Dangerous connections

the spread of infectious diseases on dynamic networks

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Dangerous connections

the spread of infectious diseases on dynamic networks

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de verspreiding van infectieziekten over dynamische netwerken

(met een samenvatting in het Nederlands)

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To diversity in science

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Chapter 1

Introduction

Infectious diseases, such as the Black Death and smallpox, have shaped human history. This is not just true for the past. Emerging infectious diseases, such as SARS and Ebola, have shown their devastating impact on society [1]. Such outbreaks remind us that the fight against infectious diseases is certainly not over. In everyday life, living in the developed world, it is easy to forget that infectious diseases still play an important role. Unfortunately, in large parts of the world, infectious diseases such as malaria, measles, and HIV still have major impact on population health [2–4].

Effective control measures require good understanding of transmission pathways. The usual process of scientific investigation is to observe a phenomenon, hypothesize an explanation, and design an experiment to test this hypothesis. In infectious disease epidemiology it is often not possible or ethical to do experiments. In such cases, mathematical modelling comes in helpful. Mathematical modelling has proven to be very useful in understanding infectious disease dynamics [5–7].

Dangerous connections

In studying the transmission dynamics of infectious diseases in a population, a key component is the contact process. Each contact, where the definition of a contact is very much context dependent (see Chapter 12 'What is contact' of [8]), generates a possibility of transmission of infection. In traditional infectious disease modelling random mixing is often assumed. Individuals randomly make contacts with one another in the population. In the large population limit, this means that two individuals meet no more than once. This assumption on the contact process has proven to work well in understanding transmission dynamics of e.g. respiratory infections and host-vector diseases such as malaria and dengue [6].

On the other hand, in case of sexually transmitted infections (STI), such as HIV, a contact between two individuals is a sexual act. As a rule, individuals engage in sexual partnerships and have multiple sexual contacts with the same partner before separation. In such a case, the contact pattern deviates too strongly from the random mixing assumption. It becomes essential to take the underlying sexual network structure into account.

One can imagine that network structure can have large influences on the transmission dynamics in a population. Indeed, in a monogamous population, an infectious individual can transmit infection to its susceptible partner. But then, infection cannot spread further, not until that partnership dissolves and a new partnership with a susceptible individual is formed. In that way, a partnership between two infectious individuals prevents infection to spread further. On the other hand, this is no longer the case in a population in which individuals may have concurrent partnerships (multiple partners at the same time). If an infectious individual has more than one susceptible partner at the same time then it may transmit infection to these partners. In turn, these partners may themselves have other susceptible partners to which they could then transmit infection to. It is conceivable that that STI transmission dynamics are different in a monogamous population compared to a non-monogamous population. The natural question arises: how does this impact the spread of STI in a population?

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HIV and concurrent partnerships

Do concurrent partnerships drive the HIV epidemic in sub-Saharan Africa? HIV is a sexually transmitted infection that causes AIDS. To this day, there is no cure for AIDS. Fortunately, with the right therapy, the virus can be controlled for a long time. In most parts of the world, HIV remains concentrated in specific high risk groups such as injecting drug users, men who have sex with men, and sex workers. In contrast, in sub-Saharan Africa, HIV prevalence remains high and is widespread among *heterosexual* populations. In this region, the main mode of transmission is through heterosexual contact [9].

Could concurrent partnerships offer an explanation for the large difference between the spread of HIV in sub-Saharan Africa and the rest of the world? About a decade ago, this was one of the hypotheses that has been put forward [10]. It has been a topic of debate for a long time now [10–17]. On the one hand, modelling studies [18–21] consistently show the potential impact of concurrency on the spread of infection. On the other hand, empirical evidence is inconclusive [22–24].

Incidentally, note that concurrency is not the only risk factor that has been considered in relation to HIV epidemics in sub-Saharan Africa. Sexual behaviour patterns are considered besides concurrency, e.g. transactional sex, age-mixing of younger women with older men. But also biological factors are considered, e.g. male circumcision and co-infection with other diseases such as other STI, malaria, tuberculosis [25–28]. There is no consensus on what the main drivers of HIV epidemics are nor did we try to investigate all this. To me, it seems likely that there are many different factors that play a role in HIV epidemics, from sexual behaviour to biological to political and financial factors, and concurrency is probably not *the* driver of HIV epidemics in sub-Saharan African countries. Note that we speak about 'sub-Saharan Africa' throughout the thesis, ignoring the diversity in populations in that region. While we were motivated by the concurrency debate, our aim was to understand the impact of concurrent partnerships on the spread of STI on a qualitative level using a mathematical modelling approach.

When it comes to concurrency, results from empirical studies are mixed. Some empirical work suggests that concurrent partnerships are positively correlated to HIV prevalence (e.g. [22]) while others suggest that no association exists (e.g. [23]). Then again, there is also an empirical study suggesting that traditional polygyny, the practise of concurrency where women are monogamous but men may not be, is negatively correlated to HIV prevalence [24]. One immediate conclusion that we can draw from all this is that it is not clearly understood how concurrent partnerships may impact the spread of STI. Therefore, we aimed to develop a flexible mathematical framework for a dynamic network and the spread of infection to understand the effect of concurrent partnerships on the spread of STI. Before we discuss the modelling aspects, let us first have a closer look at concurrency.

Difficulties in studying concurrency are manifold. Aside from aspects associated with empirical studies, also in theoretical settings, it is not easy to study concurrency. One of the issues with concurrency is that it is a network property, which makes it difficult to study in isolation from other network properties [11, 29, 30]. Moreover, while concur-

rency is a very intuitive notion, to compare the level of concurrency in different populations with each other we need a rigorous definition. On the one hand, we want to capture concurrency in the population at some fixed point in time. On the other hand, the concurrency time-window also plays a role. For example, which of the following individuals contributes more to concurrency: an individual who retains the same five partners during its entire lifetime or an individual who has two concurrent partners at any time, but twenty partners in its lifetime? We need to capture all those aspects mathematically by considering both the number of concurrent partners of an individual at a particular point in time and the time it spends in such a concurrent state.

Furthermore, there are many forms of concurrency. One form that we already mentioned is polygyny, a traditional form of concurrency. Based on their findings, Reniers and Watkins [24] hypothesized that some forms of concurrency might have a benign effect on HIV transmission dynamics in a population. In polygynous populations, concurrency is very gender asymmetric. Women do not have any concurrent partnerships but men may. How does this affect the population? Do we need to compare this to a population with the same mean number of concurrent partnerships but then evenly distributed among both genders?

The difficulty in translating the intuitive notion of concurrency to a rigorous definition can also be seen in literature. There is no consensus on an indicator for the level of concurrency in the population, e.g. [31–34]. As a consequence, it is often difficult to fairly compare different studies with each other, complicating the debate on concurrent partnerships. As there is no consensus in indicators for concurrency, when we studied epidemiological questions in relation to concurrency in Part II, we use the partnership-based concurrency index as an indicator for concurrency. This measure was first considered in [35]. We introduced this index in Chapter 2. It measures the mean number of additional partners that an individual in a randomly chosen partnership has.

In order to study how concurrency impacts the spread of STI in a population we needed a mathematical model for the underlying sexual network. We aimed to formulate models for the spread of infection on *dynamic* networks that are amenable to analysis in the large population limit. An important advantage of such simple models is that only a few parameters need to be considered to study how network properties such as concurrency impact transmission dynamics.

Networks

Sexual networks can be viewed as a collection of nodes (vertices), that represent individuals, and links (edges), that represent partnerships between individuals. Networks have attracted a lot of attention in many different research areas. Many structures can be viewed as a network, such as neural networks, transportation networks, and food webs [36–38]. In more mathematical language, any structure that can be captured by vertices and edges representing the entities and connections of interest, respectively, can in principle be viewed as a network. Next to the network structure, we may also be interested in some sort of dynamical process taking place on these networks, e.g. the spread of an STI on a sexual

network.

However, next to properties that networks may share with each other, there are also fundamental differences. In case of an STI, the network of connections of interest are the sexual partnerships. These connections are obviously very different from e.g. the (directed) connections in the twitter network where the connections are between 'followers' and anyone can connect to anyone else. These networks also have very different structure: twitter networks have a power-law distribution while sexual networks usually do not. So there are many differences and subtleties involved in modelling and research questions related to networks. In this thesis our focus was specifically on modelling and analyzing sexual networks and the spread of infectious diseases on these networks.

Now let us turn to sexual networks and STI. Consider the sexual network structure in a population and suppose an STI is introduced in the population from the outside. Next to transmission dynamics, the network itself may also be changing over time by individuals entering and leaving the population and partnerships forming and dissolving over time. Depending on the time scales of transmission dynamics relative to partnership-, and demographic changes, we can make different assumptions about the network dynamics. In this thesis (Chapter 4) we considered three situations that are characterized by the relative time scales.

When disease dynamics are fast relative to any partnership- or demographic changes then we may assume the network to be *static*. Epidemics on static networks have been much investigated and there is well-established general theory on static configuration networks [37, 39–42]. On the other hand, if disease dynamics are on the time scale of partnership changes but fast relative to any demographic changes, then we need a model for a network that is dynamic without demographic turnover. Then finally, when disease dynamics are on the time scale of partnership- and demographic changes, such as with HIV, then we need to consider networks that are dynamic both in partnership-formation and -separation and demographic turnover. Epidemics on *dynamic* networks are much harder to describe and analyze. Some statistical description of the network structure is needed before one can start modelling infection on the network. Currently, simulation studies of special cases prevail [20, 43–46] but the developments of more general frameworks have attracted more attention [47–51] and this thesis.

The class of network models that we consider in this thesis is based on the configuration network construction. Individuals are in some sense a collection of a fixed number of *binding sites* for partners. In static networks, what we call 'binding sites' here are often called 'half-edges' or 'stubs'. We use the term binding sites as we think this to be more appropriate for dynamic networks. The idea of the static configuration network construction is as follows (but see e.g. [42] for a mathematically rigorous construction). In a finite population of individuals, two binding sites (or half-edges) are randomly connected to each other and the owners of these binding sites are then in a partnership with each other. This process is repeated until no more (or only one) free binding sites exist. This yields a static network. In the large population limit the relative probability of any self-loops or multiple partnerships between two individuals becomes zero. In the dynamic network cases, free binding sites are connected through this construction and existing partnerships can dissolve (and, in the case with demography, individuals can enter and leave the pop-

ulation).

The dynamic network with demography can be seen as a generalization of pair-formation models. In the epidemiological context these were first introduced by Dietz and Hadeler in [52] and extended by various people in different ways [19, 53–56]. These pair-formation models describe partnership- and demographic changes in monogamous populations. Our models can be seen as generalizing from individuals having at most one partner at a time to allowing individuals to be in multiple partnerships at a time. In our modelling framework, the number of binding sites of an individual determine the maximum of simultaneous partnerships it may have.

As the motivation for this thesis comes from the debate on concurrency and HIV, as also given away by the thesis title, our main focus was on networks that were dynamic in both partnership- and demographic changes (all chapters except for Chapter 4). However, the framework presented in Chapter 4 is much more general and other network dynamics can easily be considered.

The infectious disease

Assumptions on the contact structure are an important part in modelling transmission dynamics. We have argued that, for STI, one should take into account some kind of network structure that allows for repeated contacts between the same individuals. Another important component is the infectious disease. While much attention is paid to the contact structure in literature, in particular to network [57–59], assumptions on the infectious disease is generally less discussed.

Traditionally, in modelling infectious disease dynamics, compartmental models are used (but see e.g. the seminal paper by Kermack and McKendrick [60]). In such compartmental models, individuals are classified in a finite number of stages; e.g. in the well-established SIR model, individuals are Susceptible, Infectious, or Recovered. Implicitly this assumes that an infectious individual has a constant infectiousness that immediately drops to zero after an exponentially distributed amount of time.

Compartmental models often lead to a description in terms of ordinary differential equations (ODE). Much existing mathematical theory can then be used to analyze these systems of ODE. Moreover, outside the mathematics community, ODE are also well accepted to describe models of dynamical processes. They are the predominant building blocks for models in the infectious disease epidemiology community.

In this thesis we also use compartmental models to describe the infectious disease (with an exception in Chapter 4). As with the random mixing assumption for contacts, mathematical convenience is of course an important motivation to use compartments for the infectious disease. Besides that, the simplifying assumptions on both contact structure and infectious disease have proven to be successful in understanding transmission dynamics [6, 7] (see also Section **Dangerous connections**). So it is not without reason that these assumptions are so widely used. However, I want to stress here that one should keep in mind the assumptions that are made implicitly when using compartmental models.

1

Characterizing infectious disease dynamics

By formulating the models mathematically, we can study the disease dynamics on the network by characterizing and analyzing epidemiological quantities. Depending on the specific epidemiological question under consideration one may be interested in different aspects of the transmission dynamics in a population, e.g. the beginning of an epidemic outbreak or the end of an outbreak.

Arguably, one of the most important quantities in infectious disease epidemiology is the basic reproduction ratio R_0 [8]. It is a threshold parameter with a threshold value of one for the epidemic to take off (in deterministic models this is with probability one). It can be interpreted as the expected number of secondary cases generated by one typical newly infected individual at the beginning of an epidemic. R_0 is often of great interest to public health officials as it has an individual-level interpretation. In this way it gives some indication on e.g. how much effort is needed to reduce the number of new infections generated by one individual to control an epidemic.

An important part of this thesis is dedicated to the characterization of R_0 (Chapters 3 and 4). What is important to keep in mind here is that, for any given system that describes an infectious disease model, there can be more than one threshold parameter (with threshold value of one) for the disease free steady state. However, we are generally interested in not just any threshold parameter but threshold parameters that have a biological interpretation (as 'reproduction' numbers, where 'reproduction' does not have just one meaning). Moreover, we are interested in proofs: is the quantity that is derived purely based on the interpretation on the individual level really a threshold parameter for the stability of the disease free steady state of the population-level system?

The most 'standard' way to characterize R_0 is the next-generation-matrix approach [8] where R_0 is the dominant eigenvalue of a matrix $K = (k_{ij})$. The elements k_{ij} can be interpreted as the expected number of new infectious cases of type i caused by a newly infected case of type j in the beginning of the epidemic and, if one is lucky, one can derive this matrix K based purely on the interpretation. This is the approach that we take in Chapter 3. However, this does not immediately provide a proof for the threshold behaviour of R_0 for the disease free steady state of the population-level system. In Chapter 3 it takes quite some work, via contrived linear algebra arguments, to provide this proof. In Chapter 4 we take a different approach to derive the same threshold parameter R_0 by considering 'reproduction opportunities'. The proof comes more or less for free!

If $R_0 > 1$ then an epidemic can take off in the population. In the case that an infection can establish itself in the population, i.e. become endemic, we are typically interested in the endemic disease prevalence. In the case of a closed population and an infection with recovery, eventually, no one in the population is infectious any more and there is an end to the epidemic outbreak. In such settings we are interested in the final size of the outbreak: what fraction of the population was ever infected? Ideally we would want to have explicit expressions for such epidemiological quantities in terms of model parameters. In case that this is not possible, we are interested in providing some sort of useful characterizations. The final size and endemic equilibrium are investigated and discussed in Chapter 4.

Binding site models for infectious disease dynamics

The title of this thesis is borrowed from Chapter 4 which also forms the heart of this thesis. We already mentioned 'binding sites' in the context of networks. In Chapter 4, using binding sites, we provide a structured way to formulate models for infectious disease spread on networks. We distinguish three different levels: (1) binding sites, (2) individuals, and (3) the population. Systematic model formulation relates the three different levels to each other. In Chapters 2 and 3, we make use of the binding site level but the model formulation is on the individual and population level without fully exploiting the binding site level. This is done in Chapter 4, where we make explicit how the three different levels are related in more generality.

In the tradition of physiologically structured population models [61–63], the formulation starts on the individual level. Individuals can be in a finite number of states that contain information about partners. Information about partners of partners is not included and a 'mean field at distance one' assumption is needed; properties about partners of partners can be obtained by averaging over the population.

On the binding site and individual level, population-level influences are captured in environmental variables. A key assumption is that individuals are collections of a fixed number of conditionally independent binding sites. The binding site dynamics are captured by only a few equations.

Individual-level probabilities are obtained from binding-site-level probabilities by combinatorics while population-level fractions are obtained by averaging over individuals in the population. So also population-level fractions be expressed in terms of binding site probabilities. In this way, binding site probabilities determine the dynamics on the individual- and population-level. Moreover, the equations describing the binding-site dynamics allow us to characterize epidemiological quantities such as R_0, r, the final size, and the endemic equilibrium.

The strength of the binding site formalism is that it provides a way to deal with the spread of infection on networks in a precise and systematic way. At the same time, the framework is flexible and allows for several meaningful generalizations (Chapter 5). Moreover, the class of models is amenable to analysis. The formalism provides a way to deal with dynamic networks that are dynamic in both partnership changes *and* demographic changes. The binding site models allow for a better understanding of the spread of infection on networks which makes them powerful in studying epidemiological questions (Part II). Therefore, I believe that the binding site models are an important addition to the mathematical modelling toolbox.

Outline

This thesis roughly consists of two parts. In Part I we focus on model formulation and mathematical analysis. In Part II we turn our focus to the investigation of epidemiological questions using the models of the first part. As one can deduce from the number of

pages of the first part compared to the second part, the main focus of this thesis was on mathematical modelling and analysis.

In Chapter 2 we introduce the dynamic network model that formed the basis for the other chapters in this thesis. The model is described and analyzed and several network statistics are characterized. Next, the infectious disease model is introduced in Chapter 3. In this chapter, an SI infection is superimposed on the dynamic network of Chapter 2. We characterize R_0 using the next-generation-matrix approach on the infectious binding site level. A large part of the chapter is devoted to proving that R_0 defined in this way is a threshold parameter with threshold value of one for the population-level system of ODE. In Chapter 4 we explicitly write down the systematic approach that we take in our model formulation. In essence, there are five steps involved in connecting the binding-site, individual, and population level to each other. We illustrate this method by considering, on three different time scales, an SIR infection superimposed on a network. Finally, in Chapter 5 we consider several generalizations of the dynamic network model. We show how, by using the steps of Chapter 4, the generalizations can be implemented. Due to the flexibility of the modelling framework, really only the bookkeeping becomes more involved.

Note added in proof. Unfortunately, life is not a bed roses. It turns out that not all generalizations are so straightforward. The how and why can be found in Section 6.2 of Chapter 5, which was added at a very late stage.

In part II we apply the models to study epidemiological questions. First, in Chapter 6, we study the association between concurrency and R_0. We show that an increase in concurrency, while keeping other key network statistics fixed, can move the epidemic threshold R_0 from below to above the threshold value of one. Next, in Chapter 7, motivated by the findings of Reniers and Watkins [24] in their empirical study on HIV prevalence and polygyny, we investigated the effect of asymmetry in concurrent partnerships in men and women on the infectious disease dynamics in the population. We looked at the most asymmetric situation of a polygynous population and compared this with more symmetric situations. We found that asymmetry in concurrent partnerships is associated with a lower R_0 in the beginning of the epidemic, a lower relative contribution of the acute phase of infection to R_0, as well as lower prevalence in the endemic situation.

Outlook and take home message

This thesis ends with a general discussion in Chapter 8. For the readers that will never make it that far, I end this introduction with a summary of the main points of discussion of Chapter 8.

In Chapter 8, I go in depth into some of the model assumptions, some more technical issues, possibilities for generalizations, etcetera. That part of the discussion relates very much to the content of this thesis. I also draw some more general conclusions that relate more broadly to mathematical modelling in infectious disease dynamics, and this is what I want to end this introduction with.

First of all, the binding site formalism developed in Chapter 4 offers a novel way to deal with models for the spread of infectious diseases on networks in a rigorous and precise way. The systematic approach makes it easy to understand the mechanisms underlying the model. The toolbox is especially useful in modelling *dynamic* networks that also incorporate *demography*. The binding-site framework is also an excellent starting point for many different possible generalizations (Chapter 5) and applications in relation to networks (static and dynamic) and transmission dynamics.

Note added in proof. Since writing this I have discovered that things are not all as straightforward as they seemed. See Section 6.2 in Chapter 5 for a discussion on generalizing to partnership capacity as a random variable.

Now let us turn our attention to the question that all readers probably have at this point in the introduction: does concurrency drive HIV epidemics in sub-Saharan Africa and can polygyny really be protective? In Chapter 6 we showed that concurrency can move the epidemic threshold R_0 from below to above the threshold value of one. In Chapter 7 we showed that gender asymmetry in concurrent partnerships, and especially polygyny, is associated with lower levels of HIV prevalence. In this way, the two modelling studies contributed to a better understanding of the role that concurrent partnerships *can* play in generalized HIV epidemics in sub-Saharan Africa. Moreover, the strength of these two studies lies also on the methodological side. We carefully defined different scenarios that enabled us to study the effect of a specific property on the disease dynamics.

However, it is important to keep in mind that the two modelling studies in Part II were qualitative in nature, and therefore not describing what is going on in *reality* (in reality, concurrency is most likely not the only risk factor; see also Section **HIV and concurrent partnerships**). One should not confuse models with reality, and models can never replace empirical research (they can however complement empirical work, but more on that in Chapter 8). So, in the end, my answer to the concurrency question for now is: further investigations are needed.

What I did learn from this thesis is that the concurrency question is difficult to investigate, despite, or perhaps because, concurrency being very intuitive. There are many factors that one needs to take into account. Even with simple models, with only few parameters to control, it is hard to study concurrency as an isolated property. There is more than one way to do so. This was also one of the challenges in this thesis: how do we compare populations with each other in a fair way? Our answer to this question resulted in the methods used in Chapters 6 and 7. This is discussed in more detail in Chapter 8.

When doing applied research (applied from the point of view of mathematics, extremely theoretical from the point of view of infectious disease epidemiology) there needs to be a balance in satisfying scientific curiosity and relevant applications. One can easily argue that the balance in this thesis was less on the applications and much more on the theoretical explorations. This has led to a lot of interesting and enjoyable mathematical models and analysis. But in many ways this was also the safe route to take. Not having to deal with reality and all its complexity makes life a lot easier as reality is not that easily captured in mathematics.

So, reality is complex. But this is exactly what we want models for: to simplify! [64]

It is easy to get carried away and end up with a model that does not resemble the real world in any way. It is my belief that this was not the case here. Although the binding site framework is caricatural there is enough reality in the models to be useful. Our models capture some of the essential features of a real world sexual network, i.e. demographic changes and partnerships dynamics. I did spend an awful lot of time failing to prove a conjecture about the existence and uniqueness of the endemic steady state (but really, if one has an easy numerical way to determine the endemic steady state, then who cares?). In the end, I can say that this failure ended up for the best as it resulted in Chapter 4.

So, on the one hand one needs to translate behavioural and biological processes into models in a way that balances simplicity and capturing reality. On the other hand, one needs to formulate models mathematically. This gives rise to challenges related to model analysis. Then again, one wants to use the models to answer relevant epidemiological questions. In order to do so, a translation from the mathematics to the interpretation needs to be made. Each of these aspects come with their own challenges. It is exactly that diversity in problems that makes infectious disease dynamics, or more generally mathematical biology, so exciting and challenging to work in.

In this thesis we let the interpretation guide our analysis. In particular with relation to R_0, we took on many different perspectives: from the population to individuals to binding sites, both the infectious and susceptible perspective. I believe that this is one of the strengths of this thesis: we did not limit ourselves to one view. I would highly recommend exploiting many different views (in mathematical modelling and beyond). It can prove worthwhile to move away from the standard.

Finally, there are different aims one can have with models. One may want models that are very detailed and are good at predictions. But a super complicated 'black box' that makes excellent predictions is rather unsatisfying in my opinion. Ideally, I would like mathematical models to enhance our understanding of different mechanisms at play. This thesis has hopefully made a small contribution to that.

Part I

Model formulation and analysis

Chapter 2

Dynamic concurrent partnership networks incorporating demography

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Abstract

We introduce a population model that incorporates

- demographic turnover
- individuals that are involved in a dynamically varying number of simultaneous partnerships

From a mathematical point of view we deal with continuous-time Markov chains at the individual level, with the interaction between individuals captured by a global variable describing opportunities for new partnerships. We show that for large time a stationary distribution is attained and we deduce various statistical features of that distribution, with particular attention for concurrency, i.e. the overlap in time of multiple partnerships of one and the same individual. Our ultimate motivation is to model the spread of sexually transmitted infections in the population, for which the present paper serves as a prelude.

1 The motivation

For a long time now, there has been a debate about the possible impact of concurrent partnerships (the overlap in time of multiple partnerships of one and the same individual) on the transmission dynamics of HIV, especially in the high prevalence areas of Southern Africa. In those regions, HIV transmission is mainly by way of heterosexual contact. In recent years, the hypothesis that concurrent partnerships are an important driver of that high prevalence has been put forward [10, 14, 17] and contested [11, 13]. At the same time, [24] showed a negative association between HIV prevalence and population prevalence of polygynous marriages in an ecological study of several sub Saharan African countries.

In the debate about the influence of concurrency, mathematical modeling results have played a pivotal role [17, 18, 20, 21, 35, 65]. In the work by Morris and Kretzschmar [35, 65], the impact of concurrency was investigated in simulations that aimed to isolate the effect of concurrency from other network influences. Quantitative measures for the level of concurrency in a population were suggested, that could then be related to observed degree distributions on the one hand, and to specific simulation results on the other hand. However, a mathematical framework suitable for deriving analytic results about the impact of concurrency on HIV transmission is still lacking. This is due to the difficulties in deriving explicit analytical results for a full dynamic network model. Indeed, most analytical results for networks to date have been derived for static networks with strong restrictions on their structure.

Here we propose a mathematical formulation of a multiple dynamic partnership formation and separation process that leads to a configuration network in a population with demographic turnover. In other words, we define a dynamic process of link formation and dissolution and demographic turnover, and analyse its dynamics. We find that the long term dynamics yields a stationary network structure and we determine the most relevant statistical properties of this structure.

The proposed model is a direct generalization of the pair formation models describing purely monogamous populations to pair formation models where individuals are allowed to have more than one partner at a time. Pair formation models for sequentially monogamous populations were first introduced into epidemiology by Dietz and Hadeler [52] and extended in various ways [19, 53–56].

The generalization allows us to formulate a quantitative definition of concurrency that measures the number of partners an individual typically has during his/her life course when the population composition is in steady state. Concurrency at the population level is thus linked to parameters describing individual behaviour such as the rate of engaging in partner relations and the rate of dissolving such relations. In other words, we investigate how these rates shape the structure of the network. This will then lay the foundation for interpreting results in terms of individual behaviour when, in follow-up work, we study transmission of an infection across the network (we are, so far, apart from [49, 66], not aware of any analytical work on disease transmission across dynamic networks with demography (see e.g. [44, 47, 50, 51, 67–69] for models incorporating dynamic relations

in a demographically closed population)).

The structure of the paper is as follows. In the next section we specify the model assumptions in detail. Section 3 is devoted to showing that for large time a stationary distribution is attained and in Section 4 some elementary statistical features of that distribution are derived. In Section 5 we present a motivated definition of two different concurrency indices and deduce an explicit formula in terms of the model parameters for each of these. Next, we discuss ways to normalize the 'total magnitude' of partner ties and present a quantitative comparison of the two indices. The final section is devoted to a short description of heterosexual and heterogeneous variants of the dynamic partner model. Seven short appendices contain the more technical aspects of various results presented in the main text.

2 Formulation of the model

Even though an individual practising monogamy may accumulate quite a few partners during life, it has at most one partner at a time. We say that an individual has partnership capacity n if the maximum number of simultaneous partners equals n. So, in case of a monogamous individual, $n = 1$.

Partnership capacity can be interpreted as an implementation of a social norm. The obvious example is of course monogamy, but in some sub-Saharan African populations having a second steady partner, next to your husband or wife, is accepted ($n = 2$) [70], while, in others, men may have multiple partners but women are supposed to be monogamous (a system called polygyny) [71, 72].

It is convenient to think in terms of binding sites. When an individual with partnership capacity n has k partners, with $0 \leq k \leq n$, we say that k binding sites are 'occupied' and $n - k$ binding sites are 'free' and that the individual is in state k. (In [50] free binding sites are called dormant.) A key assumption will be that binding sites of an individual will behave independently from one another (we realize that this is a weakness of the model; yet it is exactly this assumption that makes the model tractable). Another key assumption will be that partnership formation is supply driven in the sense that the rate at which a free binding site becomes occupied is proportional to the population-level frequency of free binding sites.

In this paper we focus on a homosexual population in which every individual has the same partnership capacity n. In Section 6 we briefly discuss the generalization to heterosexual and heterogeneous populations.

The model specification begins at the individual level. As long as an individual does not die, it is involved in a Markov process that changes its number of partners. There are $n + 1$ states, corresponding to $0, 1, \ldots, n$ partners (hence it is convenient to use these numbers to indicate the states). Rather than studying the realizations of the process, we study the probabilities p_k that the state equals k, as a function of time between time of birth and time of death. We consider a very large population and, as usual, arrive at a deterministic description by interpreting the probability as a fraction.

Consider one individual and suppose it does not die in the period under consideration,

then any one of its occupied binding sites becomes free with probability per unit of time $\sigma + \mu$. Here σ corresponds to 'separation' and μ to 'death of partner'. At the population level we can consider the pool of binding sites, and each binding site is either occupied or free. The fraction of free binding sites will be denoted by F. Note that here $F = F(t)$ even though eventually we shall work with constant F (but only after we deduce that F does indeed become constant). We assume that a free binding site becomes occupied with probability per unit of time $m(F) = \rho F$. (Note that, by working with the *fraction*, the possible influence of population size is incorporated in the parameter ρ. Also note that all our results extend to non-decreasing continuous non-negative functions $m(F)$ satisfying $m(1) > 0$.) At recruitment into the sexually active population ('birth' for short) the individual has no partner at all, i.e. $k = 0$.

We now list the possible state transitions of an individual and the rates at which they occur:

$$\begin{aligned} k &\to k+1 \qquad \text{with rate } \rho(n-k)F, \\ k &\to k-1 \qquad \text{with rate } (\sigma+\mu)k. \end{aligned} \tag{2.1}$$

Let $A = A(F)$ denote the corresponding $(n+1) \times (n+1)$ tridiagonal matrix. Let $p_k(t_b, a)$ denote the probability that an individual, born at time t_b, is in state k at age a. Then, as long as the individual does not die, we have

$$\frac{\partial p}{\partial a}(t_b, a) = A\big(F(t_b + a)\big)p(t_b, a). \tag{2.2}$$

We supplement (2.2) with the initial condition

$$p(t_b, 0) = \begin{pmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{pmatrix}. \tag{2.3}$$

Now we turn to the population level. We assume that there is a constant population birth rate and that the lifetime of an individual is exponentially distributed with parameter μ. In other words, we assume a stationary age distribution with probability density function

$$a \mapsto \mu e^{-\mu a}.$$

There is no need to specify the population birth rate or, for that matter, the population size, as the one and only nonlinear process, i.e. the formation of new partnerships, is defined in terms of fractions. So if one aims to compare populations of different size, there are two key issues:

- are both large enough to warrant a deterministic description?
- if so, can we take the same parameter ρ for both or should we adjust this parameter to the absolute size?

Let $P_k(t)$ denote the fraction of the population that is in state k at time t. Then, in a deterministic description of a large population,

$$\begin{aligned} P_k(t) &= \mu \int_0^\infty e^{-\mu a} p_k(t-a,a)da \\ &= \mu \int_{-\infty}^t e^{-\mu(t-\alpha)} p_k(\alpha, t-\alpha)d\alpha. \end{aligned} \tag{2.4}$$

We now define

$$F(t) = \frac{1}{n}\sum_{k=0}^{n}(n-k)P_k(t). \tag{2.5}$$

Finally, consider an individual with free binding sites. We assume, in accordance with (2.5), that a newly acquired partner at time t will have state $k+1$ with probability

$$\frac{(n-k)P_k(t)}{\sum_{l=0}^{n}(n-l)P_l(t)}. \tag{2.6}$$

(A potential partner with state k has $(n-k)$ free binding sites. Immediately after a match is made it will have state $k+1$. The denominator serves to renormalize into a probability distribution.) We shall show in Lemma 2 below that this assumption gives us information on the state of an individual in a randomly chosen partnership.

3 The analysis

The dynamics of partnerships in the population are governed by the fraction of free binding sites F. Due to the assumption of independence between binding sites, the dynamics of F decouple as stated in our first lemma (the proof is presented in A).

Lemma 1. *The fraction of free binding sites F satisfies the differential equation*

$$\frac{dF}{dt} = \mu + (\sigma+\mu)(1-F) - \rho F^2 - \mu F. \tag{3.1}$$

It follows from Lemma 1 that

$$F(t) \to \bar{F},$$

for $t \to \infty$, where

$$\bar{F} = \frac{\sqrt{(\sigma+2\mu)(4\rho+\sigma+2\mu)} - (\sigma+2\mu)}{2\rho}. \tag{3.2}$$

Note that this fraction of free binding sites does not depend on the partnership capacity n.

This convergence motivates us to concentrate on (2.2)-(2.3) and (2.4) with F constant and equal to $\bar{F}$ (see also Remark 1 below). Note that in that case the matrix A in (2.2) is constant as well, and hence the argument t_b of p no longer matters. Therefore we drop this argument t_b and write $p = p(a)$ from now on. The argument t of $P_k(t)$ given by (2.4) also no longer matters and we write P_k instead.

For constant F, we can easily find the explicit solution to (2.2)-(2.3). Let $\epsilon(a)$ denote the probability that a binding site is occupied at age a, given that the 'owner' of this binding site is alive. Then ϵ satisfies

$$\begin{aligned} \frac{d\epsilon}{da} &= \rho\bar{F}(1-\epsilon) - (\sigma+\mu)\epsilon, \\ \epsilon(0) &= 0. \end{aligned} \tag{3.3}$$

This initial value problem has the explicit solution

$$\epsilon(a) = \frac{\rho\bar{F}}{\rho\bar{F}+\sigma+\mu}\big(1 - e^{-(\rho\bar{F}+\sigma+\mu)a}\big). \tag{3.4}$$

Conditional on the individual being alive, binding sites are independent from one another. Therefore

$$p_k(a) = \binom{n}{k}\epsilon(a)^k\big(1-\epsilon(a)\big)^{n-k}. \tag{3.5}$$

See B for a proof that (3.5) satisfies (2.2)-(2.3).

Combining (2.4) and (3.5) we obtain

$$P_k = \binom{n}{k}\mu\int_0^\infty e^{-\mu a}\epsilon(a)^k\big(1-\epsilon(a)\big)^{n-k}da. \tag{3.6}$$

If the binding-unbinding process is fast on the time scale set by the life time of the individuals, the fact that at birth an individual has no partners at all has negligible effect. More precisely, we have

$$P_k \to \binom{n}{k}(1-\tilde{F})^k\tilde{F}^{n-k}, \tag{3.7}$$

as $\mu/\sigma \to 0$ while ρ/σ remains constant, where

$$\tilde{F} = \frac{1}{2\rho}(\sqrt{\sigma(4\rho+\sigma)} - \sigma) \tag{3.8}$$

is the nonnegative solution of

$$\sigma(1-F) - \rho F^2 = 0$$

(in a population without demographic turnover, the left hand side describes the rate of change of the fraction of free binding sites F). So in that limit the fractions P_k follow a binomial distribution. See C for the details.

In Figure 1 we have plotted some graphs of $k \mapsto P_k$ and the approximation (3.7) for ratios σ/ρ and σ/μ and partnership capacity n.

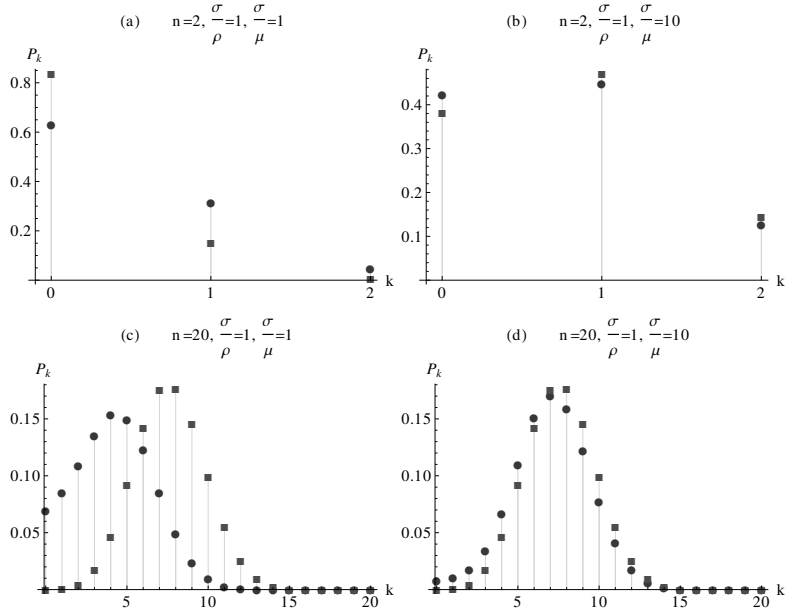

Figure 1: The probability distribution $(P_k)_{k=0}^n$ given by (3.6) (blue circles) and the approximation (3.7) (purple squares) for different ratios of σ/μ and σ/ρ and variable n. See also Table 1.

Next, choose a partnership at random from the pool of all partnerships and consider one of the two partners (by exchangeability it does not matter which one). For convenience, let us call this individual v. By assumption (2.6) in Section 2 we know the probability distribution of the state of v at the moment the partnership was formed (without this assumption, all we would know is that v has at least one partner since information about the state of partners is not incorporated in our model description). The following lemma, whose proof we provide in D, describes the probability distribution of the state of v at the time we sample the partnership in which v is involved.

Lemma 2. *Choose an individual by first sampling a partnership from the pool of all partnerships and next choosing one of the two partners. The probability that this individual has m partners equals*

$$Q_m = \frac{mP_m}{\sum_{l=1}^n lP_l}, \tag{3.9}$$

This lemma will be very useful when we consider the partnership-based concurrency index κ_P in Section 5.2.

To conclude this section, we summarize our findings.

Theorem 1. *The population structure stabilizes: a random individual has k partners with probability P_k given by* (3.6) *and a random partner has m partners with probability Q_m given by* (3.9)*.*

Remark 1. *Both the model formulation and the analysis avoid the subtle issues associated with initial conditions. Strictly speaking, we have only derived the stable structure for individuals that are born in a world with constant $\bar{F}$ and for partnerships that are formed between such individuals. In [73, Section 2.5] a full proof is given for a related, but somewhat different model. It involves arguments about ω-limit sets.*

4 Partnership dynamics and individual life history: some statistics

The Markov-chain description at the individual level allows us to determine certain expected values quite easily. First of all, the expected life time of an individual is

$$1/\mu.$$

Since binding sites behave independently, the expected duration of a partnership is

$$1/(\sigma + 2\mu).$$

We will write λ for 1 over the expected duration of a partnership, i.e.

$$\lambda := \sigma + 2\mu. \tag{4.1}$$

For constant F, we can write (2.4) as

$$P_k = \frac{\text{mean time an individual spends in state } k}{\text{mean life time}}, \tag{4.2}$$

i.e. the proportion of the population that is in state k is proportional to the mean time an individual spends in state k, a form called the 'microcosm principle' by Mollison [74].

If we consider a population snapshot, then, by Theorem 1, the mean number of partners of an individual in this snapshot is given by

$$\sum_{k=1}^{n} kP_k.$$

The relation (4.2) provides an interpretation of this quantity in terms of the life of an individual.

Consistency requires that

$$\sum_{k=1}^{n} kP_k = n(1 - \bar{F}) \tag{4.3}$$

(indeed, both sides represent the expected number of occupied binding sites of an individual) and this relation does indeed follow from the definition (2.5) of F.

We can also determine the expected lifetime number of partners, which we denote by θ. Note that, in our deterministic setting (with population size $\to \infty$), an individual encounters the same partner twice with probability zero.

Let X denote the lifetime number of partners of a newborn individual. Then $X = X_1 + \ldots + X_n$, where X_j is the number of times binding site j switches from free to occupied in the life of the newborn individual. The binding sites $1, \ldots, n$ are subject to an identical stochastic process of binding and unbinding, but are *dependent* by way of the stopping of this process when the individual dies. However, we are interested in the expected value of X and $\theta := \mathbb{E}(X) = \mathbb{E}(X_1 + \ldots + X_n) = n\,\mathbb{E}(X_1)$, where $\mathbb{E}(X_1)$ is the expected number of times the newborn binding site with label 1 becomes occupied. The binding site will leave the pool of binding sites at rate μ (since the corresponding individual dies at this rate), becomes occupied at rate $\rho\bar{F}$ and becomes free at rate $\sigma + \mu$.

We first show that the Markov property implies the consistency condition

$$\mathbb{E}(X_1) = \frac{\rho\bar{F}}{\rho\bar{F} + \mu}\left(1 + \frac{\sigma + \mu}{\sigma + 2\mu}\,\mathbb{E}(X_1)\right).$$

Here, $(\rho\bar{F})/(\rho\bar{F} + \mu)$ is the probability that the free binding site becomes occupied. If the binding site becomes occupied, then the binding site can become occupied again if it becomes free first. The latter occurs with probability $(\sigma + \mu)/(\sigma + 2\mu)$. Due to the memoryless property, the additional expected number of times the binding site will become occupied is again equal to $\mathbb{E}(X_1)$. Solving for $\mathbb{E}(X_1)$ we obtain the expected lifetime number of partners of a newborn (and thus single) individual:

$$\theta = n\,\mathbb{E}(X_1) = \frac{\rho\bar{F}(\sigma + 2\mu)n}{\mu(\rho\bar{F} + \sigma + 2\mu)} = \frac{\lambda}{\mu}n(1 - \bar{F}), \tag{4.4}$$

where the last equality follows from the definition of λ $(= \sigma + 2\mu)$ and the fact that the equation defining $\bar{F}$ can be written in the form

$$\frac{\rho\bar{F}}{\rho\bar{F} + \sigma + 2\mu} = 1 - \bar{F}. \tag{4.5}$$

We see that for a newborn individual, the expected lifetime number of partners times the fraction

$$\frac{\text{expected duration of one partnership}}{\text{expected life length}}$$

$\big(= \theta(1/\lambda)/(1/\mu) = n(1 - \bar{F})\big)$ equals the expected number of occupied binding sites of an individual at one point in time. Note that the ratio of the expected durations above corresponds to the probability that we 'catch' a particular partner in a snapshot. Thus the identity makes perfect sense.

Next, we can also determine the expected number of times an individual has a partnerless period. Note that each individual will start its life as a single, so it will start out with a partnerless period. There will be individuals who will remain single their entire life, and these will therefore have one long partnerless period.

An individual in the single state acquires a partner at rate $\rho\bar{F}n$ (since it has n free binding sites which may become occupied). As a partnerless period may also end by death, the expected duration of a partnerless period is

$$\ell := 1/(\rho\bar{F}n + \mu), \tag{4.6}$$

The expected total time an individual spends in the single state is given by

$$\int_0^\infty e^{-\mu a} p_0(a) da = P_0/\mu,$$

so the expected number of partnerless periods is the expected total time an individual spends in the single state divided by the expected time of one partnerless period. Since all individuals start their life in the single state, and we are interested only in the expected number of single periods of individuals that have had at least one partner, we want to exclude the first partnerless period. The expected number is therefore given by

$$M := P_0(\rho\bar{F}n + \mu)/\mu - 1. \tag{4.7}$$

In Table 1 the statistics are summarized that correspond to the distributions $(P_k)_k$ that are plotted in Figure 1.

Figure	**a**	**b**	**c**	**d**
n	2	2	20	20
σ/ρ	1	1	1	1
σ/μ	1	10	1	10
θ	1.25	8.42	12.52	84.24
$(1/\lambda)/(1/\mu)$	0.33	0.08	0.33	0.08
$\bar{F}$	0.79	0.65	0.79	0.79
$\ell/(1/\mu)$	0.39	0.07	0.01	0.05
M	0.63	4.94	0.17	0.12
Mean $\sum_{k=0}^{n} kP_k$	0.41	0.70	4.17	7.02
Variance $\sum_{k=0}^{n} k^2 P_k - (\sum_{k=0}^{n} kP_k)^2$	0.34	0.46	5.82	4.86

Table 1: Table with some mean values belonging to parameter choices of Figure 1 with ratios σ/μ and σ/ρ fixed. Note that $(1/\lambda)/(1/\mu)$ represents the mean duration of a partnership as a fraction of the mean lifetime $1/\mu$. Note that the fraction of free binding sites $\bar{F}$ does not depend on the parameter n.

5 Defining concurrency for individuals and partnerships

We now have the framework for defining measures of concurrency at the individual and population level. At the individual level we are interested in measuring the overlap of

partnerships in time, at the population level we want to know how many partnerships are concurrent to others at a given time.

5.1 The individual-based concurrency index

In this section we will consider a measure for the concurrency of partners of an individual that takes into account both the number of partners an individual has and the duration of the period it has these partners (we shall see that we can relate that to a population-snapshot statistic).

Consider one individual. Suppose we would know its partner history (i.e. the number of partners at any moment between birth and death). We can then divide its life in intervals of constant composition of the group of partners. The concurrency score is the overlap between partnerships during the periods that the individual has at least one partner. We weigh a period in which the individual has k partners with $k-1$ times the length of this period. Note that this ensures that a period in which the individual has only one partner has weight zero since it then has no overlapping partnerships. The concurrency index κ_I is the concurrency score of the average newborn individual. In our setting it is given by

$$\kappa_I = \frac{\sum_{k=1}^{n}(k-1)\int_0^\infty e^{-\mu a}p_k(a)da}{\sum_{k=1}^{n}\int_0^\infty e^{-\mu a}p_k(a)da}.$$

It follows at once from (2.4) that tracing the life of an individual to determine κ_I yields the same answer as taking a population snapshot does:

$$\kappa_I = \frac{\sum_{k=1}^{n}(k-1)P_k}{\sum_{k=1}^{n}P_k} = \frac{n(1-\bar{F})}{1-P_0} - 1,$$

where the second equality follows from (4.3). We conclude that κ_I is equal to the expected number of partners minus one of a nonsingle individual at any one point in time.

We call κ_I the individual-based concurrency index, as we sample an individual at random from the pool of individuals having at least one partner and then count how many partners this individual has.

In a population in which all individuals are monogamous, i.e. $n = 1$, we will have $\kappa_I = 0$ (note that we always have $\kappa_I \geq 0$). The larger κ_I is, the higher the level of concurrency in the population.

5.2 The partnership-based concurrency index

The aim of this section is to introduce the partnership-based concurrency index κ_P. The operational definition is as follows: choose a partnership at random from the pool of all partnerships, focus on one of the two partners and count how many partners it has besides the 'known' partner.

According to Lemma 2, the expected number κ_P is given by

$$\begin{aligned}\kappa_P &= \frac{\sum_{m=1}^{n}(m-1)mP_m}{\sum_{l=1}^{n} lP_l} \\ &= \frac{\sum_{m=1}^{n} m^2P_m - \left(\sum_{m=1}^{n} mP_m\right)^2}{\sum_{l=1}^{n} lP_l} + \sum_{m=1}^{n} mP_m - 1,\end{aligned}$$

or, in other words, by the variance/mean+mean-1 (variance and mean are taken with respect to the distribution $(P_k)_k$).

Note that in a monogamous population ($n = 1$), κ_P is equal to zero, and $\kappa_P > 0$ for $n > 1$.

In Appendix E we derive the identity

$$\sum_{k=1}^{n} k^2P_k = n(1-\bar{F})\left(1 + \frac{2\rho\bar{F}(n-1)}{2(\rho\bar{F}+\sigma+\mu)+\mu}\right). \tag{5.1}$$

We can therefore write κ_P as

$$\kappa_P = \frac{2\rho\bar{F}(n-1)}{2(\rho\bar{F}+\sigma+\mu)+\mu}. \tag{5.2}$$

In Table 2 the concurrency indices κ_I and κ_P are compared for ratios σ/μ and σ/ρ and partnership capacity n, corresponding to the distribution $(P_k)_k$ in 1 and the statistics in Table 1.

Figure	**a**	**b**	**c**	**d**
n	2	2	20	20
σ/ρ	1	1	1	1
σ/μ	1	10	1	10
κ_I	0.14	0.18	3.49	4.59
κ_P	0.24	0.36	4.57	6.85

Table 2: Table comparing the two concurrency indices κ_I and κ_P for ratios σ/μ and σ/ρ and partnership capacity n. The letters (a)-(d) correspond to the letters in Figure 1 and Table 1.

5.3 Comparing the individual- and partnership-based concurrency indices

We now investigate κ_I and κ_P as functions of the partnership capacity n, the expected lifetime number of partners θ, and the expected duration of a partnership $1/\lambda$ and we compare the two indices.

We first consider the individual-based concurrency index κ_I. We can express κ_I as a

function of n, θ, and λ in the following way:

$$\kappa_I(n,\theta,\lambda) = \frac{\theta}{\lambda}\left(1-\int_0^\infty e^{-a}\left(1-\frac{\lambda\theta\left(1-e^{-\frac{\lambda(\lambda-1)n+\theta}{\lambda n-\theta}a}\right)}{\lambda(\lambda-1)n+\theta}\right)^n\right)^{-1}-1. \tag{5.3}$$

Note that θ and λ have to satisfy the restrictions $\lambda n-\theta>0$ and $\lambda>1$ in order for (5.3) to make sense.

Now consider the partnership-based concurrency index κ_P. This concurrency index can be expressed as a function of n, θ, and λ in the following way:

$$\kappa_P(n,\theta,\lambda) = \frac{2(n-1)\lambda\theta}{n\lambda(2\lambda-1)+\theta}. \tag{5.4}$$

See Appendix F for the derivation of (5.3) and (5.4).

In Figure 2 we compare the two concurrency indices as functions of n, while keeping $\theta=10$ and $\lambda=10$ fixed. In Figure 3 the corresponding distributions $(P_k)_k$ are given for some n. We see that for different n the distribution $(P_k)_k$ can look pretty similar while the concurrency indices are not the same.

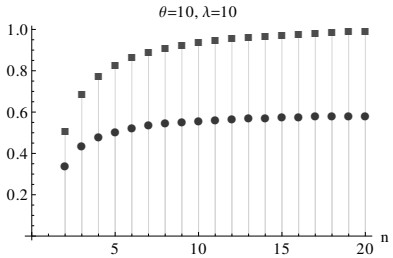

Figure 2: Comparing the two concurrency indices κ_I given by (5.3) (blue circles) and κ_P given by (5.4) (purple squares) for different n while keeping $\lambda=10$ and $\theta=10$ fixed.

6 Outlook

The model presented in this paper incorporates demographic turnover and individuals that are involved in a dynamically varying number of simultaneous partnerships, where the total number of partners of one individual at some point in time is limited by the partnership capacity. On the individual level, the number of partners is following a continuous-time Markov chain. The statistics of this chain is coupled to the population level by a global variable F, the fraction of free binding sites, that describes opportunities for new partnerships.

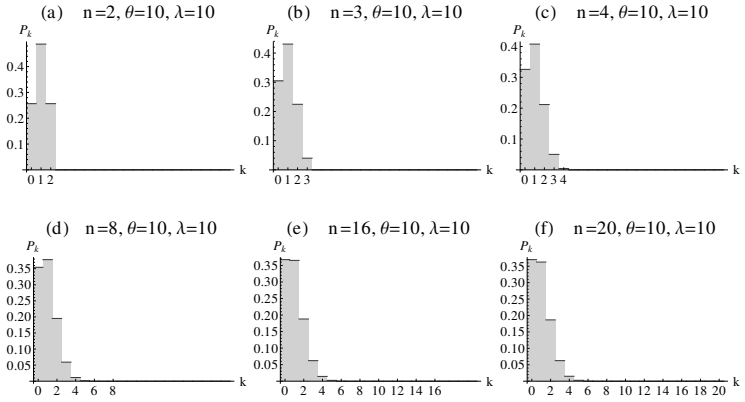

Figure 3: The distribution of the P_k given by (3.6) when keeping $\theta = 10$ and $\lambda = 10$ fixed. See Figure 2 for the corresponding concurrency indices.

For large time a stationary distribution P_k for the number of partners of an individual is attained. Various important statistical properties of this distribution were obtained in Section 4.

We captured concurrency in a population with two measures κ_I and κ_P. One measure, κ_I, the individual-based concurrency index, considers the number of partners of a randomly chosen nonsingle individual. The other, κ_P, the partnership-based concurrency index, considers the number of partners of an individual in a randomly chosen partnership.

6.1 Generalizations

However caricatural the model presented in this paper may be, it is flexible enough to allow for several meaningful generalizations. Below, we will give a short discussion of a few possibilities. See also [75].

First of all, we could relax the assumption of all individuals having the same partnership capacity n by considering partnership capacity as a random variable N (where partnership capacity of an individual does not change during its life). If we specify the distribution of N, then we only need to include averaging with respect to n in Section 2. The state of an individual is then given by (n, k) where n denotes the individual's partnership capacity and k is the number of occupied binding sites, $n \geq 1$ and $0 \leq k \leq n$.

We can also very easily generalize the framework presented for a homosexual population to one for a heterosexual population. In that case we distinguish between males, denoted by m, and females, denoted by f, where males and females may differ in partnership capacities n_m and n_f, respectively. The state of an individual is then given by (g, k), where $g \in \{m, f\}$ denotes the gender of the individual and k is the number of occupied binding sites (if $g = m$ then $0 \leq k \leq n_m$ and if $g = f$ then $0 \leq k \leq n_f$). We will then have two population-level quantities F_f and F_m, the fraction of free binding

sites belonging to a female and male individual, respectively. The rate at which a male individual acquires a new partner will then involve F_f, while the rate at which a female individual acquires a new partner will involve F_m.

It is also possible to distinguish between two (or multiple) types of partnerships. Although individuals may have multiple partners at the same time, it is reasonable to assume that during their lifetime they engage in only a few (or maybe only one) steady partnership into which they invest much time, while other partnerships are more fleeting. We can then make the distinction between casual and steady partnerships. One could imagine that each individual will have n_s steady binding sites (reserved for steady partnerships) and n_c casual binding sites (reserved for casual partnerships). These binding sites will typically have different rates of becoming occupied and, likewise, different dissolution rates. The state of an individual will then be given by (k_s, k_c), where k_s and k_c denote the number of occupied steady and occupied casual binding sites, respectively, $0 \leq k_s \leq n_s$ and $0 \leq k_c \leq n_c$. Note that here we postulate symmetry: the partners agree on whether or not their partnership is casual. At the cost of increased complexity one could relax this.

Of course, several generalizations can be combined. For example, in the framework presented, one could consider a heterosexual population in which individuals may have steady and casual partnerships and their steady and casual partnership capacities are given by random variables $N_{g,t}$ with $g \in \{m, f\}$ being the gender of an individual and $t \in \{s, c\}$ is the type of binding site (steady or casual). Obviously the bookkeeping becomes far more complicated in such cases.

6.2 Indicators to measure concurrency in practice

In [32] it is recommended to use as the main indicator of concurrency the proportion of all adults in the population having more than one sexual partnership at a point in time. In our setting this corresponds to

$$\sum_{k=2}^{n} P_k.$$

In particular when individuals with $k > 2$ are not infrequent, our index κ_I is probably more informative, but we appreciate the practical difficulty of reliably determining the state k of individuals in a population survey based on interviews.

UNAIDS (2010) also mentions the cumulative prevalence indicator, defined as the proportion of all adults that have had concurrent partnerships at any point in a certain time window, e.g. the past year. We expect that it is possible to determine this quantity in the context of our model by using the kind of calculations presented in D.

6.3 Infection dynamics

In future work we will study the transmission of infection along the dynamic partnership network formulated in this paper. We then have a model for the spread of sexually transmitted infections in a population. The two concurrency indices defined in this paper will

be used to study the impact of concurrency on the spread of sexually transmitted infections by investigating how the concurrency indices relate to epidemiological quantities such as R_0. See e.g. [76] for some R_0 calculations.

Acknowledgements

We would like to thank Joel Miller and an anonymous reviewer for suggestions.

A Proof of lemma 1

The differential equation (3.1) for F makes intuitive sense (each term has a clear interpretation). So there is no need for a justification. But our aim in this appendix is to show that our formal framework does indeed agree in detail with that intuition.

By algebraic manipulation, we prove that F satisfies (3.1). The definition of F gives

$$\begin{aligned}
\frac{dF}{dt}(t) &= \frac{1}{n}\sum_{k=0}^{n}(n-k)\frac{dP_k}{dt}(t) \\
&= \frac{1}{n}\sum_{k=0}^{n}(n-k)\mu p_k(t,0) \\
&\quad - \frac{1}{n}\sum_{k=0}^{n}(n-k)\mu^2\int_{-\infty}^{t} e^{-\mu(t-\alpha)}p_k(\alpha,t-\alpha)d\alpha \\
&\quad + \frac{1}{n}\sum_{k=0}^{n}(n-k)\mu\int_{-\infty}^{t} e^{-\mu(t-\alpha)}\frac{\partial p_k}{dt}(\alpha,t-\alpha)d\alpha \\
&= \mu - \mu F(t) - \rho F(t)\frac{1}{n}\sum_{k=0}^{n}(n-k)\mu\int_{-\infty}^{t} e^{-\mu(t-\alpha)}p_k(\alpha,t-\alpha)d\alpha \\
&\quad + (\sigma+\mu)\frac{1}{n}\sum_{k=0}^{n}k\mu\int_{-\infty}^{t} e^{-\mu(t-\alpha)}p_k(\alpha,t-\alpha)d\alpha \\
&= \mu - \mu F(t) - \rho\big(F(t)\big)^2 + (\sigma+\mu)(1-F(t)).
\end{aligned}$$

B Solution of (2.2)-(2.3)

We show that p defined by (3.5) indeed satisfies (2.2)-(2.3). First of all, since $\epsilon(0)=0$, we find that $p_0(0)=1$ and $p_k(0)=0$ for $k>0$.

On the one hand, for $a>0$, differentiating (3.5) with respect to a we obtain

$$\frac{dp_k}{da} = \binom{n}{k}k\frac{d\epsilon}{da}\epsilon^{k-1}(1-\epsilon)^{n-k} - \binom{n}{k}(n-k)\frac{d\epsilon}{da}\epsilon^{k}(1-\epsilon)^{n-k-1}$$

$$= \binom{n}{k}\epsilon^k(1-\epsilon)^{n-k}$$
$$\left(-(\sigma+\mu)k + \rho\bar{F}k\frac{1-\epsilon}{\epsilon} + (\sigma+\mu)(n-k)\frac{\epsilon}{1-\epsilon} - \rho\bar{F}(n-k)\right),$$

where we have used that $\frac{d\epsilon}{da} = \rho\bar{F}(1-\epsilon) - (\sigma+\mu)\epsilon$. On the other hand, considering $(Ap)_k$, we find

$$\begin{aligned}
&\rho\bar{F}(n-(k-1))p_{k-1} - \rho\bar{F}(n-k)p_k \\
&-(\sigma+\mu)kp_k + (\sigma+\mu)(k+1)p_{k+1} \\
&= \binom{n}{k-1}\epsilon^{k-1}(1-\epsilon)^{n-(k-1)}\rho\bar{F}(n-(k-1)) \\
&- \binom{n}{k}\epsilon^k(1-\epsilon)^{n-k}((\sigma+\mu)k + \rho\bar{F}(n-k)) \\
&+ \binom{n}{k+1}\epsilon^{k+1}(1-\epsilon)^{n-(k+1)}(\sigma+\mu)(k+1) \\
&= \binom{n}{k}\epsilon^k(1-\epsilon)^{n-k} \\
&\left(-(\sigma+\mu)k + \rho\bar{F}k\frac{1-\epsilon}{\epsilon} + (\sigma+\mu)(n-k)\frac{\epsilon}{1-\epsilon} - \rho\bar{F}(n-k)\right),
\end{aligned}$$

which is exactly the same expression as we obtained above by differentiating (3.5) with respect to a.

C P_k in the limit of $\mu/\sigma \to 0$

In this appendix we will show that (3.7) holds.

Write

$$P_k = \binom{n}{k}\int_0^\infty e^{-\alpha}\epsilon(\alpha/\mu)^k\left(1-\epsilon(\alpha/\mu)\right)^{n-k}d\alpha.$$

Note that

$$\frac{\rho\bar{F}}{\mu} + \frac{\sigma}{\mu} + 1 = \frac{1}{2}\left(\sqrt{\left(\frac{\sigma}{\mu}+2\right)\left(4\frac{\rho}{\mu}+\frac{\sigma}{\mu}+2\right)} + \frac{\sigma}{\mu}\right) \to \infty,$$

and

$$\rho\bar{F} = \frac{1}{2}\left(\sqrt{(\sigma+2\mu)(4\rho+\sigma+2\mu)} - (\sigma+2\mu)\right) \to \rho\tilde{F}$$

as $\mu/\sigma \to 0$ (where $\tilde{F}$ is given by (3.8)). By using (3.4) we see that, for $\alpha > 0$,

$$\begin{aligned}\epsilon(\alpha/\mu) &= \frac{\rho\bar{F}}{\rho\bar{F}+\sigma+\mu}\left(1-e^{-\left(\frac{\rho\bar{F}}{\mu}+\frac{\sigma}{\mu}+1\right)\alpha}\right)\\ &\to \frac{\rho\tilde{F}}{\rho\tilde{F}+\sigma},\end{aligned}$$

as $\mu/\sigma \to 0$. Since $\epsilon(\alpha/\mu) = 0$ for $\alpha = 0$, convergence is nonuniform. We find that

$$\frac{\rho\tilde{F}}{\rho\tilde{F}+\sigma} = 1-\tilde{F}, \tag{C.1}$$

by the equation defining $\tilde{F}$. Hence

$$\begin{aligned}P_k &= \binom{n}{k}\int_0^\infty e^{-\alpha}\epsilon(\alpha/\mu)^k\left(1-\epsilon(\alpha/\mu)\right)^{n-k}d\alpha\\ &\to \binom{n}{k}(1-\tilde{F})^k\tilde{F}^{n-k}\int_0^\infty e^{-\alpha}d\alpha\\ &= \binom{n}{k}(1-\tilde{F})^k\tilde{F}^{n-k}\end{aligned}$$

as $\mu/\sigma \to 0$. Note that, although we do not have uniform convergence, we do have dominated convergence ($|e^{-\alpha}\left(\epsilon(\alpha/\mu)\right)^k\left(1-\epsilon(\alpha/\mu)\right)^{n-k}| \le e^{-\alpha}$ for all $\alpha \ge 0$), so we may interchange limit and integration.

D Proof of Lemma 2

In this section we provide a proof for Lemma 2. First, note that every partnership exists for an exponentially distributed amount of time with parameter $\sigma + 2\mu$ (either one of the two individuals involved in the partnership may die or the partnership dissolves by separation). So partnerships have a stable age distribution with density $\alpha \mapsto (\sigma+2\mu)e^{-(\sigma+2\mu)\alpha}$, where α is the time elapsed since the partnership was formed.

Now pick a partnership at random. For convenience, denote this partnership with $u-v$, the individual under consideration being v. Let time be such that $u-v$ was formed at time $t = 0$.

As long as the partnership $u-v$ exists, we know that v does not die and that one of its n binding sites is occupied (by the $u-v$ partnership). The other binding sites behave independently. Therefore, the possible state transitions of v and the corresponding rates are given by

$$\begin{aligned}&k \to k+1 \quad \text{with rate } \rho(n-k)\bar{F}\\ &k \to k-1 \quad \text{with rate } (\sigma+\mu)(k-1)\end{aligned}$$

Let B denote the corresponding $(n+1) \times (n+1)$ tridiagonal matrix. Let $\pi_k(t)$ denote the probability that v has state k at time t (note that $\pi_0(t) = 0$ for all t since we assume that $u - v$ exists for the period under consideration). Then

$$\frac{d\pi}{dt}(t) = B\pi$$

with initial condition $\pi_0(0) = 0$ and

$$\pi_{k+1}(0) = \frac{(n-k)P_k}{\sum_{l=0}^{n}(n-l)P_l} = \frac{(n-k)P_k}{n\bar{F}},$$

for $0 \leq k \leq n-1$ (the second equality follows from (4.3)). This initial condition follows from the assumption we have made on the state of a newly acquired individual (2.6) in Section 2.

Formally, we obtain the solution

$$\pi(t) = e^{tB}\pi(0).$$

Let I denote the $(n+1) \times (n+1)$ identity matrix. The 'age' of the partnership $u - v$ is exponentially distributed with parameter $\sigma + 2\mu$. Therefore, the probability that v has state m at the moment we pick the partnership $u - v$ from the pool of partnerships, is the mth component of the vector

$$\begin{aligned}
&(\sigma+2\mu)\int_0^\infty e^{-t(\sigma+2\mu)I}\pi(t)dt \\
=&(\sigma+2\mu)\int_0^\infty e^{t(B-(\sigma+2\mu)I)}\pi(0)dt \\
=&-(\sigma+2\mu)\big(B-(\sigma+2\mu)I\big)^{-1}\pi(0).
\end{aligned}$$

We shall show that the mth component of this vector equals Q_m, with Q_m given by (3.9). Let Q denote the vector corresponding to the probabilities Q_m. Note that $\sum_{l=0}^{n} lP_l = n(1-\bar{F})$ (see (4.3)). So $Q_m = mP_m/n(1-\bar{F})$. We need to show that

$$\Big(-(\sigma+2\mu)\big(B-(\sigma+2\mu)I\big)^{-1}\pi(0)\Big)_m = Q_m, \tag{D.1}$$

or equivalently,

$$-(\sigma+2\mu)\pi_m(0) = \big(\big(B-(\sigma+2\mu)I\big)Q\big)_m.$$

We first elaborate the right hand side:

$$\begin{aligned}
&\big(\big(B-(\sigma+2\mu)I\big)Q\big)_m\\
&=\rho(n-m+1)\bar{F}Q_{m-1}-\big(\rho(n-m)\bar{F}\\
&\quad+(\sigma+\mu)(m-1)\big)Q_m-(\sigma+2\mu)Q_m+(\sigma+\mu)mQ_{m+1}\\
&=\frac{1}{n(1-\bar{F})}\Big(\rho(n-m+1)\bar{F}(m-1)P_{m-1}-\big(\rho(n-m)\bar{F}\\
&\qquad\qquad+(\sigma+\mu)m+\mu\big)mP_m+(\sigma+\mu)m(m+1)P_{m+1}\Big)\\
&=\frac{m}{n(1-\bar{F})}\Big(\rho(n-m+1)\bar{F}P_{m-1}-\big(\rho(n-m)\bar{F}+(\sigma+\mu)m+\mu\big)P_m\\
&\quad+(\sigma+\mu)(m+1)P_{m+1}\Big)-\frac{1}{n(1-\bar{F})}\rho(n-m+1)\bar{F}P_{m-1}\\
&=-\frac{1}{n(1-\bar{F})}\rho(n-m+1)\bar{F}P_{m-1}.
\end{aligned}$$

In the last equality we have used that

$$\begin{aligned}
&\rho(n-m+1)\bar{F}P_{m-1}-\big(\rho(n-m)\bar{F}\\
&\quad+(\sigma+\mu)m+\mu\big)P_m+(\sigma+\mu)(m+1)P_{m+1}\\
=&\mu\int_0^\infty e^{-\mu a}\rho(n-m+1)\bar{F}p_{m-1}(a)da\\
&-\mu\int_0^\infty e^{-\mu a}\big(\rho(n-m)\bar{F}+(\sigma+\mu)m+\mu\big)p_m(a)da\\
&+\mu\int_0^\infty e^{-\mu a}(\sigma+\mu)(m+1)p_{m+1}(a)da\\
=&\mu\int_0^\infty e^{-\mu a}\left(-\mu p_m(a)+(Ap(a))_m\right)da\\
=&\mu\int_0^\infty e^{-\mu a}\left(-\mu p_m(a)+\frac{dp_m}{da}(a)\right)da\\
=&0.
\end{aligned}$$

Here we have used (2.2) with F constant and equal to $\bar{F}$.

So it remains to show that

$$\begin{aligned}
&-\frac{1}{n(1-\bar{F})}\rho(n-m+1)\bar{F}P_{m-1}\\
=&-(\sigma+2\mu)\pi_m(0)\\
=&-\frac{\sigma+2\mu}{n\bar{F}}(n-m+1)P_{m-1},
\end{aligned}$$

or, equivalently,

$$(n-m+1)P_{m-1}\big(\rho\bar{F}^2-(\sigma+2\mu)(1-\bar{F})\big)=0$$

By definition of $\bar{F}$, $\rho\bar{F}^2-(\sigma+2\mu)(1-\bar{F})=0$. Therefore (D.1) holds.

E The second moment $\sum_{k=1}^{n} k^2 P_k$

In order to derive (5.1) we first we note that, by (3.6),

$$\begin{aligned}\sum_{k=1}^{n} k^2 P_k &= \sum_{k=1}^{n} k^2 \binom{n}{k} \mu \int_0^\infty e^{-\mu a}\epsilon(a)^k(1-\epsilon(a))^{n-k}da \\ &= \mu\int_0^\infty e^{-\mu a}\left(\sum_{k=1}^{n} k^2\binom{n}{k}\epsilon(a)^k(1-\epsilon(a))^{n-k}\right)da.\end{aligned}$$

Next, we see that

$$\begin{aligned}&\sum_{k=1}^{n} k^2\binom{n}{k}\epsilon(a)^k(1-\epsilon(a))^{n-k} \\ &= \sum_{k=1}^{n} k\frac{n!}{(n-k)!(k-1)!}\epsilon(a)^k(1-\epsilon(a))^{n-k} \\ &= \sum_{m=0}^{n-1}\frac{n!}{(n-m-1)!m!}\epsilon(a)^{m+1}(1-\epsilon(a))^{n-m-1} \\ &\quad+\sum_{m=1}^{n-1} m\frac{n!}{(n-m-1)!m!}\epsilon(a)^{m+1}(1-\epsilon(a))^{n-m-1}.\end{aligned}$$

The first sum can be further simplified as follows

$$\begin{aligned}&\sum_{m=0}^{n-1}\frac{n!}{(n-m-1)!m!}\epsilon(a)^{m+1}(1-\epsilon(a))^{n-m-1} \\ &= n\epsilon(a)\sum_{m=0}^{n-1}\frac{(n-1)!}{(n-1-m)!m!}\epsilon(a)^m(1-\epsilon(a))^{n-1-m} \\ &= n\epsilon(a).\end{aligned}$$

For the second sum we have

$$\begin{aligned}&\sum_{m=1}^{n-1} m\frac{n!}{(n-m-1)!m!}\epsilon(a)^{m+1}(1-\epsilon(a))^{n-m-1} \\ &= \sum_{k=0}^{n-2}\frac{n!}{(n-2-k)!k!}\epsilon(a)^{k+2}(1-\epsilon(a))^{n-2-k}\end{aligned}$$

$$= n(n-1)\epsilon(a)^2 \sum_{k=0}^{n-2} \binom{n-2}{k} \epsilon(a)^k (1-\epsilon(a))^{n-2-k}$$
$$= n(n-1)\epsilon(a)^2.$$

So we obtain

$$\sum_{k=1}^{n} k^2 P_k = \mu n \int_0^\infty e^{-\mu a} \epsilon(a)(1 + (n-1)\epsilon(a)) da,$$

which can be calculated explicitly using (3.4) for $\epsilon(a)$:

$$\mu \int_0^\infty e^{-\mu a} \epsilon(a) da = \frac{\rho \bar{F}}{\rho \bar{F} + \sigma + 2\mu}$$

and

$$\mu \int_0^\infty e^{-\mu a} \epsilon(a)^2 da = \frac{2(\rho \bar{F})^2}{(\rho \bar{F} + \sigma + 2\mu)(2(\rho \bar{F} + \sigma + \mu) + \mu)}.$$

Finally, if we use relation (4.5), then (5.1) follows.

F Concurrency measures κ_I and κ_P as functions of partnership capacity n, expected lifetime number of partners θ and expected partnership duration $1/\lambda$

In this appendix we provide the details of the derivation of (5.3) and (5.4).

We scale time such that $\mu = 1$ and we denote the scaled parameters again by ρ, σ, and λ. So

$$\lambda = \sigma + 2$$

and

$$\theta = \frac{\rho \bar{F} \lambda n}{\rho \bar{F} + \lambda}.$$

Next we rewrite (3.2) as

$$\rho \bar{F} = \frac{1}{2}(\sqrt{\lambda(4\rho + \lambda)} - \lambda)$$

and conclude that

$$\theta = \frac{(\sqrt{\lambda(4\rho + \lambda)} - \lambda)\lambda n}{(\sqrt{\lambda(4\rho + \lambda)} + \lambda}. \tag{F.1}$$

Hence

$$\begin{aligned}
(\sqrt{\lambda(4\rho+\lambda)}-\lambda)\lambda n &= \theta(\sqrt{\lambda(4\rho+\lambda)}+\lambda)\\
\sqrt{\lambda(4\rho+\lambda)}(\lambda n-\theta) &= \lambda(\lambda n+\theta)\\
\lambda(4\rho+\lambda) &= \frac{\lambda^2(\lambda n+\theta)^2}{(\lambda n-\theta)^2}\\
4\rho &= \frac{\lambda(\lambda n+\theta)^2}{(\lambda n-\theta)^2}-\lambda\\
\rho &= \frac{\lambda^2\theta n}{(\lambda n-\theta)^2}. \qquad \text{(F.2)}
\end{aligned}$$

From the second equality it follows that $\lambda n-\theta>0$ should hold since ρ, θ, $\lambda>0$.

We shall now write the concurrency indices κ_I and κ_P as functions of n, θ, and λ. Substituting expression (F.2) for ρ we can write $\bar{F}$ as

$$\begin{aligned}
\bar{F} &= \left(\sqrt{\lambda\left(4\frac{\lambda^2\theta n}{(\lambda n-\theta)^2}+\lambda\right)}-\lambda\right)\frac{(\lambda n-\theta)^2}{2\lambda^2\theta n}\\
&= \left(\sqrt{\lambda^2\frac{2\lambda\theta n+\lambda^2n^2+\theta^2}{(\lambda n-\theta)^2}}-\lambda\right)\frac{(\lambda n-\theta)^2}{2\lambda^2\theta n}\\
&= \left(\lambda\frac{\lambda n+\theta}{\lambda n-\theta}-\lambda\right)\frac{(\lambda n-\theta)^2}{2\lambda^2\theta n}\\
&= \frac{2\lambda\theta}{\lambda n-\theta}\frac{(\lambda n-\theta)^2}{2\lambda^2\theta n}\\
&= \frac{\lambda n-\theta}{\lambda n}, \qquad \text{(F.3)}
\end{aligned}$$

where we have used that $\lambda n-\theta>0$. Combination of (F.2) and (F.3) yields

$$\rho\bar{F} = \frac{\lambda^2\theta n}{(\lambda n-\theta)^2}\frac{\lambda n-\theta}{\lambda n} = \frac{\lambda\theta}{\lambda n-\theta}. \qquad \text{(F.4)}$$

Next, note that

$$\begin{aligned}
\rho\bar{F}+\sigma+1 &= \frac{\lambda^2\theta n}{(\lambda n-\theta)^2}\frac{\lambda n-\theta}{\lambda n}+\lambda-1\\
&= \frac{\lambda\theta}{\lambda n-\theta}+\lambda-1\\
&= \frac{\lambda(\lambda-1)n+\theta}{\lambda n-\theta}, \qquad \text{(F.5)}
\end{aligned}$$

where we used (F.4) and the definition of λ in the first equality.

Let's first focus on $\kappa_I = n(1-\bar{F})/(1-P_0) - 1$. We can express the numerator of κ_I as a function of n, θ, and λ, viz. $n(1-\bar{F}) = \theta/\lambda$. For the denominator we consider P_0 given by

$$P_0 = \int_0^\infty e^{-a}(1-\epsilon(a))^n da,$$

where

$$\epsilon(a) = \frac{\rho\bar{F}}{\rho\bar{F}+\sigma+1}\left(1-e^{-(\rho\bar{F}+\sigma+1)a}\right)$$

(recall that we have scaled $\mu = 1$). We want to express $\epsilon(a)$ as a function of n, θ, and λ as well. Using (F.3), (F.2), and (F.5) we can write

$$\epsilon(a,n,\theta,\lambda) = \frac{\lambda\theta}{\lambda(\lambda-1)n+\theta}\left(1-e^{-\frac{\lambda(\lambda-1)n+\theta}{\lambda n-\theta}a}\right).$$

Finally we see that (5.3) holds.

Now, for the concurrency measure κ_P, consider (5.2), with the scaling $\mu = 1$. Using (F.2), (F.3), and (F.5) we can write

$$\begin{aligned}\kappa_P(n,\theta,\lambda) &= 2(n-1)\frac{\frac{\lambda\theta}{\lambda n-\theta}}{2\frac{\lambda(\lambda-1)n+\theta}{\lambda n-\theta}+1}\\ &= \frac{2(n-1)\lambda\theta}{n\lambda(2\lambda-1)+\theta},\end{aligned}$$

so we see that (5.4) holds.

Chapter 3

SI infection on a dynamic partnership network: characterization of R_0

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Abstract

We model the spread of an SI (Susceptible $\rightarrow$ Infectious) sexually transmitted infection on a dynamic homosexual network. The network consists of individuals with a dynamically varying number of partners. There is demographic turnover due to individuals entering the population at a constant rate and leaving the population after an exponentially distributed time. Infection is transmitted in partnerships between susceptible and infected individuals. We assume that the state of an individual in this structured population is specified by its disease status and its numbers of susceptible and infected partners. Therefore the state of an individual changes through partnership dynamics and transmission of infection. We assume that an individual has precisely n 'sites' at which a partner can be bound, all of which behave independently from one another as far as forming and dissolving partnerships are concerned. The population level dynamics of partnerships and disease transmission can be described by a set of $(n+1)(n+2)$ differential equations. We characterize the basic reproduction ratio R_0 using the next-generation-matrix method. Using the interpretation of R_0 we show that we can reduce the number of states-at-infection n to only considering three states-at-infection. This means that the stability analysis of the disease-free steady state of an $(n+1)(n+2)$-dimensional system is reduced to determining the dominant eigenvalue of a 3×3 matrix. We then show that a further reduction to a 2×2 matrix is possible where all matrix entries are in explicit form. This implies that an explicit expression for R_0 can be found for every value of n.

1 Introduction

The role that concurrent partnerships might play in the spread of HIV in sub-Saharan Africa is the subject of an ongoing debate. While simulation studies have shown the large impact that concurrency potentially has on the epidemic growth rate and the endemic prevalence of HIV [17, 20, 21, 35, 65], the empirical evidence for such a relationship is inconclusive [11, 22–24].

Mathematical modelling results have played a key role in fuelling the debate [17, 18, 20, 21, 35, 65]. However, a mathematical framework suitable to derive analytical results is still lacking. At present, simulation studies prevail, and general theory is mainly focused on static networks [40, 50, 76–79]. This motivated us to develop and analyse a mathematical model for the spread of an SI (Susceptible–Infectious) infection along a dynamic network.

In a previous paper (Chapter 2) a model for a dynamic sexual network of a homosexual population is presented that incorporates demographic turnover and allows for individuals to have multiple partners at the same time, with the number of partners varying over time. This network model can be seen as a generalization of the pair formation models (that describe sequentially monogamous populations) to situations where individuals are allowed more than one partner at a time. Pair formation models were first introduced into epidemiology by Dietz and Hadeler (1988) and extended in various ways [19, 53–56, 80]. In the present generalization, individuals have at most n partners at a time. We call n the partnership capacity. In the partnership network individuals are, essentially, collections of n 'binding sites' where binding sites can be either 'free' or 'occupied' (by a partner). In the case that $n = 1$ we recover the pair formation model of a monogamous population.

Consider an individual in the sexual network. Since individuals may have several partners simultaneously, the risk of acquiring infection depends on that individual's partners, but also on their partners, and so on. We would need to keep track of the entire network to fully characterize the risk of infection to an individual. Here we introduce an approximation rather than taking full network information into account: we assume that properties concerning partners of partners can be obtained by averaging over the population. This approximation is termed the 'mean field at distance one' assumption ('mean field at distance one' should be read as one term; from here on we write this without quotation marks). This assumption relates to what is called 'effective degree' in [76], where transmission of infection along a static network is studied (we are, apart from [49, 66], not aware of any analytical work so far, on disease transmission across dynamic networks with demography (see e.g. [47, 51, 67, 68, 79, 81] and references therein for models incorporating dynamic partnerships in a demographically closed population).

The mean field at distance one assumption is a moment closure approximation obtained by ignoring certain correlations between the states of two individuals that are in a partnership and, as a consequence, this assumption is inconsistent with the assumptions that underlie the partnership network (see e.g. [48, 78, 81, 82] and references therein for different moment closure approximations on networks). However, this assumption allows us to write down a closed system of ODEs to describe an approximation of the SI infec-

tion on the partnership network. If a partnership capacity n is given, then we have an $(n+1)(n+2)$ dimensional system of ODEs.

A large part of the paper is devoted to characterizing the basic reproduction number R_0 and proving its threshold character for the nonlinear system of ODEs. This system is quite large already for small n. However, by considering only states-at-infection and using the next-generation matrix approach, R_0 can be characterized as the dominant eigenvalue of an $n \times n$ matrix. Using the interpretation we can further reduce this and R_0 can ultimately be characterized as the dominant eigenvalue of a 2×2 matrix where the entries of this matrix are explicit, and therefore also R_0 has an explicit expression. In fact, we are able to interpret R_0 in terms of individuals (which are considered in the model specification) and in terms of binding sites.

The structure of the paper is as follows. First, in Section 2, we consider the partnership network of Chapter 2 and summarize the main results needed for this paper. Next, in Section 3 we superimpose an SI-infection on the network and specify the model assumptions. Particular attention is given to the mean field at distance one assumption. The rest of the paper is devoted to characterizing the basic reproduction number R_0. For this, in Section 4, we first consider the linearisation of the system.

In Section 5, which constitutes the core of the paper, we characterize R_0 in terms of newly infected binding sites that produce newly infected binding sites. We introduce a transition matrix Σ and a transmission matrix T and define R_0 as the dominant eigenvalue of the next generation matrix $-T\Sigma^{-1}$ [8, Section 7.2]. The building blocks for an explicit expression for R_0 are presented in Appendix C. We also show that R_0 thus defined can be interpreted as the basic reproduction ratio for individuals, since individuals can be considered to be collections of n binding sites. Section 5 can be read independently of the rest of the paper.

The characterization of R_0 in Section 5 does not, by itself, provide a mathematical proof that the disease-free steady state is stable for $R_0 < 1$ and unstable for $R_0 > 1$. We provide such a proof in Section 6. The proof is based on the Perron-Frobenius theory of spectral properties of positive and positive-off-diagonal irreducible matrices. In particular we use that

- $\mathrm{sign}(R_0 - 1) = \mathrm{sign}(r)$ where r is the Malthusian parameter (i.e. the dominant eigenvalue) of the matrix $T + \Sigma$

- the linearised system derived in Section 4 can be mapped in a natural way to the binding-site system defined by the matrices Σ and T, while preserving positivity.

The final Section 7 provides conclusions and plans for future work. Some more technical calculations are left for the six appendices. In particular, in Appendix B we show with explicit calculations for the case $n = 2$ (suggested to us by Pieter Trapman, (personal communication, 26 August, 2013)) that states of partners are not independent of one another, implying that the mean field at distance one assumption yields only an approximate and not an exact description.

2 The partnership network

In this section we will give a summary of the specification of the partnership network and of the main results presented in Chapter 2.

Consider a population of homosexual individuals – all with partnership capacity n. The partnership capacity is the maximum number of simultaneous partners an individual may have. One may think of an individual as having n binding sites. Binding sites are either 'occupied' (by a partner) or 'free'. We assume that *binding sites of an individual behave independently from one another* as far as forming and dissolving partnerships are concerned. Furthermore, individuals enter ('birth') and leave ('death') the sexually active population.

The model specification begins at the individual level. The state of an individual is given by k, the number of occupied binding sites, $k = 0, \ldots, n$. Consider one individual born at time t_b and suppose it does not die in the time interval under consideration. An occupied binding site becomes free at rate $\sigma + \mu$, where σ corresponds to 'separation' and μ to 'death of partner'. A free binding site becomes occupied at rate ρF, where F denotes the fraction of free binding sites in the pool of all binding sites in the population. The possible state transitions and the rates at which they occur are:

$$\begin{aligned} k &\to k+1 \qquad \text{with rate } \rho(n-k)F, \\ k &\to k-1 \qquad \text{with rate } (\sigma+\mu)k. \end{aligned}$$

The probability that an individual is in state k at age a is denoted by $p_k(t_b, a)$, where t_b denotes the time of birth. A newborn individual has n free binding sites, i.e.

$$p(t_b, 0) = \begin{pmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{pmatrix}.$$

Let $A = A(F)$ denote the matrix corresponding to the state transitions described above. So, as an example, for $n = 2$, the matrix A is as follows:

$$A = \begin{pmatrix} -2\rho F & \sigma+\mu & 0 \\ 2\rho F & -(\rho F+\sigma+\mu) & 2(\sigma+\mu) \\ 0 & \rho F & -2(\sigma+\mu) \end{pmatrix}.$$

Note that, throughout this paper, we will use the convention that, for a transition matrix $M = (m_{ij})$, m_{ij} denotes the probability per unit of time at which a transition from j to i is made (instead of the transition from i to j, as it is common in the stochastic community.)

Then, as long as the individual does not die, we have

$$\frac{\partial p}{\partial a}(t_b, a) = A(F(t_b + a))p(t_b, a).$$

We assume a stationary age distribution which is exponential with parameter μ, so it has probability density function

$$a \mapsto \mu e^{-\mu a}. \tag{2.1}$$

Then, in a deterministic description of a large population, the fraction of the population in state k at time t is

$$P_k(t) = \int_0^\infty \mu e^{-\mu a} p_k(t-a, a) da = \int_{-\infty}^t \mu e^{-\mu(t-\alpha)} p_k(\alpha, t-\alpha) d\alpha. \tag{2.2}$$

The fraction of free binding sites F is defined as

$$F(t) = \frac{1}{n} \sum_{k=0}^{n} (n-k) P_k(t). \tag{2.3}$$

Due to the assumption of independence of binding sites with respect to partnership dynamics, the dynamics of F decouple as stated in Lemma 1 below (the proof is presented in Chapter 2).

Lemma 1. *The fraction of free binding sites F satisfies the differential equation*

$$\frac{dF}{dt} = \mu + (\sigma + \mu)(1 - F) - \rho F^2 - \mu F. \tag{2.4}$$

Consequently,

$$F(t) \to \bar{F},$$

for $t \to \infty$, where

$$\bar{F} = \frac{\sqrt{(\sigma + 2\mu)(4\rho + \sigma + 2\mu)} - (\sigma + 2\mu)}{2\rho}. \tag{2.5}$$

This convergence to $\bar{F}$ motivates us to take F constant and equal to $\bar{F}$ (note , incidentally, that $\bar{F}$ does not depend on the partnership capacity n). As a consequence the argument t_b in $p_k(t_b, a)$ no longer matters and $P_k(t) = P_k$ is independent of time. In fact, one finds that

$$P_k = \binom{n}{k} \int_0^\infty \mu e^{-\mu a} \epsilon(a)^k (1 - \epsilon(a))^{n-k} da,$$

where

$$\epsilon(a) = \frac{\rho \bar{F}}{\rho \bar{F} + \sigma + \mu} (1 - e^{-(\rho \bar{F} + \sigma + \mu) a})$$

is the probability that a binding site is occupied at age a, given that the 'owner' of the binding site is alive. We can get rid of the integral by using the binomium of Newton to expand $\epsilon(a)^k(1-\epsilon(a))^{n-k}$ and compute the integral of an exponential function:

$$P_k = \binom{n}{k}\mu\left(\frac{\rho\bar{F}}{\rho\bar{F}+\sigma+\mu}\right)^n \sum_{j=0}^{n-k}\sum_{i=0}^{k}\binom{n-k}{j}\binom{k}{i}(-1)^i \left(\frac{\sigma+\mu}{\rho\bar{F}}\right)^j \frac{1}{\mu+(\rho\bar{F}+\sigma+\mu)(n-k-j+i)}. \tag{2.6}$$

So we have explicit expressions for the degree distribution $P=(P_k)_{k=0}^n$.

There are two probability distributions that play a more important role in the characterization of R_0. First, consider an individual that acquires a new partner. We assume, in accordance with (2.3), that this newly acquired partner will have state k with probability

$$q_k = \frac{(n-k+1)P_{k-1}}{\sum_{l=0}^n (n-l)P_l} = \frac{(n-k+1)P_{k-1}}{n\bar{F}}. \tag{2.7}$$

(A potential partner with state $k-1$ has $(n-k+1)$ free binding sites. Immediately after a match is made it will have state k. The denominator serves to renormalise into a probability distribution.) This assumption gives us information on the state of an individual in a randomly chosen partnership, as expressed in the next lemma.

Lemma 2. *Choose an individual by first sampling a partnership from the pool of all partnerships and next choosing one of the two partners at random. The probability that this individual has k partners equals*

$$Q_k = \frac{kP_k}{\sum_{l=1}^n lP_l} = \frac{kP_k}{n(1-\bar{F})}. \tag{2.8}$$

Note that Lemma 2 does *not* imply that the states of the two individuals in this partnership are independent of one another. Indeed, they are not. Information about the number of partners of one of the individuals provides some information about the duration of the partnership and thus influences the probability that the other individual has k partners (or, in other words, there exists degree correlation in this network); see Appendix B for explicit calculations for $n=2$.

Note that the model specification is deterministic in the sense that it concerns expected values for a population of infinite size. Partnership formation is at random between two free binding sites. As a consequence of mass action and infinite population size, partnership formation with oneself or multiple partnerships with the same individual occur with probability zero. For the same reason clustering does not occur in the network. It should be possible to formulate a stochastic version for a population of size N and derive the present description by considering the limit $N\to\infty$. We conjecture that all the previous statements hold in the limit. In particular clustering disappears in the limit, i.e. the probability that a path of a fixed finite length contains a loop goes to zero in the limit.

Finally, to summarize, we have three degree distributions, i.e. probability distributions for the number of partners of an individual, that we will use throughout this paper:

- $P = (P_k)$ for a random individual,
- $q = (q_k)$ for an individual who just acquired a partner (but is otherwise randomly chosen),
- $Q = (Q_k)$ for an individual in a randomly chosen partnership.

3 Superimposing transmission of an infectious disease

We consider an SI infection spreading on the dynamic sexual network described in Section 2. We assume that individuals become infectious at the very instant that they become infected and stay infectious (with the same infectiousness) for the rest of their life.

3.1 i-states and i-dynamics

The model specification begins at the i-level (i for individual). We classify individuals as either susceptible (indicated by the symbol $-$) or infectious (indicated by $+$). We assume that the $\pm$ classification has no influence whatsoever on partnership formation and separation nor on the probability per unit of time of dying.

The state of an individual is now a triple (x, k_-, k_+), where x is either $+$ or $-$ and k_- and k_+ are nonnegative integers with $0 \leq k_- + k_+ \leq n$. The x specifies whether the individual itself is susceptible or infectious, k_- specifies the number of its susceptible partners, and k_+ specifies the number of its infectious partners.

3.1.1 Demographic change of i-states

Consider an individual and suppose it does not die in the period under consideration. There are two types of state transitions: those that contribute to demography and those that involve transmission of infection.

We let F_- denote the fraction of the total pool of binding sites that is free and belongs to a susceptible individual and let F_+ denote the fraction that is free and belongs to an infectious individual so $F_- + F_+ = \bar{F}$. We shall say that a binding site is susceptible or infectious if the 'owner' is so.

The possible state transitions and corresponding rates that involve partnership formation, separation, and death of a partner are as follows:

$(\pm, k_-, k_+) \to (\pm, k_- - 1, k_+)$	with rate $(\sigma + \mu)k_-$ (separation from or death of a susceptible partner),
$(\pm, k_-, k_+) \to (\pm, k_-, k_+ - 1)$	with rate $(\sigma + \mu)k_+$ (separation from or death of an infectious partner),

$(\pm, k_-, k_+) \to (\pm, k_- + 1, k_+)$ with rate $\rho F_-(n - k_- - k_+)$
(acquisition of a new partner
who happens to be susceptible),
$(\pm, k_-, k_+) \to (\pm, k_-, k_+ + 1)$ with rate $\rho F_+(n - k_- - k_+)$
(acquisition of a new partner
who happens to be infectious).

3.1.2 Transmission (mean field at distance one)

Next, consider the transmission events. A susceptible having a binding site that is occupied by an infectious partner, gets infected by this partner at rate β. There is more than one way in which transmission events show up as i-level state transitions. First of all, we have the possibility that a susceptible individual u gets infected by one of its infectious partners. This occurs at rate β times the number of infectious partners u has, i.e.,

$$(-, k_-, k_+) \to (+, k_-, k_+) \qquad \text{with rate } \beta k_+.$$

Here we have assumed that the frequency of sex acts within one partnership does not depend on concurrent other partnerships.

It is also possible that a partner v of u (with u either susceptible or infectious) becomes infected by one of v's infectious partners (which includes u if u is infectious). Of course the probability that this happens depends on the actual configuration in terms of number of partners of v and their infection status. That information is, however, not incorporated in our description.

Therefore, we assume that we can average over all possibilities (we call this 'mean field at distance one'). This assumption is an approximation that we make in order to close the infectious disease model within our limited bookkeeping framework; we will come back to this in more detail in Section 3.2.2. More concretely we assume that rates $\Lambda_\pm(t)$ exist such that

$$\begin{aligned} (-, k_-, k_+) &\to (-, k_- - 1, k_+ + 1) \qquad \text{with rate } \beta\Lambda_-(t)k_-, \\ (+, k_-, k_+) &\to (+, k_- - 1, k_+ + 1) \qquad \text{with rate } \beta\Lambda_+(t)k_-, \end{aligned} \tag{3.1}$$

and that we can specify $\Lambda_\pm(t)$ as appropriate population averages. But before we can provide this specification in Section 3.2.2, we have to define the relevant population-level quantities. For this we need to first consider the i-level dynamics.

3.1.3 i-level dynamics

We have now described all i-states and the possible changes in i-states. The i-level dynamics are as follows. Newborn individuals are in state $(-, 0, 0)$ (we call this the i-state-at-birth), i.e. at birth an individual is susceptible and has no partner at all. Let $p_\ell(t_b, a)$ denote the probability that an individual born at time t_b is in state ℓ at age a given that the individual does not die in the period under consideration, where ℓ is any allowed triple

$(\pm, k_-, k_+)$. By choosing a way to order the ℓ's, we can think of p as a vector. This ordering then also allows us to construct a matrix

$$B = B(F_\pm, \Lambda_\pm)$$

on the basis of the transition rates that are described in Sections 3.1.1 and 3.1.2.

Then the matrix B allows us to describe the dynamics of p. As long as the individual does not die,

$$\frac{\partial p}{\partial a}(t_b, a) = B\big(F_\pm(t_b + a), \Lambda_\pm(t_b + a)\big)\, p(t_b, a), \tag{3.2}$$

with

$$p(t_b, 0) = \begin{pmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{pmatrix} \tag{3.3}$$

if $(-, 0, 0)$ is chosen as the first triple in our list.

Finally, as an example, we write out the matrix B for $n = 2$. If we order the twelve states $(\pm, k_-, k_+)$ as $(-,0,0)$, $(-,1,0)$, $(-,2,0)$, $(-,0,1)$, $(-,1,1)$, $(-,0,2)$, $(+,0,0)$, $(+,1,0)$, $(+,2,0)$, $(+,0,1)$, $(+,1,1)$, $(+,0,2)$, then B is of the form

$$B = \begin{pmatrix} B_1 & 0 \\ B_2 & B_3 \end{pmatrix},$$

with the B_i being 6×6 matrices. B_1 describes the transitions between $-$ states:

$$B_1 = \begin{pmatrix} (B_1)_{11} & \sigma+\mu & 0 & \sigma+\mu & 0 & 0 \\ 2\rho F_- & (B_1)_{22} & 2(\sigma+\mu) & 0 & \sigma+\mu & 0 \\ 0 & \rho F_- & (B_1)_{33} & 0 & 0 & 0 \\ 2\rho F_+ & \beta\Lambda_- & 0 & (B_1)_{44} & \sigma+\mu & 2(\sigma+\mu) \\ 0 & \rho F_+ & 2\beta\Lambda_- & \rho F_- & (B_1)_{55} & 0 \\ 0 & 0 & 0 & \rho F_+ & \beta\Lambda_- & (B_1)_{66} \end{pmatrix},$$

with $(B_1)_{jj} = -\sum_{i=1}^{6} \big((B_1)_{ij} + (B_2)_{ij}\big)$, and where B_2 describes the transitions from $-$ to $+$ states:

$$B_2 = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \beta & 0 & 0 \\ 0 & 0 & 0 & 0 & \beta & 0 \\ 0 & 0 & 0 & 0 & 0 & 2\beta \end{pmatrix},$$

and B_3 describes the transitions between $+$ states:

$$B_3 = \begin{pmatrix} (B_3)_{11} & \sigma+\mu & 0 & \sigma+\mu & 0 & 0 \\ 2\rho F_- & (B_3)_{22} & 2(\sigma+\mu) & 0 & \sigma+\mu & 0 \\ 0 & \rho F_- & (B_3)_{33} & 0 & 0 & 0 \\ 2\rho F_+ & \beta\Lambda_+ & 0 & (B_3)_{44} & \sigma+\mu & 2(\sigma+\mu) \\ 0 & \rho F_+ & 2\beta\Lambda_+ & \rho F_- & (B_3)_{55} & 0 \\ 0 & 0 & 0 & \rho F_+ & \beta\Lambda_+ & (B_3)_{66} \end{pmatrix},$$

with $(B_3)_{jj} = -\sum_{i=1}^{6}(B_3)_{ij}$. So in this way, one can construct the matrix B explicitly.

3.2 Bookkeeping on the p-level and feedback

We have now specified the i-level dynamics. In this section we consider the p-level (p for population) and the feedback to the i-level via the variables $F_\pm$ and $\Lambda_\pm$.

3.2.1 Bookkeeping

In a deterministic description of a large population

$$P_\ell(t) = \int_0^\infty \mu e^{-\mu a} p_\ell(t-a,a)da = \int_{-\infty}^{t} \mu e^{-\mu(t-\alpha)} p_\ell(\alpha, t-\alpha)d\alpha, \tag{3.4}$$

is the fraction of the population that is in state ℓ at time t. In Section 3.3 we rewrite these identities as differential equations.

3.2.2 Feedback

It remains to provide the feedback relations that express the individual level input variables $F_\pm(t)$ and $\Lambda_\pm(t)$ in terms of output variables at the population level. Directly from the interpretation it follows that we should take

$$F_\pm(t) = \frac{1}{n}\sum_{k_+=0}^{n}\sum_{k_-=0}^{n-k_+}(n-k_--k_+)P_{(\pm,k_-,k_+)}(t). \tag{3.5}$$

The only unknown terms left are the mean field at distance one rates $\Lambda_\pm(t)$. In the remainder of this section we define these rates and explain why our description is not exact.

Consider a transition $(\pm,k_-,k_+) \to (\pm,k_- - 1,k_+ + 1)$. This transition occurs when a susceptible partner v of the focus individual u in state $(\pm,k_-,k_+)$ gets infected. The rate at which v gets infected depends on the number of infectious partners v has. However, we only know that v is a susceptible partner of u.

Note that we can not distinguish between two susceptible partners v_1 and v_2 of an individual u and that the states of v_1 and v_2 are correlated in the same way with the state of u. In particular, the probability that v_1 is in state $(-,m_-,m_+)$ is equal to the probability

that v_2 is in that state. Therefore, we are interested in probabilities $\lambda(m_+|(\pm, k_-, k_+))$, where $\lambda(m_+|(\pm, k_-, k_+))$ denotes the conditional probability that a susceptible partner of an individual in state $(\pm, k_-, k_+)$ has itself m_+ infectious partners. The force of infection on a susceptible individual with m_+ partners is βm_+. Therefore, by averaging over all possibilities, we obtain the following rates for the corresponding transitions:

$$(-, k_-, k_+) \to (-, k_- - 1, k_+ + 1)$$

with rate

$$k_- \sum_{m_+=0}^{n-1} \beta m_+ \lambda(m_+|(-, k_-, k_+)),$$

and

$$(+, k_-, k_+) \to (+, k_- - 1, k_+ + 1)$$

with rate

$$k_- \sum_{m_+=1}^{n} \beta m_+ \lambda(m_+|(+, k_-, k_+)).$$

We now make the simplifying assumption that the probability that a susceptible partner of u has m_+ infectious partners does not depend on the exact state of u but only on u being susceptible or infectious. More precisely, we assume that we can approximate $\lambda(m_+|(\pm, k_-, k_+))$ by

$$\lambda_\pm(m_+),$$

where $\lambda_-(m_+)$ is the conditional probability that v has m_+ infectious partners, given that v is susceptible and v is a partner of susceptible individual u and $\lambda_+(m_+)$ is that same conditional probability when v is a partner of infectious individual u. In fact, as we explain in Appendix B, the probabilities $\lambda_\pm(m_+)$ are really an approximation of $\lambda(m_+|(\pm, k_-, k_+))$ as these probabilities ignore correlations of u and v, i.e. between the states of two individuals that are in a partnership. Note that for certain static networks one can actually justify the mean field at distance one assumption for SI and SIR infection (but presumably not for SIS), see [83, 84].

Assuming a two-type version of (2.8) we define

$$\lambda_-(m_+) = \frac{\sum_{m_-=1}^{n-m_+} m_- P_{(-,m_-,m_+)}(t)}{\sum_{l_+=0}^{n-1} \sum_{l_-=1}^{n-l_+} l_- P_{(-,l_-,l_+)}(t)}, \tag{3.6}$$

with the convention that $\lambda_-(m_+) = 0$ if the denominator equals zero, and

$$\lambda_+(m_+) = \frac{\sum_{m_-=0}^{n-m_+} m_+ P_{(-,m_-,m_+)}(t)}{\sum_{l_+=1}^{n} \sum_{l_-=0}^{n-l_+} l_+ P_{(-,l_-,l_+)}(t)}, \tag{3.7}$$

with the convention that $\lambda_+(1) = 1$ and $\lambda_+(m_+) = 0$ for $m_+ > 1$, if the denominator equals zero. The explanation of (3.6) and (3.7) is as follows. In both cases, we consider the probability that the state of v is $(-, m_-, m_+)$, given that v is susceptible and v has a partner u. In the case of (3.6), u is susceptible, so, if we also take into account that u is one of the m_- susceptible partners of v, the probability that v is in state $(-, m_-, m_+)$ is

$$\frac{m_- P_{(-,m_-,m_+)}(t)}{\sum_{l_+=0}^{n-1} \sum_{l_-=1}^{n-l_+} l_- P_{(-,l_-,l_+)}(t)}$$

cf. Lemma 2. Similarly, in the case of (3.7), we 'arrive' at v via its link to the *infectious* u, so then the probability that v is in state $(-, m_-, m_+)$ is

$$\frac{m_+ P_{(-,m_-,m_+)}(t)}{\sum_{l_+=0}^{n-1} \sum_{l_-=1}^{n-l_+} l_+ P_{(-,l_-,l_+)}(t)}.$$

In both cases, the denominator serves to normalize.

The mean field at distance one terms $\Lambda_\pm$ in (3.1) are now specified by

$$\Lambda_-(t) = \sum_{m_+=1}^{n-1} m_+ \lambda_-(m_+) \tag{3.8}$$

with $\lambda_-(m_+)$ given by (3.6), and

$$\Lambda_+(t) = \sum_{m_+=1}^{n} m_+ \lambda_+(m_+) = 1 + \sum_{m_+=2}^{n} (m_+ - 1)\lambda_+(m_+), \tag{3.9}$$

with $\lambda_+(m_+)$ given by (3.7). (For mean field at distance one terms also see [76].)

Note that, from an individual-based perspective, (3.8) and (3.9) are the only formulas consistent with our assumption that u's susceptible partners are subject to a force of infection $\beta\Lambda_\pm$ depending only on t and u's infection status $\pm$ (and not on the number of susceptible and infectious partners of u cf. Appendix B). Hence our choice of the term 'mean field at distance one' for the latter assumption.

3.3 The p-level differential equations

In a deterministic description of a large population, $P_(\pm, k_-, k_+)$ denotes the fraction of the population in state $(\pm, k_-, k_+)$ We take as the convention that the $P_{(\pm,k_-,k_+)}$ should be interpreted as zero when $k_- + k_+ > n$, $k_- < 0$, or $k_+ < 0$. By differentiation of (3.4) and using (3.2)-(3.3) for p, we obtain the following set of $(n + 1)(n + 2)$ differential

equations:

$$
\begin{aligned}
&\frac{dP_{(-,0,0)}}{dt} = \mu - (\rho\bar{F}n + \mu)P_{(-,0,0)} + (\sigma+\mu)(P_{(-,1,0)} + P_{(-,0,1)}) \\
&\frac{dP_{(-,k_-,k_+)}}{dt} = \\
&\quad - \Big(\rho\bar{F}(n-k_- - k_+) + (\sigma+\mu)(k_- + k_+) \\
&\qquad + \beta k_+ + \beta\Lambda_- k_- + \mu\Big)P_{(-,k_-,k_+)} \\
&\quad + \rho F_-(n-k_- - k_+ + 1)P_{(-,k_- -1,k_+)} \\
&\quad + \rho F_+(n-k_- - k_+ + 1)P_{(-,k_-,k_+ -1)} \\
&\quad + (\sigma+\mu)\Big((k_- + 1)P_{(-,k_- +1,k_+)} + (k_+ + 1)P_{(-,k_-,k_+ +1)}\Big) \\
&\quad + \beta\Lambda_-(k_- + 1)P_{(-,k_- +1,k_+ -1)} \\
&\frac{dP_{(+,k_-,k_+)}}{dt} = \\
&\quad - \Big(\rho\bar{F}(n-k_- - k_+) + (\sigma+\mu)(k_- + k_+) + \beta\Lambda_+ k_- + \mu\Big)P_{(+,k_-,k_+)} \\
&\quad + \rho F_-(n-k_- - k_+ + 1)P_{(+,k_- -1,k_+)} \\
&\quad + \rho F_+(n-k_- - k_+ + 1)P_{(+,k_-,k_+ -1)} \\
&\quad + (\sigma+\mu)\Big((k_- + 1)P_{(+,k_- +1,k_+)} + (k_+ + 1)P_{(+,k_-,k_+ +1)}\Big) \\
&\quad + \beta\Lambda_+(k_- + 1)P_{(+,k_- +1,k_+ -1)} + \beta k_+ P_{(-,k_-,k_+)}.
\end{aligned}
$$

Choose the same ordering of the ℓ's as before with the i–states in Section 3.2 and let P denote the corresponding vector of the variables P_ℓ. In matrix notation, we have

$$
\frac{dP}{dt} = \mu\mathbf{1}_{(-,0,0)} + B\big(F_\pm, \Lambda_\pm\big)P - \mu P, \tag{3.10}
$$

where $\mathbf{1}_{(-,0,0)}$ is the indicator function of $(-,0,0)$, and B is the matrix corresponding to the rates of the state transitions described in Sections 3.1.1 and 3.1.2.

3.3.1 Consistency relations

The P_ℓ are related to each other by:

$$
\sum_{k_+=0}^{n}\sum_{k_-=0}^{n-k_+} k_+ P_{(-,k_-,k_+)}(t) = \sum_{k_+=0}^{n}\sum_{k_-=0}^{n-k_+} k_- P_{(+,k_-,k_+)}(t), \tag{3.11}
$$

This is evident from the interpretation, since both terms denote the number of SI partnerships, i.e. the number of partnerships involving an infectious and a susceptible individual. The proof of (3.11) starts by differentiating both left- and right hand side with respect to t

and continues by inserting components of (3.10); this is worked out for a similar situation in [76, Appendix B].

We have assumed that the infectious disease has no influence on the partnership formation and separation or on the probability per unit of time of dying. Therefore, the disease-free partnership network is embedded in (3.10) and the fraction of individuals in the population in state k at time t is equal to

$$P_k(t) = \sum_{k_-+k_+=k} \big(P_{(-,k_-,k_+)}(t) + P_{(+,k_-,k_+)}(t)\big). \tag{3.12}$$

Furthermore, the dynamics of partnerships in the population are governed by the sum of the fraction of free susceptible and the fraction of free infectious binding sites, which is equal to the total fraction of free binding sites, i.e. $F_-(t) + F_+(t) = F(t)$. As a consequence, the set characterized by

$$F_-(t) + F_+(t) = \bar{F} \tag{3.13}$$

is invariant and attracting. Therefore, also in the network with infection superimposed, we consider $F(t)$ constant and equal to $\bar{F}$ (see Lemma 1). Likewise, we can consider the left hand side of (3.12) as constant in time and given by (2.6).

4 Linearisation and the map L

In this section we linearise system (3.10) around the disease-free equilibrium. Next we show that we can reduce the dimension of the linearised system and consider only the variables $P_{(-,k_-,1)}$ and $P_{(+,k_-,k_+)}$. In Section 6 we will use this reduced linearised system to prove that the basic reproduction number R_0, that we characterize in Section 5, indeed provides a threshold value of 1 for the disease free steady state of the nonlinear system (3.10) to become unstable. To this end we define a map L in subsection 4.2, which allows us to relate, in the linearisation, population-level fractions of individuals (that we consider in the present section) to fractions of binding sites (that we consider in Section 5).

4.1 Linearisation

Note that the disease-free equilibrium is given by

$$P_{(-,k,0)}(t) = P_k,$$

$0 \le k \le n$, and $P_\ell(t) = 0$ for all triplets ℓ not of the form $(-, k, 0)$.

Next, note that we can use relationship (3.13) in order to replace F_- by $\bar{F} - F_+$ (note that this last expression does not involve any variable of the form $P_{(-,k,0)}$). Next, we can reduce the dimension of the system by $n + 1$ by eliminating the $P_{(-,k,0)}$, $k = 0, \ldots, n$, from the system using relation (3.12).

Consider the differential equations for $P_{(-,k_-,1)}$, $0 \leq k_- \leq n-1$, explicitly given by

$$\begin{aligned}\frac{dP_{(-,k_-,1)}}{dt} = \\ &-\Big(\rho\bar{F}(n-k_--1)+(\sigma+\mu)(k_-+1)+\beta+\beta\Lambda_-k_-+\mu\Big)P_{(-,k_-,1)}\\ &+\rho(\bar{F}-F_+)(n-k_-)P_{(-,k_--1,1)}+\rho F_+(n-k_-)P_{(-,k_-,0)}\\ &+(\sigma+\mu)\Big((k_-+1)P_{(-,k_-+1,1)}+2P_{(-,k_-,2)}\Big)\\ &+\beta\Lambda_-(k_-+1)P_{(-,k_-+1,0)}\end{aligned}$$

(as one can verify by writing out the relevant part of (3.10)).

Then the only nonlinear terms are those that involve F_+ or $\Lambda_\pm$ as a factor. In these differential equations we find, among the nonlinear terms,

$$\rho F_+(n-k_-)P_{(-,k_-,0)} \tag{4.1}$$

and

$$\beta\Lambda_-(k_-+1)P_{(-,k_-+1,0)}. \tag{4.2}$$

Trusting that it does not lead to confusion we will denote the variables in the linearisation of (3.10) by the same symbols as the variables in the nonlinear system.

Linearisation of (4.1) yields

$$\rho F_+(n-k_-)P_{k_-}$$

where P_{k_-} is the fraction of the population in state k_- in the disease-free network and F_+ is defined as in (3.5), only now for the variables of the linearised system. For (4.2), similarly replace $P_{(-,k_-+1,0)}$ by P_{k_-+1} but next use the identity

$$(k_-+1)P_{k_-+1} = Q_{k_-+1}\sum_m mP_m$$

(cf. (2.8)). In the definition (3.8) of Λ_- we take linearisation into account by adapting the denominator of the expression for λ_- in (3.6). More precisely, we replace that denominator by

$$\sum_m mP_m.$$

Note that this cancels the identical factor in the numerator. The upshot is that this sum leads to the linearisation of (4.2) being equal to

$$\beta Q_{k_-+1}\sum_{j_+=0}^{n-1}\sum_{j_-=1}^{n-j_+} j_+j_-P_{(-,j_-,j_+)}. \tag{4.3}$$

In all other nonlinear terms, whenever F_+ or $\Lambda_\pm$ multiplies P_ℓ and P_ℓ is zero in the disease free steady state, simply put F_+ respectively $\Lambda_\pm$ equal to their values in the disease-free equilibrium, i.e.

$$\begin{aligned} F_+ &= 0 \\ \Lambda_- &= 0 \\ \Lambda_+ &= 1, \end{aligned}$$

to obtain the corresponding term for the linearised system.

Thus we deduce that the linearised system is given by

$$\begin{cases} \dfrac{dP_{(-,k_-,1)}}{dt} &= -\Big(\rho\bar{F}(n-k_- -1) + (\sigma+\mu)(k_-+1) \\ &\qquad + \mu + \beta\Big)P_{(-,k_-,1)} \\ &\quad + \rho F_+(n-k_-)P_{k_-} + \rho\bar{F}(n-k_-)P_{(-,k_- -1,1)} \\ &\quad + 2(\sigma+\mu)P_{(-,k_-,2)} + (\sigma+\mu)(k_-+1)P_{(-,k_-+1,1)} \\ &\quad + \beta Q_{k_-+1}\sum_{j_+=0}^{n-1}\sum_{j_-=1}^{n-j_+} j_+ j_- P_{(-,j_-,j_+)}, \\ \dfrac{dP_{(+,k_-,k_+)}}{dt} &= -\Big(\rho\bar{F}(n-k_- -k_+) + (\sigma+\mu)(k_+ + k_-) \\ &\qquad + \mu + \beta k_-\Big)P_{(+,k_-,k_+)} \\ &\quad + \rho\bar{F}(n-k_- -k_+ +1)P_{(+,k_- -1,k_+)} \\ &\quad + (\sigma+\mu)(k_-+1)P_{(+,k_-+1,k_+)} \\ &\quad + (\sigma+\mu)(k_++1)P_{(+,k_-,k_++1)} \\ &\quad + \beta k_+ P_{(-,k_-,k_+)} + \beta(k_-+1)P_{(+,k_-+1,k_+-1)}, \\ \text{and for } k_+ \geq 2, & \\ \dfrac{dP_{(-,k_-,k_+)}}{dt} &= -\Big(\rho\bar{F}(n-k_- -k_+) + (\sigma+\mu)(k_- + k_+) \\ &\qquad + \mu + \beta k_+\Big)P_{(-,k_-,k_+)} \\ &\quad + \rho\bar{F}(n-k_- -k_+ +1)P_{(-,k_- -1,k_+)} \\ &\quad + (\sigma+\mu)(k_-+1)P_{(-,k_-+1,k_+)} \\ &\quad + (\sigma+\mu)(k_++1)P_{(-,k_-,k_++1)}. \end{cases} \tag{4.4}$$

Remark 1. *In Lemma 3 below we will show that we can simplify expression* (4.3) *to*

$$\beta Q_{k_-+1}\sum_{j_-=0}^{n-1} j_- P_{(-,j_-,1)}.$$

Intuitively, one would expect that, in the linearisation, for $k_+ \geq 2$, $P_{(-,k_-k_+)}(t) = 0$ for all t if $P_{(-,k_-k_+)}(0) = 0$. Indeed, in the beginning of an epidemic very few individuals in the population are infectious. It is already very unlikely for a susceptible individual to have an infectious partner, so the probability that a susceptible individual has more than one infectious partner should be negligible. That this is indeed the case, is established in the following lemma.

Lemma 3. *In the linearised system* (4.4)*, if* $P_{(-,k_-k_+)}(0) = 0$*, then*

$$P_{(-,k_-,k_+)}(t) \equiv 0,$$

for $k_+ \geq 2$*.*

Proof. We prove the lemma in four steps

Step 1. Observe first that the differential equations for $P_{(-,k_-,k_+)}$, $k_+ \geq 2$, form a closed system, i.e. they do not depend on the remaining variables (see (4.4)).

Step 2. Observe that this closed system has a certain hierarchical structure, viz. the subsystem for the variables

$$P_{(-,j,n-k)},$$

$0 \leq j \leq k$, depO.ends on the variables of the subsystems with a lower value of k, but not on the variables of any subsystem with a higher value of k (the reason is that both F_+ and Λ_- were put equal to zero to derive the equations that we consider; recall that we focus on $n - k \geq 2$).

Step 3. For $k = 0$ we have

$$\frac{dP_{(-,0,n)}}{dt} = -\big((\sigma + \mu)n + \mu + \beta n\big)P_{(-,0,n)}$$

so, if $P_{(-,0,n)}(0) = 0$, then $P_{(-,0,n)} \equiv 0$.

Step 4. Consider $k = 1$. The diagram in Figure 1 shows at once that the zero state is globally stable, i.e. if $P_{(-,j,n-1)}(0) = 0$, then $P_{(-,j,n-1)} \equiv 0$, $j = 0, 1$.

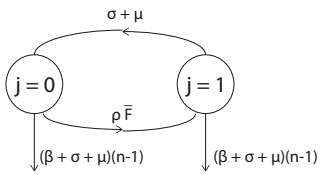

Figure 1: Diagram that shows that, if $P_{(-,j,n-1)}(0) = 0$, then $P_{(-,j,n-1)} \equiv 0$, $j = 0, 1$.

For $k = 2$, we have the diagram in Figure 2, which shows that if $P_{(-,j,n-2)}(0) = 0$, then $P_{(-,j,n-2)} \equiv 0$, $j = 0, 1, 2$.

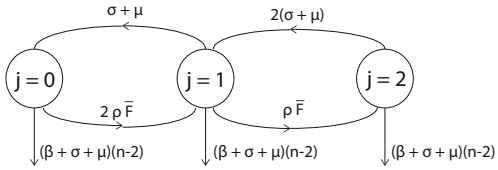

Figure 2: Diagram that shows that, if $P_{(-,j,n-2)}(0) = 0$, then $P_{(-,j,n-2)} \equiv 0$, $j = 0, 1, 2$.

By continuing in this way we establish that for all k with $0 \leq k \leq n-2$, if $P_{(-,j,n-k)}(0) = 0$, then $P_{(-,j,n-k)} \equiv 0$, $j = 0, 1, \ldots, k$. □

It follows that we are left to deal with the stability of the following linear system:

$$
\begin{cases}
\dfrac{dP_{(-,k_-,1)}}{dt} &= -\Big(\rho\bar{F}(n-k_- -1) + (\sigma+\mu)(k_-+1) + \mu + \beta\Big)P_{(-,k_-,1)} \\
&\quad + \rho F_+(n-k_-)P_{k_-} + \rho\bar{F}(n-k_-)P_{(-,k_- -1,1)} \\
&\quad + (\sigma+\mu)(k_-+1)P_{(-,k_-+1,1)} \\
&\quad + \beta Q_{k_-+1}\sum_{l_-=1}^{n} l_- P_{(-,l_-,1)} \\
\dfrac{dP_{(+,k_-,1)}}{dt} &= -\Big(\rho\bar{F}(n-k_- -1) + (\sigma+\mu)(k_-+1) \\
&\qquad + \mu + \beta k_-\Big)P_{(+,k_-,1)} + \rho\bar{F}(n-k_-)P_{(+,k_- -1,1)} \\
&\quad + (\sigma+\mu)(k_-+1)P_{(+,k_-+1,1)} + 2(\sigma+\mu)P_{(+,k_-,2)} \\
&\quad + \beta(k_-+1)P_{(+,k_-+1,0)} + \beta P_{(-,k_-,1)}
\end{cases}
$$

and for $k_+ = 0$ and $k_+ \geq 2$,

$$
\begin{cases}
\dfrac{dP_{(+,k_-,k_+)}}{dt} &= -\Big(\rho\bar{F}(n-k_- -k_+) + (\sigma+\mu)(k_- + k_+) \\
&\qquad + \mu + \beta k_-\Big)P_{(+,k_-,k_+)} \\
&\quad + \rho\bar{F}(n-k_- -k_+ +1)P_{(+,k_- -1,k_+)} \\
&\quad + (\sigma+\mu)(k_-+1)P_{(+,k_-+1,k_+)} \\
&\quad + (\sigma+\mu)(k_++1)P_{(+,k_-,k_+ +1)} \\
&\quad + \beta(k_-+1)P_{(+,k_-+1,k_+ -1)}.
\end{cases}
\tag{4.5}
$$

Recall definition (3.5) of F_+. In the reduced linearised system (4.5) we are left with variables $P_{(-,k_-,1)}$ and $P_{(+,k_-,k_+)}$, $k_-, k_+ \geq 0$, $0 \leq k_- + k_+ \leq n$. Therefore, (4.5) is a closed system. Furthermore, note that the dimension of the system is $n + (n+1)(n+2)/2 = (n^2+5n+2)/2$ (where the contribution n comes from the $P_{(-,k_-,1)}$ and the $(n+1)(n+2)/2$ from the $P_{(+,k_-,k_+)}$).

4.2 The map L

Order the P_ℓ in some appropriate way, and denote the corresponding vector by P. We define a linear map L from $\mathbb{R}^{(n^2+5n+2)/2}$ to $\mathbb{R}^{n+2}$ as follows:

$$L(P) = \begin{pmatrix} \sum_{k_+=0}^{n} \sum_{k_-=0}^{n-k_+} (n-k_- - k_+) P_{(+,k_-,k_+)} \\ \left(P_{(-,j-1,1)}\right)_{j=1}^{n} \\ \sum_{k_+=0}^{n} \sum_{k_-=0}^{n-k_+} k_+ P_{(+,k_-,k_+)} \end{pmatrix}. \tag{4.6}$$

Note that L maps the positive P-cone to the positive cone in $\mathbb{R}^{n+2}$. In fact, if P is in the interior of the positive cone, i.e. all vector elements are strictly positive, then

$$\sum_{k_+=0}^{n} \sum_{k_-=0}^{n-k_+} (n-k_- - k_+) P_{(+,k_-,k_+)} > 0,$$

since $n - k_- - k_+ \geq 0$ for all $k_- + k_+ < n$, and $P_{(+,k_-,k_+)} > 0$ for all k_- and k_+,

$$P_{(-,j,1)} > 0,$$

and

$$\sum_{k_+=0}^{n} \sum_{k_-=0}^{n-k_+} k_+ P_{(+,k_-,k_+)} > 0,$$

since $P_{(+,k_-,k_+)} > 0$ for all k_- and we sum over $k_+ = 0, 1, 2, \ldots, n$. In particular it follows that if $L(P) = 0$, then $P = 0$. We shall use this linear operator L in Section 6.

5 Dynamics of the binding sites of an infectious individual: characterization of R_0

By exploiting that an individual can be considered as a collection of n binding sites that behave independently from one another as far as separation or acquiring a new partner is concerned and by using our mean field at distance one assumption, we are able to characterize R_0 in terms of binding sites. In this section we only use the interpretation of the model and we do not use the system (3.10) or its reduced linearisation (4.5). We characterize R_0 as the dominant eigenvalue of a next-generation matrix (NGM) that we construct using the interpretation of the model.

The entries in the NGM can be viewed as expected offspring values for a multi-type branching process [85, 86], with the two matrix-indices specifying the type at birth of, respectively, offspring and parent. Several slightly different branching processes may yield the same NGM and for the deterministic theory (which is what we deal with here) there is no need to choose one of these as 'the' underlying process. A branching process corresponding to the NGM is subcrititcal when $R_0 < 1$ and supercritical when $R_0 > 1$. But

does such a branching process indeed correspond to the linearisation of (3.10) in the disease free steady state? Especially for $n > 1$ this is a nontrivial question. In Section 6 we will therefore prove that R_0, as computed from the NGM, is indeed a threshold parameter with threshold value one for (3.10).

First, in Section 5.1, we consider the case $n = 1$. In Section 5.2 we generalize the transition and transmission scheme to $n > 1$, and in Section 5.3 we characterize R_0 on the level of binding sites. We conclude this section by showing in Section 5.4 that R_0 also has an interpretation in terms of individuals. The explicit expression for R_0 and the remainder of its derivation is left for Appendix C.

Consider the usual setting for determining R_0, i.e. suppose that we have a population in which only a few individuals are infectious and all others are susceptible. We are interested in the expected number of secondary cases caused by one 'typical' infectious case.

5.1 The case $n = 1$

First, consider a population of individuals with partnership capacity $n = 1$. Then each individual has exactly one binding site. If we now consider an infectious individual, then its binding site can be in one of three states:

- A — free
- B — occupied by a susceptible partner
- C — occupied by an infectious partner

Please note that we recycle symbols: the A here has nothing to do with the matrix A of Section 2 and the B here has nothing to do with the matrix B in (3.2) of Section 3. In Figure 3 the possible state transitions and corresponding rates for an infectious individual are given. Note that it is highly unlikely that an infectious individual acquires an infectious partner in the beginning of an epidemic, and therefore there is no transition from A to C.

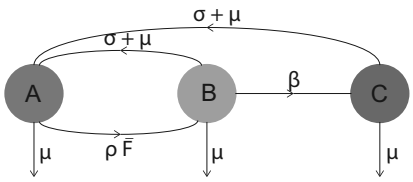

Figure 3: Flow chart describing the possible transitions between states A, B and C and their corresponding rates. Note that, in the beginning of the epidemic, only a few individuals in the population are infectious. Therefore the probability that an infectious individual acquires an infectious partner is zero. This is represented in the flowchart where there is no direct arrow from A to C.

We can characterize R_0 by constructing an NGM K_1 that involves a transmission part T_1 and a transition part Σ_1.

Recall that we use the convention that, for a transition matrix $M = (m_{ij})$, m_{ij} denotes the probability per unit of time at which a transition from j to i occurs (instead of the transition from i to j, as it is common in the stochastic community).

The matrices T_1 and Σ_1 are obtained as follows. Consider an infectious individual, and order the states as A, B, C. Then the transitions of the individual's binding site are described by the following matrix Σ_1 (see Figure 3 for its graphical representation):

$$\Sigma_1 = \begin{pmatrix} -(\rho\bar{F} + \mu) & \sigma + \mu & \sigma + \mu \\ \rho\bar{F} & -(\beta + \sigma + 2\mu) & 0 \\ 0 & \beta & -(\sigma + 2\mu) \end{pmatrix}. \tag{5.1}$$

Here $(\Sigma_1)_{xy}$ is the rate at which a transition from a binding site in state y to state x occurs, $x, y \in \{A, B, C\}$, $x \neq y$, and for the diagonal elements we have $(\Sigma_1)_{xx} = -(\mu + \sum_{y \neq x}(\Sigma_1)_{yx})$.

Consider an infectious individual u with its binding site in state B. If u infects its susceptible partner v, then the binding site of u transits from B to C. This transition is represented by $(\Sigma_1)_{CB} = \beta > 0$. In addition to this transition, an additional C binding site is created. Indeed, v is now also an infectious individual who has a binding site occupied by an infectious partner (namely u). This shows that one transition from B to C always creates one additional C binding site in the population. Accordingly we define the transmission matrix T_1:

$$T_1 = \beta \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 1 & 0 \end{pmatrix}. \tag{5.2}$$

Using T_1 and Σ_1 we can construct the NGM K_1:

$$K_1 = T_1(-\Sigma_1)^{-1}.$$

The basic reproduction number R_0 is defined as the dominant eigenvalue of K_1 [8, Section 7.2].

In the present case we can, quite easily, give an explicit expression for R_0. Note that T_1 has one-dimensional range spanned by the vector $(0, 0, 1)'$. Therefore $(0, 0, 1)'$ is the eigenvector corresponding to the dominant eigenvalue R_0. We find K_1 applied to this vector by first constructing $(-\Sigma_1)^{-1}$ applied to this vector. This can be done by either treating it as a linear algebra problem or we can use the interpretation for it: $\big(-(\Sigma_1)^{-1}(0, 0, 1)'\big)_x$ is the mean time spent in state x when starting in state C, $x = A$, B, C (in fact we only use $x = B$). We find that

$$(-\Sigma_1)^{-1} \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix} = \begin{pmatrix} \frac{\sigma+\mu}{\mu(\rho\bar{F}+\sigma+2\mu)} \\ \frac{\rho\bar{F}(\sigma+\mu)}{\mu(\beta+\sigma+2\mu)(\rho\bar{F}+\sigma+2\mu)} \\ \frac{\beta(\rho\bar{F}+\mu)+\mu(\rho\bar{F}+\sigma+2\mu)}{\mu(\beta+\sigma+2\mu)(\rho\bar{F}+\sigma+2\mu)} \end{pmatrix},$$

and subsequently,

$$K_1 \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix} = \frac{\beta\rho\bar{F}(\sigma+\mu)}{\mu(\beta+\sigma+2\mu)(\rho\bar{F}+\sigma+2\mu)} \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix},$$

from which we conclude that

$$R_0 = \frac{\beta\rho\bar{F}(\sigma+\mu)}{\mu(\beta+\sigma+2\mu)(\rho\bar{F}+\sigma+2\mu)}. \tag{5.3}$$

Alternatively, we can characterize R_0 by first step analysis; see Appendix A for the details or [8, Section 7.8] or [50, formula (3.1.9)] or [80, Section 4.1]. However, this does not have such a nice generalization to $n > 1$ as the ABC scheme does.

5.2 Generalization of the transition and transmission matrix: $n > 1$

Now consider the case $n > 1$. In this case, an individual is a collection of n binding sites. These binding sites may be free, occupied by a susceptible or occupied by an infectious individual, i.e. in states A, B, or C, respectively. An infectious individual can infect a susceptible individual in the population if it has a binding site that is occupied by a susceptible individual. In that case, that binding site becomes occupied by an infectious individual. Similar to the $n = 1$ situation we observe that if a binding site makes a transition from 'occupied by a susceptible individual' to C, it creates a new infectious individual in the population. However, we need to know in which states the n binding sites of this new infectious individual are. Obviously, one new infectious binding site is in state C, viz. the binding site still occupied by its epidemiological parent. In order to know the states of the other $n-1$ binding sites, we need to know the number of (susceptible) partners of this individual at epidemiological birth.

Naively, motivated by Lemma 2, one would think (as we did at first) that the number of partners of a newly infected individual is k (i.e. 1 binding site in state C, $k-1$ binding sites in state B and $n-k$ binding sites in state A) with probability Q_k. The computation of the corresponding R_0 is rather straightforward (using the method explained in Appendix A for $n = 1$). However, one can check numerically that the stability switch of the disease free steady state of (3.10) does *not* coincide with $R_0 = 1$ when R_0 is defined in this manner. We conclude that the premise is wrong. In retrospect this makes sense. First of all, we know that q differs from Q, where q and Q are defined by (2.7) and (2.8), respectively. In our model description we keep track of the number of partners of an individual. We use mean field at distance one for the partners of partners of this individual (and this shows up in the $\Lambda_\pm$ in the transmission events). So we need to do the same when characterizing R_0 and also take into account the partners of susceptible partners. Therefore, we need to extend the information that is tracked in the scheme.

We generalize the ABC scheme of Section 5.1 as follows. Consider an infectious binding site. Then this binding site can be in one of $n+2$ states:

- A — free

- B_j — occupied by a susceptible partner that has j partners in total, $j = 1, \ldots, n$
- C — occupied by an infectious partner.

Let $\boldsymbol{B}$ denote the collection of all states B_j. We denote the transition matrix of the states A, B_j, $j = 1, \ldots, n$, and C by Σ (see Figure 4 for the corresponding flowchart), where

$$\Sigma = \begin{pmatrix} -(\rho\bar{F} + \mu) & \boldsymbol{\sigma + \mu} & \sigma + \mu \\ \rho\bar{F}\boldsymbol{q} & \Sigma_{\boldsymbol{B}} & \mathbf{0} \\ 0 & \boldsymbol{\beta} & -(\sigma + 2\mu) \end{pmatrix}, \tag{5.4}$$

where $\mathbf{0}$ denotes the n dimensional zero vector, $\boldsymbol{\sigma+\mu}$ and $\boldsymbol{\beta}$ both denote an n-dimensional row vector, namely

$$\begin{aligned} \boldsymbol{\sigma + \mu} &= (\sigma + \mu)\begin{pmatrix} 1 & 1 & \cdots & 1 \end{pmatrix}, \\ \boldsymbol{\beta} &= \beta\begin{pmatrix} 1 & 1 & \cdots & 1 \end{pmatrix}. \end{aligned}$$

The vector $\boldsymbol{q}$ is the probability vector with elements q_k given by (2.7), and $\Sigma_{\boldsymbol{B}}$ is an $n \times n$ matrix describing the transitions between the states $B_1, \ldots, B_n$ and out of $\boldsymbol{B}$; see Figure 4 for the corresponding flowchart.

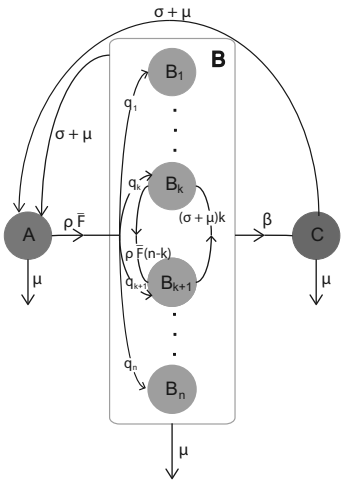

Figure 4: Flow chart describing the possible transitions between states A, B_j, $j = 1, \ldots, n$, and C and their corresponding rates.

Let's describe $\Sigma_{\boldsymbol{B}}$ more carefully. The matrix $\Sigma_{\boldsymbol{B}}$ describes the transitions between the B_j and out of $\boldsymbol{B}$. Thus $\Sigma_{\boldsymbol{B}}$ is an $n \times n$ tridiagonal matrix with negative diagonal entries and positive off-diagonal entries. More specifically,

$$\begin{aligned} (\Sigma_{\boldsymbol{B}})_{j-1,j} &= (\sigma + \mu)(j - 1), \\ (\Sigma_{\boldsymbol{B}})_{j,j} &= -(\beta + \rho\bar{F}(n - j) + (\sigma + \mu)j + \mu), \\ (\Sigma_{\boldsymbol{B}})_{j+1,j} &= \rho\bar{F}(n - j). \end{aligned}$$

Indeed, a susceptible individual with 1 infectious and $j-1$ susceptible partners loses one of these susceptible partners at rate $(\sigma+\mu)(j-1)$, acquires a new susceptible partner at rate $\rho\bar{F}(n-j)$, and, since it can also become infectious, lose its infectious partner, or die (these last three mark transitions out of $\boldsymbol{B}$), the rate out of B_j is $(\Sigma_{\boldsymbol{B}})_{j,j} = -(\beta + \rho\bar{F}(n-j) + (\sigma+\mu)j + \mu)$.

The other elements of Σ have the following interpretation. Note that, in the beginning of an epidemic, a binding site in state A acquires a susceptible partner at rate $\rho\bar{F}$. The probability that, just after the moment of acquisition, this susceptible partner has in total j partners is q_j in accordance with (2.7). Therefore, the rate at which a binding site in state A transits to state B_j is $(\Sigma)_{B_j,A} = \rho\bar{F}q_j$. In a similar way one can use the interpretation (and the flowchart in Figure 4) to find the other entries for the matrix Σ.

Finally, we need to construct the transmission matrix T. A transmission corresponds to a transition $B_j \to C$, i.e. if an infectious individual u with a binding site in B_j infects its partner v. This is included in the matrix Σ since $(\Sigma)_{C,B_j} = \beta > 0$. The transmission matrix T includes the binding sites of the newly infected partner v. Concerning the binding sites of v, since it is now infectious, we observe that it has one binding site in C, $n-j$ binding sites in A and $j-1$ binding sites will be occupied by susceptible individuals, i.e. $j-1$ binding sites will be in the set $\boldsymbol{B}$ (see Figure 5 for an illustration where u has a binding site in B_2 that changes state to C and v is the newly infected individual with one binding site in C, one binding site in A and one binding site occupied by a susceptible individual). All that is left to specify are the states of the $j-1$ binding sites in $\boldsymbol{B}$, i.e. we need to know how many partners these susceptible partners of v have (in Figure 5 on p. 65: how many partners does w have).

The probability that a partner w of v has k partners depends on the state of v, where v is in state $(+, j-1, 1)$ immediately after infection by u. However, as another manifestation of the mean field at distance one assumption, we approximate this probability by only taking into account that the susceptible individual w has at least one partner v. Therefore, we assume that w has k partners with probability Q_k (cf. Lemma 2). In other words, we assume that a binding site of v occupied by a susceptible partner, i.e. a binding site in the set $\boldsymbol{B}$, is in state B_k with probability Q_k.

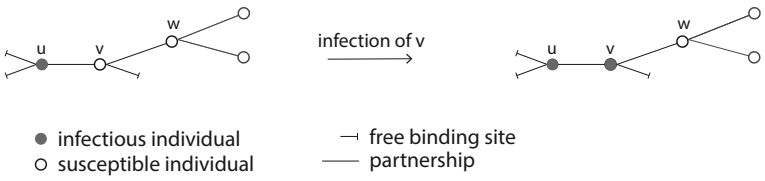

Figure 5: Illustration of the construction of T for $n=3$. Suppose we start with an individual with two binding sites in A and one binding site in B_2. Then u has one susceptible partner v. If u infects v, then v will have one binding site in C, one binding site in A, and one binding site will be occupied by a susceptible partner w. In the example, w has three partners in total and therefore the binding site of v would be in state B_3. However, information about the partners of w is not incorporated in our model description and therefore we assume that w has three partners with probability Q_3.

Accordingly, we define the transmission matrix T as follows:

$$T = \beta\begin{pmatrix} 0 & \phi_1 & \cdots & \phi_n & 0 \end{pmatrix}, \tag{5.5}$$

where ϕ_j is the $n+2$ vector

$$\phi_j = \begin{pmatrix} n-j \\ (j-1)\boldsymbol{Q} \\ 1 \end{pmatrix} = (n-j)\psi_A + (j-1)\psi_{\boldsymbol{B}} + \psi_C, \tag{5.6}$$

$j = 1, \ldots, n$, where

$$\psi_A = \begin{pmatrix} 1 \\ \mathbf{0} \\ 0 \end{pmatrix}, \quad \psi_{\boldsymbol{B}} = \begin{pmatrix} 0 \\ \boldsymbol{Q} \\ 0 \end{pmatrix}, \quad \psi_C = \begin{pmatrix} 0 \\ \mathbf{0} \\ 1 \end{pmatrix}, \tag{5.7}$$

and $\boldsymbol{Q}$ is the probability vector with components Q_k given by (2.8). Note that the ϕ_j are a linear combination of the ψ_x, $x \in \{A, \boldsymbol{B}, C\}$. We conclude that the range of T is spanned by $\psi_A, \psi_{\boldsymbol{B}}, \psi_C$.

In Section 5.4 we shall show that we can identify the ϕ_j with an individual in state $(+, j-1, 1)$, which allows us to interpret R_0 in terms of individuals. But first, in Section 5.3, we focus on the interpretation in terms of binding sites.

5.3 R_0 in terms of binding sites

Now that we have defined the transition matrix Σ and the transmission matrix T, we are ready to define the basic reproduction ratio R_0 for $n > 1$ as the dominant eigenvalue of the matrix

$$T(-\Sigma)^{-1}.$$

In order to underpin this, consider variables X_A, X_{B_j}, and X_C, where X_A, X_{B_j}, and X_C are the fractions of the total binding-site population in states A, B_j, and C, respectively. Then, based on the interpretation, X_A, X_{B_j}, and X_C should satisfy the following system of differential equations:

$$\frac{d}{dt}\begin{pmatrix} X_A \\ X_{B_1} \\ \vdots \\ X_{B_n} \\ X_C \end{pmatrix} = (T+\Sigma)\begin{pmatrix} X_A \\ X_{B_1} \\ \vdots \\ X_{B_n} \\ X_C \end{pmatrix}. \tag{5.8}$$

It follows that the zero state $(X_A, X_{B_1}, \ldots, X_{B_n}, X_C)' = 0$ switches stability at $R_0 = 1$. We formulate this as

Theorem 2. *R_0, defined as the dominant eigenvalue of $T(-\Sigma)^{-1}$, is a threshold parameter with threshold value one for the zero state of* (5.8).

Note that $T(-\Sigma)^{-1}$ is an $(n+2)\times(n+2)$ matrix. Also, elements $\left(T(-\Sigma)^{-1}\right)_{xy}$ can be interpreted as the expected number of binding sites in x created by one binding site in y, where $x, y \in \{A, B_1, \ldots, B_n, C\}$. This gives us an interpretation of R_0 in terms of binding sites $A, B_1, \ldots, B_n, C$. However, we can reduce the characterization of R_0 to a problem involving a 3×3 matrix by averaging the B_j in the right way (and this allows us to consider binding sites in A, $\boldsymbol{B}$, C only). We show this in the remainder of this subsection.

Consider the 3×3 matrix $K = (k_{x,y})$ where the $k_{x,y}$, $x, y = A, \boldsymbol{B}, C$, are defined by

$$T(-\Sigma)^{-1}\psi_y = \sum_{x=A,\boldsymbol{B},C} k_{x,y}\psi_x. \tag{5.9}$$

Then R_0 is also the dominant eigenvalue of K. We formulate this in a theorem.

Theorem 3. *R_0, defined as the dominant eigenvalue of K, where K is defined by* (5.9)*, is a threshold parameter with threshold value one for the zero state of* (5.8)*.*

Proof. We have defined R_0 as the dominant eigenvalue of $T(-\Sigma^{-1})$ and this R_0 is a threshold parameter of the linear system corresponding to the matrix $T + \Sigma$ according to Theorem 2. We will show that $T(-\Sigma^{-1})$ and K have the same dominant eigenvalue.

The range of T is spanned by three linearly independent vectors ψ_A, $\psi_{\boldsymbol{B}}$, ψ_C. If $T(-\Sigma)^{-1}v = \lambda v$, with $\lambda \neq 0$, $v \neq 0$, then v lies in the range of T, i.e. $v = \sum_y w_y\psi_y$, with at least one of the $w_y \neq 0$. Therefore,

$$\begin{aligned} T(-\Sigma)^{-1}v &= T(-\Sigma)^{-1}\left(\sum_y w_y\psi_y\right) \\ &= \sum_x \sum_y k_{x,y}w_y\psi_x, \end{aligned}$$

where the summation is over x or $y \in \{A, \boldsymbol{B}, C\}$. On the other hand, this is equal to

$$\lambda v = \lambda \sum_x w_x\psi_x.$$

Since the ψ_x are linearly independent, it follows that

$$\sum_y k_{x,y}w_y = \lambda w_x,$$

for all $x = A, \boldsymbol{B}, C$. In matrix notation:

$$Kw = \lambda w,$$

where $w = (w_x)$ is a three-dimensional vector, not equal to the zero vector. We conclude that if λ is a nonzero eigenvalue of $T(-\Sigma)^{-1}$, then λ is also a nonzero eigenvalue of K. To find the dominant eigenvalue R_0 of $T(-\Sigma)^{-1}$, we can focus on the 3×3 matrix $K = (k_{x,y})$. □

Consider the definition of K given by (5.9). This definition allows for an interpretation of the elements $k_{x,y}$. Indeed, $k_{x,y}$ can be interpreted as the expected number of binding sites in x created by one binding site in y, with $x, y \in \{A, \boldsymbol{B}, C\}$. Therefore, we call K the NGM on the level of binding sites, and R_0 can be interpreted as the expected number of secondary cases caused by a typical newly infected binding site in the beginning of an epidemic. Note that when x or y equals $\boldsymbol{B}$ we specify a probability distribution rather than a specific state.

The relation (5.9) completely characterizes the matrix K. However, using the interpretation, we can give explicit expressions for the entries of K; see Appendix C. In this appendix it is also shown that, in order to find R_0, we can reduce K to a 2×2 matrix and calculate the dominant eigenvalue of this smaller matrix. By combining (C.4)-(C.6), (C.8), and (C.10)-(C.12) we then find R_0 given as an explicit function of the model parameters.

We have characterized R_0 in terms of binding sites, both by considering all possible states $\{A, B_1, \ldots, B_n, C\}$ and by considering $\{A, \boldsymbol{B}, C\}$. This allows for an interpretation of R_0 in terms of binding sites. As we next show, we may also interpret R_0 in terms of individuals.

5.4 R_0 in terms of individuals

The model description is on the level of individuals, so it is only sensible that, in this section, we concern ourselves with the interpretation of R_0 in terms of individuals, i.e. the interpretation of R_0 as the expected number of secondary cases caused by a typical newly infected *individual* (rather than binding site) in the beginning of an epidemic.

Individuals can be considered as collections of n binding sites. We find the relation between the binding site level and the individual level as follows. Recall (5.6), where we see in the second equality that the ϕ_j are a linear combination of the ψ_A, $\psi_{\boldsymbol{B}}$, and ψ_C. Note that ϕ_j is a collection of n infectious binding sites, $n - j$ in state A, 1 in state C, and $j - 1$ in states B_l, $l = 0, \ldots, n$ (and where the infectious binding site is in state B_l with probability Q_l). We can identify ϕ_j with an individual in state $(+, j - 1, 1)$. Note that the $(+, j - 1, 1)$ are the possible states of an individual at epidemiological birth. For the case $n = 1$, we have $\phi_1 = \psi_C$ only (which corresponds to the only state-at-epi-birth $(+, 0, 1)$ since an infectious individual at epi-birth is in a partnership with its epidemiological partner).

This observation allows us to also give an interpretation to R_0 for individuals. Indeed, consider $K^{\text{ind}} = ((k^{\text{ind}})_{ij})$, where the $(k^{\text{ind}})_{ij}$ are characterized by

$$T(-\Sigma^{-1})\phi_j = \sum_{i=1}^{n} (k^{\text{ind}})_{ij} \phi_i. \tag{5.10}$$

Element $(k^{\text{ind}})_{ij}$ is then the expected number of secondary cases in state i caused by one infectious individual in state j. Here i and j are of the form $(+, m, 1)$, $m = 0, \ldots, n - 1$. To arrive at the interpretation of R_0 on the individual-level, we can prove that the

dominant eigenvalue of K^{ind} (which is the NGM on individual level) equals the dominant eigenvalue R_0 of K; see Appendix E for the details.

The matrix K^{ind} is completely characterized by the identity (5.10). But, as in the case of K, we can use the interpretation to give a more explicit expression for the entries of K^{ind}; see Appendix F.

5.5 R_0: equivalence of different interpretations

In Section 5.3 R_0 is defined as the dominant eigenvalue of $T(-\Sigma)^{-1}$. Theorem 3 states that R_0 is also the dominant eigenvalue of the ABC-NGM K, where K is defined by (5.9), and in Appendix C we show that, in order to find the dominant eigenvalue of K, we can reduce K to a 2×2 matrix $\tilde{K}$. Finally, in Appendix E, we show that R_0 is also the dominant eigenvalue of the NGM K^{ind} on individual level. We summarize this in (5.11), where $\Leftrightarrow$ refers to 'has the same dominant eigenvalue'.

$$T(-\Sigma^{-1}) \iff \begin{array}{c} K \\ \Updownarrow \\ \tilde{K} \end{array} \iff K^{\text{ind}} \tag{5.11}$$

In the next section we prove that R_0 defined in this way is indeed a threshold for the stability of the disease-free steady state of the nonlinear system (3.10), by using L defined in (4.6) to relate the linearisation of (3.10) to (5.8).

6 Proof that R_0 is a threshold parameter

Recall that, using the mean field at distance one assumption, we have written down a system of differential equations to describe the transmission of the infectious disease across the dynamic network. We will refer to the system (3.10) of differential equations for the fractions of the population of individuals in states ℓ, $\ell = (\pm, k_-, k_+)$ as the P-system. In Section 4 we have linearised this system around the disease-free steady state and we were able to restrict this linearised system to the fractions $P_{(-,k,1)}$ and $P_{(+,k_-,k_+)}$. In Section 5 we considered binding sites of an infectious individual (in the linearisation!) and these binding sites could be in A, $\boldsymbol{B}$, and C. This led to the ABC-system (5.8). R_0, defined as the dominant eigenvalue of K, is a threshold for the stability of the zero state of (5.8); this was formulated in Theorem 3. In this section we will prove that R_0 is also a threshold for the stability of the disease-free steady state of system (3.10). We do so by relating the reduced linearisation (4.5) of the P-system to the ABC-system (5.8).

6.1 The case $n = 1$

For $n = 1$ the proof is relatively easy, since there is no distinction between 'individual' and 'binding site'. As the proof provides guiding lines for the general case, we present it first.

If we write out (4.5) for $n = 1$ we obtain the system of four ODE:

$$\begin{aligned}
\frac{dP_{(-,0,1)}}{dt} &= -(\sigma + 2\mu + \beta)P_{(-,0,1)} + \rho F_+ P_0 \\
\frac{dP_{(+,0,0)}}{dt} &= -(\rho\bar{F} + \mu)P_{(+,0,0)} + (\sigma + \mu)P_{(+,1,0)} + (\sigma + \mu)P_{(+,0,1)} \\
\frac{dP_{(+,1,0)}}{dt} &= -(\sigma + 2\mu + \beta)P_{(+,1,0)} + \rho\bar{F}P_{(+,0,0)} \\
\frac{dP_{(+,0,1)}}{dt} &= -(\sigma + 2\mu)P_{(+,0,1)} + \beta P_{(+,1,0)} + \beta P_{(-,0,1)}.
\end{aligned}$$

The consistency relation (3.11), which for $n = 1$ reduces to

$$P_{(-,0,1)} = P_{(+,1,0)}, \tag{6.1}$$

is reflected in the fact that the first and third equation of the system of ODEs are identical (recall that, for $n = 1$, $\bar{F}$ equals P_0 and F_+ equals $P_{(+,0,0)}$). Using (6.1) we reduce to the three-dimensional system

$$\begin{aligned}
\frac{dP_{(+,0,0)}}{dt} &= -(\rho\bar{F} + \mu)P_{(+,0,0)} + (\sigma + \mu)P_{(+,1,0)} + (\sigma + \mu)P_{(+,0,1)} \\
\frac{dP_{(+,1,0)}}{dt} &= -(\sigma + 2\mu + \beta)P_{(+,1,0)} + \rho\bar{F}P_{(+,0,0)} \\
\frac{dP_{(+,0,1)}}{dt} &= -(\sigma + 2\mu)P_{(+,0,1)} + 2\beta P_{(+,1,0)}.
\end{aligned}$$

To finish the proof, we only need to observe that the corresponding matrix is exactly $\Sigma_1 + T_1$, with Σ_1 defined in (5.1) and T_1 in (5.2).

Indeed, recall the three states A, B, and C that we defined for the binding site of an infectious individual in Section 5.1 and the population level fractions X_A, X_B, X_C in states A, B, and C. Since individuals have exactly one binding site we identify the fractions of binding sites with fractions of individuals:

$$\begin{aligned}
X_A &= P_{(+,0,0)} \\
X_B &= P_{(+,1,0)} \\
X_C &= P_{(+,0,1)}.
\end{aligned}$$

With this identification, the linearisation of the P-system equals the (linear) ABC-system. Therefore, not only is there a stability switch of the disease-free state of the ABC-system at $R_0 = 1$ (see also Theorem 3), but in fact there is also a stability switch for the disease-free state of the system at $R_0 = 1$.

To enhance the understanding, we present the main ingredients of the proof once more, but now by way of pictures. Figure 3 depicts the possible states and state transitions for an *infectious* individual. The corresponding part of the transition matrix is Σ_1. The corresponding p-level variables are P_ℓ with indices $\ell = (+,0,0), (+,1,0), (+,0,1)$.

This $+$ part of the P-vector does not form a closed system. Indeed, an individual in state $(-,0,1)$ has probability per unit of time β to jump to $(+,0,1)$, as indicated in Figure 6.

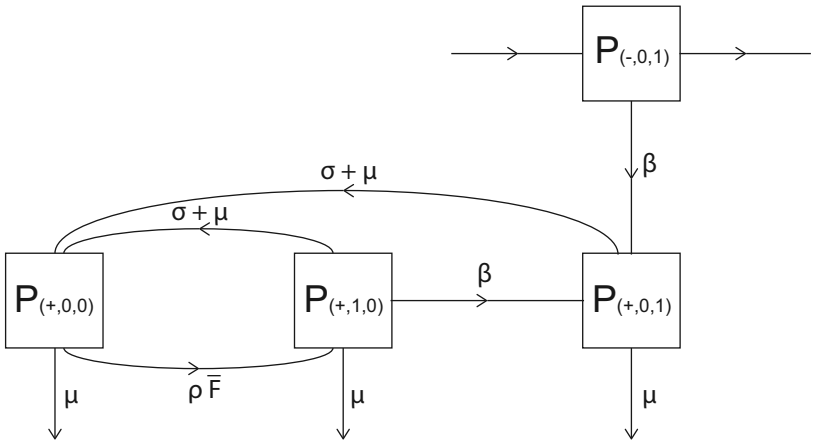

Figure 6: Flow chart representing part of the linearised system of ODEs (4.5) for the p-level fractions.

When this jump occurs, the responsible partner (the 'epidemiological parent') jumps from $(+,1,0)$ to $(+,0,1)$. The interpretation underlying this last statement is mathematically reflected in the consistency relation (6.1). Using (6.1) we reduce the flow chart of Figure 6 to the one depicted in Figure 7. The corresponding matrix is $\Sigma_1 + T_1$.

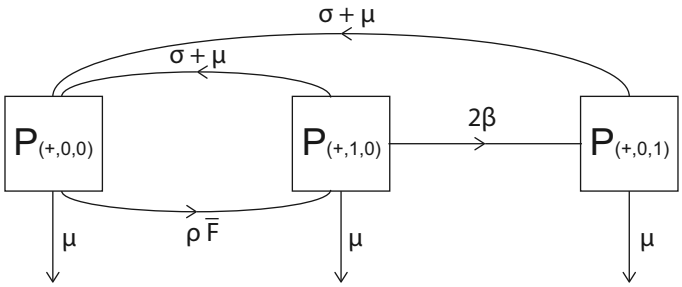

Figure 7: Flow chart of Figure 6 with $P_{(-,0,1)}$ eliminated. Note that this figure does not allow for an individual-level interpretation; the rate at which an individual in state $(+,1,0)$ infects its susceptible partner is β (compare with Figure 3). But the flow from population-level fraction $P_{(+,1,0)}$ to $P_{(+,0,1)}$ is with rate 2β since it implicitly captures the inflow from $P_{(-,0,1)}$.

6.2 Generalization: $n > 1$

In general, for $n > 1$, we can express X_A, X_{B_j}, and X_C in terms of the linearised P-system by:

$$\begin{aligned} X_A &= \sum_{k_+=0}^{n} \sum_{k_-=0}^{n-k_+} (n - k_- - k_+) P_{(+,k_-,k_+)} \\ X_{B_j} &= P_{(-,j-1,1)} \\ X_C &= \sum_{k_+=0}^{n} \sum_{k_-=0}^{n-k_+} k_+ P_{(+,k_-,k_+)}. \end{aligned}$$

The explanation is as follows. An individual in state $(+, k_-, k_+)$ is infectious and has $n - k_- - k_+$ free binding sites and k_+ binding sites occupied by infectious partners. Summing over all possible states $(+, k_-, k_+)$ we obtain the number of binding sites in, respectively, states A and C. For the number of binding sites in state B_j we observe that an individual in $(-, j-1, 1)$ has j partners in total and one infectious partner. This infectious individual therefore has a binding site occupied by a susceptible partner who has j partners in total, i.e. a binding site in state B_j. The total number of binding sites in state B_j is therefore $P_{(-,j-1,1)}$.

So the map L defined in (4.6) maps the P-variables to the X_{ABC}-variables, i.e. we have the linear transformation

$$\begin{pmatrix} X_A \\ X_{B_1} \\ \vdots \\ X_{B_n} \\ X_C \end{pmatrix} = LP. \tag{6.2}$$

By differentiating LP and using (4.5), we obtain the linear system of differential equations (5.8) for X_A, X_{B_j}, and X_C.

It remains to prove that the stability switch of the zero state of the ABC-system occurs if and only if the disease-free state of the P-system (3.10) switches stability. This will be shown in the remainder of this section.

We know that R_0 is a threshold parameter for the zero state of the ABC-system (see Theorem 3), i.e.

$$\operatorname{sign}(R_0 - 1) = \operatorname{sign}(r_{ABC}), \tag{6.3}$$

where r_{ABC} is the spectral bound of $T + \Sigma$, i.e. $r_{ABC} = \sup\{\operatorname{Re}(\lambda) \colon \lambda \in \sigma(T + \Sigma)\}$, and $\sigma(T + \Sigma)$ is the spectrum of $T + \Sigma$.

So in order to show that R_0 is a threshold for the disease free state of the P-system, it suffices to show that

$$\operatorname{sign}(r_{ABC}) = \operatorname{sign}(r_P). \tag{6.4}$$

Here r_P is the spectral bound of M_P where M_P is the matrix corresponding to the right-hand side of (4.5). In fact we will show that $r_{ABC} = r_P$.

We will proceed as follows. First we shall prove that r_{ABC} and r_P are dominant eigenvalues of the matrices $T+\Sigma$ and M_P, respectively, in the sense that these eigenvalues are uniquely characterized by the positivity of the eigenvector (up to a multiplicative positive constant).

We show in Lemma's 4 and 5 that $T + \Sigma$ and M_P are irreducible matrices. This then allows us to conclude that the dominant eigenvalues of M_P and $T + \Sigma$ are real and uniquely characterized by a positive eigenvector (see e.g. Theorem 2.5 of [87]). In other words, there exists a real eigenvalue r_P for M_P for which it holds that $r_P > \text{Re } \lambda$ for any eigenvalue $\lambda \neq r_P$ of M_P and r_P is uniquely defined by the positivity of the corresponding eigenvector (and similarly with r_{ABC} replacing r_P and $T + \Sigma$ replacing M_P).

In Lemma's 4 and 5 below we use that a matrix $M = (m_{xy})$ is irreducible if and only if variable x communicates with variable y ($x \leftrightarrow y$) for all variables x and y, i.e. there is a path from x to y ($x \to y$), i.e. there are variables y_1, y_2, …, y_n such that $m_{y,y_n} \cdots m_{y_2,y_1} m_{y_1,x} > 0$, and a path from y to x ($y \to x$), i.e. there are variables x_1, x_2, …, x_k such that $m_{y,x_k} \cdots m_{x_2,x_1} m_{x_1,y} > 0$. Note that the somewhat unusual notation is due to our convention that m_{xy} denotes the transition from y to x (instead of the transition from x to y, as it is common in the stochastic community).

Lemma 4. *$T + \Sigma$ is an irreducible matrix.*

Proof. The flowchart describing the matrix Σ is presented in Figure 4. We immediately see from this figure that from any state x there is a path to any other state y, with $x, y \in \{A, B_1, B_2, \ldots, B_n, C\}$. It follows that Σ is irreducible. Since T is nonnegative, also $T + \Sigma$ is irreducible. □

Lemma 5. *M_P is an irreducible matrix.*

Proof. With respect to a splitting of P into $-$ components and $+$ components, M_P is a block matrix that consists of four matrices M_1, M_2, M_3, M_4:

$$M_P = \begin{array}{c} \\ - \\ + \end{array} \begin{array}{c} \begin{array}{cc} - & + \end{array} \\ \begin{pmatrix} M_1 & M_3 \\ M_2 & M_4 \end{pmatrix} \end{array}.$$

The matrices M_2 and M_3 are non-negative matrices, not equal to the zero matrix, while M_1 and M_4 are positive off-diagonal. We show that M_1 and M_4 are irreducible, and that this implies that M_P is irreducible.

Consider M_1. This matrix consists of the rates corresponding to the possible flows of the $-$ variables, i.e. population-level fractions of the form $P_{(-,k,1)}$ (and rates $\beta + \sigma + 2\mu$ out of the $-$ states, that we do not need to consider here). In Figure 8 part of the possible flows and corresponding rates are represented graphically. From Figure 8 we immediately see that, from any variable $P_{(-,k,1)}$, one can find a path to any other variable $P_{(-,l,1)}$, or

in other words, $P_{(-,k,1)} \rightarrow P_{(-,l,1)}$ for all $k, l = 0, \ldots, n-1$. Therefore M_1 is an irreducible matrix.

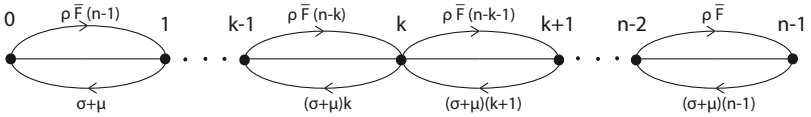

Figure 8: Graphical representation of part of matrix M_1 (point k represents fraction $P_{(-,k,1)}$) showing that $x \rightarrow y$ for all $x, y = P_{(-,l,1)}$, i.e. M_1 is irreducible. Part of M_1 that is being ignored is e.g. the rates $\beta + \sigma + 2\mu$ out of each variable $P_{(-,k_-,1)}$ leaving the $-$ system.

Consider the matrix M_4. This matrix consists of the rates corresponding to the possible flows of the $+$ variables. i.e. population-level fractions of the form $P_{(+,k_-,k_+)}$. In Figure 9 a graphical representation of part of the possible flows are given and in Figure 10 the rates corresponding to these flows are given. These figures show (literally) that M_4 is irreducible.

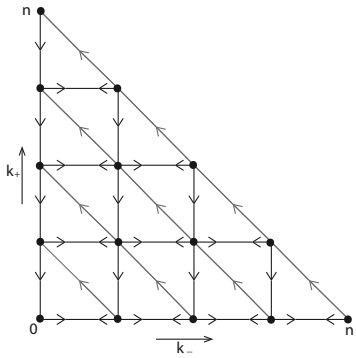

Figure 9: Graphical representation of the possible flows incorporated in the matrix M_4 (coordinate (k_-, k_+) represents fraction $P_{(+,k_-,k_+)}$), ignoring the death rate μ out of each fraction.

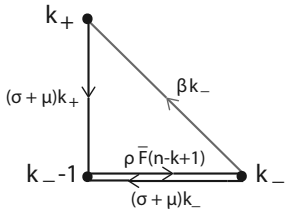

Figure 10: Rates corresponding to the flows of Figure 9, ignoring the death rate μ out of each variable.

Finally, consider two variables $x^- = P_{(-,k,1)}$, $x^+ = P_{(-,l_-,l_+)}$ of the matrix M_P. We show that $x^- \leftrightarrow x^+$.

Since M_2 and M_3 are non-negative and non-zero, there are variables y^-, y^+, z^-, z^+ such that $y^- \to y^+$ and $z^+ \to z^-$. Note that, in terms of interpretation, the nonzero elements of M_2 correspond to infection of $-$ individuals by one of their $+$ partner, i.e. transitions with rate β from fractions $P_{(-,j_-,1)}$ to $P_{(+,j,1)}$. The nonzero elements of M_3 correspond to the feed into the $P_{(-,j_-,1)}$ category via the F_+ terms from fractions $P_{(+,k_-,k_+)}$.

We find a path from $x^- \to x^+$ through y^- and y^+, i.e.

$$x^- \to y^- \to y^+ \to x^+,$$

and a path from $x^+ \to x^-$ through z^+ and z^-, i.e.

$$x^+ \to z^+ \to z^- \to x^-.$$

Note that the paths $x^- \to y^-$, $y^+ \to x^+$, $x^+ \to z^+$, and $z^- \to x^-$ exist since M_1 and M_4 are irreducible.

Since any two variables x^- and x^+ of M_P communicate, i.e. $x^- \leftrightarrow x^+$, M_P is irreducible. □

We now have all the ingredients to prove that R_0 is a threshold parameter for the disease free state of (3.10).

Since M_P is an irreducible positive off-diagonal matrix, we know that M_P has a real dominant eigenvalue r_P with corresponding positive eigenvector v, i.e.

$$M_P\, v = r_P\, v.$$

Then how does this relate to $T + \Sigma$? On the one hand we find that

$$\frac{d}{dt}LP = L\frac{dP}{dt} = LM_P P,$$

on the other hand $LP = X$ and (5.8) holds. Therefore

$$LM_P P = (T + \Sigma)LP, \tag{6.5}$$

and it follows that

$$r_P Lv = LM_P\, v = (T + \Sigma)Lv.$$

We have seen in Section 4 that if v is strictly positive then so is Lv. Furthermore, since $T + \Sigma$ is an irreducible positive off-diagonal matrix (see Lemma 4), the Malthusian parameter of $T + \Sigma$ is uniquely characterized by a positive eigenvector. Therefore r_P is also the Malthusian parameter of $T + \Sigma$ with corresponding eigenvector Lv, i.e.

$$r_P = r_{ABC}. \tag{6.6}$$

Finally, (6.4) together with Theorem 3 shows that R_0 is a threshold parameter of the P-system.

6.3 Characterization of the Malthusian parameter r $(= r_{ABC} = r_P)$

In this section we characterize the initial exponential growth rate $r = r_{ABC} = r_P$ (recall (6.6)). The Malthusian parameter r satisfies

$$(T + \Sigma)v = rv \quad \Leftrightarrow \quad Tv = (rI - \Sigma)v.$$

So $(rI - \Sigma)v$ lies in the range of T, i.e.

$$(rI - \Sigma)v = w$$

with

$$w = d_A\psi_A + d_B\psi_{\boldsymbol{B}} + d_C\psi_C, \tag{6.7}$$

where the d_x are some constants, not all equal to zero, and the ψ_x are defined in (5.7), $x = A, \boldsymbol{B}, C$. This is equivalent to

$$v = (rI - \Sigma)^{-1}w.$$

Therefore

$$T(rI - \Sigma)^{-1}w = w,$$

where w is defined by (6.7), so

$$\sum_x d_x T(rI - \Sigma)^{-1}\psi_x = \sum_x d_x\psi_x. \tag{6.8}$$

Since the range of T is spanned by ψ_x, we also have that, for certain constants $(m_r)_{yx}$,

$$T(rI - \Sigma)^{-1}\psi_x = \sum_y (m_r)_{yx}\psi_y. \tag{6.9}$$

The Malthusian parameter r then needs to satisfy

$$M_r d = d,$$

where $M_r = ((m_r)_{xy})$ is a 3×3 matrix characterized by (6.9), with matrix elements $(m_r)_{xy}$ depending on the unknown r. Identity (6.9) fully characterizes elements $(m_r)_{xy}$, but, as in the case of K and K^{ind}, we can use the interpretation to give explicit expressions for the entries of M_r, in the last paragraph of Appendix C we outline how this can be done.

Finally, consider the case $n = 1$, then r satisfies

$$T_1(rI - \Sigma_1)^{-1}w = w, \tag{6.10}$$

where Σ_1 and T_1 are defined in (5.1) and (5.2), respectively. Since the range of T_1 is spanned by ψ_C, we see that $w = \psi_C$. We find that

$$T_1(rI - \Sigma_1)^{-1} \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ \frac{\beta\rho\bar{F}(\sigma+\mu)}{(r+\mu)(r+\beta+\sigma+2\mu)(r+\rho\bar{F}+\sigma+2\mu)} \end{pmatrix}.$$

It then follows from (6.10) that we find r by solving the following third-order polynomial in r:

$$\beta\rho\bar{F}(\sigma+\mu) = (r+\mu)(r+\beta+\sigma+2\mu)(r+\rho\bar{F}+\sigma+2\mu).$$

7 Looking back and ahead

The overall aim of our research is to formulate and analyse models for the spread of an infectious disease across a network that is dynamic in the double sense that individuals come (by birth) and go (by death) and that links/partnerships are formed and broken. In particular our aim is to investigate the role of concurrency in the spread of sexually transmitted infections.

In Chapter 2 we introduced a class of doubly dynamic network models that are relatively simple to describe, that involve just a few parameters, and for which one can calculate many statistics exactly in explicit detail. The next step, taken here, is superimposing the spread of an infection. In order to retain the simplicity, we again characterize individuals by their dynamic degree (i.e. the current number of their partners), but now include the disease status (S versus I) of the individual itself and of its partners. In this bookkeeping scheme we need to account for the infection of a partner by one of its other partners, but the scheme itself does not provide information about partners of partners. Thus we faced a closing problem. The mean field at distance one assumption provided a natural solution.

Originally we thought that this was an assumption because we had not yet found a way to prove it. In a late stage Pieter Trapman pointed the way to the current Appendix B, showing that the assumption is inconsistent with the model itself. We then realised that, in essence, our bookkeeping scheme constitutes a first order description that we close by making the (inconsistent) mean field at distance one assumption. So the deterministic system studied here provides at best an approximation to the large system size limit of a stochastic model.

The great advantage of the deterministic system of dimension $(n+1)(n+2)$ is that it is amenable to analysis. The fact that binding sites operate to some extent independently from each other enables a reduction of the dimension from $(n+1)(n+2)$ to 2 in the characterization of R_0. Indeed, we characterized the basic reproduction number R_0 as the dominant eigenvalue of a 3×3 matrix with elements describing the expected numbers of newly infected binding sites of three different types generated by one infected binding site of either type during its life time. We could then further reduce the 3×3 matrix to a

2×2 matrix which lead to an explicit expression for the dominant eigenvalue R_0. We also verified that the basic reproduction number R_0 defined in this way is indeed a threshold parameter for the stability of the disease free steady state of the nonlinear system of model equations. This is done by establishing a relationship between the exponential growth rate r of the epidemic in the linearised system and the quantity R_0 on the level of binding sites.

The characterization of r and R_0 opens up the route for investigating the impact of concurrency on the transmission of the SI infection in the dynamic network. We can now study how r and R_0 depend on the capacity n when fixing all other parameters at constant values. Furthermore, the relationship between concurrency measures on the one hand and R_0, r, and the endemic steady state on the other, can be analysed. This will be explored in a follow-up paper. (Concerning the endemic steady state, we will need to derive the equations that characterize it, to investigate the uniqueness and to prove that existence requires $R_0 > 1$.)

There are a number of generalisations of the network model that are both useful and feasible. The extension to a heterosexual population requires only the distinction between males and females and some assumptions on the symmetry or asymmetry in rates and partnership capacity between the two sexes. We expect that all results presented here carry, mutatis mutandis, over to that situation. No doubt the model can also be extended to the situation that n is a random variable with a prescribed distribution.

Other generalisations pertain to the description of infectiousness. An obvious example is a model with two consecutive stages I_1 and I_2, where infectiousness is characterised by β_i in stage I_i. Other compartmental epidemic models could be considered as well, such as SIR and SIS. Inclusion of the impact of the disease on mortality is very relevant in the context of HIV. Unfortunately it might turn out to be very hard.

The most stringent limitation of our framework is the assumption that having a partner does not influence an individual's propensity to enter into a new partnership or its contact rate in other ongoing partnerships. This is clearly at odds with reality (although equally clearly it is an impossible task to disentangle the manifold ways in which dependence 'works' in reality). Dependence destroys the basis on which our analytic approach rests.

Be that as it may, we view the work presented here as a first step towards a framework for studying the impact of dynamic network structure on the transmission of an infectious disease.

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A R_0 for $n = 1$: alternative method

We can also characterize R_0 for the case $n = 1$ in the following way. An individual at epidemiological birth is in state C with probability one (since it has its epidemiological parent as partner) and each time it visits C (which is only possible by jumping from B to C since the probability to encounter an infectious individual is zero at the beginning of an epidemic) a new infectious individual is created; recall Figure 3. So, for R_0, we simply need to count the expected number of times to visit C when starting in C. This can be done by exploiting the Markov property:

$$R_0 = \pi_{CC}(1 + R_0), \tag{A.1}$$

where π_{CC} is the probability to ever enter state C when starting in state C. Let π_{xy} denote the probability to ever enter state x when starting in y, $x, y \in \{A, B, C\}$. We find π_{CC} by first-step analysis:

$$\begin{aligned}
\pi_{CC} &= \frac{\sigma + \mu}{\sigma + 2\mu}\pi_{CA} \\
\pi_{CA} &= \frac{\rho\bar{F}}{\rho\bar{F} + \mu}\pi_{CB} \\
\pi_{CB} &= \frac{\beta}{\beta + \sigma + 2\mu} + \frac{\sigma + \mu}{\beta + \sigma + 2\mu}\pi_{CA}.
\end{aligned}$$

Solving for π_{CC} we find

$$\pi_{CC} = \frac{\beta\rho\bar{F}(\sigma + \mu)}{(\sigma + 2\mu)\big(\rho\bar{F}(\beta + \mu) + \mu(\beta + \sigma + 2\mu)\big)}.$$

This yields the same expression (5.3) as the ABC scheme does.

B Correlation between the states of two partners

Consider a randomly chosen partnership. For convenience we call the individuals in the partnership u and v. Then, without knowing anything about v, the probability that u is in state k, $k \geq 1$, is given by Q_k (Lemma 2), i.e.

$$P(u \text{ in state } k) = Q_k.$$

In other words, Q_k is the probability that an individual is in state k given that it has at least one partner.

Let's study this partnership in more detail. The states of u and v are independent of each other at the moment $t = 0$ when the partnership uv is formed, i.e.

$$\begin{aligned}
&P(u \text{ in state } k \text{ and } v \text{ in state } l \text{ at } t = 0) \\
&= P(u \text{ in state } k \text{ at } t = 0)P(v \text{ in state } l \text{ at } t = 0) \\
&= q_k q_l,
\end{aligned}$$

cf. assumption (2.7).

As long as we condition on the existence of the partnership uv the remaining binding sites of u behave independently of the remaining binding sites of v and consequently there is independence of the states of u and v at any time $t = s$ in the partnership, i.e.

$$\begin{aligned}&P(u \text{ in state } k \text{ and } v \text{ in state } l \text{ at } t = s)\\ &= P(u \text{ in state } k \text{ at } t = s)P(v \text{ in state } l \text{ at } t = s).\end{aligned}$$

However, if we do *not* specify the duration so far of the partnership, then we find dependence between the states of u and v:

$$\begin{aligned}&P(u \text{ in state } k \text{ and } v \text{ in state } l)\\ &= \int_0^\infty (\sigma + 2\mu)e^{-(\sigma+2\mu)s}\\ &\qquad P(u \text{ in state } k \text{ at } t = s \text{ and } v \text{ in state } l \text{ at } t = s)ds\\ &= \int_0^\infty (\sigma + 2\mu)e^{-(\sigma+2\mu)s}\\ &\qquad P(u \text{ in state } k \text{ at } t = s)P(v \text{ in state } l \text{ at } t = s)ds\\ &\neq P(u \text{ in state } k)P(v \text{ in state } l)\\ &= Q_k Q_l.\end{aligned}$$

Here the density $(\sigma + 2\mu)e^{-(\sigma+2\mu)s}$ accounts for the conditioning on the uv partnership remaining in existence. We show the inequality with explicit calculations for $n = 2$. In this case, individuals can have 0, 1, or 2 partners. Choose a partnership at random from the population and label the partners u and v. Since $n = 2$, u and v both have one additional binding site that can be either free or occupied. This gives us three possible states for the partnership uv, we denote these states by x_{11}, x_{12}, and x_{22}; see Figure B.1.

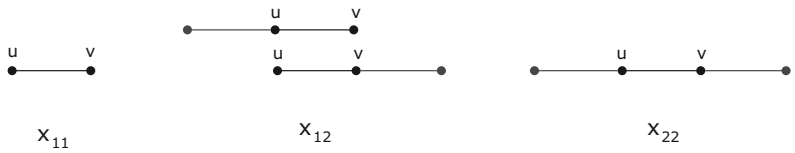

Figure B.1: The three possible configurations for the partnership uv concerning additional partners when $n = 2$.

Let $\pi(t)$ denote the probability distribution for the configuration of the partnership uv at time t given that uv exists for the period under consideration.

At $t = 0$ the probability distribution of the different configurations is given by

$$\pi(0) = \begin{pmatrix} q_1^2 \\ 2q_1q_2 \\ q_2^2 \end{pmatrix}.$$

Given that the partnership uv exists for the time interval under consideration, the transitions and the corresponding rates are represented by the flowchart in Figure B.2. We denote the corresponding transition matrix by M.

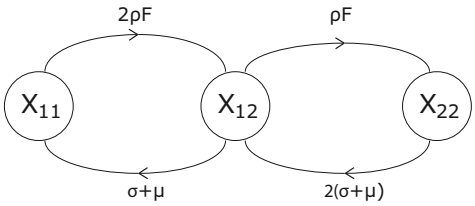

Figure B.2: The flowchart for the three possible configurations for the partnership uv concerning additional partners given that uv exists for the period under consideration.

Note that the 'age' of the partnership uv is exponentially distributed with parameter $\sigma + 2\mu$. Therefore the probability distribution for the configuration of partnership uv at the moment we pick the partnership from the pool of partnerships is

$$(\sigma + 2\mu) \int_0^\infty e^{-t(\sigma+2\mu)I} \pi(t) dt \tag{B.1}$$

$$= (\sigma + 2\mu) \int_0^\infty e^{t(M-(\sigma+2\mu)I)} \pi(0) dt \tag{B.2}$$

$$= -(\sigma + 2\mu)(M - (\sigma + 2\mu)I)^{-1} \pi(0)$$

$$= \begin{pmatrix} Q_1^2 + c \\ 2Q_1 Q_2 - 2c \\ Q_2^2 + c \end{pmatrix}, \tag{B.3}$$

where

$$c = \frac{(\rho F \mu)^2}{(\sigma + 2\mu)(2\rho F + 3\sigma + 4\mu)(2\rho F + 2\sigma + 3\mu)^2}.$$

The states of u and v are independent of one another iff $c = 0$

Note that $c = 0$ if $\mu = 0$ and $\mu = 0$ corresponds to a dynamic network without demography. One should, however, not conclude that demography necessarily leads to correlation. We assumed that individuals are born single. One can think of other ways of incorporating demography, e.g. individuals having k partners at birth with probability equal to the degree distribution [48]. Adopting this rule creates a partnership network where, when disease is *not* considered, the correlation is zero between the degrees of two partners (in essence this rule makes 'death' the same as rewiring of partnerships after an exponentially distributed amount of time and then basically a dynamic network in a closed population is considered [50]).

C The matrix elements $k_{x,y}$ of K and a characterization of R_0 by a 2×2 matrix

In this appendix we use the interpretation to guide us in deriving explicit expressions for the $k_{x,y}$ and in that way we derive an explicit expression for R_0.

First of all, as explained below, the following equalities hold:

$$(-\Sigma)^{-1}\psi_A = \begin{pmatrix} \frac{\sigma+2\mu}{\mu(\rho\bar{F}+\sigma+2\mu)} \\ \frac{\rho\bar{F}(\sigma+2\mu)}{\mu(\rho\bar{F}+\sigma+2\mu)}(-\Sigma_{\boldsymbol{B}})^{-1}q \\ \frac{\beta}{(\beta+\sigma+2\mu)(\sigma+2\mu)}\,\frac{\rho\bar{F}(\sigma+2\mu)}{\mu(\rho\bar{F}+\sigma+2\mu)} \end{pmatrix}, \tag{C.1}$$

$$(-\Sigma)^{-1}\psi_{\boldsymbol{B}} = \begin{pmatrix} 0 \\ (-\Sigma_{\boldsymbol{B}})^{-1}Q \\ 0 \end{pmatrix} + \begin{pmatrix} \frac{\sigma+\mu}{\mu(\rho\bar{F}+\sigma+2\mu)} \\ \frac{\rho\bar{F}(\sigma+\mu)}{\mu(\rho\bar{F}+\sigma+2\mu)}(-\Sigma_{\boldsymbol{B}})^{-1}q \\ \frac{\beta(\rho\bar{F}+\mu)}{\mu(\beta+\sigma+2\mu)(\rho\bar{F}+\sigma+2\mu)} \end{pmatrix}, \tag{C.2}$$

$$(-\Sigma)^{-1}\psi_C = \begin{pmatrix} \frac{\sigma+\mu}{\mu(\rho\bar{F}+\sigma+2\mu)} \\ \frac{\rho\bar{F}(\sigma+\mu)}{\mu(\rho\bar{F}+\sigma+2\mu)}(-\Sigma_{\boldsymbol{B}})^{-1}q \\ \frac{\beta(\rho\bar{F}+\mu)}{\mu(\beta+\sigma+2\mu)(\rho\bar{F}+\sigma+2\mu)} + \frac{1}{\beta+\sigma+2\mu} \end{pmatrix}. \tag{C.3}$$

Indeed, if we multiply the right-hand side of each of these equalities with the matrix Σ, where Σ is defined in (5.4), we obtain $-\psi_x$, $x = A, \boldsymbol{B}, C$.

The elements $-\Sigma^{-1}\psi_x$, $x = A, \boldsymbol{B}, C$, also have an interpretation. The interpretation of $(-\Sigma^{-1}\psi_A)_{B_k}$ is as follows. Consider a binding site in state A. The probability for the binding site to be in state A in the time interval $[0, \tau]$ is

$$\left[e^{\tau\Sigma_1} \begin{pmatrix} 1 \\ 0 \\ 0 \end{pmatrix} \right]_A,$$

where Σ_1 is defined in (5.1). It enters the set $\boldsymbol{B}$ at rate $\rho\bar{F}$. The probability that the binding site is in state B_k upon entering $\boldsymbol{B}$ is q_k. The probability to remain in B_k in the time interval $[\tau, s]$ is the kth component of

$$e^{(s-\tau)\Sigma_{\boldsymbol{B}}}q.$$

By integrating over all possible s we find the expectation:

$$\begin{aligned}
&\int_0^\infty \int_0^s \left[e^{\tau\Sigma_1} \begin{pmatrix} 1 \\ 0 \\ 0 \end{pmatrix} \right]_A \rho\bar{F} e^{(s-\tau)\Sigma_{\boldsymbol{B}}} q \, \mathrm{d}\tau \, \mathrm{d}s \\
&= \rho\bar{F} \left[-\Sigma_1^{-1} \begin{pmatrix} 1 \\ 0 \\ 0 \end{pmatrix} \right]_A (-\Sigma_{\boldsymbol{B}})^{-1} q \\
&= \frac{\rho\bar{F}(\sigma+2\mu)}{\mu(\rho\bar{F}+\sigma+2\mu)} (-\Sigma_{\boldsymbol{B}})^{-1} q.
\end{aligned}$$

The kth component is then the mean time a binding site that starts in state A will spend in state B_k. Similarly, one can interpret $(-\Sigma^{-1}\psi_C)_{B_k}$.

Finally, we show how to derive (C.2) by exploiting the interpretation of $-\Sigma^{-1}\psi_{\boldsymbol{B}}$ (this is the most complicated case and it involves all building blocks for the other cases).

First note that $(e^{s\Sigma}\psi_x)_y$ is the probability to be in state y at time s when one starts life in state x, so $\left((-\Sigma)^{-1}\psi_x\right)_y$, $x, y = A, \boldsymbol{B}, C$ is the mean time spent in state y when the binding site starts its life in state x. Therefore

$$\int_0^\infty e^{s\Sigma}\psi_x ds = (-\Sigma)^{-1}\psi_x,$$

There are flows out of $\boldsymbol{B}$ to A and C with rates $\sigma+\mu$ and β, respectively. There is also a flow in to $\boldsymbol{B}$ from A with rate $\rho\bar{F}$. Note that the transition matrix between state A, set $\boldsymbol{B}$, and state C is exactly Σ_1, where Σ_1 is defined in (5.1).

We shall use the inverse $(-\Sigma_1)^{-1}$ in the following calculations. Using linear algebra or interpretation, we obtain

$$\begin{aligned}
&(-\Sigma_1)^{-1} \\
&= \begin{pmatrix}
\frac{\sigma+2\mu}{\mu(\rho\bar{F}+\sigma+2\mu)} & \frac{\sigma+\mu}{\mu(\rho\bar{F}+\sigma+2\mu)} & \frac{\sigma+\mu}{\mu(\rho\bar{F}+\sigma+2\mu)} \\
\frac{\rho\bar{F}(\sigma+2\mu)}{\mu(\beta+\sigma+2\mu)(\rho\bar{F}+\sigma+2\mu)} & \frac{(\rho\bar{F}+\mu)(\sigma+2\mu)}{\mu(\beta+\sigma+2\mu)(\rho\bar{F}+\sigma+2\mu)} & \frac{(\rho\bar{F}+\mu)(\sigma+2\mu)}{\mu(\beta+\sigma+\mu)(\rho\bar{F}+\sigma+2\mu)} \\
\frac{\beta\rho\bar{F}}{\mu(\beta+\sigma+2\mu)(\rho\bar{F}+\sigma+2\mu)} & \frac{\beta(\rho\bar{F}+\mu)}{\mu(\beta+\sigma+2\mu)(\rho\bar{F}+\sigma+2\mu)} & \frac{\beta(\rho\bar{F}+\mu)+\mu(\rho\bar{F}+\sigma+2\mu)}{\mu(\beta+\sigma+2\mu)(\rho\bar{F}+\sigma+2\mu)}
\end{pmatrix}.
\end{aligned}$$

The mean time a binding site born in one of the states B_j in the set $\boldsymbol{B}$, spends in state A is given by

$$\left[(-\Sigma_1)^{-1} \begin{pmatrix} 0 \\ 1 \\ 0 \end{pmatrix} \right]_A = \frac{\sigma+\mu}{\mu(\rho\bar{F}+\sigma+2\mu)},$$

while the mean future time a binding site presently in $\boldsymbol{B}$ spends in state C is

$$\left[(-\Sigma_1)^{-1} \begin{pmatrix} 0 \\ 1 \\ 0 \end{pmatrix} \right]_C = \frac{\beta(\rho\bar{F}+\mu)}{\mu(\beta+\sigma+2\mu)(\rho\bar{F}+\sigma+2\mu)}.$$

To determine the mean time spent in the set $\boldsymbol{B}$, when starting life in $\boldsymbol{B}$, is a bit more complicated. First of all, a binding site that starts life in $\boldsymbol{B}$ starts life in state B_j with probability Q_j, $j = 1, \ldots, n$. The mean time it then spends in state B_k without leaving the set $\boldsymbol{B}$ is given by

$$((-\Sigma_{\boldsymbol{B}})^{-1}Q)_k.$$

Next, the binding site in $\boldsymbol{B}$ leaves $\boldsymbol{B}$ and enters A with probability

$$\frac{\sigma+\mu}{\beta+\sigma+2\mu}.$$

If that is the case, then the mean future time it spends in B_k is, by first step analysis,

$$((-\Sigma)^{-1}\psi_A)_{B_k} = \frac{\rho\bar{F}(\sigma+2\mu)}{\mu(\rho\bar{F}+\sigma+2\mu)}((-\Sigma_{\boldsymbol{B}})^{-1}q)_k.$$

Similarly, the probability to enter state C from $\boldsymbol{B}$ is

$$\frac{\beta}{\beta+\sigma+2\mu}$$

and the mean time it will spend in B_k is

$$((-\Sigma)^{-1}\psi_C)_{B_j} = \frac{\rho\bar{F}(\sigma+\mu)}{\mu(\rho\bar{F}+\sigma+2\mu)}\big((-\Sigma_{\boldsymbol{B}})^{-1}q)_j.$$

Therefore, the mean time spent in state B_k after leaving $\boldsymbol{B}$ is

$$\begin{aligned}
&\frac{\sigma+\mu}{\beta+\sigma+2\mu}\frac{\rho\bar{F}(\sigma+2\mu)}{\mu(\rho\bar{F}+\sigma+2\mu)}[(-\Sigma_{\boldsymbol{B}})^{-1}q]_k \\
&\quad+\frac{\beta}{\beta+\sigma+2\mu}\frac{\rho\bar{F}(\sigma+\mu)}{\mu(\rho\bar{F}+\sigma+2\mu)}[(-\Sigma_{\boldsymbol{B}})^{-1}q]_k \\
=&\frac{\rho\bar{F}(\sigma+\mu)}{\mu(\rho\bar{F}+\sigma+2\mu)}((-\Sigma_{\boldsymbol{B}})^{-1}q)_k.
\end{aligned}$$

This explains (C.2).

The matrix T is given by (5.5). By multiplying with (C.1), (C.2), and (C.3), we obtain the first column of K

$$\begin{pmatrix} k_{AA} \\ k_{\boldsymbol{B}A} \\ k_{CA} \end{pmatrix} = \frac{\beta\rho\bar{F}(\sigma+2\mu)}{\mu(\rho\bar{F}+\sigma+2\mu)} \begin{pmatrix} \sum_{k=1}^n (n-k)[(-\Sigma_{\boldsymbol{B}})^{-1}q]_k \\ \sum_{k=1}^n (k-1)[(-\Sigma_{\boldsymbol{B}})^{-1}q]_k \\ \sum_{k=1}^n [(-\Sigma_{\boldsymbol{B}})^{-1}q]_k \end{pmatrix}, \tag{C.4}$$

the second column of K is given by

$$\begin{aligned}
\begin{pmatrix} k_{A\boldsymbol{B}} \\ k_{\boldsymbol{B}\boldsymbol{B}} \\ k_{C\boldsymbol{B}} \end{pmatrix} &= \beta \begin{pmatrix} \sum_{k=1}^n (n-k)[(-\Sigma_{\boldsymbol{B}})^{-1}Q]_k \\ \sum_{k=1}^n (k-1)[(-\Sigma_{\boldsymbol{B}})^{-1}Q]_k \\ \sum_{k=1}^n [(-\Sigma_{\boldsymbol{B}})^{-1}Q]_k \end{pmatrix} \\
&\quad + \frac{\beta\rho\bar{F}(\sigma+\mu)}{\mu(\rho\bar{F}+\sigma+2\mu)} \begin{pmatrix} \sum_{k=1}^n (n-k)[(-\Sigma_{\boldsymbol{B}})^{-1}q]_k \\ \sum_{k=1}^n (k-1)[(-\Sigma_{\boldsymbol{B}})^{-1}q]_k \\ \sum_{k=1}^n [(-\Sigma_{\boldsymbol{B}})^{-1}q]_k \end{pmatrix},
\end{aligned} \tag{C.5}$$

and the third column is

$$\begin{pmatrix} k_{AC} \\ k_{\boldsymbol{B}C} \\ k_{CC} \end{pmatrix} = \frac{\beta\rho\bar{F}(\sigma+\mu)}{\mu(\rho\bar{F}+\sigma+2\mu)} \begin{pmatrix} \sum_{k=1}^{n}(n-k)[(-\Sigma_{\boldsymbol{B}})^{-1}q]_k \\ \sum_{k=1}^{n}(k-1)[(-\Sigma_{\boldsymbol{B}})^{-1}q]_k \\ \sum_{k=1}^{n}[(-\Sigma_{\boldsymbol{B}})^{-1}q]_k \end{pmatrix}. \tag{C.6}$$

Note that the elements k_{xy}, $x, y = A, \boldsymbol{B}, C$ involve the vectors $(-\Sigma_{\boldsymbol{B}})^{-1}q$ and $(-\Sigma_{\boldsymbol{B}})^{-1}Q$.

We can simplify the sums $\sum_{k=1}^{n}[(-\Sigma_{\boldsymbol{B}})^{-1}q]_k$ and $\sum_{k=1}^{n}[(-\Sigma_{\boldsymbol{B}})^{-1}Q]_k$. Note that

$$\sum_{k=1}^{n}[(-\Sigma_{\boldsymbol{B}})^{-1}]_{kl} = \frac{1}{\beta+\sigma+2\mu},$$

since $(-\Sigma_{\boldsymbol{B}})_{kl}$ is the mean time to spent in state k when starting life in state l, by summing over all possible states $k \in \boldsymbol{B}$, we obtain the mean time to spent in $\boldsymbol{B}$ when starting in some state $l \in \boldsymbol{B}$ (this is of course equal to 1 over the rate of leaving $\boldsymbol{B}$). Therefore, for any probability distribution $\mathbb{P}$,

$$\begin{aligned} \sum_{k=1}^{n}[(-\Sigma_{\boldsymbol{B}})^{-1}\,\mathbb{P}]_k &= \sum_{l=1}^{n}\left(\sum_{k=1}^{n}[(-\Sigma_{\boldsymbol{B}})^{-1}]_{kl}\right)\mathbb{P}_l \\ &= \frac{1}{\beta+\sigma+2\mu}\sum_{l=1}^{n}\mathbb{P}_l \\ &= \frac{1}{\beta+\sigma+2\mu}, \end{aligned}$$

where the last equality holds since $\mathbb{P}$ is a probability distribution. So

$$\sum_{k=1}^{n}[(-\Sigma_{\boldsymbol{B}})^{-1}q]_k = \sum_{k=1}^{n}[(-\Sigma_{\boldsymbol{B}})^{-1}Q]_k = \frac{1}{\beta+\sigma+2\mu}, \tag{C.7}$$

which we can use to simplify K.

Observe that the sum of the first and second row of K is $n-1$ times the third row of K, i.e.

$$k_{A,y} + k_{\boldsymbol{B},y} = (n-1)\cdot k_{C,y},$$

and the third column is a multiple of the first column, i.e.

$$k_{x,C} = \frac{\sigma+\mu}{\sigma+2\mu}k_{x,A}.$$

So we find that, of the three eigenvalues that K has, at least one equals zero. Moreover, using (C.7),

$$k_{CA} = \frac{\beta\rho F(\sigma+2\mu)}{\mu(\beta+\sigma+2\mu)(\rho F+\sigma+2\mu)},$$

and

$$k_{C\boldsymbol{B}} = \frac{\beta}{\beta+\sigma+2\mu}\left(1+\frac{\rho F(\sigma+\mu)}{\mu(\rho F+\sigma+2\mu)}\right).$$

To find the dominant eigenvalue of K we can therefore reduce K to the 2×2 matrix $\tilde{K}$:

$$\begin{aligned}\tilde{K} &= \begin{pmatrix} k_{AA}+\frac{\sigma+\mu}{\sigma+2\mu}k_{CA} & k_{A\boldsymbol{B}}+\frac{\sigma+\mu}{\sigma+2\mu}k_{C\boldsymbol{B}} \\ k_{\boldsymbol{B}A} & k_{\boldsymbol{BB}}\end{pmatrix} \\ &= \begin{pmatrix} k_{AA}+\frac{\beta\rho F(\sigma+\mu)}{\mu(\beta+\sigma+2\mu)(\rho F+\sigma+2\mu)} & k_{A\boldsymbol{B}}+\frac{\beta(\rho F+\mu)(\sigma+\mu)}{\mu(\beta+\sigma+2\mu)(\rho F+\sigma+2\mu)} \\ k_{\boldsymbol{B}A} & k_{\boldsymbol{BB}}\end{pmatrix}. \end{aligned} \tag{C.8}$$

Note that

$$\begin{aligned}\sum_k (n-k)[-\Sigma_{\boldsymbol{B}}^{-1}\,\mathbb{P}]_k &= (n-1)\sum_k [-\Sigma_{\boldsymbol{B}}^{-1}\,\mathbb{P}]_k - \sum_k (k-1)[-\Sigma_{\boldsymbol{B}}^{-1}\,\mathbb{P}]_k \\ &= \frac{n-1}{\beta+\sigma+2\mu} - \sum_k (k-1)[-\Sigma_{\boldsymbol{B}}^{-1}\,\mathbb{P}]_k, \end{aligned} \tag{C.9}$$

where $\mathbb{P}$ is the probability distribution q or Q, and we have used (C.7) in the second equality. Therefore, the only ingredients left in order to arrive at a completely explicit expression for the dominant eigenvalue R_0 of the 2×2 matrix $\tilde{K}$ are explicit expressions for the sums $\sum_{k=1}^n (k-1)[(-\Sigma_{\boldsymbol{B}})^{-1}q]_k$ and $\sum_{k=1}^n (k-1)[(-\Sigma_{\boldsymbol{B}})^{-1}Q]_k$.

In the remainder of this appendix we show that

$$\begin{aligned}\sum_k (k-1)[-\Sigma_{\boldsymbol{B}}^{-1}q]_k &= \frac{(n-1)\rho\bar{F}}{(\rho\bar{F}+\sigma+\mu)(\beta+\sigma+2\mu)} \\ &\quad - \frac{(n-1)Y}{\rho F+2\sigma+3\mu+\beta}, \end{aligned} \tag{C.10}$$

and

$$\begin{aligned}\sum_k (k-1)[-\Sigma_{\boldsymbol{B}}^{-1}Q]_k &= \frac{(n-1)\rho\bar{F}}{(\rho\bar{F}+\sigma+\mu)(\beta+\sigma+2\mu)} \\ &\quad - \frac{(n-1)Y(\sigma+2\mu)}{(\rho\bar{F}+2\sigma+3\mu)(\beta+\rho\bar{F}+2\sigma+3\mu)}, \end{aligned} \tag{C.11}$$

where

$$Y = \frac{\rho\bar{F}\mu(\rho\bar{F}+2\sigma+3\mu)}{(\sigma+2\mu)(\rho\bar{F}+\sigma+\mu)(2\rho\bar{F}+2\sigma+3\mu)}. \tag{C.12}$$

We obtain an explicit expression for R_0 by using (C.9) and plugging (C.10) and (C.11) (together with (C.12)) into (C.4) and (C.5). Next, plug these into (C.8) and use that the dominant eigenvalue of a 2×2 matrix is

$$\frac{\mathrm{tr}+\sqrt{\mathrm{tr}^2-4\,\det}}{2}$$

(where tr and det denote the trace and determinant of $\tilde{K}$, respectively).

Finally, in the remainder of this appendix we will show (C.10) and (C.11) by straightforward computations that we divide up in four lemma's (for the first of these we only sketch the proof).

We need the following ingredients. Let M be the matrix corresponding to the state transitions between the states B_k, $k = 1, \ldots, n$; see Figure C.1. Then

$$\Sigma_{\boldsymbol{B}} = M - (\beta + \sigma + 2\mu)I.$$

Furthermore, e^{tM} denotes the fundamental solution of

$$\frac{d\pi}{dt} = M\pi. \tag{C.13}$$

We also use the relationship between q and Q:

$$Q = (\sigma + 2\mu) \int_0^\infty e^{-(\sigma+2\mu)t} e^{tM} q dt \tag{C.14}$$

(see proof of Lemma 2 in Chapter 2).

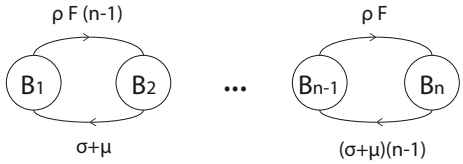

Figure C.1: State transitions and corresponding rates between states $B_1, \ldots, B_n$; the corresponding transition matrix is denoted M.

We need the probability distribution q for $n = 2$: $q^{(2)} = (q_1^{(2)}, q_2^{(2)})^t$ where the superscript (2) is to distinguish the $n = 2$ probabilities from general $n > 2$.

$$\begin{aligned} q_1^{(2)} &= \frac{\rho\bar{F}\mu + (\sigma + 2\mu)(2\sigma + 3\mu)}{(\sigma + 2\mu)(2\rho\bar{F} + 2\sigma + 3\mu)}, \\ q_2^{(2)} &= \frac{\rho\bar{F}(2\sigma + 3\mu)}{(\sigma + 2\mu)(2\rho\bar{F} + 2\sigma + 3\mu)}. \end{aligned} \tag{C.15}$$

Finally, we use two probabilities for binding sites. Consider one binding site. Conditioning on the individual staying alive till at least time t, $\epsilon_0(t)$ and $\epsilon_1(t)$ denote the probabilities that the binding site is occupied at time t, given that, respectively, it was free or occupied at time $t = 0$. So ϵ_i, $i = 0, 1$, satisfies

$$\frac{d\epsilon_i}{dt} = \rho\bar{F}\epsilon_i - (\sigma + \mu)(1 - \epsilon_i)$$

with initial conditions $\epsilon_0(0) = 0$ and $\epsilon_1(0) = 1$. Solving these, we find

$$\begin{aligned}\epsilon_0(t) &= \frac{\rho\bar{F}}{\rho\bar{F}+\sigma+\mu} - \frac{\rho\bar{F}}{\rho\bar{F}+\sigma+\mu}e^{-(\rho\bar{F}+\sigma+\mu)t},\\ \epsilon_1(t) &= \frac{\rho\bar{F}}{\rho\bar{F}+\sigma+\mu} + \frac{\sigma+\mu}{\rho\bar{F}+\sigma+\mu}e^{-(\rho\bar{F}+\sigma+\mu)t}.\end{aligned} \tag{C.16}$$

Lemma 6.

$$\sum_{k=2}^{n}(k-1)(e^{tM})_{kj} = (n-j)\epsilon_0(t) + (j-1)\epsilon_1(t), \tag{C.17}$$

Sketch of proof. Consider a randomly chosen partnership between two individuals u and v. Then $(e^{tM})_{kj}$ is the probability for u to be in state k given that it starts life in j (here: 'life starts' at the moment uv is formed). Then $\sum_{k=2}^{n}(k-1)(e^{tM})_{kj}$ is the expected number of partners of u, minus partner v, at time t given that u started life in j. Conditioning on the existence of uv, the other $n-1$ binding sites of u behave independently of one another.

Since u starts life in state j, there are $j-1$ binding sites that have probability $\epsilon_1(t)$ to be occupied at time t and $n-j$ binding sites that have probability $\epsilon_0(t)$ to be occupied at time t. Therefore, the expected number of occupied binding sites of u minus the binding site occupied by v at time t is exactly the right hand side of (C.17). □

We now consider the expected number of 'other' partners of an individual that just acquired a new partner in the following lemma.

Lemma 7.

$$\sum_{k=1}^{n}(k-1)q_k = (n-1)q_2^{(2)},$$

with $q_2^{(2)}$ *given by* (C.15).

Proof. The probability q_k is given by (2.7) with

$$P_{k-1} = \binom{n}{k-1}\int_0^\infty \mu e^{-\mu a}(1-\epsilon_0(a))^{n-k+1}\epsilon_0(a)^{k-1}da.$$

Then

$$\begin{aligned}&(k-1)(n-k+1)P_{k-1}\\ &= \frac{n!}{(k-2)!(n-k)!}\int_0^\infty \mu e^{-\mu a}\big(1-\epsilon_0(a)\big)\epsilon_0(a)(1-\epsilon_0(a))^{n-k}\epsilon_0(a)^{k-2}da\\ &= n(n-1)\int_0^\infty \mu e^{-\mu a}\big(1-\epsilon_0(a)\big)\epsilon_0(a)\binom{n-2}{k-2}\big(1-\epsilon_0(a)\big)^{n-k}\epsilon_0(a)^{k-2}da\end{aligned}$$

If we now take the sum $\sum_k (k-1)q_k$, then we obtain

$$\begin{aligned}\sum_{k=2}^{n}(k-1)q_k &= \frac{n(n-1)}{n\bar{F}}\int_0^\infty \mu e^{-\mu a}(1-\epsilon_0(a))\epsilon_0(a)da \\ &= \frac{n-1}{2\bar{F}}P_1^{(2)} \\ &= (n-1)q_2^{(2)},\end{aligned}$$

which we wanted to show. □

Lemma 8.

$$\sum_{k=2}^{n}(k-1)(e^{tM}q)_k = (n-1)\left(\frac{\rho F}{\rho F+\sigma+\mu} - Ye^{-t(\rho\bar{F}+\sigma+\mu)}\right),$$

where Y is the positive constant (C.12)*.*

Proof. We combine Lemma 6 and 7.

$$\begin{aligned}\sum_{k=2}^{n}(k-1)(e^{tM}q)_k &= \sum_{k=2}^{n}(k-1)\sum_{j=1}^{n}(e^{tM})_{kj}q_j \\ &= \sum_{j=1}^{n}q_j\sum_{k=2}^{n}(k-1)(e^{tM})_{kj} \\ \text{(Lemma 6)} &= \sum_{j=1}^{n}q_j\Big((n-j)\epsilon_0(t)+(j-1)\epsilon_1(t)\Big) \\ \text{(Lemma 7)} &= (n-1)(1-q_2^{(2)})\epsilon_0(t)+(n-1)q_2^{(2)}\epsilon_1(t) \\ &= (n-1)\Big(q_1^{(2)}\epsilon_0(t)+q_2^{(2)}\epsilon_1(t)\Big).\end{aligned}$$

Finally, one can use (C.15) and (C.16) in the last step to arrive at the explicit expression. □

Lemma 9. *The equalities* (C.10) *and* (C.11) *hold.*

Proof. Putting all the pieces together, we obtain

$$\begin{aligned}&\sum_{k=2}^{n}(k-1)[-\Sigma_{\boldsymbol{B}}^{-1}q]_k \\ =&\sum_k(k-1)\left(\int_0^\infty e^{-(\beta+\sigma+2\mu)t}e^{tM}qdt\right)_k \\ =&\sum_k(k-1)\int_0^\infty e^{-(\beta+\sigma+2\mu)t}(e^{tM}q)_k dt\end{aligned}$$

$$
\begin{aligned}
&= \int_0^\infty e^{-(\beta+\sigma+2\mu)t} \sum_k (k-1)(e^{tM}q)_k dt \\
&\overset{\text{(Lemma 8)}}{=} \int_0^\infty e^{-(\beta+\sigma+2\mu)t}(n-1)\left(\frac{\rho F}{\rho F+\sigma+\mu} - Y e^{-t(\rho\bar{F}+\sigma+\mu)}\right) dt \\
&= \frac{(n-1)\rho\bar{F}}{(\rho\bar{F}+\sigma+\mu)(\beta+\sigma+2\mu)} - \frac{(n-1)Y}{\rho F+2\sigma+3\mu+\beta}.
\end{aligned}
$$

and for the sum involving Q, we use (C.14), and then find

$$
\begin{aligned}
&\sum_{k=2}^n (k-1)[-\Sigma_{\boldsymbol{B}}^{-1}Q]_k \\
&= \sum_k (k-1)\left(\int_0^\infty e^{-(\beta+\sigma+2\mu)t} e^{tM} Q dt\right)_k \\
&= \sum_k (k-1)\left(\int_0^\infty e^{-(\beta+\sigma+2\mu)t} e^{tM}(\sigma+2\mu)\int_0^\infty e^{-(\sigma+2\mu)\tau} e^{\tau M} q d\tau dt\right)_k \\
&= (\sigma+2\mu)\sum_k (k-1)\left(\int_0^\infty \int_0^\infty e^{-(\beta+\sigma+2\mu)t} e^{-(\sigma+2\mu)\tau} e^{(t+\tau)M} q d\tau dt\right)_k \\
&= (\sigma+2\mu)\int_0^\infty \int_0^\infty e^{-(\beta+\sigma+2\mu)t} e^{-(\sigma+2\mu)\tau} \sum_k (k-1)\left(e^{(t+\tau)M}q\right)_k d\tau dt \\
&\overset{\text{(Lemma 8)}}{=} (\sigma+2\mu)\int_0^\infty \int_0^\infty \Big[e^{-(\beta+\sigma+2\mu)t} e^{-(\sigma+2\mu)\tau} \\
&\quad (n-1)\left(\frac{\rho F}{\rho F+\sigma+\mu} - Y e^{-(t+\tau)(\rho\bar{F}+\sigma+\mu)}\right)\Big] d\tau dt \\
&= \frac{(n-1)\rho\bar{F}}{(\rho\bar{F}+\sigma+\mu)(\beta+\sigma+2\mu)} - \frac{(n-1)Y(\sigma+2\mu)}{(\rho\bar{F}+2\sigma+3\mu)(\beta+\rho\bar{F}+2\sigma+3\mu)}.
\end{aligned}
$$

□

Finally, we note that we can use the method described in this appendix to find explicit expressions for the matrix entries of the 3×3 matrix M_r, that are characterized by identity (6.9). Note that we can find expressions for the $T(rI-\Sigma)^{-1}\psi_x$, $x = A, \boldsymbol{B}, C$ by simply replacing $-\Sigma_{\boldsymbol{B}}$ by $rI - \Sigma_{\boldsymbol{B}}$ in the calculations in this appendix. This allows us to characterize $(m_r)_{xy}$. We refrain from elaborating the details.

D Mean field at distance one - bounds for R_0

As explained in the main text, the mean field at distance one assumption is a moment closure approximation as we ignore certain correlations between the states of two individuals in a partnership. One may wonder how well 'the real R_0' (presuming it can be defined, when no assumption is made about the degree distribution of the partners of an individual at epi-birth) is approximated by R_0 as derived under the mean field at distance

one assumption. Note that here we focus on the mean field at distance one assumption in the linearised system only.

In this appendix we provide lower- and upper bounds for 'the real R_0' for the case $n = 2$ with numerical values presented in Figure D.1.

Consider a randomly chosen partnership with partners u and v. Assume that the partnership is formed at time $t = 0$. Then, as long as we condition on the existence of partnership uv, the states of u and v are independent from one another at time $t = s$ (as also explained in Appendix B). The probability that u is in state 1 or 2 at time s is given by the probability distribution

$$e^{sM}q,$$

$s \geq 0$, where

$$M = \begin{pmatrix} -\rho\bar{F} & \sigma+\mu \\ \rho\bar{F} & -(\sigma+\mu) \end{pmatrix}.$$

For $s = 0$, this yields initial condition q, for $s \to \infty$ we obtain probability distribution

$$q^{\infty} = \begin{pmatrix} \frac{\sigma+\mu}{\rho\bar{F}+\sigma+\mu} \\ \frac{\rho\bar{F}}{\rho\bar{F}+\sigma+\mu} \end{pmatrix}.$$

Then

$$\begin{aligned} q_2 &\leq P(v \text{ has degree 2 at time } s \mid u \text{ has degree } k \text{ at time } s) = \left(e^{sM}q\right)_2 \\ &\leq q_2^{\infty} \end{aligned}$$

(note that the equality holds since the degrees of u and v are independent of one another as long as we specify the duration of the partnership uv). Therefore

$$q_2 \leq P(v \text{ has degree 2} \mid u \text{ has degree } k) \leq q_2^{\infty}, \tag{D.1}$$

$k = 1, 2$ (recall that we condition on the existence of partnership uv). Under the mean field at distance one assumption, we say that

$$P(v \text{ has degree 2} \mid u \text{ has degree } k) = Q_2.$$

As we will explain now, (D.1) provides us with a bandwidth for 'the real R_0' (in which the mean field at distance one R_0 also falls).

The mean field at distance one assumption manifests itself in the distribution Q, which plays a role in elements $k_{A\boldsymbol{B}}$ and $k_{\boldsymbol{BB}}$. For $n = 2$, we find $\sum_{k=1}^{n}(n-k)[-\Sigma_{\boldsymbol{B}}^{-1}Q]_k = [-\Sigma_{\boldsymbol{B}}^{-1}Q]_1$ and $\sum_{k=1}^{n}(k-1)[-\Sigma_{\boldsymbol{B}}^{-1}Q]_k = [-\Sigma_{\boldsymbol{B}}^{-1}Q]_2$.

If we replace Q by a probability distribution $\mathbb{P}$ in (C.8) (and keep all other elements equal) then we deal with $[-\Sigma_{\boldsymbol{B}}^{-1}\mathbb{P}]_j$, $j = 1, 2$. Using (C.7) we find that $[-\Sigma_{\boldsymbol{B}}^{-1}\mathbb{P}]_1 + [-\Sigma_{\boldsymbol{B}}^{-1}\mathbb{P}]_2 = 1/(\beta+\sigma+2\mu)$ holds so we can eliminate $[-\Sigma_{\boldsymbol{B}}^{-1}\mathbb{P}]_1$. (All other elements in (C.8) do not concern the mean field at distance one assumption, so for any assumption

on the degree distribution of the partners of an individual at epi-birth, these will be the the same.) We can then express the dominant eigenvalue λ of $\tilde{K}$ as a function of $[-\Sigma_{\boldsymbol{B}}^{-1}\,\mathbb{P}]_2$ using the explicit formula for the dominant eigenvalue of a 2×2 matrix. This is then a monotonically increasing function of $[-\Sigma_{\boldsymbol{B}}^{-1}\,\mathbb{P}]_2$.

Furthermore, one can check that

$$\begin{aligned}[-\Sigma_{\boldsymbol{B}}^{-1}\,\mathbb{P}]_2 &= [-\Sigma_{\boldsymbol{B}}^{-1}]_{21}(1-\mathbb{P}_2) + [-\Sigma_{\boldsymbol{B}}^{-1}]_{22}\,\mathbb{P}_2 \\ &= [-\Sigma_{\boldsymbol{B}}^{-1}]_{21} + ([-\Sigma_{\boldsymbol{B}}^{-1}]_{22} - [-\Sigma_{\boldsymbol{B}}^{-1}]_{21})\,\mathbb{P}_2,\end{aligned}$$

where $[-\Sigma_{\boldsymbol{B}}^{-1}]_{22} \geq [-\Sigma_{\boldsymbol{B}}^{-1}]_{21}$ (note that $\Sigma_{\boldsymbol{B}} = M - (\beta+\sigma+2\mu)I$), so $[-\Sigma_{\boldsymbol{B}}^{-1}\,\mathbb{P}]_2$ is a monotonically increasing function of $\mathbb{P}_2$. Using (D.1) we then find

$$[-\Sigma_{\boldsymbol{B}}^{-1}q]_2 \leq [-\Sigma_{\boldsymbol{B}}^{-1}Q]_2 \leq [-\Sigma_{\boldsymbol{B}}^{-1}q^{\infty}]_2,$$

and we find a lower (upper) bound by replacing $\mathbb{P}$ by q (q^{∞}) for 'the real R_0' which we can compare with the dominant eigenvalue R_0 of (C.8). We evaluate this numerically in Figure D.1 to get some indication of how well the mean field at distance assumption performs.

We believe that this can be generalized to obtain a bandwidth for R_0 for $n > 2$ by considering expected values but we have not elaborated the details.

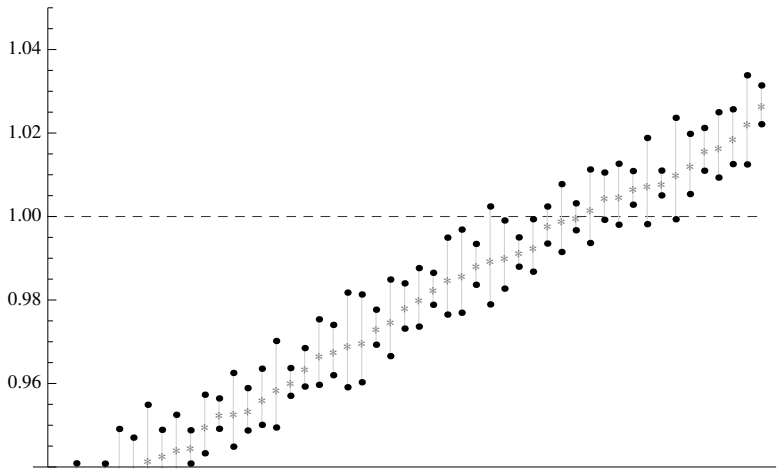

Figure D.1: For different values of parameters ρ, σ, μ, β, the basic reproduction number R_0 is determined together with a lower and an upper bound for 'the real R_0'. We focus here on parameter values for which R_0 lies around threshold value 1.

E The dominant eigenvalue of K equals the dominant eigenvalue of K^{ind}

We have defined R_0 on the binding-site level as the dominant eigenvalue of a NGM K. In this section we prove that K and K^{ind}, the NGM on the individual level, have the same dominant eigenvalue R_0. Therefore, R_0 has an interpretation on both the binding site and the individual level.

Lemma 10. *K^{ind} and K have the same dominant eigenvalue R_0.*

Proof. With the $3 \times n$ matrix G given by

$$G = \begin{pmatrix} n-1 & n-2 & \cdots & 1 & 0 \\ 0 & 1 & \cdots & n-2 & n-1 \\ 1 & 1 & \cdots & 1 & 1 \end{pmatrix} \tag{E.1}$$

the identity

$$GK^{\text{ind}} = KG \tag{E.2}$$

holds. Since $T \geq 0, T \neq 0, -\Sigma^{-1} >> 0, \psi, \phi_i \geq 0, \psi, \phi \neq 0$, we know that $(k^{\text{ind}})_{xy} > 0$ and $k_{ij} > 0$ for all x, y. Therefore K^{ind} and K are primitive matrices.

Now suppose that v is the eigenvector corresponding to eigenvalue R_0, then $K^{\text{ind}}v = R_0 v$ implies that

$$K(Gv) = R_0(Gv).$$

Since v can be chosen as a strictly positive vector (as it belongs to the dominant eigenvalue of a primitive matrix) and G is non-negative and non-zero, Gv is also strictly positive. Therefore, Gv is the (strictly positive) eigenvector corresponding to the eigenvalue R_0 of K. Since K is primitive, it must also be the dominant eigenvalue of K.

On the other hand, suppose w is the eigenvector corresponding to the dominant eigenvalue λ of K^t (where ^{t} denotes the transpose of K), so $K^t w = \lambda w$. Then we can choose w strictly positive, as K is primitive. Then

$$(K^{\text{ind}})^t(G^t w) = \lambda(G^t w).$$

So we see that λ is an eigenvalue of $(K^{\text{ind}})^t$ (and therefore also of K^{ind}) with strictly positive eigenvector $G^t w$. Therefore, λ is the dominant eigenvalue of K^{ind}, i.e. $\lambda = R_0$. □

F Characterizing the matrix elements $(k^{\text{ind}})_{ij}$

The matrix elements $(k^{\text{ind}})_{ij}$ of the matrix K^{ind} are uniquely characterized in (5.10). However, as in the case with K, we can give more explicit expressions for $(k^{\text{ind}})_{ij}$ using the interpretation.

Indeed, $(k^{\text{ind}})_{ij}$ can be interpreted as the expected number of secondary cases in state i caused by one individual in state j, where i and j are of the form $(+, m, 1)$, $m = 0, \ldots, n-1$. A newly infected individual in state $j = (+, m, 1)$ has m susceptible partners, where each of these partners is in state $k = (-, l, 1)$ with probability Q_l (as a consequence of the mean field at distance one assumption). The probability that an individual in state k gets infected and has state-at-epi-birth $i = (+, m', 1)$ is $[\beta(-\Sigma_{\boldsymbol{B}})^{-1}]_{ik}$. On top of the secondary cases caused by infecting existing partners, the newly infected individual can also cause secondary cases among the partners that it acquires after epi-birth. A newly acquired partner is in state $k = (-, l, 1)$ with probability q_l, and the probability that this individual gets infected and has state-at-epi-birth i is again $[\beta(-\Sigma_{\boldsymbol{B}})^{-1}]_{ik}$. The expected additional lifetime number of partners of an individual in state $j = (+, m, 1)$ is $n - m - 1$ times the expected lifetime number of partners of a free binding site plus $m + 1$ times the expected additional lifetime number of partners of an occupied binding site, where the expected lifetime number of partners of a free binding site is

$$\frac{\rho\bar{F}(\sigma + 2\mu)}{\mu(\rho\bar{F} + \sigma + 2\mu)},$$

while the expected additional lifetime number of partners of an occupied binding site is

$$\frac{\sigma + \mu}{\sigma + 2\mu} \frac{\rho\bar{F}(\sigma + 2\mu)}{\mu(\rho\bar{F} + \sigma + 2\mu)} = \frac{\rho\bar{F}(\sigma + \mu)}{\mu(\rho\bar{F} + \sigma + 2\mu)}.$$

Using this interpretation of the matrix elements $(k^{\text{ind}})_{ij}$ we find

$$K^{\text{ind}} = \beta(-\Sigma_{\boldsymbol{B}})^{-1}(Qr^t + qs^t), \tag{F.1}$$

with $s = (s_k)$ and $r = (r_k)$ are n-dimensional vectors, where r is the second row of the matrix G defined in (E.1), i.e.

$$r_k = k - 1,$$

$k = 1, \ldots, n$, and

$$s_k = \left((n - k) + k\frac{\sigma + \mu}{\sigma + 2\mu}\right) \frac{\rho\bar{F}(\sigma + 2\mu)}{\mu(\rho\bar{F} + \sigma + 2\mu)}.$$

In order to prove that K^{ind}, defined by (5.10), satisfies (F.1), we use results from Appendix C. First of all, ϕ_j can be written as

$$\phi_j = (n - j)\psi_A + (j - 1)\psi_{\boldsymbol{B}} + \psi_C.$$

Therefore,

$$\begin{aligned}T(-\Sigma)^{-1}\phi_j =&(n-j)T(-\Sigma)^{-1}\psi_A + (j-1)T(-\Sigma)^{-1}\psi_{\boldsymbol{B}} + T(-\Sigma)^{-1}\psi_C\\ =&(n-j)\sum_x k_{xA}\psi_x + (j-1)\sum_x k_{x,\boldsymbol{B}}\psi_x + \sum_x k_{xC}\psi_i\\ =&\big((n-j)k_{AA} + (j-1)k_{A\boldsymbol{B}} + k_{AC}\big)\psi_A\\ &+\big((n-j)k_{\boldsymbol{B}A} + (j-1)k_{\boldsymbol{BB}} + k_{\boldsymbol{B}C}\big)\psi_{\boldsymbol{B}}\\ &+\big((n-j)k_{CA} + (j-1)k_{C\boldsymbol{B}} + k_{CC}\big)\psi_C.\end{aligned}$$

Now, we can expand this using the characterization of the k_{xy} of Appendix C. The coefficient of ψ_C is

$$\begin{aligned}&(n-j)k_{CA} + (j-1)k_{C\boldsymbol{B}} + k_{CC}\\ =&(n-j)\frac{\beta\rho\bar{F}(\sigma+2\mu)}{\mu(\rho\bar{F}+\sigma+2\mu)}\sum_{i=1}^n[(-\Sigma_{\boldsymbol{B}})^{-1}q]_i + (j-1)\sum_{i=1}^n[(-\Sigma_{\boldsymbol{B}})^{-1}Q]_i\\ &+(j-1)\frac{\beta\rho\bar{F}(\sigma+\mu)}{\mu(\rho\bar{F}+\sigma+2\mu)}\sum_{i=1}^n[(-\Sigma_{\boldsymbol{B}})^{-1}q]_i\\ &+\frac{\beta\rho\bar{F}(\sigma+\mu)}{\mu(\rho\bar{F}+\sigma+2\mu)}\sum_{i=1}^n[(-\Sigma_{\boldsymbol{B}})^{-1}q]_i\\ =&\beta\bigg((n-j)\frac{\rho\bar{F}(\sigma+2\mu)}{\mu(\rho\bar{F}+\sigma+2\mu)} + j\frac{\rho\bar{F}(\sigma+\mu)}{\mu(\rho\bar{F}+\sigma+2\mu)}\bigg)\sum_{i=1}^n[(-\Sigma_{\boldsymbol{B}})^{-1}q]_i\\ &+\beta(j-1)\sum_{i=1}^n[(-\Sigma_{\boldsymbol{B}})^{-1}Q]_i\\ =&\sum_{i=1}^n\beta\left([(-\Sigma_{\boldsymbol{B}})^{-1}q]_i s_j + [(-\Sigma_{\boldsymbol{B}})^{-1}Q]_i r_j\right)\\ =&\sum_{i=1}^n\beta\big[(-\Sigma_{\boldsymbol{B}})^{-1}(qs^t + Qr^t)\big]_{ij}.\end{aligned}$$

On the other hand,

$$\begin{aligned}T(-\Sigma)^{-1}\phi_j &= \sum_{i=1}^n(k^{\text{ind}})_{ij}\phi_i\\ &= \sum_{i=1}^n(n-i)(k^{\text{ind}})_{ij}\psi_A + \sum_{i=1}^n(i-1)(k^{\text{ind}})_{ij}\psi_{\boldsymbol{B}} + \sum_{i=1}^n(k^{\text{ind}})_{ij}\psi_C.\end{aligned}$$

Therefore

$$(k^{\text{ind}})_{ij} = \beta\big[(-\Sigma_{\boldsymbol{B}})^{-1}(qs^t + Qr^t)\big]_{ij}.$$

Chapter 4

Dangerous connections: on binding site formulations for infectious disease models

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Abstract

We formulate models for the spread of infection on networks that are amenable to analysis in the large population limit. We distinguish three different levels: (1) binding sites, (2) individuals, and (3) the population. In the tradition of physiologically structured population models, the formulation starts on the individual level. Influences from the 'outside world' on an individual are captured by environmental variables. These environmental variables are population level quantities. A key characteristic of the network models is that individuals can be decomposed into a number of conditionally independent components: each individual has a fixed number of 'binding sites' for partners. The Markov chain dynamics of binding sites are described by only a few equations. In particular, individual-level probabilities are obtained from binding-site-level probabilities by combinatorics while population-level quantities are obtained by averaging over individuals in the population. Thus we are able to characterize population-level epidemiological quantities, such as R_0, r, the final size, and the endemic equilibrium, in terms of the corresponding variables.

The title of this paper is inspired by Van Baalen en Jansen [88] and in this spirit we propose as an alternative subtitle: 'the epidemiology of private risk and common threat'.

1 Introduction

Consider an empirical network consisting of individuals that form partnerships with other individuals. Suppose an infectious disease can be transmitted from an infectious individual to any of its susceptible partners and thus spread over the network. Consider an individual in the network at a particular point in time. We are interested in the disease status of the individual, but also in the presence of the infection in its immediate surroundings that are formed by the individual's partners. We may label this individual by listing

- its disease status in terms of the S, I, R classification, where, as usual, S stands for susceptible, I for infectious and R for recovered (implying immunity)
- how many partners this individual has
- the disease status of these partners

In this spirit, we may provide a statistical description of the network at a particular point in time by listing, for each such label, the fraction of the population carrying it.

Is it possible to predict the future spread of the disease on the basis of this statistical description? The answer is 'no', simply because the precise network structure is important for transmission and we cannot recover the structure from the description. But if we are willing to make assumptions about the structure (and to consider the limit of the number of individuals going to infinity), the answer might be 'yes'. And even if the true answer is still 'no', we may indulge in wishful thinking and answer 'to good approximation'.

When considering an outbreak of a rapidly spreading disease, we can consider the network as static. If we are willing to assume that the network is constructed by the configuration procedure [41, 42], the answer is indeed 'yes' [83, 84, 89]. But if the disease spreads at the time scale of formation and dissolution of partnerships, we need to take these partnership dynamics into account and next indeed rely on wishful thinking (though the answer may very well be 'yes'). In case of HIV, the disease spreads on the time scale of demographic turnover and this motivated our earlier work (Chapters 2 and 3) that also takes birth and death into account (here we know that the answer is 'no', see Appendix B of Chapter 3).

In the rest of this introduction we first discuss the model formulation used and the relation between our work and existing literature. Next, we consider three different settings based on the time scales of disease spread, partnership dynamics, and demographic turnover. Individuals are decomposed into conditionally independent components (the 'binding sites') and we discuss how the dynamics of these binding sites can be specified. We end the introduction with an outline of the structure of the rest of the paper.

Physiologically Structured Population Models

As in our earlier paper (Chapter 3), our model formulation is in the tradition of physiologically structured population models (PSPM [61–63]). This means that we start from the notion of state at the individual level, called i-state (where i stands for individual). Model specification involves, first of all, a description of changes in time of the i-state as influenced by i-state itself and the relevant environmental variables that capture the influence of the outside world. Next the model specifies the impact of individuals on the environmental variables. Thus the feedback loop that creates density dependence, i.e. dependence among individuals, is described in a two step procedure. To lift the i-level model to the population level (p-level) is just a matter of bookkeeping, see [90] for a recent account.

In the setting considered here, i-state ranges over a finite set. As a consequence, the p-level equations are ordinary differential equations (ODE). These ODE describe, apart from death and birth of individuals, the dynamical changes of i-state, i.e. how individuals jump back and forth between the various states. In the spirit of the theory of Markov chains [91], we describe an individual not by its actual state but by the probability distribution, i.e. the probability of being in the various states. Equating a p-level fraction to an i-level probability provides the link between the two levels.

The approach of both earlier work and this paper is to *pretend* that the label can be considered as the i-state, the information about the individual that is relevant for predicting its future. The i-state contains information about partners, but not about partners of partners. Implicitly this entails that we use a mean field description of partners of partners. We call this the 'mean field at distance one' assumption. The description of partners of partners is incorporated in an environmental variable, the information about the 'outside world' that is relevant for a prediction of the future of the individual.

A rather special feature of the models considered here is that i-state involves a number of conditionally independent components: the binding sites. An individual has binding sites for partners. Two free binding sites can be joined together to form a partnership between two individuals (see Fig. 1 on p. 101 for an illustration). In graph theory the words 'half-edge' or 'stub' are often used. We think that for static networks these terms capture the essence much better than the word 'binding site'. But the latter provides, in our opinion, a better description for dynamic networks. The fact that our research started with dynamic networks is responsible for our choice of terminology.

It is attractive to model the dynamics of one binding site and next use combinatorics to describe the full i-state. It is precisely this aspect that we did not yet elaborate in Chapter 3 but highlight now. It is precisely this aspect that uncovers the link/relationship between the work of [76] and Chapter 3 on the one hand and the edge-based modelling approach of Volz, Miller and co-workers [50, 79, 92–94] on the other hand.

Volz and Miller focus on the binding site (=half-edge/stub) and individual level and draw p-level conclusions by a clever use of probabilistic arguments to determine the relevant environmental variables. Lindquist et al. [76] systematically formulate and analyze the p-level equations. In Chapter 3 we too emphasized the p-level equations, but used the i-level version to derive an expression for R_0. The link between the two was established by somewhat contrived linear algebra arguments. In the present paper we build our way

upwards from binding site - via individual - to population level. One of the secondary aims of this paper is to show that the systematic methodology of PSPM is also very useful when i-state space is discrete, rather than a continuum, and when i-state involves multiple identical components.

Figure 1: An illustration of binding sites with three individuals u, v, and w. In this example, u, v, and w have four, three, and two binding sites for partners, respectively. On the left, all binding sites are free. On the right, a partnership between u and w is formed and they both have one occupied binding site.

Three network cases

Now, consider a network. An epidemic starts when, at some point in time, a small fraction of the population is infected from outside. Our idealized description shifts the 'point in time' towards $-\infty$ while letting the fraction become smaller and smaller. In other words, our story starts 'far back' in time when all individuals are still susceptible (see Appendix A for elucidation). We consider three different situations, characterized by the relation between the time scales of, respectively, transmission, partnership dynamics and demographic turnover:

I The disease dynamics are fast relative to any partnership- or demographic changes. The network is static and everyone is susceptible at time $t = -\infty$.

II The disease dynamics are on the same time scale as the partnership dynamics, but fast relative to demographic turnover. In this network individuals can acquire and lose partners over time. Everyone is susceptible at time $t = -\infty$.

III The disease dynamics and partnership- and demographic changes are on the same time scale. Here the age of an individual matters and we assume that, at birth, an individual enters the population as a susceptible without any partners.

We assume that infection is transmitted from an infectious individual to a susceptible partner at rate β and infectious individuals recover at rate γ (but see Section 2.5 for a far more general setting). We also assume that infection does *not* influence the partnership dynamics or the probability per unit of time of dying in any way.

Each individual in the population is assumed to have a so-called partnership capacity n which denotes the number of binding sites it has (so n is the maximum number of simultaneous partners it may have). Throughout the life of the individual this partnership capacity does not change. An individual with partnership capacity n can be thought of as having n binding sites for partners (in Fig. 1, individuals u, v, and w have partnership capacities 4, 3, and 2, respectively). We call the individual to which a binding site belongs

its owner. For the purpose of this paper, we will assume that all individuals have the same partnership capacity n. One can easily generalize this by allowing individuals to have different partnership capacities; in that case, one only needs to average over n in the correct way (see Section 2.5 for the static case).

Binding sites

An individual with partnership capacity n is to some extent just a collection of n binding sites. These n binding sites are coupled through the disease status (or death) of their owner. We assume that this is the only manner in which the binding sites of an individual are coupled. As long as the disease status of the owner does not change (and the owner does not die), binding sites behave independently of one another and the 'rules' for changes in binding site states are the same for each binding site. Obviously the latter depends on the network dynamics under consideration (either case I, II, or III). As a port to the world, a binding site can be in one of four states:

- 0 - free
- 1 - occupied by a susceptible partner
- 2 - occupied by an infectious partner
- 3 - occupied by a recovered partner.

Here (and in the remainder of this introduction) our formulation is precise for case II while sometimes requiring minor adaptations to capture cases I and III.

A key component of the model is the description of the dynamics of a binding site. The state of an individual is specified by listing its disease status and the states of each of its n binding sites. So it makes sense to first consider a binding site as a separate and independent entity and to only take the dependence (by way of a change in the disease status of the owner) into account when we combine n binding sites into one individual.

The case of a susceptible binding site (i.e. a binding site with a susceptible owner) is, as will become clear, far more important than the other cases. This is partly due to our assumption that all individuals start out susceptible, i.e. are susceptible at time $t = -\infty$ (I and II) or at birth (III). The dynamics of a susceptible binding site are described by a differential equation for the variable $x(t) = (x_i(t))$, $i = 0, 1, 2, 3$. Here x_i can be interpreted as the probability that a binding site is susceptible and has state i at time t, given that its owner does not become infected through one of its other $n - 1$ binding sites (in other words, by conditioning on the individual not getting infected through its $n - 1$ other binding sites, the only way the individual could get infected is through the binding site under consideration). In particular, *given that its owner does not become infected through one of its other binding sites*,

$$\bar{x}(t) = x_0(t) + x_1(t) + x_2(t) + x_3(t) \tag{1.1}$$

is the probability that the binding site is susceptible at time t (or, in other words, that the owner is not infected along this binding site before time t). Accordingly, the probability that an *individual* is susceptible at time t is equal to

$$\bar{x}(t)^n. \tag{1.2}$$

In order to arrive at a closed system of equations for x, we need to go through several steps. The variable x contains information about a partner. Consequently the dynamics of x is partly determined by partners of partners, hence by one or more environmental variables. The 'mean field at distance one' assumption yields expressions for environmental variables in terms of subpopulation sizes (for a given label, the corresponding subpopulation size is the fraction of the population that carries this label). In turn, p-level fractions can be expressed in terms of i-level probabilities. And since a susceptible individual is in essence a collection of n conditionally i.i.d. binding sites, we can use combinatorics to express i-level probabilities in terms of binding-site-level probabilities as incorporated in x.

The exchangeability of the binding sites is broken by the infection event. There is exactly one binding site along which infection took place, viz. the binding site occupied by the individual's epidemiological parent, and for this binding site we know with certainty that it is in state 2 at time of infection t_+. We call the binding site through which the change in the owner's disease status occurred the 'exceptional' binding site. The other $n-1$ binding sites are i.i.d. and, at time t_+, they are distributed according to $x(t_+)$. Recovery (and death) is an event that occurs at a constant rate for an infectious individual so they are independent of binding site states. Therefore, also after recovery, there remains exactly one exceptional binding site, viz. the one through which transmission occurred. See also Fig. 2 for an illustration of the exceptional binding site.

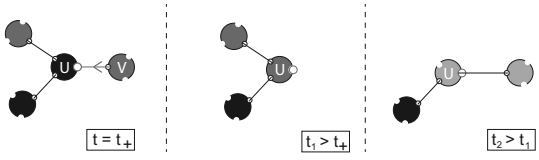

Figure 2: An illustration of the exceptional binding site. Susceptible, infectious, and recovered individuals are displayed in black, red, and blue, respectively. Three time points in the life of individual u are displayed. Suppose u is susceptible and becomes infected by an infectious partner v at time t_+. From that moment on, the binding site along which transmission occurred is the exceptional binding site. This binding site remains exceptional throughout u's life and no other binding site can become exceptional, regardless of whether or not v is still a partner or u is still infectious.

Structure of the paper

In Sections 2, 3, and 4 below, we will discuss the three network model cases I, II, and III separately. For each of the three cases we will explain how the model can be formulated and described in terms of susceptible binding sites. By considering the susceptible

binding site perspective we can write a closed system of only a few equations that fully determine the dynamics of i-level probabilities and p-level fractions. This system is then used to determine epidemiological quantities of interest: R_0, r, the final size (in cases I and II), and the endemic steady state (in case III). In all three cases, an explicit expression can be given for R_0. In case I, one can derive a simple scalar equation for the final size. In cases II and III, we could only implicitly characterize the final size and endemic equilibrium, respectively.

In Section 2 case I of a static network is considered. This is the simplest case among the three. The relative simplicity allows for the derivation of an ODE system for susceptible binding sites directly from the interpretation. This will be the first way in which we formulate the model for this case. But case I will also serve to illustrate the systematic procedure for model formulation in the spirit of PSPM. This systematic procedure allows us to connect the three different levels, viz. (1) binding sites, (2) individuals, and (3) the population, to each other.

In network case I, since it is relatively simple, one can derive a one-dimensional renewal equation from which R_0, r, and the final size almost immediately follow. This renewal equation will be treated in Section 2.5 for a much more general class of infectious disease models than only SIR.

Part of the systematic procedure in cases II and III focuses on infectious binding sites. We use case I to illustrate the model formulation concerning infectious (and recovered) binding sites, even though, for case I these are not needed to obtain a closed system for susceptible binding sites. However, depending on the network features of interest (e.g. fractions of infectious individuals) one may still want to consider infectious (and recovered) binding sites.

In network cases II and III, there are also network dynamics in absence of infection due to partnership changes (and demographic changes). We will only describe the essential characteristics of the network dynamics that we use in this paper. Certainly, much more can be said about the networks in absence of infection (Chapter 2).

Finally, in Section 5 we discuss the issues that we have encountered in the three different network cases and pose some open problems. We end the discussion by considering a few generalizations that can easily be implemented using the systematic model formulation of Section 2.2.

2 Part I: static network

2.1 Model formulation

We derive a closed system of ODE for x purely on the basis of the interpretation of binding sites (without explicitly taking into account i-level probabilities or p-level fractions). The relatively simple setting of a static network allows us to do so. We are able to consider a binding site as a separate and independent entity all throughout its susceptible life. Implicitly, this uses (2.8) below. One can show that the system of ODE for x indeed captures the appropriate large population limit of a stochastic SIR epidemic on a

configuration network. This requires quite some work; see [83, 84, 89].

Consider a susceptible binding site and assume its owner does not become infected through one of its other $n-1$ binding sites for the period under consideration. If a susceptible binding site is in state 2, it can become infected by the corresponding infectious partner. This happens at rate β and when it happens, the binding site is no longer susceptible so it 'leaves' the x-system. It is also possible that the infectious partner recovers. This happens at rate γ. Finally, there is the possibility that a susceptible partner of a susceptible binding site becomes infectious (corresponding to a transition from state 1 to state 2). The rate at which this occurs depends on the number of infectious partners that this susceptible partner has. So here we use the mean field at distance one assumption: we average over all possibilities at the p-level to obtain one rate at which a susceptible partner of a susceptible binding site becomes infected. More specifically, we assume that there is a rate $\beta\Lambda_-(t)$ at which a susceptible partner of a susceptible binding site becomes infected at time t. Here $\Lambda_-(t)$ has the interpretation of the expected number of infectious partners of a susceptible partner of a susceptible individual.

Then, putting together the various assumptions described above, the dynamics of x is governed by the following system (please note that the environmental variable Λ_- is a p-level quantity that we have yet to specify):

$$\frac{dx(t)}{dt} = M\big(\Lambda_-(t)\big)x(t), \tag{2.1}$$

with 'far past' conditions

$$x_1(-\infty) = 1, \quad x_2(-\infty) = 0 = x_3(-\infty),$$

and

$$M(\Lambda_-) = \begin{pmatrix} -\beta\Lambda_- & 0 & 0 \\ \beta\Lambda_- & -(\beta+\gamma) & 0 \\ 0 & \gamma & 0 \end{pmatrix}. \tag{2.2}$$

To express Λ_- in terms of x we use the interpretation. Consider a susceptible partner v of a susceptible individual u. Then, since u is susceptible, we know that v has at most $n-1$ binding sites that are possibly in state 2 (i.e. occupied by infectious partners). Since v is known to be susceptible, also all its binding sites are susceptible (in the sense that their owner v is). The probability that a binding site is susceptible at time t is $\bar{x}$ with

$$\bar{x}(t) = x_1(t) + x_2(t) + x_3(t) \tag{2.3}$$

(recall (1.1) and note that in case I we have $x_0(t) = 0$). The probability that a binding site is in state 2, given that the binding site is susceptible, is $x_2(t)/\bar{x}(t)$. Therefore,

$$\Lambda_-(t) = (n-1)\frac{x_2(t)}{\bar{x}(t)}. \tag{2.4}$$

By inserting (2.4) into (2.1) we find that the x-system is fully described by an ODE system in terms of the x-variables only:

$$\begin{aligned} x_1' &= -\beta(n-1)\frac{x_2}{\bar{x}}x_1 \\ x_2' &= \beta(n-1)\frac{x_2}{\bar{x}}x_1 - (\beta+\gamma)x_2 \\ x_3' &= \gamma x_2, \end{aligned} \tag{2.5}$$

with 'far past' conditions

$$x_1(-\infty) = 1, \quad x_2(-\infty) = 0 = x_3(-\infty).$$

Remark 1. *In the pioneering paper [93] an equivalent system of three coupled ODE was introduced to describe the binding-site level of the model. The variables of Volz are connected to our x-system as follows: $\theta = \bar{x}$, $p_S = x_1/\bar{x}$ and $p_I = x_2/\bar{x}$.*

4

2.2 Systematic procedure for closing the feedback loop

Before analyzing (2.5) in the next section, we describe a systematic procedure, consisting of five steps, for deriving the complete model formulation. A key aim is to rederive the crucial relationship (2.4) in a manner that can be extended to the dynamic networks. Thus the present section serves to prepare for a quick and streamlined presentation of the cases II and III in Sections 3 and 4, respectively. The various steps reveal the relation between binding site probabilities, i-level probabilities and p-level fractions. In addition we introduce some notation.

step 1. Susceptible binding sites: x-probabilities
The first step is to describe the dynamics of x while specifying the environmental variable Λ_- only conceptually, i.e. in terms of the interpretation. We then arrive at system (2.1)-(2.2).

Next, we introduce $P_{(d,\boldsymbol{k})}(t)$, denoting the fraction of the population with label $(d, \boldsymbol{k})$. Here $\boldsymbol{k} = (k_1, k_2, k_3)$ denotes the number of partners of an individual with each of the different disease statuses, i.e. k_1 susceptible, k_2 infectious, and k_3 recovered partners. Furthermore, $d \in \{-, +, *\}$ denotes the disease status of the individual itself, with $-$ corresponding to S, $+$ to I, and $*$ to R.

In the second step, the environmental variable Λ_- is, on the basis of its interpretation, redefined in terms of p-level fractions $P_{(-,\boldsymbol{k})}(t)$.

step 2. Environmental variables: definition in terms of p-level fractions
The mean field at distance one assumption concerns the environmental variable Λ_-. This variable is interpreted as the mean number of infectious partners of a susceptible individual that has at least one susceptible partner (see also Fig. 3). We define it in terms of

p-level fractions as follows:

$$\Lambda_-(t) = \sum_{\boldsymbol{m}} m_2 \, \frac{m_1 P_{(-,\boldsymbol{m})}(t)}{\sum_{\boldsymbol{k}} k_1 P_{(-,\boldsymbol{k})}(t)}. \tag{2.6}$$

Here the sums are over all possible configurations of $\boldsymbol{m}$ and $\boldsymbol{k}$ with $0 \leq m_1+m_2+m_3 \leq n$, $0 \leq k_1 + k_2 + k_3 \leq n$. The second factor in each term of this sum denotes the probability that a susceptible partner of a susceptible individual is in state $(-, \boldsymbol{m})$. The number of infectious partners is then given by m_2, and we find the expected number of infectious partners Λ_- by summing over all possibilities.

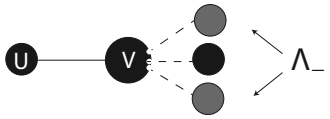

Figure 3: The susceptible partner v of a susceptible individual u has a mean number of infectious partners Λ_-.

In the third step, we let $p_{(-,\boldsymbol{k})}(t)$ denote the probability that an individual is in state $(-, \boldsymbol{k})$ at time t. This i-level probability can be expressed in terms of x-probabilities.

step 3. i-level probabilities in terms of x-probabilities
We need to take into account the number of possible configurations of the individual's binding sites such that there are exactly k_1 binding sites in state 1, k_2 binding sites in state 2, (and then automatically, there are $k_3 = n - k_1 - k_2$ binding sites in state 3). The number of possibilities is equal to

$$\binom{n}{k_1+k_2}\binom{k_1+k_2}{k_1} = \frac{n!}{k_1!\,k_2!\,k_3!},$$

The probability to have a specific configuration of the n binding sites in the different states is obtained by simply multiplying the x-probabilities:

$$x_1^{k_1} x_2^{k_2} x_3^{k_3}.$$

Therefore,

$$p_{(-,\boldsymbol{k})}(t) = \frac{n!}{k_1!\,k_2!\,k_3!} \left(x_1^{k_1}\, x_2^{k_2}\, x_3^{k_3} \right)(t) \tag{2.7}$$

is the probability that an individual is, at time t, susceptible with k_1 susceptible, k_2 infectious, and k_3 recovered partners. The solution of the x-system then gives us a complete Markovian description of the i-state dynamics of susceptible individuals.

In this setting of a static network age does not play a role. Therefore, i-level probabilities can immediately be linked to p-level fractions in step 4 below.

step 4. p-level fractions in terms of i-level probabilities
The i-level probabilities and p-level fractions coincide, i.e.

$$P_{(d,\boldsymbol{k})}(t) = p_{(d,\boldsymbol{k})}(t), \tag{2.8}$$

$d \in \{-, +, *\}$. In a way, individuals are interchangeable as they all start off in the same state at $t = -\infty$.

Finally in the last step, by combining steps 2, 3, and 4, we can express Λ_- in terms of the x-probabilities.

step 5. Environmental variables in terms of x-probabilities (combining 2, 3, 4)
By combining (2.8), and (2.7) we find that $\sum_{\boldsymbol{m}} m_2 m_1 P_{(-,\boldsymbol{m})}(t) = n(n-1)\left(x_1 x_2 \bar{x}^{n-2}\right)(t)$ and $\sum_{\boldsymbol{k}} k_1 P_{(-,\boldsymbol{k})}(t) = n\left(x_1 \bar{x}^{n-1}\right)(t)$. Then definition (2.6) yields the same expression for Λ_- as (2.4).

Finally, steps 1 to 5 together yield the closed system (2.5) of ODE for x. The dynamics of the $1/2(n+1)(n+2)$ i-level probabilities $p_{(-,\boldsymbol{k})}(t)$ are fully determined by the system of three ODE for x. We can use this three-dimensional system of ODE to determine r, R_0, and the final size as we will show in Section 2.3. In this particular case of a static network, we can do even better by considering one renewal equation for $\bar{x}$. This one equation then allows us to determine the epidemiological quantities as well. This is the topic of Section 2.5 where we consider epidemic spread on a static configuration network in greater generality.

Remark 2. *One obtains the p-level ODE system by differentiation of* (2.7) *and use of* (2.5) *and* (2.8)*. In doing so, one obtains a system of $1/2(n+1)(n+2)$ ODE for the p-level fractions concerning individuals with a $-$ disease status:*

$$\begin{aligned}\frac{dP_{(-,k_1,k_2,k_3)}}{dt} = &-(\beta k_2 + \gamma k_2 + \beta \Lambda_- k_1) P_{(-,k_1,k_2,k_3)} \\ &+ \gamma(k_2+1) P_{(-,k_1,k_2+1,k_3-1)} \\ &+ \beta \Lambda_- (k_1+1) P_{(-,k_1+1,k_2-1,k_3)},\end{aligned}$$

$k_1 + k_2 + k_3 = n$, with Λ_- defined by (2.6) *(compare with [76, eq. (13)]).*

2.3 The beginning and end of an epidemic: R_0, r, and final size

In this section we consider the beginning and end of an epidemic. We first focus on R_0 and r, so on the start of an epidemic.

Note that we can very easily find an expression for R_0 from the interpretation: when infected individuals are rare, a newly infected individual has exactly $n-1$ susceptible partners. It infects one such partner before recovering from infection with probability

$\beta/(\beta+\gamma)$. Therefore, the expected number of secondary infections caused by one newly infected individual is

$$R_0 = \frac{\beta(n-1)}{\beta+\gamma}. \tag{2.9}$$

However, even though there should be no doubt about it, this does not yield a *proof* that this expression is indeed a threshold parameter with threshold value one for the stability of the disease free steady state of the p-level system. In order to provide a proof *and* to prepare for cases II and III, we now derive R_0 and r from the binding site system (2.5).

Note that the p-level fractions $P_{(-,\boldsymbol{k})}(t)$ can be fully expressed in terms of the binding site level probabilities x_i (eqs. (2.8) and (2.7)). Furthermore, the $P_{(-,\boldsymbol{k})}(t)$ fractions, i.e. the fractions concerning individuals with a $-$ disease status, form a closed system. Therefore, a threshold parameter for the disease free steady state of the binding-site system x is also a threshold parameter for the disease free steady state of the p-level system. (This argument extends to the dynamic network cases II and III in Sections 3 and 4)

Linearization of system (2.5) in the disease free steady state $\tilde{x}_1 = 1$, $\tilde{x}_2 = 0 = \tilde{x}_3$, yields a decoupled ODE for the linearization of the ODE for x_2. To avoid any confusion, let $\hat{x}_2$ denote the *linearized* x_2 variable. Then the linearization yields

$$\hat{x}_2' = \beta(n-1)\hat{x}_2 - (\beta+\gamma)\hat{x}_2,$$

with 'far past' condition $\hat{x}_2(-\infty) = 0$. In particular, the right-hand side of the ODE for $\hat{x}_2$ depends only on $\hat{x}_2$.

To illustrate the method used in case II and III in Sections 3.3 and 4.3, we derive expressions for R_0 and r from a special form of the characteristic equation. Variation of constants for the ODE of $\hat{x}_2$ yields

$$\hat{x}_2(t) = \int_0^\infty e^{-(\beta+\gamma)\tau}\beta(n-1)\hat{x}_2(t-\tau)d\tau.$$

Substituting the ansatz $\hat{x}_2(t) = e^{\lambda t}$ yields the characteristic equation

$$1 = \int_0^\infty \beta e^{-(\beta+\gamma)\tau}(n-1)e^{-\lambda\tau}d\tau.$$

Then there is a unique real root to this equation for λ that we denote by r and call the Malthusian parameter. Evaluating the integral we find that $r = \beta(n-1) - (\beta+\gamma)$. Likewise, we can derive the expression (2.9) for R_0 by evaluating the integral with $\lambda = 0$.

Next, we consider the final size. We do so by considering the dynamics of $\bar{x}$ defined in (2.3). Recall (1.2), i.e. the probability that an individual is susceptible at time t, is given by $\bar{x}(t)^n$. We observe that, by (2.8), $\bar{x}(t)^n$ is also equal to the fraction of susceptible individuals in the population at time t. (Alternatively, one can show that $\sum_{\boldsymbol{k}} P_{(-,\boldsymbol{k})}(t) = \bar{x}(t)^n$ by combining (2.8) and (2.7).) In fact, it is possible to describe the dynamics of $\bar{x}$ in terms of only $\bar{x}$ itself. This was first observed in [95], where the Volz equations of [93] were taken as a starting point. The most important observation is the consistency relation

$$x_1 = \bar{x}^{n-1}. \tag{2.10}$$

We can use the interpretation to derive (2.10); x_1 is the probability that a susceptible binding site with owner u is occupied by a susceptible partner v, $\bar{x}^{n-1}$ is the probability that v is susceptible given that it is a partner of a susceptible individual u (see also (2.27) below).

Then, using (2.10) together with algebraic manipulation of the ODE system (2.5) (see [95] for details), one is able to find a decoupled equation for $\bar{x}$:

$$\bar{x}' = \beta\bar{x}^{n-1} - (\beta+\gamma)\bar{x} + \gamma. \tag{2.11}$$

The fraction of susceptible individuals at the end of the outbreak is determined by the probability $\bar{x}(\infty)$. Since $\bar{x}$ satisfies (2.11) and $\bar{x}(\infty)$ is a constant, we find that necessarily $\bar{x}(\infty)$ is the unique solution in $(0,1)$ of

$$0 = \beta\bar{x}(\infty)^{n-1} - (\beta+\gamma)\bar{x}(\infty) + \gamma \tag{2.12}$$

if $R_0 > 1$. The final size is given by

$$1 - \bar{x}(\infty)^n.$$

In Section 2.5 we show that one can actually describe the dynamics of the probability $\bar{x}$ for deterministic epidemics on configuration networks for a much larger class of submodels for infectiousness. The SIR infection that we consider here is a very special case of the situation considered in Section 2.5. There we show that it is possible to derive a renewal equation for $\bar{x}$. The final size equation is then obtained by simply taking the limit $t \to \infty$. We highly recommend reading Section 2.5 to understand the derivation of the renewal equation for $\bar{x}$ based on the interpretation of the model (with a minimum of calculations).

2.4 After susceptibility is lost

In the preceding section we have seen that the x-system (2.5) for susceptible binding sites is all that is needed to determine several epidemiological quantities of immediate interest. On the other hand, we might not only be interested in the fraction (1.2) of susceptibles in the population, but also in the dynamics of i-level probabilities $p_{(d,\boldsymbol{k})}(t)$ (and likewise p-level fractions $P_{(d,\boldsymbol{k})}(t)$ given by (2.8)) for $d = +, *$.

So what happens after an individual becomes infected? We work out the details for infectious individuals and only briefly describe recovered individuals. Again, we are able to formulate the model following steps 1-5 of Section 2.2 (where the word 'susceptible' should be replaced by 'infectious' or 'recovered' whenever appropriate and step 3 should be replaced by a slightly different step 3', but we will come back to this later on in this section). But now we need to take into account the exceptional binding site, i.e. the binding site through which infection was transmitted to the owner (see also Fig. 2).

In *step 1* one considers the dynamics of infectious binding sites, i.e. binding sites having infectious owners. Suppose that the owner became infected at time t_+ and that it does not recover in the period under consideration. Let $y_i^{\mathrm{e}}(t \mid t_+)$ denote the probability

for the exceptional binding site to be in state i at time t, $i = 1, 2, 3$. Similarly, $y_i(t \mid t_+)$ denotes the probability for a non-exceptional binding site to be in state i at time t, $i = 1, 2, 3$. Here the probabilities are defined only for $t \geq t_+$. Note that y and y^{e} are probability vectors, i.e. the components are nonnegative and sum to one.

Instead of 'far past' conditions we now have to take into account the distribution of binding site states at time of infection t_+. Whether or not an infectious binding site is exceptional has an influence on the state it has at epidemiological birth. Indeed, the exceptional binding site is in state 2 at time t_+ with probability 1, while the distribution of the state of a non-exceptional binding site at time t_+ is given by $x(t_+)/\bar{x}(t_+)$, i.e. we have boundary conditions

$$\begin{aligned} y_1^{\mathrm{e}}(t_+ \mid t_+) &= 0, \quad y_1(t_+ \mid t_+) = x_1(t_+)/\bar{x}(t_+), \\ y_2^{\mathrm{e}}(t_+ \mid t_+) &= 1, \quad y_2(t_+ \mid t_+) = x_2(t_+)/\bar{x}(t_+), \\ y_3^{\mathrm{e}}(t_+ \mid t_+) &= 0, \quad y_3(t_+ \mid t_+) = x_3(t_+)/\bar{x}(t_+). \end{aligned} \tag{2.13}$$

The mean field at distance one assumption again plays a role. Here, we need to deal with the environmental variable Λ_+ that is defined as the expected number of infectious partners of a susceptible partner of an infectious individual (see also Fig. 4 and compare with Fig. 3). We can redefine Λ_+ in terms of p-level fractions $P_{(-,\boldsymbol{k})}$ for susceptible individuals:

$$\Lambda_+(t) = \sum_{\boldsymbol{m}} m_2 \frac{m_2 P_{(-,\boldsymbol{m})}(t)}{\sum_{\boldsymbol{k}} k_2 P_{(-,\boldsymbol{k})}(t)}. \tag{2.14}$$

In particular, once again, Λ_+ can be expressed in terms of x by combining steps 2, 3, and 4. Using (2.14), (2.8), and (2.7) we find that

$$\Lambda_+(t) = 1 + (n-1)\frac{x_2(t)}{\bar{x}(t)} \tag{2.15}$$

(alternatively, one can find the same expression for Λ_+ in terms of x-probabilities directly from the interpretation, exactly as before in the case of Λ_-).

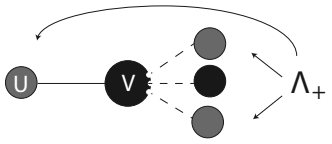

Figure 4: The susceptible partner v of an infectious individual u has a mean number of infectious partners Λ_+ (note that this number is always larger or equal to 1 since u is a partner).

The rates at which changes in the states (1, 2, 3) of infectious binding sites occur is the same for each binding site, including the exceptional one. There is a rate γ at which an infectious partner of an infectious binding site recovers (this corresponds to a change in state from 2 to 3). And there is a rate at which a susceptible partner of an infectious

binding site becomes infected (either along the binding site under consideration or by one of its other infectious partners) corresponding to a change in state from 1 to 2. The rate at which this occurs is $\beta\Lambda_+$ where Λ_+ is defined by (2.14) and hence (2.15).

Recall that we condition on the infectious binding site under consideration not recovering, therefore, these are all state changes that can occur. So we find that the dynamics of y and y^e are described by the same ODE system

$$\frac{dy(t \mid t_+)}{dt} = M_+\big(\Lambda_+(t)\big)y(t \mid t_+), \tag{2.16}$$

with

$$M_+(\Lambda_+) = \begin{pmatrix} -\beta\Lambda_+ & 0 & 0 \\ \beta\Lambda_+ & -\gamma & 0 \\ 0 & \gamma & 0 \end{pmatrix},$$

and case specific boundary conditions (2.13). Observe that this means that $y_1^{\mathrm{e}}(t \mid t_+) = 0$ for all $t \geq t_+$.This also immediately follows from the interpretation: at time t_+, the binding site is occupied by an infectious partner, the network is static, and an infectious individual can not become susceptible again.

Next, we turn to *infectious* individuals. Compared to susceptible i-level probabilities, it is more involved to express infectious i-level probabilities in terms of y^{e}- and y-probabilities. Therefore, we first consider conditional i-level probabilities before finding an expression for the unconditional probabilities. We replace step 3 by step 3'.

step 3' Infectious i-level probabilities in terms of y and y^{e}
We let $\phi_{(+,\boldsymbol{k})}(t \mid t_+)$ denote the probability that an infectious individual, infected at time t_+, is in state $(+, \boldsymbol{k})$ at time t, given no recovery. As in the case of a susceptible individual, we count the number of different configurations for the n binding sites of the individual (and we find the same expression as in the case of a susceptible individual). Next, we need to take into account that there is one exceptional binding site, and the probability that it is in state i is y_i^{e} (note that this is equal to zero for $i = 1$). The other $n-1$ binding sites are i.i.d. Suppose the exceptional binding site is in state 2, then the number of possible configurations of the individual's $n-1$ non-exceptional binding sites such that there are exactly k_1 in state 1, $k_2 - 1$ in state 2, and k_3 in state 3 is

$$\binom{n-1}{k_1+k_2-1}\binom{k_1+k_2-1}{k_1} = \frac{(n-1)!}{k_1!\,(k_2-1)!\,k_3!}.$$

The probability to have a specific configuration of the $n-1$ binding sites in the different states is obtained by multiplying the y-probabilities:

$$y_1^{k_1} y_2^{k_2-1} y_3^{k_3}.$$

We can do the same when the exceptional binding site is in state 3. Taking into account both possible states (2 and 3) for the exceptional binding site, we obtain

$$\begin{aligned}&\phi_{(+,\boldsymbol{k})}(t \mid t_+)\\ =&\frac{n!}{k_1!\,k_2!\,k_3!}\left(\frac{k_2}{n}\,y_2^{\mathrm{e}}\,y_1^{k_1}y_2^{k_2-1}y_3^{k_3}+\frac{k_3}{n}\,y_3^{\mathrm{e}}\,y_1^{k_1}y_2^{k_2}y_3^{k_3-1}\right)(t \mid t_+).\end{aligned} \tag{2.17}$$

Note that $\phi_{(+,\boldsymbol{k})}(t \mid t_+) = 0$ for $\boldsymbol{k} = (n, 0, 0)$, i.e. for all $t \geq t_+$ at least one partner is not susceptible.

A susceptible individual becomes infected at time t_+ if infection is transmitted to this individual through one of its n binding sites. Infection is transmitted at rate β. Therefore, the force of infection at time t_+, i.e. the rate at which a susceptible individual becomes infected at time t_+, equals $\beta n \frac{x_2}{\bar{x}}(t_+)$ and consequently the incidence at time t_+, i.e. the fraction of the population that becomes, per unit of time, infected at time t_+, equals

$$\beta n\left(\frac{x_2}{\bar{x}}\,\bar{x}^n\right)(t_+) = \beta n x_2 \bar{x}^{n-1}(t_+) \tag{2.18}$$

(recall that $\bar{x}^n$ is the fraction of the population that is susceptible).

Furthermore, an infectious individual that is infected at time t_+ is still infectious at time t if it does not recover in the period (t_+, t). Since the infectious period of an individual is assumed to be exponentially distributed with rate γ, the probability that this happens is

$$e^{-\gamma(t-t_+)}. \tag{2.19}$$

We then find an expression for the unconditional i-level probabilities $p_{(+,\boldsymbol{k})}(t)$ that a randomly chosen individual is in state $(+, \boldsymbol{k})$ at time t in terms of infectious binding site probabilities and the history of susceptible binding site probabilities:

$$p_{(+,\boldsymbol{k})}(t) = \int_{-\infty}^{t} e^{-\gamma(t-t_+)}\beta n x_2 \bar{x}^{n-1}(t_+)\phi_{(+,\boldsymbol{k})}(t \mid t_+)dt_+, \tag{2.20}$$

where $\phi_{(+,\boldsymbol{k})}(t \mid t_+)$ is given by (2.17). The i-level probabilities $p_{(+,\boldsymbol{k})}(t)$ are lifted to the p-level by (2.8).

In this way we can use infectious binding sites as building blocks for infectious individuals. We see that y and y^{e} explicitly depend on the dynamics of x through the boundary conditions (2.13) and the environmental variable Λ_+ (2.15). In addition, x_2 plays a role in determining the time of infection of an individual.

Remark 3. *Similar to the ODE system for $-$ individuals considered in Remark 2, one obtains the p-level ODE system by differentiation of* (2.20) *and use of* (2.16), (2.7) *and* (2.8). *In doing so, one obtains a system of* $1/2(n+1)(n+2)$ *ODE for the p-level fractions con-*

cerning individuals with a + disease status:

$$\begin{aligned}&\frac{dP_{(+,k_1,k_2,k_3)}}{dt}\\ =&\beta k_2 P_{(-,k_1,k_2,k_3)} - (\gamma k_2 + \gamma + \beta\Lambda_+ k_1)P_{(+,k_1,k_2,k_3)}\\ &+\gamma(k_2+1)P_{(+,k_1,k_2+1,k_3-1)} + \beta\Lambda_+(k_1+1)P_{(+,k_1+1,k_2-1,k_3)},\end{aligned}$$

$k_1 + k_2 + k_3 = n$, *with* Λ_+ *defined by* (2.6) *(compare with [76, eq. (13)]).*

In case of recovered individuals, one considers their binding sites and first conditions on time of infection t_+ and time of recovery t_*. Again one needs to distinguish between the exceptional and the non-exceptional binding sites. The dynamics of recovered binding sites are described by taking into account the mean field at distance one assumption for the mean number Λ_* of infectious partners of a susceptible partner of a recovered individual. Boundary conditions are given by the $y(t_* \mid t_+)$ and $y^{\mathrm{e}}(t_* \mid t_+)$ for non-exceptional and exceptional binding sites, i.e.

$$\begin{aligned}z_1^{\mathrm{e}}(t_* \mid t_+, t_*) &= 0, & z_1(t_* \mid t_+, t_*) &= y_1(t_* \mid t_+),\\ z_2^{\mathrm{e}}(t_* \mid t_+, t_*) &= y_2^{\mathrm{e}}(t_* \mid t_+), & z_2(t_* \mid t_+, t_*) &= y_2(t_* \mid t_+),\\ z_3^{\mathrm{e}}(t_* \mid t_+, t_*) &= y_3^{\mathrm{e}}(t_* \mid t_+), & z_3(t_* \mid t_+, t_*) &= y_3(t_* \mid t_+).\end{aligned}$$

The dynamics for z and z^{e} can be described by a system of ODE identical to the ODE systems for y and y^{e}, but with Λ_+ replaced by Λ_*. The environmental variable Λ_* is given by

$$\Lambda_*(t) = \sum_{\boldsymbol{m}} m_2 \frac{m_3 P_{(-,\boldsymbol{m})}(t)}{\sum_{\boldsymbol{k}} k_3 P_{(-,\boldsymbol{k})}(t)}. \tag{2.21}$$

By combining (2.21) with (2.8) and (2.7) we find

$$\Lambda_*(t) = (n-1)\frac{x_3(t)}{\bar{x}(t)}. \tag{2.22}$$

We find an expression for the probability $\psi_{(*,\boldsymbol{k})}(t \mid t_+, t_*)$ that a recovered individual, infected at time t_+ and recovered at time t_*, is in state $(*, \boldsymbol{k})$ at time $t \geq t_*$, in terms of z and z^{e} probabilities for recovered binding sites with the same reasoning as for $\phi_{(+,\boldsymbol{k})}(t \mid t_+)$ (one can simply replace ϕ by ψ, y_i by z_i, and y_i^{e} by z_i^{e} in (2.17)). Then, to arrive at an expression for the unconditional probability $p_{(*,\boldsymbol{k})}(t)$, we again need to take into account the incidence $\beta n x_2 \bar{x}^{n-1}(t_+)$ at t_+. The probability that recovery does not occur in the time interval (t_+, t_*) is given by $e^{-\gamma(t_*-t_+)}$ and the rate at which an infectious individual recovers is γ, therefore

$$\begin{aligned}&P_{(*,\boldsymbol{k})}(t) = p_{(*,\boldsymbol{k})}(t)\\ &= \int_{-\infty}^{t}\int_{-\infty}^{t_*} \gamma e^{-\gamma(t_*-t_+)}\beta n x_2 \bar{x}^{n-1}(t_+)\psi_{(*,\boldsymbol{k})}(t \mid t_+, t_*)dt_+ dt_*,\end{aligned} \tag{2.23}$$

where the first equality in (2.23) follows from (2.8).

2.5 The renewal equation for the Volz variable

So far we dealt with the SIR situation, where an individual becomes infectious immediately upon becoming infected and stays infectious for an exponentially distributed amount of time, with rate parameter γ, hence mean γ^{-1}. During the infectious period any susceptible partner is infected with rate (=probability per unit of time) β.

Here we incorporate randomness in infectiousness via a variable ξ taking values in a set Ω according to a distribution specified by a measure m on Ω. This sounds abstract at first, but hopefully less so if we mention that the SIR situation corresponds to

$$\begin{aligned} \Omega &= (0, \infty), \\ m(d\xi) &= \gamma e^{-\gamma \xi} d\xi, \end{aligned}$$

with ξ corresponding to the length of the infectious period. In this section we only consider the setting where the 'R' characteristic holds, i.e. after becoming infected, individuals can not become susceptible for infection any more.

In order to describe how the probability of transmission to a susceptible partner depends on ξ, we need the auxiliary variable τ corresponding to the 'age of infection', i.e. the time on a clock that starts when an individual becomes infected. As a key model ingredient we introduce

$$\begin{aligned} \pi(\tau, \xi) = {} & \text{the probability that transmission to a susceptible partner} \\ & \text{happens before } \tau, \text{ given } \xi. \end{aligned}$$

In the SIR example we have

$$\pi(\tau, \xi) = 1 - e^{-\beta \min(\tau, \xi)}.$$

It is important to note a certain asymmetry. On the one hand, there is dependence in the risk of infection of partners of an infectious individual u. Their risk of getting infected by u depends on the length of the infectious period of u (and, possibly, other aspects of infectiousness encoded in ξ). On the other hand, if u is susceptible, the risk that u itself becomes infected depends on the length of the infectious periods of its various infectious partners. But these partners are independent of one another when it comes to the length of their infectious period (see also [8, Section 2.3 'The pitfall of overlooking dependence']). In particular, the probability that an individual escapes infection from its partner, up to at least τ units of time after the partner became infected, equals

$$\mathcal{F}(\tau) = 1 - \int_{\Omega} \pi(\tau, \xi) m(d\xi). \tag{2.24}$$

For the Markovian SIR example (2.24) boils down to

$$\mathcal{F}(\tau) = \frac{\gamma}{\beta + \gamma} + \frac{\beta}{\beta + \gamma} e^{-(\beta + \gamma)\tau}, \tag{2.25}$$

a formula that can also be understood in terms of two competing events (transmission versus ending of the infectious period) that occur at respective rates β and γ.

As in [40] and earlier subsections, we consider a static configuration network with uniform degree distribution: every individual is connected to exactly n other individuals. At the end of this section we shall formulate the renewal equation for arbitrary degree distribution. In [40] an expression for R_0 and equations for both final size and the probability of a minor outbreak were derived. In addition, it was sketched how to formulate a nonlinear renewal equation for a scalar quantity, but the procedure is actually that complicated that the resulting equation was *not* written down.

The brilliant idea of Volz [93] is to focus on the variable $\theta(t)$ corresponding to the probability that along a randomly chosen partnership between individuals u and v *no* transmission occurred from v to u before time t, given that no transmission occurred from u to v (see also Fig. 5 for a schematic representation). Here one should think of 'probability of transmission' as being defined by π (and hence $\mathcal{F}$) and not require that the individual at the receiving end of the link is indeed susceptible (though, if it actually is, or has been, infectious, the condition of no transmission in the opposite direction is indeed a nontrivial condition).

Figure 5: Volz [93] focused on the variable $\theta(t)$ corresponding to the probability that along a randomly chosen partnership between individuals u and v *no* transmission occurred from v to u before time t, given that no transmission occurred from u to v.

The variable θ corresponds to $\bar{x}$ introduced in Section 2.1 and therefore we use that symbol also in this section. We reformulate (2.3) as

$$\begin{aligned}\bar{x}(t) = \text{prob}\{&\text{a binding site is susceptible at time } t \mid \text{its owner}\\ &\text{does not become infected through one of}\\ &\text{its other binding sites before time } t\}\end{aligned} \tag{2.26}$$

(see also Fig. 6). There is an underlying stochastic process in the definition for $\bar{x}$ that we have not carefully defined here. Yet we shall use the words from the definition to derive a consistency relation that takes the form of a nonlinear renewal equation for $\bar{x}(t)$. The renewal equation describes the stochastic process starting 'far back' in time when all individuals were still susceptible. A precise mathematical definition and an in-depth analysis of the stochastic process can be found in [84]. See [57, Sec. V] for a different way of specifying initial conditions.

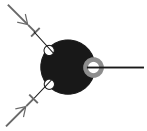

Figure 6: Schematic representation of $\bar{x}$. In this figure, the binding site under consideration is indicated in green. Its owner has three binding sites in total. It is given that no transmission occurs through its other two binding sites.

To derive the consistency relation for $\bar{x}(t)$ we shift our focus to the partner that occupies the binding site under consideration. For convenience we call the owner of the binding site under consideration u and the partner that occupies this binding site v. Then, given that u does not become infected through one of its $n-1$ other binding sites, u is susceptible at time t if (1) v is susceptible at time t or (2) v is not susceptible at time t but has not transmitted infection to u up to time t.

We begin by determining (1). Given its susceptible partner u, individual v is susceptible if its $n-1$ other binding sites are susceptible. Conditioning on its $n-1$ other binding sites not transmitting to v, a binding site of v is susceptible at time t with probability $\bar{x}(t)$. Therefore, given susceptibility of partner u, v is susceptible at time t with probability

$$\bar{x}(t)^{n-1}. \tag{2.27}$$

This just repeats the consistency relation (2.10) $x_1 = \bar{x}^{n-1}$ stating that the probability x_1 that a susceptible binding site is occupied by a susceptible partner is equal to the probability $\bar{x}^{n-1}$ that a partner of a susceptible individual is susceptible.

Next, suppose that v gets infected at some time $\eta < t$, then u is not infected by v before time t if no transmission occurs in the time interval of length $t-\eta$. The expression (2.27) has as a corollary that the probability per unit of time that v becomes infected at time η equals

$$-\frac{d}{d\eta}\big(\bar{x}(\eta)\big)^{n-1}.$$

Noting that the probability of no transmission to u in the time interval (η, t) is $\mathcal{F}(t-\eta)$ we conclude that necessarily,

$$\bar{x}(t) = \bar{x}(t)^{n-1} - \int_{-\infty}^{t} \left(\frac{d}{d\eta}\big(\bar{x}(\eta)\big)^{n-1}\right) \mathcal{F}(t-\eta)d\eta. \tag{2.28}$$

Finally, by integration by parts, we obtain the renewal equation

$$\bar{x}(t) = \mathcal{F}(\infty) - \int_{-\infty}^{t} \bar{x}(\eta)^{n-1}\mathcal{F}'(t-\eta)d\eta. \tag{2.29}$$

For a configuration network with general degree distribution (p_n) for the number of binding sites n of an individual, exactly the same arguments hold. But now there is random-

ness of n. This leads to the renewal equation (compare with (2.29))

$$\bar{x}(t) = \mathcal{F}(\infty) - \int_{-\infty}^{t} g(\bar{x}(\eta))\mathcal{F}'(t-\eta)d\eta, \tag{2.30}$$

with

$$g(x) := \frac{\sum_{n=1}^{\infty} np_n x^{n-1}}{\sum_{m=1}^{\infty} mp_m}.$$

The solution $\bar{x}(t) = 1$, $-\infty < t < \infty$, of (2.30) corresponds to the disease free situation. If we put $\bar{x}(t) = 1 - h(t)$ and assume h is small, we easily deduce that the linearized equation is given by

$$h(t) = -g'(1)\int_{-\infty}^{t} h(\eta)\mathcal{F}'(t-\eta)d\eta. \tag{2.31}$$

The corresponding Euler-Lotka characteristic equation reads

$$1 = -g'(1)\int_{0}^{\infty} e^{-\lambda\tau}\mathcal{F}'(\tau)d\tau. \tag{2.32}$$

If we evaluate the right hand side of (2.32) at $\lambda = 0$, we obtain

$$R_0 = g'(1)\big(1 - \mathcal{F}'(\infty)\big)$$

cf. [8, eq. (12.32), p. 294]. In short, the relevant characteristics of the initial phase of an epidemic outbreak are easily obtained from the linearized renewal equation (2.31) (see [96] for a study of the Malthusian parameter, i.e. the real root of (2.31)).

To derive an equation for the final size is even simpler, one takes the limit $t \to \infty$ in (2.30) to deduce

$$\bar{x}(\infty) = \mathcal{F}(\infty) + (1 - \mathcal{F}(\infty))g(\bar{x}(\infty)), \tag{2.33}$$

and next observes that the escape probability $s(\infty)$ is given by

$$s(\infty) = \sum_{n=1}^{\infty} p_n\big(\bar{x}(\infty)\big)^n$$

(to compare to [8, eqs. (12.36)-(12.38), p. 295] identify $\bar{q} = 1 - \mathcal{F}(\infty)$, $\pi = g(\bar{x}(\infty))$, and rewrite (2.33) as $\pi = g(1 - \bar{q} + \bar{q}\pi)$).

In the case that $\mathcal{F}$ is given by (2.25), the RE

$$\bar{x}(t) = \frac{\gamma}{\beta+\gamma} + \beta\int_{-\infty}^{t} g(\bar{x}(\eta))e^{-(\beta+\gamma)(t-\eta)}d\eta$$

can be transformed into an ODE for $\bar{x}$ by differentiation:

$$\bar{x}' = \beta g(\bar{x}) - (\beta+\gamma)\bar{x} + \gamma.$$

In the special case of Sections 2.1-2.4, we have $p_n = 1$ and $p_k = 0$ for all $k \neq n$ so $g(x) = x^{n-1}$ and we recover (2.11).

As explained in (O. Diekmann, M. Gyllenberg, J.A.J. Metz. Finite dimensional state representation of linear and nonlinear delay systems. *In preparation*), the natural generalization of (2.25) assumes that $\mathcal{F}$ is of the form

$$\mathcal{F}(\tau) = 1 - \int_0^\tau \boldsymbol{\beta} \cdot e^{\eta(\Sigma - \operatorname{diag} \boldsymbol{\beta})} V d\eta, \tag{2.34}$$

where, for some $m \in \mathbb{N}$, $\boldsymbol{\beta}$ and V are non-negative vectors in $\mathbb{R}^m$ while Σ is a Positive-Off-Diagonal (POD) $m \times m$ matrix. If $\mathcal{F}$ is given by (2.34), the variable

$$Q(t) := \int_{-\infty}^t g(\bar{x}(\eta)) e^{(t-\eta)(\Sigma - \operatorname{diag} \boldsymbol{\beta})} V d\eta$$

satisfies the ODE

$$\frac{dQ}{dt} = (\Sigma - \operatorname{diag} \boldsymbol{\beta})Q + g(\bar{x})V \tag{2.35}$$

and, since (2.30) can be rewritten as

$$\bar{x} = \mathcal{F}(\infty) - \boldsymbol{\beta} \cdot Q, \tag{2.36}$$

the equation (2.35) is a closed system once we replace $\bar{x}$ at the right hand side of (2.35) by the right hand side of (2.36)

So one can solve/analyze (2.35) and next use the identity (2.36) to draw conclusions about $\bar{x}$. We conclude that various ODE systems as derived in [50] are subsumed in (2.30) and can be deduced from (2.30) by a special choice of $\mathcal{F}$ and differentiation.

3 Part II: dynamic network without demographic turnover

In Section 2, only one environmental variable Λ_- is involved in the specification of the dynamics of the susceptible binding sites. In dynamic networks, additional environmental variables play a role. Notably, we have to specify the (probability distribution of the) disease status of a new partner. Before formulating the model for susceptible binding sites, we first consider the network itself in Section 3.1. This is needed in order to determine the appropriate 'far past' conditions of the susceptible binding site system.

In Section 3.2, the model formulation is divided into three subsections. First, we formulate the model in terms of susceptible binding site probabilities x by following the scheme of five steps presented in Section 2.2. This allows us to express in terms of x those environmental variables that are defined in terms of susceptible p-level fractions $P_{(-,\boldsymbol{k})}$. We then consider infectious and recovered binding site systems and these allow us to express the other environmental variables in terms of (the history of) x as well.

3.1 Network dynamics

Binding sites are either free or occupied. We denote the fraction of free binding sites in the population by F. We assume that a binding site that is free becomes occupied at rate ρF, while an occupied binding site becomes free at rate σ. Similar to Chapter 2 (set $\mu = 0$), we find that F satisfies the ODE

$$\frac{dF}{dt} = -\rho F^2 + \sigma(1 - F).$$

So we find that F converges to a constant for $t \to \infty$. Therefore, we assume that the fraction of free binding sites is constant, and this constant is again denoted by the symbol F. Then F satisfies

$$F = \frac{\sigma}{\rho F + \sigma}. \tag{3.1}$$

Although we could give an explicit expression in terms of σ and ρ for F, we prefer to state the more useful identity (3.1) that, viewed as an equation, has F as its unique positive root. The network structure, although dynamic, is stable. A randomly chosen binding site (in the pool of all binding sites) is free with probability F and occupied by a partner with probability $1 - F$. Later on we shall use that, given that a binding site is free with probability F at time τ, the probability that a binding site is free at time $\xi + \tau$ is F (and the probability that it is occupied at time $\xi + \tau$ is $1 - F$).

Finally, later on in Section 3.2.2, we also need the probability $\varphi_1(\xi)$ that a binding site is free at time $\xi + \tau$ if it is occupied at time τ. Note that, by the Markov property, this probability only depends on the length ξ of the time interval. Since $\varphi_1(\xi)$ is the unique solution of the initial value problem:

$$\begin{aligned} \varphi_1' &= -\rho F \varphi_1 + \sigma(1 - \varphi_1), \\ \varphi_1(0) &= 0, \end{aligned}$$

we have

$$\varphi_1(\xi) = \frac{\sigma}{\rho F + \sigma}\left(1 - e^{-(\rho F + \sigma)\xi}\right) = F\left(1 - e^{-(\rho F + \sigma)\xi}\right) \tag{3.2}$$

where we used (3.1) in the second equality.

3.2 Model formulation

3.2.1 Susceptibles

We describe the dynamics of susceptible binding sites in terms of x-probabilities. Consider a susceptible binding site and suppose its owner does not become infected through one of its other $n - 1$ binding sites for the period under consideration. An occupied binding site (in states 1, 2, or 3) becomes free if it loses its partner (corresponding to a transition to state 0). This occurs at rate σ. A binding site that is free, i.e. a binding site in

state 0, can acquire a partner. The rate at which this occurs is ρF where F is the fraction of free binding sites defined by (3.1). Free binding sites either have a susceptible, infectious, or recovered owner. So there are three additional environmental variables, viz. the fraction of binding sites that are free and have disease status d (i.e. having owners with disease status d), we denote these by F_d, $d \in \{-, +, *\}$. Then $F = F_- + F_+ + F_*$. Finally, there are infection and recovery events that can cause state transitions (as in the case of a static network in Section 2).

Long ago in time, by assumption, all individuals (and therefore binding sites) are susceptible. In accordance with Section 3.1 the fraction of free and susceptible binding sites is equal to F and the fraction of susceptible binding sites occupied by susceptible partners is equal to $1 - F$, i.e. we have 'far past' conditions

$$x_0(-\infty) = F, \quad x_1(-\infty) = 1 - F, \quad x_2(-\infty) = 0 = x_3(-\infty). \tag{3.3}$$

Let $\boldsymbol{F} = (F_-, F_+, F_*)$. The environmental variables $\boldsymbol{F}$ and Λ_- are p-level quantities that we have yet to specify. Putting together the various assumptions described above, the dynamics of x is governed by the system:

$$\frac{dx(t)}{dt} = M\big(\boldsymbol{F}(t), \Lambda_-(t)\big)x(t), \tag{3.4}$$

with 'far past' conditions (3.3), and

$$M(\boldsymbol{F}, \Lambda_-) = \begin{pmatrix} -\rho F & \sigma & \sigma & \sigma \\ \rho F_- & -(\beta\Lambda_- + \sigma) & 0 & 0 \\ \rho F_+ & \beta\Lambda_- & -(\beta + \sigma + \gamma) & 0 \\ \rho F_* & 0 & \gamma & -\sigma \end{pmatrix}. \tag{3.5}$$

Next, in *step 2*, we define the environmental variables in terms of p-level fractions. The definition (2.6) of Λ_- in terms of p-level fractions carries over. We define the fractions of free binding sites in terms of p-level fractions as follows:

$$F_d(t) = \frac{1}{n}\sum_{\boldsymbol{k}}(n - k_1 - k_2 - k_3)P_{(d,\boldsymbol{k})}(t), \tag{3.6}$$

where the sum is over all possible configurations of $\boldsymbol{k}$ with $0 \le k_1 + k_2 + k_3 \le n$.

In *step 3* we define the i-level probabilities $p_{(-,\boldsymbol{k})}(t)$ in terms of the x probabilities by using the conditional independence of binding sites:

$$p_{(-,\boldsymbol{k})}(t) = \frac{n!}{k_0!\,k_1!\,k_2!\,k_3!}\left(x_0^{k_0}x_1^{k_1}x_2^{k_2}x_3^{k_3}\right)(t). \tag{3.7}$$

As in the static network case I, the i-level probabilities coincide with the p-level fractions, i.e. (2.8) holds. This is *step 4* in our model formulation.

Then, in *step 5*, we can express the environmental variables Λ_- and F_- in terms of x-probabilities. By combining (3.7) with (2.8) and (2.6), we again find (2.4) to hold

(only now the x are defined by the system of ODE (3.4)). By combining (3.7) with (2.8) and (3.6) we find that

$$F_-(t) = x_0(t)\bar{x}(t)^{n-1}, \tag{3.8}$$

exactly as the interpretations of F_- and x would suggest.

Before we can specify F_+ and F_* in terms of (the history of) x we need to define p-level fractions $P_{(+,\boldsymbol{k})}(t)$ and $P_{(*,\boldsymbol{k})}(t)$. We do so in the next section where we turn to infectious and recovered binding site systems.

3.2.2 After susceptibility is lost

If an individual becomes infected at time t_+, the binding site through which infection is transmitted is from that point on 'exceptional'. Then, given that its owner became infected at time t_+ and that it does not recover for the time under consideration, we consider an infectious binding site. Let $y_i^{\mathrm{e}}(t \mid t_+)$ denote the probability that the exceptional binding site is in state i at time t and $y_i(t \mid t_+)$ this same probability for a non-exceptional binding site.

As in Section 2.4, the exceptionalness plays a role only in the states at epidemiological birth, i.e. at time t_+. The exceptional binding site is with probability one in state 2 at time t_+. The states of all other binding sites are distributed according to $x(t_+)/\bar{x}(t_+)$. Therefore, we put boundary conditions

$$\begin{aligned}
y_0^{\mathrm{e}}(t_+ \mid t_+) &= 0, \qquad & y_0(t_+ \mid t_+) &= x_0(t_+)/\bar{x}(t_+),\\
y_1^{\mathrm{e}}(t_+ \mid t_+) &= 0, \qquad & y_1(t_+ \mid t_+) &= x_1(t_+)/\bar{x}(t_+),\\
y_2^{\mathrm{e}}(t_+ \mid t_+) &= 1, \qquad & y_2(t_+ \mid t_+) &= x_2(t_+)/\bar{x}(t_+),\\
y_3^{\mathrm{e}}(t_+ \mid t_+) &= 0, \qquad & y_3(t_+ \mid t_+) &= x_3(t_+)/\bar{x}(t_+).
\end{aligned}$$

Since the individual does not recover in the period under consideration, the infectious binding sites behave independently of one another.

The dynamics of y^{e} and y are both governed by the system

$$\frac{dy(t \mid t_+)}{dt} = M_+\big(\boldsymbol{F}(t), \Lambda_+(t)\big)y(t \mid t_+), \tag{3.9}$$

with

$$M_+(\boldsymbol{F}, \Lambda_+) = \begin{pmatrix} -\rho F & \sigma & \sigma & \sigma \\ \rho F_- & -(\beta\Lambda_+ + \sigma) & 0 & 0 \\ \rho F_+ & \beta\Lambda_+ & -(\sigma+\gamma) & 0 \\ \rho F_* & 0 & \gamma & -\sigma \end{pmatrix},$$

Note that there is no rate γ of leaving the infectious state as we condition on the owner remaining infectious in the period under consideration. Furthermore, note that, contrary to the network case I of Section 2.4, the exceptional binding site can lose its epidemiological parent by separation. Therefore $y_1^{\mathrm{e}}(t \mid t_+) > 0$ for $t > t_+$.

Next, similarly to Section 2.4, by combinatorics (but now probabilities y_0^{e} and y_1^{e} are not equal to zero for $t \geq t_+$), we find that the probability $\phi_{(+,\boldsymbol{k})}(t \mid t_+)$ that an individual, infected at time t_+, is in state $(+,\boldsymbol{k})$ at time $t \geq t_+$ is given by

$$\begin{aligned}\phi_{(+,\boldsymbol{k})}(t \mid t_+) = \\ \frac{n!}{k_0!\,k_1!\,k_2!\,k_3!}\Big(\frac{k_0}{n}\,y_0^{\mathrm{e}}\,y_0^{k_0-1}y_1^{k_1}y_2^{k_2}y_3^{k_3} + \frac{k_1}{n}\,y_1^{\mathrm{e}}\,y_0^{k_0}y_1^{k_1-1}y_2^{k_2}y_3^{k_3} \\ + \frac{k_2}{n}\,y_2^{\mathrm{e}}\,y_0^{k_0}y_1^{k_1}y_2^{k_2-1}y_3^{k_3} + \frac{k_3}{n}\,y_3^{\mathrm{e}}\,y_0^{k_0}y_1^{k_1}y_2^{k_2}y_3^{k_3-1}\Big)(t \mid t_+). \qquad (3.10)\end{aligned}$$

The probability $P_{(+,\boldsymbol{k})}(t)$ that a randomly chosen individual is in state $(+,\boldsymbol{k})$ at time t is obtained by taking into account the time of infection t_+ and the probability (2.19) that an individual has not recovered time $t - t_+$ after infection. The definition (2.18) for the incidence carries over (but now with the x defined by the ODE system (3.4)). So

$$\begin{aligned}P_{(+,\boldsymbol{k})}(t) &= p_{(+,\boldsymbol{k})}(t) \\ &= \int_{-\infty}^{t} e^{-\gamma(t-t_+)}\beta n x_2 \bar{x}^{n-1}(t_+)\phi_{(+,\boldsymbol{k})}(t \mid t_+)dt_+. \qquad (3.11)\end{aligned}$$

By combining (2.8) and the expression (3.11) for $P_{(+,fOff\boldsymbol{k})}$ in terms of y and y^{e} we can redefine F_+ in terms of the history of x as we will show now. First of all, combining (3.10), (3.11) and (3.6) we express F_+ in terms of y and y^{e}:

$$\begin{aligned}F_+(t) = \frac{1}{n}\int_{-\infty}^{t} e^{-\gamma(t-t_+)}\beta n x_2 \bar{x}^{n-1}(t_+) \\ \left(y_0^{\mathrm{e}}\,\bar{y}^{n-1} + (n-1)\bar{y}^{\mathrm{e}}\,y_0\,\bar{y}^{n-2}\right)(t \mid t_+)dt_+. \qquad (3.12)\end{aligned}$$

where $\bar{y} = y_0 + y_1 + y_2 + y_3$ and $\bar{y}^{\mathrm{e}} = y_0^{\mathrm{e}} + y_1^{\mathrm{e}} + y_2^{\mathrm{e}} + y_3^{\mathrm{e}}$. Since y^{e} and y are probability vectors,

$$\bar{y}^{\mathrm{e}}(t \mid t_+) = 1 = \bar{y}(t \mid t_+).$$

Next, we consider the probabilities y_0, y_0^{e}. Note that

$$y_0^{\mathrm{e}}(t \mid t_+) = \varphi_1(t - t_+),$$

with φ_1 given by (3.2). The dynamics of y_0 are described in terms of y_0 and the history of $x_0/\bar{x}$ (by means of the boundary condition). We can solve for y_0. This yields

$$y_0(t \mid t_+) = \varphi_1(t - t_+) + \frac{x_0}{\bar{x}}(t_+)e^{-(\rho F+\sigma)(t-t_+)}$$

(note that time of infection t_+ matters in this probability and not only the length $t - t_+$ of the time interval). We can further simplify (3.12) to obtain

$$\begin{aligned}F_+(t) = \frac{1}{n}\int_{-\infty}^{t} e^{-\gamma(t-t_+)}\beta n x_2 \bar{x}^{n-1}(t_+)\Big\{\varphi_1(t - t_+) \\ + (n-1)\left(\varphi_1(t - t_+) + \frac{x_0}{\bar{x}}(t_+)e^{-(\rho F+\sigma)(t-t_+)}\right)\Big\}dt_+, \qquad (3.13)\end{aligned}$$

which only depends on the model parameters and past probabilities x_i for susceptible binding sites.

We can use the consistency condition for the total fraction of free binding sites:

$$F_*(t) = F - F_-(t) - F_+(t). \tag{3.14}$$

to express F_* in terms of the history of x (use (3.8) for F_- and (3.13) for F_+). So this specifies all environmental variables for the susceptible binding site system x in terms of (the history of x).

Next, similar to case I of Section 2.4, we consider recovered individuals and their binding sites. Suppose that the infectious individual, that was infected at time t_+, recovers at time t_*. After recovery, we still distinguish between the exceptional binding site and the $n-1$ other binding sites. We introduce probabilities $z_i^{\mathrm{e}}(t \mid t_+, t_*)$ and $z_i(t \mid t_+, t_*)$ for recovered binding sites. The y and y^{e} probabilities yield the conditions for z and z^{e} at time $t = t_*$, i.e.

$$\begin{aligned}
z_0^{\mathrm{e}}(t_* \mid t_+, t_*) &= y_1^{\mathrm{e}}(t_* \mid t_+), \qquad & z_0(t_* \mid t_+, t_*) &= y_1(t_* \mid t_+),\\
z_1^{\mathrm{e}}(t_* \mid t_+, t_*) &= y_1^{\mathrm{e}}(t_* \mid t_+), \qquad & z_1(t_* \mid t_+, t_*) &= y_1(t_* \mid t_+),\\
z_2^{\mathrm{e}}(t_* \mid t_+, t_*) &= y_2^{\mathrm{e}}(t_* \mid t_+), \qquad & z_2(t_* \mid t_+, t_*) &= y_2(t_* \mid t_+),\\
z_3^{\mathrm{e}}(t_* \mid t_+, t_*) &= y_3^{\mathrm{e}}(t_* \mid t_+), \qquad & z_3(t_* \mid t_+, t_*) &= y_3(t_* \mid t_+).
\end{aligned}$$

The dynamics of z and z^{e} are described by the system of ODE for y and y^{e}, with the mean field at distance one quantity Λ_+ replaced by Λ_* where Λ_* is defined in terms of p-level fractions by (2.21) and hence is given by (2.22) in terms of x-probabilities.

Let $\psi_{(*,\boldsymbol{k})}(t \mid t_+, t_*)$ denote the probability that a recovered individual is in state $(*, \boldsymbol{k})$ given that it was infected at time t_+ and recovered at time t_*. Then $\psi_{(*,\boldsymbol{k})}(t \mid t_+, t_*)$ can be expressed in terms of z and z^{e} by replacing ϕ in (3.10) by ψ, y_i by z_i, and y_i^{e} by z_i^{e}.

The unconditional probability $p_{(*,\boldsymbol{k})}(t)$ is then obtained by taking into account time of infection t_+ and recovery time t_*:

$$\begin{aligned}
&p_{(*,\boldsymbol{k})}(t)\\
&= \int_{-\infty}^{t} \int_{-\infty}^{t_*} \gamma e^{-\gamma(t_*-t_+)} \beta n x_{\boldsymbol{2}} \bar{x}^{n-1}(t_+) \psi_{(*,\boldsymbol{k})}(t \mid t_+, t_*) dt_+ dt_*,
\end{aligned} \tag{3.15}$$

which, by relation (2.8), is equal to the p-level fraction $P_{(*,\boldsymbol{k})}(t)$. Note that we can also use this definition of $P_{(*,\boldsymbol{k})}(t)$ to define F_* in terms of x similar to the way we did for F_+ in (3.13).

3.2.3 One renewal equation or a system of six ODE, whatever you like

We ended the model formulation in Section 3.2.1 by defining the environmental variables Λ_- and F_- in terms of x (eqs. (2.4) and (3.8)). Subsequently, in Section 3.2.2, by considering infectious binding site probabilities y, and y^{e}, we also defined F_+ and F_* in terms of

x (eqs. (3.13) and (3.14)). Combining these formulas, we find that the system describing the dynamics of susceptible binding sites is given by:

$$\begin{aligned} x_0' &= -\rho F x_0 + \sigma(x_1 + x_2 + x_3) \\ x_1' &= \rho x_0^2 \bar{x}^{n-1} - \Big(\sigma + \beta(n-1)\frac{x_2}{\bar{x}}\Big) x_1 \\ x_2' &= \rho F_+ x_0 + \beta(n-1)\frac{x_2}{\bar{x}} x_1 - (\sigma + \beta + \gamma) x_2 \\ x_3' &= \rho\big(F - x_0\bar{x}^{n-1} - F_+\big)x_0 + \gamma x_2 - \sigma x_3, \end{aligned} \tag{3.16}$$

with F_+ given by (3.13) and with 'far past' condition

$$x_0(-\infty) = F, \quad x_1(-\infty) = 1 - F, \quad x_2(-\infty) = 0 = x_3(-\infty). \tag{3.17}$$

The ODE (3.16) for x together with the expression (3.13) for F_+ yields a closed system of five equations. By substituting expression (3.13) in system (3.16), one can view (3.16) as a system of four delay differential equations. The dynamics of the $1/6(n+1)(n+2)(n+3)$ i-level probabilities (hence p-level fractions) $p_{(-,\boldsymbol{k})}$ for susceptible individuals are fully determined by this set of four delay differential equations (regardless of n).

Alternatively, we can view the solution $x(t)$ of (3.16)-(3.17) as fully determined by $F_+|_{(-\infty,t]}$. Interpreting x_2, $\bar{x}$, and x_0 at the right hand side of (3.13) in this manner, we arrive at the conclusion that the dynamics are fully determined by a single renewal equation for F_+.

One may prefer a system consisting only of ODE rather than a delay system. We can in fact reason directly in terms of the interpretation to derive an ODE for F_+. In order to do so, we first consider the fraction $I(t) = \sum_{\boldsymbol{k}} P_{(+,\boldsymbol{k})}$ of infectious binding sites in the population. This fraction decreases when infecteds recover. Infecteds recover at a constant rate γ. The fraction I increases when a susceptible individual becomes infected so there is the positive term (2.18) in the ODE for I (combine (3.7) with (2.8) and (2.18), the x are defined by the ODE system (3.4))). We find that the dynamics of I are described by the following ODE:

$$\frac{dI}{dt} = \beta n x_2 \bar{x}^{n-1} - \gamma I, \tag{3.18}$$

with 'far past' condition $I(-\infty) = 0$. Next, we consider F_+. Any infectious owner recovers at constant rate γ. In addition, partnership formation and separation affect the fraction of free infectious binding sites. There is a rate ρF at which free binding sites become occupied. The fraction of infectious binding sites that are occupied is given by $I - F_+$ and the rate at which these binding sites become free is σ. Then, finally, a susceptible individual with k_2 infectious partners becomes infected at rate βk_2, taking into account all $0 \leq k_2 \leq n$ we find probability per unit of time $\beta n x_2 \bar{x}^{n-1}$ at which a susceptible individual becomes infected. The probability that a non-exceptional binding site is free and susceptible upon infection is $x_0/\bar{x}$, so the expected fraction of free binding

sites created upon infection of a susceptible individual is $\frac{1}{n}(n-1)x_0/\bar{x}$. Hence there is a flow $\beta(n-1)x_0x_2\bar{x}^{n-2}$ into F_+. We have the following ODE for F_+:

$$\frac{dF_+}{dt} = \beta(n-1)x_0x_2\bar{x}^{n-2} - (\rho F + \gamma)F_+ + \sigma(I - F_+), \tag{3.19}$$

with 'far past' condition $F_+(-\infty) = 0$.

Alternatively, we can derive the ODE (3.19) for F_+ by differentiating (3.13) with respect to t. Note that we can express I in terms of x by first expressing it in terms of y and y^e (similar to F_+ in Section 3.2.2). This yields $I(t) = \int_{-\infty}^{t} e^{-\gamma(t-t_+)}\beta n x_2\bar{x}^{n-1}(t_+)dt_+$.

The combination of (3.16) with (3.18) and (3.19) yields a six-dimensional closed system of ODE. (Compare with the slightly different but related network model called the 'dormant contacts' model of [50]. Presumably (3.16), (3.18), (3.19) is a transformed but equivalent version of their system (3.11)-(3.16).)

Both (3.13) and (3.16)-(3.19) can be used to represent the system. In terms of the number of equations, it does not matter too much which system one considers. In the first case, one renewal equation is needed compared to six ODE in the second case. In both formulations one can determine r and R_0 with not too much effort. In Section 3.3 below, we will use a pragmatic mixture. This gives us a way of determining r and R_0 that prepares for the characterization of r and R_0 in case III in Section 4.3 (where a model formulation in terms of only ODE becomes troublesome).

3.3 The beginning and end of an epidemic: R_0, r and final size

First, just as in case I, the final size is given by

$$1 - \bar{x}(\infty)^n.$$

But while in case I we derived a simple scalar equation for $\bar{x}(\infty)$ ((2.12) or (2.33)), depending explicitly on the parameters, we did not, despite fanatical efforts, manage to derive such an equation from the implicit characterization by (3.16), (3.18), (3.19); see also Appendix A.

Next, in the rest of this section, we use the binding site level system (3.16)-(3.19) to consider the beginning of an epidemic and determine R_0 and r. The point here is not only to use (3.16)-(3.19) to find threshold parameters but to find threshold parameters with their usual interpretation of R_0 and r.

Using the same arguments as in network case I of Section 2, we find that a threshold parameter for the disease free steady state of system (3.16)-(3.19) on the binding site level is also a threshold parameter for the disease free steady state of the p-level system.

The disease free steady state of (3.16) is given by $\tilde{x}_0 = F$, $\tilde{x}_1 = 1 - F$, $\tilde{x}_2 = 0 = \tilde{x}_3$. Linearization in this state yields a decoupled system of equations for the linearized x_2 and F_+ equations. We let $\hat{x}_2$ and $\hat{F}_+$ denote the variables in the linearization in the disease free steady state. Note that, in the disease free steady state $\tilde{y}_0(t \mid t_+) = \varphi_1(t - t_+) + Fe^{-(\rho F+\sigma)(t-t_+)} = F$, i.e. in the disease free steady state, the probability that

an infectious binding site is free at time t given that it is free at time t_+ is equal to the probability F that a randomly chosen binding site is free. Then

$$\begin{aligned}\hat{x}_2' &= \rho F \hat{F}_+ + \beta(n-1)(1-F)\hat{x}_2 - (\sigma+\beta+\gamma)\hat{x}_2 \\ \hat{F}_+(t) &= \int_0^\infty e^{-\gamma\xi}\beta\hat{x}_2(t-\xi)\big(\varphi_1(\xi)+(n-1)F\big)d\xi \end{aligned} \tag{3.20}$$

which can be viewed as a linear delay differential equation for $\hat{x}_2$. In order to obtain an informative version of the corresponding characteristic equation, we rewrite it as a renewal equation for $\hat{x}_2$.

Variation of constants for the ODE for $\hat{x}_2$ yields:

$$\begin{aligned}\hat{x}_2(t) &= \int_{-\infty}^t e^{-(\sigma+\beta+\gamma)(t-\xi)}\left(\rho F\hat{F}_+(\xi)+\beta(n-1)(1-F)\hat{x}_2(\xi)\right)d\xi \\ &= \int_0^\infty e^{-(\sigma+\beta+\gamma)\xi}\left(\rho F\hat{F}_+(t-\xi)+\beta(n-1)(1-F)\hat{x}_2(t-\xi)\right)d\xi.\end{aligned}$$

Substituting (3.20) into this expression yields the renewal equation for $\hat{x}_2$:

$$\begin{aligned}\hat{x}_2(t) &= \int_0^\infty e^{-(\sigma+\beta+\gamma)\xi}\Big\{\rho F\int_0^\infty e^{-\gamma\eta}\beta\hat{x}_2(t-\xi-\eta) \\ &\qquad \big(\varphi_1(\eta)+(n-1)F\big)d\eta+\beta(n-1)(1-F)\hat{x}_2(t-\xi)\Big\}d\xi \\ &= \int_0^\infty \hat{x}_2(t-\xi)k(\xi)d\xi,\end{aligned}$$

with

$$\begin{aligned}k(\xi) &= \beta e^{-(\sigma+\beta+\gamma)\xi}(n-1)(1-F) \\ &\quad + \int_0^\xi \beta e^{-(\sigma+\beta+\gamma)\eta}e^{-\gamma(\xi-\eta)}\rho F\big(\varphi_1(\xi-\eta)+(n-1)F\big)d\eta\end{aligned}$$

(where the rearrangement of the terms in the integrals is in preparation for the interpretation). Next, we substitute the ansatz $\hat{x}_2(t)=e^{\lambda t}$, and obtain the characteristic equation

$$1 = \int_0^\infty e^{-\lambda\xi}k(\xi)d\xi, \tag{3.21}$$

There is a unique real root to (3.21) and this root is by definition the Malthusian parameter r. We define $R_0 = \int_0^\infty k(\xi)d\xi$. Then sign($r$)=sign($R_0-1$), and we find that R_0 is a threshold parameter with threshold value one for the stability of the disease free steady

state, with $R_0 = \int_0^\infty k(\xi)d\xi$ equal to

$$\begin{aligned}
&\int_0^\infty \beta e^{-(\sigma+\beta+\gamma)\xi}(n-1)(1-F)d\xi \\
&+ \int_0^\infty \int_0^\xi \beta e^{-(\sigma+\beta+\gamma)\eta} e^{-\gamma(\xi-\eta)} \rho F\big(\varphi_1(\xi-\eta) + (n-1)F\big) d\eta\, d\xi \\
=& \int_0^\infty \beta e^{-(\sigma+\beta+\gamma)\xi} d\xi \\
&\qquad \left\{(n-1)(1-F) + \int_0^\infty e^{-\gamma\tau}\rho F\big(\varphi_1(\tau) + (n-1)F\big)d\tau\right\} \qquad (3.22)
\end{aligned}$$

We can evaluate the integrals and find an explicit expression for R_0. However, the interpretation is easier in the form it is written now.

First of all, consider a newly infected individual u. Individual u transmits infection to a susceptible partner with probability $\int_0^\infty \beta e^{-(\sigma+\beta+\gamma)\xi} d\xi = \beta/(\beta+\sigma+\gamma)$. By multiplying this probability with the expected number of susceptible partners u has at epidemiological birth plus the expected number of susceptible partners u acquires during its infectious period after epidemiological birth, we obtain R_0. As we will explain now, these are exactly the two terms in $\{\cdots\}$ of (3.22).

The mean number of susceptible partners of u *at* epidemiological birth is $(n-1)(1-F)$ (note that, in addition to the susceptible partners, u has $(n-1)F$ free and 1 exceptional binding site). This is the first term in $\{\cdots\}$ of (3.22). We are left with determining the expected number of susceptible partners u acquires *after* epidemiological birth. This goes as follows. At time τ after u became infected, u has not recovered yet with probability $e^{-\gamma\tau}$. The exceptional binding site of u is free at time τ with probability $\varphi_1(\tau)$ (see (3.2)). Each of the $n-1$ non-exceptional binding sites of u are free with probability F regardless of whether they were free or occupied at epidemiological birth (recall Section 3.1). Note that a free binding site becomes occupied by a susceptible partner at rate ρF (at the beginning of the epidemic). Integrating over all possible lengths $\tau > 0$ of the infectious period, we find that $\int_0^\infty e^{-\gamma\tau}\rho F\big(\varphi_1(\tau)+(n-1)F\big)d\tau$ is the expected number of additional susceptible partners of u in its infectious period after epidemiological birth.

Note that we made the distinction of the susceptible partners *at* and *after* epidemiological birth of u but what really matters is the *total* number of susceptible partners in the infectious period of u. So really, we did not need to make any distinction between at and after epidemiological birth. But this distinction is essential in Section 4.3 of case III. The distinction here serves both to illustrate this difference with case III and as a preparation for case III.

Finally, in the same spirit, we would like to mention that rather than taking the perspective of an infectious individual/binding site, we can also take the perspective of a susceptible binding sites 'at risk' of infection, i.e. susceptible binding sites occupied by infectious partners, and interpret R_0 in that way. In the present context this does not change much. Therefore we refrain from elaborating. We leave this for Section 4.3 of case III where this different perspective leads to a major simplification compared to the 'standard' perspective of infectious binding sites that we took here.

4 Part III: dynamic network with demography

In this part, the network is not only dynamic due to partnership formation and separation but also due to demographic turnover. We assume that there is a constant per capita death rate μ and a constant population birth rate so that the population size is in equilibrium and the age of individuals is exponentially distributed with parameter μ. At birth, an individual does not have any partners. Details are presented in Chapter 2.

4.1 Network dynamics

In a world with demographic turnover, next to calendar time, also age matters. We keep track of both age a and time of birth t_b of an individual (calendar time is then given by $t = a + t_b$). When we speak about the age and time of birth of a binding site, we mean the age and time of birth of its owner. Often, we assume that the owner of a binding site does not die in the period under consideration. By assumption, at age zero, a binding site is free. A free binding site becomes occupied at rate ρF where F denotes the total fraction of free binding sites in the population. This F is assumed to be constant (see Chapter 2 for the justification) and satisfies

$$F = \frac{\sigma + 2\mu}{\rho F + \sigma + 2\mu} \tag{4.1}$$

(compare with (3.1)). If the binding site is occupied, then it becomes free at rate $\sigma + \mu$ where σ and μ represent separation and death of partner, respectively.

In this section we will also make use of the following binding site probabilities (where, as usual, we condition on the owner not dying in the period under consideration). We let $\varphi_0(a)$ denote the probability that a binding site is free at age $a + \alpha$, given that it was free at age α, and $\varphi_1(a)$ denotes the probability that a binding site is free at age $a + \alpha$, given that it is occupied at age α. Note that, by the Markov property, these probabilities only depend on the time interval a (recall that F is constant). The dynamics of φ_i as a function of a is described by

$$\frac{d\varphi_i}{da} = -\rho F \varphi_i + (\sigma + \mu)(1 - \varphi_i),$$

with initial conditions, respectively,

$$\varphi_0(0) = 1, \qquad \varphi_1(0) = 0.$$

The explicit expressions for the φ_i are given by

$$\varphi_0(a) = \frac{\sigma + \mu}{\rho F + \sigma + \mu} + \frac{\rho F}{\rho F + \sigma + \mu} e^{-(\rho F + \sigma + \mu)a}, \tag{4.2}$$

$$\varphi_1(a) = \frac{\sigma + \mu}{\rho F + \sigma + \mu} \left(1 - e^{-(\rho F + \sigma + \mu)a}\right). \tag{4.3}$$

See also (3.4) of Chapter 2 (where $\epsilon(a)$ can be identified with $1-\varphi_0(a)$) and (C.16) of Chapter 3 (where $\epsilon_0(t)$ and $\epsilon_1(t)$ can be identified with $1-\varphi_0(t)$ and $1-\varphi_1(t)$, respectively).

Furthermore, we have the identity

$$F=\int_0^\infty \mu e^{-\mu a}\varphi_0(a)da \tag{4.4}$$

(use (4.1)), expressing that a randomly chosen binding site is free with probability F. So, according to Bayes' Theorem, the probability density function of the age of (the owner of) a free binding site is given by

$$\pi_0(a)=\frac{\mu e^{-\mu a}\varphi_0(a)}{F}. \tag{4.5}$$

Similarly, the probability density function of the age of (the owner of) a randomly chosen occupied binding site is

$$\pi_1(a)=\frac{\mu e^{-\mu a}\big(1-\varphi_0(a)\big)}{1-F}. \tag{4.6}$$

(in view of the derivation of a formula for R_0 in Section 4.3 below, we remark that π_0 and π_1 should be compared to probability distributions q and Q, respectively, in Chapter 3; the difference is that q and Q concern the number of partners while π_0 and π_1 concern the age; the probability distributions, however, provide the same information).

4.2 Model formulation

4.2.1 Susceptibles

Demography does not give rise to any additional environmental variables, we still deal with the mean field at distance one variable Λ_-, and the fractions F_d of free binding sites with disease status d, $d\in\{-,+,*\}$.

We follow the steps 1-5 of Section 2.2. In *step 1* we consider x-probabilities. Consider a susceptible binding site, born at time t_b, and suppose that its owner, for the period under consideration, does not die and does not become infected through one of its other $n-1$ binding sites. The dynamics of x as a function of age are described by the following system of equations:

$$\frac{dx(a\mid t_b)}{da}=M\big(\boldsymbol{F}(t_b+a),\Lambda_-(t_b+a)\big)x(a\mid t_b), \tag{4.7}$$

with $M(\boldsymbol{F},\Lambda_-)$ given by

$$\begin{pmatrix} -\rho F & \sigma+\mu & \sigma+\mu & \sigma+\mu\\ \rho F_- & -(\beta\Lambda_-+\sigma+\mu) & 0 & 0\\ \rho F_+ & \beta\Lambda_- & -(\beta+\sigma+\mu+\gamma) & 0\\ \rho F_* & 0 & \gamma & -(\sigma+\mu)\end{pmatrix}. \tag{4.8}$$

An individual is assumed to be susceptible without any partners at birth (and therefore the same applies to all its binding sites). So we have the birth conditions

$$x_0(0 \mid t_b) = 1, \quad x_1(0 \mid t_b) = 0 = x_2(0 \mid t_b) = x_3(0 \mid t_b). \tag{4.9}$$

Given the environmental variables $\boldsymbol{F}$ and Λ_-, we can formally view $x(a \mid t_b)$ as a function of the environmental variables:

$$x(a \mid t_b) = \Phi(a, t_b, \boldsymbol{F}, \Lambda_-),$$

i.e. $x(a \mid t_b)$ is completely determined by

$$\boldsymbol{F}|_{[t_b, t_b+a]}, \quad \text{and} \quad \Lambda_-|_{[t_b, t_b+a]}.$$

We now define the environmental variables in terms of p-level fractions. Note that Λ_- has the exact same interpretation as in network cases I and II. It should therefore come as no surprise that the definition of Λ_- in terms of p-level fractions is again (2.6). The fractions of free binding sites with disease status d are again defined by (3.6). This is *step 2*.

Next, in *step 3*, we define the i-level probabilities $p_{(-,\boldsymbol{k})}(a \mid t_b)$ in terms of x. As long as no infection occurs and the owner does not die, binding sites with the same owner are i.i.d. with distribution x. Therefore

$$p_{(-,\boldsymbol{k})}(a \mid t_b) = \frac{n!}{k_0!\, k_1!\, k_2!\, k_3!} \left(x_0^{k_0} x_1^{k_1} x_2^{k_2} x_3^{k_3} \right)(a \mid t_b) \tag{4.10}$$

(compare with eq. (3.7) and note that we condition on the survival of the individual).

In *step 4* we relate p-level fractions $P_{(d,\boldsymbol{k})}(t)$ to i-level probabilities $p_{(d,\boldsymbol{k})}(a \mid t_b)$. In order to do so, we use the stationary age distribution with density $a \mapsto \mu e^{-\mu a}$. The fraction of the population that is in state $(d, \boldsymbol{k})$ at time t is obtained by adding all individuals in that state that are born before time t and are still alive at time t. We find that

$$\begin{aligned} P_{(d,\boldsymbol{k})}(t) &= \int_{-\infty}^{t} \mu e^{-\mu(t-t_b)} p_{(d,\boldsymbol{k})}(t - t_b \mid t_b) dt_b \\ &= \int_0^{\infty} \mu e^{-\mu a} p_{(d,\boldsymbol{k})}(a \mid t - a) da, \end{aligned} \tag{4.11}$$

$d \in \{-, +, *\}$.

In *step 5*, we express the environmental variables Λ_- and F_- in terms of x. This can be done by combining (4.10) and (4.11) with (2.6) (for Λ_-) or (3.6) (for F_-). We find that

$$\Lambda_-(t) = (n-1) \frac{\int_0^{\infty} \mu e^{-\mu a} x_1 x_2 \bar{x}^{n-2}(a \mid t - a) da}{\int_0^{\infty} \mu e^{-\mu a} x_1 \bar{x}^{n-1}(a \mid t - a) da}, \tag{4.12}$$

and

$$F_-(t) = \int_0^{\infty} \mu e^{-\mu a} x_0 \bar{x}^{n-1}(a \mid t - a) da. \tag{4.13}$$

In order to complete *step 5* (expressing the environmental variables F_+ and Λ_- in terms of x) we need to consider infectious and recovered binding sites.

4.2.2 After susceptibility is lost

Consider a binding site that was born at time t_b and infected at age a_+ and remains alive and infectious for the period under consideration. Note that age a_+ for this individual corresponds to calendar time $t_+ = t_b + a_+$. Let $y_i^{\mathrm{e}}(a \mid t_b, a_+)$ denote the probability that the exceptional binding site is in state i at age a and $y_i(a \mid t_b, a_+)$ the same probability for a non-exceptional binding site.

Then, at age a_+, the exceptional binding site is for certain in state 2, while the other $n-1$ binding site states are distributed according to $x(a_+ \mid t_b)/\bar{x}(a_+ \mid t_b)$:

$$\begin{aligned}
y_0^{\mathrm{e}}(a_+ \mid t_b, a_+) &= 0, \qquad & y_0(a_+ \mid t_b, a_+) &= \frac{x_0}{\bar{x}}(a_+ \mid t_b),\\
y_1^{\mathrm{e}}(a_+ \mid t_b, a_+) &= 0, \qquad & y_1(a_+ \mid t_b, a_+) &= \frac{x_1}{\bar{x}}(a_+ \mid t_b),\\
y_2^{\mathrm{e}}(a_+ \mid t_b, a_+) &= 1, \qquad & y_2(a_+ \mid t_b, a_+) &= \frac{x_2}{\bar{x}}(a_+ \mid t_b),\\
y_3^{\mathrm{e}}(a_+ \mid t_b, a_+) &= 0, \qquad & y_3(a_+ \mid t_b, a_+) &= \frac{x_3}{\bar{x}}(a_+ \mid t_b).
\end{aligned}$$

The dynamics of infectious binding sites are described by:

$$\frac{dy(a \mid t_b, a_+)}{da} = M_+\big(\boldsymbol{F}(t_b + a), \Lambda_+(t_b + a)\big) y(a \mid t_b, a_+), \tag{4.14}$$

with

$$M_+(\boldsymbol{F}, \Lambda_+) = \begin{pmatrix} -\rho F & \sigma + \mu & \sigma + \mu & \sigma + \mu \\ \rho F_- & -(\beta\Lambda_+ + \sigma + \mu) & 0 & 0 \\ \rho F_+ & \beta\Lambda_+ & -(\sigma + \mu + \gamma) & 0 \\ \rho F_* & 0 & \gamma & -(\sigma + \mu) \end{pmatrix}.$$

Again, there is no rate γ in $M_+(\boldsymbol{F}, \Lambda_+)$ of leaving the system of infectious binding sites as we assume that infectious binding sites remain infectious in the period under consideration.

In (4.14) we can consider Λ_+ as 'known'. Indeed, by combining (2.14) with (4.11) and (4.10), we can express Λ_+ in terms of x as follows:

$$\Lambda_+(t) = 1 + (n-1)\frac{\int_0^\infty \mu e^{-\mu a} x_2^2 \bar{x}^{n-2}(a \mid t-a)da}{\int_0^\infty \mu e^{-\mu a} x_2 \bar{x}^{n-1}(a \mid t-a)da}. \tag{4.15}$$

We now set out to derive an expression for F_+. The probability $\phi_{(+,\boldsymbol{k})}(t_b, a \mid a_+)$ that an individual, born at time t_b and infected at age a_+, is in state $(+, \boldsymbol{k})$ at age $a \geq a_+$ is given by

$$\begin{aligned}
&\phi_{(+,\boldsymbol{k})}(a \mid t_b, a_+) = \\
&\quad \frac{n!}{k_0!\,k_1!\,k_2!\,k_3!}\left(\frac{k_0}{n}\, y_0^{\mathrm{e}}\, y_0^{k_0-1} y_1^{k_1} y_2^{k_2} y_3^{k_3} + \frac{k_1}{n}\, y_1^{\mathrm{e}}\, y_0^{k_0} y_1^{k_1-1} y_2^{k_2} y_3^{k_3}\right.\\
&\qquad \left. + \frac{k_2}{n}\, y_2^{\mathrm{e}}\, y_0^{k_0} y_1^{k_1} y_2^{k_2-1} y_3^{k_3} + \frac{k_3}{n}\, y_3^{\mathrm{e}}\, y_0^{k_0} y_1^{k_1} y_2^{k_2} y_3^{k_3-1}\right)(a \mid t_b, a_+).
\end{aligned} \tag{4.16}$$

The contribution to the incidence of individuals of age a_+, born at time t_b and alive for the period under consideration, is given by

$$\beta n x_2 \bar{x}^{n-1}(a_+ \mid t_b),$$

where the reasoning is similar to cases I and II. Then, taking into account all possible ages of infection $0 \leq a_+ \leq a$, and the probability that as yet recovery did not occur, the probability that an individual, born at time t_b, is in state $(+, \boldsymbol{k})$ at age a is given by

$$p_{(+,\boldsymbol{k})}(a \mid t_b) = \int_0^a e^{-\gamma(a-a_+)} \beta n x_2 \bar{x}^{n-1}(a_+ \mid t_b) \phi_{(+,\boldsymbol{k})}(a \mid t_b, a_+) da_+.$$

The p-level fractions $P_{(+,\boldsymbol{k})}(t)$ at time t are obtained through relation (4.11). In this way, the dynamics of infectious binding sites describe the dynamics of infectious individuals and the population of such individuals.

In particular, we find that F_+ is defined in terms of infectious (and susceptible) binding sites as follows:

$$F_+(t) = \frac{1}{n} \int_0^\infty \mu e^{-\mu a} \int_0^a e^{-\gamma(a-a_+)} \beta n x_2 \bar{x}^{n-1}(a_+ \mid t-a) \\ \left(y_0^{\mathrm{e}} \bar{y}^{n-1} + (n-1) \bar{y}^{\mathrm{e}} y_0 \bar{y}^{n-2}\right)(a \mid t-a, a_+) da_+ da.$$

Since y^{e} and y are probability vectors, they sum to one: $\bar{y}^{\mathrm{e}}(a|t_b, a_+) = 1 = \bar{y}(a|t_b, a_+)$. Moreover, with φ_1 given by (4.3), since

$$y_0^{\mathrm{e}}(a \mid t_b, a_+) = \varphi_1(a - a_+), \tag{4.17}$$

$$y_0(a \mid t_b, a_+) = y_0^{\mathrm{e}}(a \mid t_b, a_+) + \frac{x_0}{\bar{x}}(a_+ \mid t_b)\, e^{-(\rho F + \sigma + \mu)(a-a_+)}, \tag{4.18}$$

we can express F_+ in terms of the history of x:

$$F_+(t) = \frac{1}{n} \int_0^\infty \mu e^{-\mu a} \int_0^a e^{-\gamma(a-a_+)} \beta n x_2 \bar{x}^{n-1}(a_+ \mid t-a) \\ \left\{\varphi_1(a-a_+) + (n-1)\Big(\varphi_1(a-a_+) \right. \\ \left. + \frac{x_0}{\bar{x}}(a_+ \mid t-a)\, e^{-(\rho F+\sigma+\mu)(a-a_+)}\Big)\right\} da_+ da. \tag{4.19}$$

We can use the consistency condition for the total fraction of free binding sites:

$$F_*(t) = F - F_-(t) - F_+(t). \tag{4.20}$$

to express F_* in terms of the history of x by using (4.13) and (4.19).

Thus we have specified all environmental variables for (4.7) in terms of (the history of) x. For completeness we briefly consider recovered binding sites.

Suppose a recovered binding site was born at time t_b, infected at age a_+, and recovered at age a_* (and as usual, suppose its owner does not die in the period under consideration).We consider probabilities $z_i^{\mathrm{e}}(a \mid t_b, a_+, a_*)$ and $z_i(a \mid t_b, a_+, a_*)$ for recovered

exceptional and non-exceptional binding sites in state i, respectively. The y and y^{e} probabilities yield the conditions for z and z^{e} at age $a = a_*$, i.e.

$$\begin{aligned}
z_0^{\mathrm{e}}(a_* \mid t_b, a_+, a_*) &= y_1^{\mathrm{e}}(a_* \mid t_b, a_+), \quad z_0(a_* \mid t_b, a_+, a_*) = y_1(a_* \mid t_b, a_+),\\
z_1^{\mathrm{e}}(a_* \mid t_b, a_+, a_*) &= y_1^{\mathrm{e}}(a_* \mid t_b, a_+), \quad z_1(a_* \mid t_b, a_+, a_*) = y_1(a_* \mid t_b, a_+),\\
z_2^{\mathrm{e}}(a_* \mid t_b, a_+, a_*) &= y_2^{\mathrm{e}}(a_* \mid t_b, a_+), \quad z_2(a_* \mid t_b, a_+, a_*) = y_2(a_* \mid t_b, a_+),\\
z_3^{\mathrm{e}}(a_* \mid t_b, a_+, a_*) &= y_3^{\mathrm{e}}(a_* \mid t_b, a_+), \quad z_3(a_* \mid t_b, a_+, a_*) = y_3(a_* \mid t_b, a_+).
\end{aligned}$$

The dynamics for z and z^{e} can be described by a system of ODE similar to the ODE systems (4.14) for y and y^{e}. Only now the mean field at distance one quantity Λ_+ needs to be replaced by Λ_* where Λ_* is defined in terms of p-level fractions by (2.21). By combining (2.21) with (4.11) and (4.10) we can express Λ_* in terms of x-probabilities:

$$\Lambda_*(t) = (n-1)\frac{\int_0^\infty \mu e^{-\mu a} x_2 x_3 \bar{x}^{n-2}(a \mid t-a)da}{\int_0^\infty \mu e^{-\mu a} x_3 \bar{x}^{n-1}(a \mid t-a)da}.$$

4

Let $\psi_{(*,\boldsymbol{k})}(a \mid t_b, a_+, a_*)$ denote the probability that a recovered individual is in state $(*, \boldsymbol{k})$ given that it was born at time t_b, infected at age a_+ and recovered at age a_*, and does not die in the period under consideration. Then $\psi_{(*,\boldsymbol{k})}(a \mid t_b, a_+, a_*)$ can be expressed in terms of z and z^{e} by replacing ϕ by ψ, y_i by z_i, and y_i^{e} by z_i^{e} in (4.16).

The probability $p_{(*,\boldsymbol{k})}(a \mid t_b)$ is then obtained by taking into account all possibilities for age of infection a_+ and age of recovery a_*:

$$\begin{aligned}
p_{(*,\boldsymbol{k})}(a \mid t_b) = \int_{a_*=0}^{a} \int_{a_+=0}^{a_*} &\gamma e^{-\gamma(a_*-a_+)} \beta n x_2 \bar{x}^{n-1}(a_+ \mid t_b)\\
&\psi_{(*,\boldsymbol{k})}(a \mid t_b, a_+, a_*) da_+ da_*.
\end{aligned}$$

Finally, by relation (4.11), we obtain

$$P_{(*,\boldsymbol{k})}(t) = \int_0^\infty \mu e^{-\mu a} p_{(*,\boldsymbol{k})}(a \mid t-a)da.$$

4.2.3 A system of three renewal equations

To summarize, by replacing F_* by (4.20), we are left with three environmental variables Λ_-, F_-, and F_+ which are defined by

$$\Lambda_-(t) = (n-1)\frac{\int_0^\infty \mu e^{-\mu a} x_1 x_2 \bar{x}^{n-2}(a \mid t-a)da}{\int_0^\infty \mu e^{-\mu a} x_1 \bar{x}^{n-1}(a \mid t-a)da}, \tag{4.21}$$

$$F_-(t) = \int_0^\infty \mu e^{-\mu a} x_0 \bar{x}^{n-1}(a \mid t-a)da, \tag{4.22}$$

$$F_+(t) = \frac{1}{n}\int_0^\infty \mu e^{-\mu a}\int_0^a e^{-\gamma(a-a_+)}\beta n x_2 \bar{x}^{n-1}(a_+ \mid t-a)$$
$$\Big\{\varphi_1(a-a_+) + (n-1)\Big(\varphi_1(a-a_+)$$
$$+ \frac{x_0}{\bar{x}}(a_+ \mid t-a)\, e^{-(\rho F+\sigma+\mu)(a-a_+)}\Big)\Big\} da_+ da. \tag{4.23}$$

Recall that $x(a \mid t-a)$ is completely determined by

$$F_-|_{[t-a,t]}, \quad F_+|_{[t-a,t]}, \quad \text{and} \quad \Lambda_-|_{[t-a,t]},$$

via (4.7)-(4.9). Therefore (4.21)-(4.23) is a closed system of three renewal equations.

Together, the three renewal equations (4.21)-(4.23) fully determine the dynamics of i-level probabilities $p_{(-,\boldsymbol{k})}(a \mid t_b)$ and p-level fractions $P_{(-,\boldsymbol{k})}(t)$. (Note that there are in total $1/6(n+1)(n+2)(n+3)$ states of the form $(-,\boldsymbol{k})$, with $\boldsymbol{k} = (k_1,k_2,k_3)$, $0 \le k_1+k_2+k_3 \le n$.)

One may not particularly like renewal equations to work with. However, the ODE system (4.7) has t_b as a parameter, so is not finite dimensional. Therefore, contrary to Section 3, in order to describe the model with a closed finite system of ODE one needs to turn to p-level fractions $P_{(-,\boldsymbol{k})}$ and $P_{(+,\boldsymbol{k})}$ (the p-level system of ODE can be written down directly from the interpretation; see also Chapter 3 and Remarks 2 and 3). Together with the definition of the environmental variables $F_\pm$ and $\Lambda_\pm$ in terms of p-level fractions, the system is then closed. However, there are in total $1/3(n+1)(n+2)(n+3)$ variables of the form $P_{(\pm,\boldsymbol{k})}$.

As the system of three renewal equations (4.21)-(4.23) has a clear interpretation, and R_0, r, and the endemic steady state can very nicely be characterized from this system (see Section 4.3 below), we strongly advocate this formulation of the model rather than a (very high-dimensional) system with only ODE.

4.3 The beginning of an epidemic: R_0 and r

To describe the beginning of an epidemic, we are interested in characterizing R_0 and r. We have done so for the full p-level ODE system in Chapter 3. In this paper, the characterization of R_0 involved the dynamics of infectious binding sites in the beginning of the epidemic. This infectious binding site system was then, via a linear map, coupled to the linearized p-system to show that the definition of R_0 via the interpretation indeed yields a threshold parameter with threshold value one for the p-level system.

In this section, we use the system of three renewal equations (4.21)-(4.23) to characterize R_0 and r. Using the same arguments as in Sections 2.3 and 3.3 of network cases I and II, we deduce that, in order to find a threshold parameter for the disease free steady state of the p-level system, we can focus on a threshold parameter for the stability of the disease free steady state of the binding site level system (4.7). Hence we can focus on (4.21)-(4.23).

The linearization of (4.21)-(4.23) involves the linearization of (4.7). The disease free steady state of (4.7) is given by $\tilde{x}_0(a \mid t_b) = \varphi_0(a)$, $\tilde{x}_1(a \mid t_b) = 1-\varphi_0(a)$, $\tilde{x}_2(a \mid t_b) =$

$0 = \tilde{x}_3(a \mid t_b)$, where $\varphi_0(a)$, the probability that a binding site is free at age a given that it was born free (i.e. free at age 0), is given by (4.2).

We again put a $\wedge$ on the symbols to denote the variables in the linearized system. The ODE for the linearized variable $\hat{x}_2$ is straightforward:

$$\begin{aligned}\frac{d\hat{x}_2}{da}(a \mid t_b) &= \rho\hat{F}_+(t_b + a)\varphi_0(a) + \beta\hat{\Lambda}_-(t_b + a)\big(1 - \varphi_0(a)\big) \\ &\quad - (\sigma + \mu + \beta + \gamma)\hat{x}_2(a \mid t_b), \\ \hat{x}_2(0 \mid t_b) &= 0.\end{aligned} \tag{4.24}$$

In the following we condition (as usual) on the owner of the binding site staying alive in the period under consideration. The probability $y_0^{\mathrm{e}}(a \mid t_b, a_+)$ is independent of t_b and given by (4.17). On the other hand, $y_0(a \mid t_b, a_+)$ in the disease free steady state can be interpreted as the probability that a binding site is free at age a given that it is free at age a_+ with probability $\varphi_0(a_+)$. But this is equal to the probability $\varphi_0(a)$ that a binding site is free at age a given that it was born free at age 0 (since then, the probability that it is free at age a_+ is exactly $\varphi_0(a_+)$). So we find that, in the disease free steady state,

$$y_0(a \mid t_b, a_+) = \varphi_1(a - a_+) + e^{-(\rho F + \sigma + \mu)(a - a_+)}\varphi_0(a_+) = \varphi_0(a),$$

where the first equality follows from simply evaluating (4.18) in the disease free steady state and the second can be deduced (as above) from the interpretation (or by algebraic manipulation). So we find that $\hat{F}_+$ satisfies

$$\begin{aligned}\hat{F}_+(t) = \frac{1}{n}\int_0^\infty \mu e^{-\mu a}\int_0^a e^{-\gamma(a - a_+)}\beta n\hat{x}_2(a_+ \mid t - a) \\ \Big(\varphi_1(a - a_+) + (n - 1)\varphi_0(a)\Big)da_+ da.\end{aligned} \tag{4.25}$$

Next, linearization of Λ_- yields

$$\hat{\Lambda}_-(t) = \frac{1}{1 - F}\int_0^\infty \mu e^{-\mu a}(n - 1)\big(1 - \varphi_0(a)\big)\hat{x}_2(a \mid t - a)da, \tag{4.26}$$

where we used relation (4.4) between F and φ_0.

We now derive two renewal equations for $\hat{F}_+$ and $\hat{\Lambda}_-$. Variation of constants yields an expression for $\hat{x}_2$ in terms of $\hat{F}_+$ and $\hat{\Lambda}_-$:

$$\begin{aligned}\hat{x}_2(a \mid t_b) = \int_0^a e^{-(\sigma + \mu + \beta + \gamma)(a - \alpha)} \\ \Big(\rho\hat{F}_+(t_b + \alpha)\varphi_0(\alpha) + \beta\hat{\Lambda}_-(t_b + \alpha)\big(1 - \varphi_0(\alpha)\big)\Big)\,d\alpha.\end{aligned} \tag{4.27}$$

We substitute this in the expressions for $\hat{F}_+$ and $\hat{\Lambda}_-$ to find the system of two renewal

equations:

$$\begin{aligned}\hat{F}_+(t) = &\int_0^\infty \int_0^a \int_0^{a_+} \mu e^{-\mu a} e^{-\gamma(a-a_+)} \beta e^{-(\sigma+\mu+\beta+\gamma)(a_+-\alpha)} \\ &\Big(\rho \hat{F}_+(t-a+\alpha)\varphi_0(\alpha) + \beta \hat{\Lambda}_-(t-a+\alpha)\big(1-\varphi_0(\alpha)\big)\Big) \\ &\Big(\varphi_1(a-a_+) + (n-1)\varphi_0(a)\Big) d\alpha da_+ da \\ \hat{\Lambda}_-(t) = &\frac{1}{1-F}\int_0^\infty \int_0^a \mu e^{-\mu a}(n-1)\big(1-\varphi_0(a)\big) e^{-(\sigma+\mu+\beta+\gamma)(a-\alpha)} \\ &\Big(\rho \hat{F}_+(t-a+\alpha)\varphi_0(\alpha) + \beta \hat{\Lambda}_-(t-a+\alpha)\big(1-\varphi_0(\alpha)\big)\Big)\, d\alpha da.\end{aligned}$$

In preparation for defining and interpreting R_0 we write these integrals in convolution form:

$$\begin{aligned}\hat{F}_+(t) = &\int_0^\infty \int_0^\infty \int_0^\infty \beta e^{-(\sigma+2\mu+\beta+\gamma)\xi} e^{-(\gamma+\mu)\tau} \\ &\Big(\rho F \hat{F}_+(t-\tau)\pi_0(\alpha) + \beta(1-F)\hat{\Lambda}_-(t-\tau)\pi_1(\alpha)\Big) \\ &\big(\varphi_1(\tau) + (n-1)\varphi_0(\tau+\xi+\alpha)\big) d\alpha d\xi d\tau \qquad (4.28) \\ \hat{\Lambda}_-(t) = &\frac{1}{1-F}\int_0^\infty \int_0^\infty (n-1)\big(1-\varphi_0(\tau+\alpha)\big) e^{-(\sigma+2\mu+\beta+\gamma)\tau} \\ &\Big(\rho F \hat{F}_+(t-\tau)\pi_0(\alpha) \\ &\quad + \beta(1-F)\hat{\Lambda}_-(t-a+\alpha)\pi_1(\alpha)\Big) d\alpha d\tau. \qquad (4.29)\end{aligned}$$

(the π_0 and π_1 appear by multiplying with F/F and $(1-F)/(1-F)$). This is a system of two renewal equations of the form

$$\tilde{b}(t) = \int_0^\infty \tilde{K}(\tau)\tilde{b}(t-\tau)d\tau, \qquad (4.30)$$

with non-negative kernel $\tilde{K}$.

From these two renewal equations (4.28) and (4.29), we can obtain the characteristic equation and deduce threshold parameters r and R_0. We define

$$R_0 = \text{dominant eigenvalue of } \int_0^\infty \tilde{K}(\tau)d\tau. \qquad (4.31)$$

Note that $\int_0^\infty \tilde{K}(\tau)$ is a 2×2 matrix that can be evaluated explicitly so we have an explicit expression for R_0. We define r to be the real root (if it exists) of the *characteristic*

4

equation

$$\det\left(I - \int_0^\infty e^{-\lambda\tau}\tilde{K}(\tau)d\tau\right) = 0 \tag{4.32}$$

such that the spectral radius of $\int_0^\infty e^{-\lambda\tau}\tilde{K}(\tau)d\tau$ equals 1. Note that r is necessarily the rightmost solution of the characteristic equation (4.32).

Then r is a threshold parameter with threshold value zero for the stability of the disease free steady state of the system of renewal equations (4.21)-(4.23). Furthermore $\text{sign}(R_0 - 1) = \text{sign}(r)$ so the definition (4.31) of R_0 indeed has the right threshold property.

For $R_0 > 1$, to see that $\text{sign}(R_0 - 1) = \text{sign}(r)$, one uses that each matrix element of $\int_0^\infty e^{-\lambda\tau}K(\tau)d\tau$ is a strictly monotonically decreasing function of λ and therefore the dominant eigenvalue of $\int_0^\infty e^{-\lambda\tau}K(\tau)d\tau$ is strictly monotonically decreasing as a function of λ [97],[8, Section 8.2 the intrinsic growth rate]. For $R_0 < 1$, one uses that the rightmost real solution r of (4.32) (if it exists) is strictly less than zero and this establishes the stability of the disease free steady state [98–100].

In the epidemic context, 'reproduction' corresponds to transmission of the infectious agent to another host. The definition of (and the derivation of an expression for) R_0 in Chapter 3 is in this spirit: it follows infectious binding sites in time and counts how many new infectious binding sites are formed when transmission occurs. A slight modification of the derivation in Chapter 3 is required to generalize from SI to SIR. We did check that (4.31) is identical to the appropriately modified version of the dominant eigenvalue of (C.8) in Appendix C of Chapter 3.

Yet we would like to have a direct interpretation of the would-be reproduction number (4.31). To achieve this, it is helpful to think in terms of reproduction 'opportunities'. In the present context, these consist of $+-$ links. In Chapter 3 the spotlight is on the $+$ side of the link. The present bookkeeping scheme focuses on x, so on $-$ binding sites. So now the spotlight is on the $-$ side of the link. The difference is just a matter perspective. A key point, however, is that after transmission the link disappears from the x stage. This forces us to formulate the interpretation in terms of reproduction opportunities rather than reproductions. (Note that, in traditional epidemiological models involving the random mixing assumption, contacts between individuals are instantaneous so there are no $-+$ links or 'reproduction opportunities' in the above sense.)

We distinguish two birth-types of $-+$ links, according to the way they originate:

Type 0 the $-+$ link was formed when a $-$ binding site and a $+$ binding site linked up

Type 1 the $-+$ link is a transformed $--$ link (one of the two owners got infected by one of its other partners)

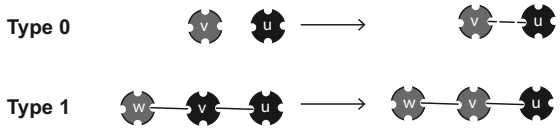

Figure 7: The two birth-types of $+-$ links between individuals u and v.

The relevant difference is the age distribution of the $-$ binding site at the 'birth' of the $-+$ link (see Fig. 7):

- for type 0 this distribution has density π_0 since the $-$ binding site was free until that moment
- for type 1 this distribution has density π_1 since the $-$ binding site was (and remains) occupied

So the density of the age distribution of the $-$ binding site at birth depends on the birth-type, making it necessary to distinguish between the two birth-types 0 and 1, such in contrast to case II.

In the nonlinear setting, the total rate in the population at which $-+$ links of type 0 are formed is equal to $\rho F_- \sum k_0 P_{(+,\boldsymbol{k})} = \rho F_- n F_+$ (note the $-+$ asymmetry here, which is in preparation for the linearization). The rate at which type 1 $-+$ links are formed is equal to $\beta \sum k_1 k_2 P_{(-,\boldsymbol{k})}$, respectively. Indeed, the expected number of free infectious binding sites in the population is $\sum k_0 P_{(+,\boldsymbol{k})}$, and the rate at which a free and infectious binding site acquires a susceptible partner is ρF_-. The expected number $- - +$ configurations per 'middle' $-$ individual is $\sum k_1 k_2 P_{(-,\boldsymbol{k})}$ (see also Fig. 8) and the rate of transmission is β.

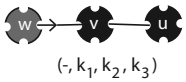

Figure 8: An example of a $- - +$ configuration: u is one of the k_1 $-$ partners of the 'middle' $-$ individual v in state $(-, k_1, k_2, k_3)$ and w is one of the k_2 $+$ partners of v.

Linearization in the disease free steady state yield $\rho F \sum k_0 \hat{P}_{(+,\boldsymbol{k})} = \rho F n \hat{F}_+$ and $\beta \sum k_1 \hat{P}_{(-,k_1,1,0)} = \beta n(1-F)\hat{\Lambda}_-$, respectively (use p-level definition (2.6) for Λ_-). These observations motivate us to scale the two renewal equations (4.28) and (4.29). Let

$$\begin{aligned} b_0 &\coloneqq \rho F n \hat{F}_+, \\ b_1 &\coloneqq \beta n(1-F)\hat{\Lambda}_-. \end{aligned} \tag{4.33}$$

That such a rescaling does not affect the definition of r and R_0 follows from the following observation:

Observation. *In general, if we have a system of renewal equations of the form* (4.30)*, we may 'scale' $\tilde{b}$, i.e. put $\tilde{b}_i = c_i b_i$ and consider the renewal equation*

$$b(t) = \int_0^\infty K(\tau) b(t-\tau) d\tau$$

with $K(\tau) := C^{-1}\tilde{K}(\tau)C$ and C the diagonal matrix with non-zero entries $C_{ii} = c_i$. Then

$$\det\left(I - \int_0^\infty e^{-\lambda\tau}\tilde{K}(\tau)d\tau\right) = \det\left(I - \int_0^\infty e^{-\lambda\tau}K(\tau)d\tau\right).$$

Moreover, the matrices $\int_0^\infty \tilde{K}(\tau)d\tau$ and $\int_0^\infty K(\tau)d\tau = C^{-1}\int_0^\infty \tilde{K}(\tau)d\tau C$ are similar, so they have the same eigenvalues. In particular, they have the same dominant eigenvalue R_0.

4

Rescaling (4.33) yields a system of renewal equations

$$b(t) = \int_0^\infty K(\tau) b(t-\tau) d\tau \tag{4.34}$$

with $b = (b_0\ b_1)^T$, and $K = (K_{ij})$ a 2×2 matrix with matrix elements

$$\begin{aligned}
K_{00}(\tau) &= \int_0^\infty \int_0^\infty \pi_0(\alpha)\beta e^{-(\sigma+2\mu+\beta+\gamma)\xi} e^{-(\mu+\gamma)\tau} \\
&\qquad \rho F\big(\varphi_1(\tau) + (n-1)\varphi_0(\tau+\xi+\alpha)\big) d\alpha d\xi \\
K_{01}(\tau) &= \int_0^\infty \int_0^\infty \pi_1(\alpha)\beta e^{-(\sigma+2\mu+\beta+\gamma)\xi} e^{-(\mu+\gamma)\tau} \\
&\qquad \rho F\big(\varphi_1(\tau) + (n-1)\varphi_0(\tau+\xi+\alpha)\big) d\alpha d\xi \\
K_{10}(\tau) &= \int_0^\infty \pi_0(\alpha) e^{-(\sigma+2\mu+\beta+\gamma)\tau} \beta(n-1)\big(1-\varphi_0(\tau+\alpha)\big) d\alpha \\
K_{11}(\tau) &= \int_0^\infty \pi_1(\alpha) e^{-(\sigma+2\mu+\beta+\gamma)\tau} \beta(n-1)\big(1-\varphi_0(\tau+\alpha)\big) d\alpha.
\end{aligned} \tag{4.35}$$

(Again we note that each of these four integrals can be evaluated explicitly.)

We now explain how (4.35) can be interpreted in terms of reproduction opportunities of types 0 and 1. A $-+$ link has no 'descendants' when transmission does not occur. When transmission occurs, it has at that very moment descendants of type 1, because the 'other' partners of the owner u of the $-$ link then all of a sudden are connected to a $+$ individual. In addition, it has descendants of type 0 when empty binding sites of u get occupied (necessarily by a $-$ partner, since we consider the initial phase when $+$ individuals are rare). Note that we should follow all binding sites of u until u either

dies or becomes removed, since occupied binding sites may become free, occupied again, etcetera.

We now compute the expected number of descendants of either type for a $-+$ link given that the owner u of the $-$ binding site has age a at the birth of the $-+$ link. The force of infection on u along the link equals β as long as

- the $+$ partner is alive and infectious
- separation did not occur
- u is alive and not yet infected

Hence the probability per unit of time that u is infected at age $\alpha + \tau$ is given by $\beta e^{-(\mu+\gamma+\sigma+\mu+\beta)\tau}$.

When u is infected at age $\alpha + \tau$ an expected number $(n-1)\big(1-\varphi_0(\alpha+\tau)\big)$ of offspring of type 1 is produced. A schematic representation is given in Fig. 9. This is how $\int_0^\infty K_{10}(\tau)d\tau$ and $\int_0^\infty K_{11}(\tau)d\tau$ in (4.35) can be interpreted.

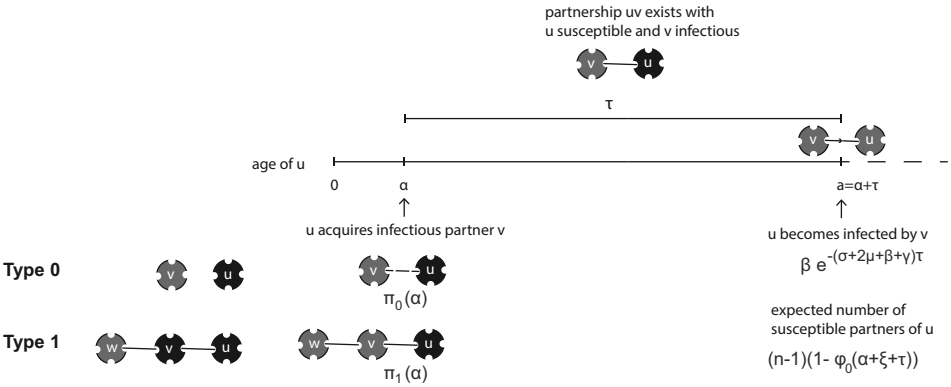

Figure 9: The production of type 1 offspring.

Offspring of type 0 are (potentially) produced by both free and occupied (at the time of infection) binding sites of u. To calculate the mean number of offspring of type 0, suppose u is infected at age $\alpha + \xi$. Then u is alive and infectious at age $\alpha + \xi + \tau$ with probability $e^{-(\gamma+\mu)\tau}$. The expected number of free binding sites it has at age $\alpha + \tau + \xi$ is equal to $\varphi_1(\xi) + (n-1)\varphi_0(\tau + \xi + \alpha)$. A free binding site becomes occupied at rate ρF. Integrating over all possible $\tau > 0$, we find that the expected offspring of type 0 is

$$\int_0^\infty e^{-(\gamma+\mu)\tau}\rho F\big(\varphi_1(\tau) + (n-1)\varphi_0(\tau+\xi+\alpha)\big)d\tau.$$

This is how $\int_0^\infty K_{00}(\tau)d\tau$ and $\int_0^\infty K_{01}(\tau)d\tau$ in (4.35) can be interpreted. A schematic representation is given in Fig. 10.

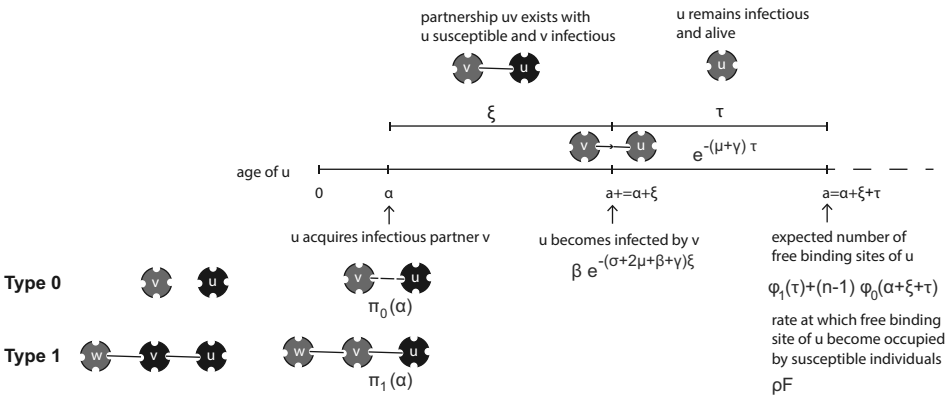

Figure 10: The production of type 0 offspring.

4

The infectious binding site perspective

In Chapter 3 the focus was on infectious binding sites. As exhibited by the densities π_0 and π_1 of the age-distribution of $-$ individuals in the birth-types of $-+$ links, it matters whether a newly created $-+$ links is type 0 or type 1. To take this into account, in Chapter 3, we kept track of the number of partners of susceptible partners of infectious binding sites. This led to the reduction to a 2×2 next-generation-matrix involving mean times spent with a susceptible partner with k partners, $k = 1, \ldots, n$, (in the form of the inverse of an $n \times n$ matrix). We were able to find an explicit expression for R_0 although it required quite a lot of work to deal with this $n \times n$ inverse matrix.

The results in this paper teach us that, to take into account the birth-types of $-+$ links, we can also keep track of the age of susceptible partners rather than partners of partners. While age can be anything from zero to infinity, it can only move forward in time, i.e. individuals can only grow older. The same 2×2 NGM is obtained in a much more straightforward manner.

Whether doing the bookkeeping of partners of partners or of the age of partners, a big downside of taking the infectious binding site perspective is that it takes quite some work to *prove* that so-obtained R_0 is actually a threshold parameter for the stability of the disease free steady state of the p-level system (see Chapter 3). This comes almost for free when taking the $-$ perspective as we did in this paper.

Finally note that, whether we consider actual 'reproductions' (taking the $+$ perspective) or 'reproduction opportunities' (taking the $-$ perspective), both yield the exact same threshold parameter R_0 so in that sense it does not matter which perspective we take. However, while the *the dominant eigenvalue* R_0 of the next-generation-matrix is the same with both perspectives, the *matrices* themselves are different. And so are the underlying interpretations.

4.4 Endemic steady state

Let $E = (F_+, F_*, \Lambda_-)$ be the vector of environmental variables. Note that we use consistency relation (4.20) to substitute environmental variable F_* for F_-. This choice of environmental variables leads to the disease free steady state corresponding to $E = (0, 0, 0)$. Then we have a system of three renewal equations for E.

Let

$$\begin{aligned}
G_1(E)(t) &:= \int_0^\infty \mu e^{-\mu a} \int_0^a e^{-\gamma(a-a_+)} \beta x_2(a_+ \mid t-a) \\
&\quad \Big(n \frac{\sigma+\mu}{\rho F+\sigma+\mu} \left(1 - e^{-(\rho F+\sigma+\mu)(a-a_+)}\right) \bar{x}(a_+ \mid t-a)^{n-1} \\
&\quad + (n-1) e^{-(\rho F+\sigma+\mu)(a-a_+)} \left(x_0 \bar{x}^{n-2}\right)(a_+ \mid t-a) \Big) da_+ da, \\
G_2(E)(t) &:= F - \int_0^\infty \mu e^{-\mu a} \left(x_0 \bar{x}^{n-1}\right)(a \mid t-a) da - G_1(E), \\
G_3(E)(t) &:= (n-1) \frac{\int_0^\infty \mu e^{-\mu a} \left(x_1 x_2 \bar{x}^{n-2}\right)(a \mid t-a) da}{\int_0^\infty \mu e^{-\mu a} \left(x_1 \bar{x}^{n-1}\right)(a \mid t-a) da}.
\end{aligned}$$

where $x(a \mid t-a)$ is completely determined by $E|_{[t-a,a]}$ via (4.7)-(4.9). Therefore,

$$\begin{pmatrix} F_+ \\ F_* \\ \Lambda_- \end{pmatrix} = \begin{pmatrix} G_1(F_+, F_*, \Lambda_-) \\ G_2(F_+, F_*, \Lambda_-) \\ G_3(F_+, F_*, \Lambda_-) \end{pmatrix} \tag{4.36}$$

is a closed system of three renewal equations.

In endemic equilibrium, the environmental variable E is constant (note that, if E is constant, then also p-level fractions are constant and binding-site- and i-level probabilities are constant as functions of time of birth t_b). So the endemic steady state is characterized as a solution to the fixed point problem (4.36) where now the symbols denote the values of constant functions. The fixed point problem always has a trivial solution given by the disease free steady state $E = (0, 0, 0)$. Note that a solution E to (4.36) needs to have biological meaning. Therefore, we only consider solutions that satisfy $F_+, F_* \geq 0$, $0 \leq F_+ + F_* \leq F$, and $0 \leq \Lambda_- \leq n-1$.

Conjecture: If $R_0 < 1$, then the only solution to the fixed point problem is the trivial solution. If $R_0 > 1$, then there is a unique nontrivial solution.

Open problem: Prove (or disprove) the conjecture.

In Appendix B we elaborate on an unsuccessful attempt at a proof of the conjecture for the simpler case of an SI infection, rather than an SIR infection, obtained by setting $\gamma = 0$. This attempt tried to use Krasnoselskii's method [101] (see also [102]).

Note that the three-dimensional fixed point problem (4.36) provides a way to find the endemic steady state numerically. Furthermore, even though we did not manage to prove the conjecture, numerical investigations strongly suggest that all conditions for Krasnoselskii's method are satisfied and that the conjecture holds true.

5 Conclusions and discussion

In this paper we formulated binding site models for the spread of infection on networks. The binding sites serve as building blocks for individuals. In fact we considered three different levels: (1) binding sites, (2) individuals, and (3) the population. On both the binding site and individual level, we have a Markov chain description of the dynamics, where feedback from the population is captured by environmental variables. These environmental variables are population-level quantities. By lifting the individual level to the population level (where the model is deterministic), the feedback loop can be closed. In the end, this leads to a model description in terms of susceptible binding sites in case I and in terms of just environmental variables in cases II and III.

The systematic model formulation leads, in all three cases, to only a few equations that determine the binding site, individual, and the population dynamics. Moreover, from these equations we derive the epidemiological quantities of interest, i.e. R_0, r, the final size (in cases I and II) and the endemic steady state (in case III).

Quite a general understanding is enhanced by an elaboration of the interpretation of R_0 in a specific context. In cases I and II we have taken the obvious perspective of a $+$ binding site to do so. But in case III, cf. Section 4.3, we reasoned in terms of 'reproduction opportunities'. These consist of $+-$ links. From these links we took the $-$ perspective. Somewhat surprisingly, this turned out to lead quickly and efficiently to a simple interpretation. Moreover, the derivation of R_0 follows from the system of equations in a natural manner. One can adopt the $-$ perspective in cases I and II too, but there it does not change much. Yet we wouldn't be surprised if the $-$ perspective turns out to be powerful in other dynamic network models of infectious disease transmission.

Several open problems remain. Although we are able to implicitly characterize the final size in case II, we have not been able to make it more explicit. We would like a characterization in the same spirit as (2.33) for case I, but we have not succeeded and our optimism subsided. A more useful characterization of the endemic steady state was given for case III as a three-dimensional fixed point problem. Unfortunately, we have not (yet) been able to prove the existence and uniqueness of a nontrivial fixed point for $R_0 > 1$ (and that no such fixed point exists for $R_0 < 1$) and therefore we posed this as a conjecture in Section 4.4.

Of another nature are open problems related to the mean field at distance one assumption. While, in case I, the mean field at distance one assumption is proven to be exact in the appropriate large population limit of a stochastic SIR epidemic on a configuration network, it remains an open problem whether or not this also holds for the dynamic network case II (we conjecture it does). In the dynamic network case III, we know that the mean field at distance one assumption is really an approximation of the true dynamics

as we pointed out in the introduction of this paper. What we have not discussed is how good or bad of an approximation it is. In particular, are there conditions for which the approximation works nicely and can we understand intuitively the extent to which this assumption violates the truth?

In both cases II and III, we ended the model formulation with renewal equations. In case II one can just as easily consider a system of ODE, and we represented this view also in the section title 3.2.3. In case III, a system of ODE clearly becomes inconvenient. An ODE formulation in that case would require at least $1/3(n+1)(n+2)(n+3)$ variables, while, by considering a system of renewal equations, only three equations are needed. More importantly, the system of renewal equations has the huge advantage that R_0 and r more or less immediately follow from the linearization of the system in the disease free steady state. The calculations are straightforward, the expressions are interpretable biologically, and the proof that R_0 and r are threshold parameters for the disease free steady state of the p-level system comes more or less for free.

By distinguishing the three different levels, and formulating the model on the binding site level, one can easily consider several generalizations (see also Chapters 2 and 3 for a discussion). In principle, any generalization that maintains the (conditional) independence assumption for binding sites of an individual easily fits within this framework. One can think of generalizations concerning the network or generalizations concerning the infectious disease. For the infectious disease, one can easily take any compartmental model such as SIR, SEIR, SI, SI_1I_2 (as long as infected individuals can not return to the susceptible class within their lifetime). The main difference is in the different states that a binding site can be in. Generalizations of the network that one can think of are (i) a heterosexual population rather than a homosexual population, (ii) allowing for different n in the population, i.e. letting n be a random variable (which we already considered in the static network case in Section 2.5) (iii) allowing for multiple types of binding sites, e.g. binding sites for casual and steady partnerships, and combinations of the three. One can formulate models incorporating these generalizations by following the five steps described in Section 2.2. The main added difficulty is in the bookkeeping that becomes more involved. But in terms of the characterization of R_0 and the endemic steady state, mathematically speaking the situation does not become more complex.

Finally, in the current framework, and as usual in literature, demographic turnover as considered in case III takes the individual's age to be exponentially distributed. This assumption is mainly for mathematical convenience and is not realistic for many populations. We believe that it is possible to relax the assumption on the age distribution to consider more general survival functions. In that case, lifting the i-level to the p-level changes, and one needs to take into account the age of partners (but hopefully this may be done by simply averaging in the right way). Moreover, in the current framework, disease does not impact mortality. In the context of HIV, disease-related mortality is certainly very relevant. We believe that the framework presented in this paper provides a way to incorporate this by means of the infectious y binding sites. While these generalizations relating to the demographic process are less straightforward to implement than the ones described in the previous paragraph, the current framework provides an excellent starting point.

Acknowledgements

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A Do 'far past' conditions single out a unique solution?

In this paper we duck the responsibility of rigorously showing that the systems that we introduce have, modulo translation, at most one epidemiologically relevant (i.e. positive) solution. The aim of this appendix is to sketch the underlying ideas and to provide some references.

Linearization of an epidemic system in the disease free steady state leads to a linear system that leaves a cone, characterized by positivity, invariant. Perron-Frobenius theory, or its infinite dimensional Krein-Rutman variant, yields the existence of a simple eigenvalue r such that

(i) the corresponding eigenvector is positive

(ii) Re $\lambda < r$ for all eigenvalues $\lambda \neq r$

The theory of stable and unstable manifolds yields a nonlinear analogue: the nonlinear system has exactly one orbit that is tangent to the eigenvector corresponding to eigenvalue r. If $r > 0$ then this orbit belongs to the unstable manifold and tends to the disease free steady state for $t \to -\infty$. If $r < 0$ then the orbit belongs to the stable manifold and tends to the disease free steady state for $t \to +\infty$. Our interest is in the case $r > 0$.

Note that one orbit of an autonomous dynamical system corresponds to a family of solutions that are translates of each other. See [103] for an early example of this type of result (but note that the proof in that paper has a flaw; see [104, Section 7] for a flawless proof).

These ideas apply directly to the three-dimensional ODE system (2.5) in case I. For the scalar renewal equation (2.30) we can refer to Section 7 of [104] provided that we are willing to assume that $\mathcal{F}'$ has compact support. For the ODE system of case II there exists an eigenvalue zero (corresponding to conservation of binding sites). This eigenvalue zero creates havoc. Presumably, the difficulties can be overcome by the introduction of a tailor-made cone, but we did not elaborate this in all required detail. The alternative is to consider the scalar renewal equation (3.13) for F_+ and to combine ideas from [105] with theory developed in [106]. This combination should, we think, also cover the system of renewal equations (4.21)-(4.23) for case III.

B Endemic steady state: unsuccessful attempt at a proof

We explain our attempt to prove the conjecture of Section 4.4 about the existence and uniqueness of solutions to the fixed point problem (4.36) for the simpler case of an SI

infection rather than an SIR infection (set $\gamma = 0$). We only need to consider two environmental variables, rather than three, as we will explain. This attempt to prove the conjecture uses the sublinearity method of [101] (see also [102]), the idea of which for one dimension is represented in Fig. B.1.

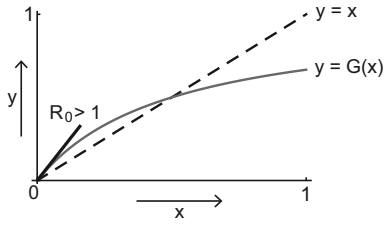

Figure B.1: Krasnoselskii's method generalizes the geometric arguments in one dimension to multiple dimensions.

First of all, if $\gamma = 0$, then x satisfies

$$\begin{aligned}
\frac{dx_0}{da}(a \mid t_b) &= -\rho F x_0(a \mid t_b) + (\sigma + \mu)\big(x_1(a \mid t_b) + x_2(a \mid t_b)\big) \\
\frac{dx_1}{da}(a \mid t_b) &= \rho(F - F_+)(t_b + a)x_0(a \mid t_b) \\
&\quad - (\sigma + \mu + \beta\Lambda_-(t_b + a))x_1(a \mid t_b) \\
\frac{dx_2}{da}(a \mid t_b) &= \rho F_+(t_b + a)x_0(a \mid t_b) + \beta\Lambda_-(t_b + a)x_1(a \mid t_b) \\
&\quad - (\sigma + \mu + \beta)x_2(a \mid t_b)
\end{aligned} \tag{B.1}$$

with boundary condition

$$x_0(0 \mid t_b) = 1, \quad x_1(0 \mid t_b) = 0 = x_2(0 \mid t_b). \tag{B.2}$$

As before in Section 4, $x(a \mid t_b)$ is completely determined by

$$F_+|_{[t_b, t_b + a]}, \quad \text{and} \quad \Lambda_-|_{[t_b, t_b + a]},$$

via (B.1)-(B.2). In particular, there are now only two environmental variables F_+ and Λ_-. These environmental variables satisfy renewal equations. Let

$$\begin{aligned}
G_1(F_+, \Lambda_-)(t) &= F - \int_0^\infty \mu e^{-\mu a} x_0 \bar{x}^{n-1}(a \mid t - a)da, \\
G_2(F_+, \Lambda_-)(t) &= (n-1)\frac{\int_0^\infty \mu e^{-\mu a} x_1 x_2 \bar{x}^{n-2}(a \mid t - a)da}{\int_0^\infty \mu e^{-\mu a} x_1 \bar{x}^{n-1}(a \mid t - a)da},
\end{aligned}$$

then we obtain a fixed point problem for the environmental variables F_+ and Λ_-:

$$\begin{pmatrix} F_+ \\ \Lambda_- \end{pmatrix} = \begin{pmatrix} G_1(F_+, \Lambda_-) \\ G_2(F_+, \Lambda_-) \end{pmatrix}. \tag{B.3}$$

Note that in endemic equilibrium the environment is constant, i.e. $F_+(t) = \bar{F}_+$, $\Lambda_-(t) = \bar{\Lambda}_-$. Therefore x no longer depends on time of birth. In what follows we write $x = x(a)$.

The fixed point problem (B.3) can be related to R_0 by considering the linearizaton of the right hand side of (B.3) in the disease free steady state $(F_+, \Lambda_-) = (0, 0)$. Indeed, the linearization $DG(0, 0)$ has dominant eigenvalue R_0.

Next, Krasnoselskii's method uses the monotonicity of G_1 and G_2 in both variables F_+ and Λ_- and strict sublinearity for both G_1 and G_2, i.e. $G_i(t(F_+, \Lambda_-)) > tG_i(F_+, \Lambda_-)$ for all $0 < t < 1$. $i = 1, 2$).

Monotonicity and sublinearity of G_1 in both variables F_+ and Λ_- is easily proven. One can show that the derivatives of x_0, x_1, and $x_1 + x_2$ with respect to F_+ and Λ_- are nonpositive while the mixed second order derivatives are all nonnegative. Then one can easily prove that the derivatives $D_iG_1(F_+, \Lambda_-) \geq 0$ showing that G_1 is a monotonically increasing function of both F_+ and Λ_-. Sublinearity can be proven by showing that the function $f(t) = G_1(t(F_+, \Lambda_-)) - tG_1(F_+, \Lambda_-)$ satisfies $f''(t) < 0$ for $0 < t < 1$.

We work out only the proof to show that $D_1G_1(F_+, \Lambda_-) \geq 0$. The derivative of G_1 with respect to F_+ is equal to

$$D_1G_1(F_+, \Lambda_-) = -\int_0^\infty \mu e^{-\mu a} \left(\frac{\partial dx_0}{\partial F_+} \bar{x}^{n-1} + (n-1) \frac{\partial \bar{x}}{\partial F_+} x_0 \bar{x}^{n-2} \right) (a) da. \quad \text{(B.4)}$$

Here $\partial x / \partial F_+$ satisfies:

$$\begin{aligned} &\frac{d}{da} \frac{\partial x}{\partial F_+} = M(F_+, \Lambda_-) \frac{\partial x}{\partial F_+} + A_1 x \\ &\frac{\partial x}{\partial F_+}(0) = 0, \end{aligned} \quad \text{(B.5)}$$

with

$$M(F_+, \Lambda_-) = \begin{pmatrix} -\rho F & \sigma + \mu & \sigma + \mu \\ \rho(F - F_+) & -(\sigma + \mu + \beta\Lambda_-) & 0 \\ \rho F_+ & \beta\Lambda_- & -(\sigma + \mu + \beta) \end{pmatrix}$$

and

$$A_1 = \rho \begin{pmatrix} 0 & 0 & 0 \\ -1 & 0 & 0 \\ 1 & 0 & 0 \end{pmatrix}.$$

To prove that x_0, x_1, and $x_1 + x_2$ are monotonically decreasing functions of F_+, we prove that the derivatives with respect to F_+ are nonpositive. Working out (B.5) we find that

$$\begin{aligned} \frac{d}{da} \frac{\partial x_0}{\partial F_+} &= -\rho F \frac{\partial x_0}{\partial F_+} + (\sigma + \mu) \left(\frac{\partial x_1}{\partial F_+} + \frac{\partial x_2}{\partial F_+} \right) \\ \frac{d}{da} \frac{\partial x_1}{\partial F_+} &= \rho(F - F_+) \frac{\partial x_0}{\partial F_+} - (\sigma + \mu + \beta\Lambda_-) \frac{\partial x_1}{\partial F_+} - \rho x_0 \\ \frac{d}{da} \left(\frac{\partial x_1}{\partial F_+} + \frac{\partial x_2}{\partial F_+} \right) &= \rho F \frac{\partial x_0}{\partial F_+} - (\sigma + \mu + \beta) \left(\frac{\partial x_1}{\partial F_+} + \frac{\partial x_2}{\partial F_+} \right) + \beta \frac{\partial x_1}{\partial F_+}, \end{aligned}$$

where $x_0 \geq 0$. All off-diagonal terms and the inhomogeneous term are ≤ 0, and the initial conditions for $\partial x_0/\partial F_+$, $\partial x_1/\partial F_+$, and $\partial x_1/\partial F_+ + \partial x_2/\partial F_+$ are equal to zero. Therefore we find that $\partial x_0/\partial F_+(a), \partial x_1/\partial F_+(a), \partial x_1/\partial F_+(a) + \partial x_2/\partial F_+(a) \leq 0$ for all a, and also $\partial \bar{x}/\partial F_+(a) \leq 0$. Similarly, if we replace F_+ by Λ_- in the partial derivative and $-\rho x_0$ by $-\beta x_1$ then we also find that x_0, x_1, and x_1+x_2 are monotonically decreasing functions of Λ_-. Together with (B.4) this shows that G_1 is monotonically increasing in both F_+ and Λ_-, i.e. $D_1 G_1(F_+, \Lambda_-) \leq 0$ and $D_2 G_1(F_+, \Lambda_-) \leq 0$.

Remark 4. *The variable x_2 is not necessarily monotone in F_+ or Λ_-. One can find parameter values for which we find that $\partial x_2/\partial E(a)$, $E = F_+, \Lambda_-$, is neither nonpositive nor nonnegative as a function of a.*

Note that the feedback function G_2 for Λ_- involves x_2. The arguments to prove monotonicity and sublinearity do not seem to work for G_2. Numerical investigation strongly suggest that G_2 is indeed monotonically increasing as a function of both F_+ and Λ_- as well as sublinear. So far, we have not been able to provide a proof.

Nevertheless, once we show that both G_1 and G_2 are monotonically increasing functions of environmental variables F_+ and Λ_- and sublinear, Krasnoselskii's method then provides a proof that for $R_0 < 1$ only the trivial solution exists and for $R_0 > 1$ there exists a unique nontrivial solution to (B.3).

Chapter 5

Generalizations of the binding site model: it's just bookkeeping

K.Y. Leung

Abstract

In this chapter we consider several straightforward generalizations of the model for the spread of infection on a dynamic network that incorporates demography (Chapters 3 and 4). These generalizations are such that the conditional independence for the binding sites of an individual are maintained. We consider generalizations related to the partnership capacity, gender, partnership types, and the infectious disease. We believe that the binding site formalism also allows for generalizations related to the demographic process. This is left for future work due to time limitations.

This chapter serves to illustrate the strength and flexibility of the binding site formalism of Chapter 4. We show that, due to the systematic approach of the formalism, implementing the generalizations boils down to doing the bookkeeping right. This can be more subtle than one might think at first, see Section 6, which was added at a very late stage (indicating that one might add to the title of this chapter: 'is it?').

1 Introduction

In Chapters 2, 3, and 4 we considered the spread of infection on a network that is dynamic in partnership formation and separation as well as demographic turnover. The model described a partnership network model for a homosexual population with one fixed partnership capacity n and one type of partnerships. The binding site formalism of Chapter 4 allows for many generalizations. In this text we will focus on generalizations that, to a certain extent, preserve the independence of binding sites of an individual.

We can subdivide the generalizations of the model in this chapter into two categories: (1) generalizations of the network and (2) generalizations of the disease. Throughout this chapter we maintain the (limiting) assumption that disease does not influence partnership dynamics or the demographic process (but we belief that this assumption can be relaxed, see Section 5 of Chapter 4).

In the following we will mostly try to stick to our conventions and notation of Chapter 4. As before, we will sometimes say that a binding site has a certain property when it is really a property of the owner of the binding site, e.g. when we say that a binding site is born at time t_b, then we really mean that the *owner* of the binding site is born at time t_b. We consider the following four generalizations:

(i) Partnership capacity as a random variable Partnership capacity n may vary between individuals. An individual has a partnership capacity n with probability $\mathbb{P}(N = n)$, $n = 1, 2, \ldots$, with N a random variable. Partnership capacity does *not* change in the course of the life of an individual.

(ii) Steady and casual partnerships There may be different partnership types in the population. To illustrate the ideas and to keep things simple we consider two types of partnerships: steady and casual. Each type of partnership may have a different acquisition and dissolution rate and transmission rates may depend on partnership type.

(iii) Heterosexual population We may want to distinguish between gender. We consider a heterosexual population where partnerships are between men and women. Men and women may have different life expectancies and the male-to-female transmission rate may be different from the female-to-male transmission rate.

(iv) Multiple stages of infection We may generalize the infectious disease to include multiple stages of infection (again, to illustrate the ideas and to keep things simple we only consider two stages of infection in this chapter). This generalization is motivated by HIV where we know the infectiousness is not constant throughout the life of an infectious individual [107]. Roughly, HIV is characterized by a initial phase of high infectiousness, which is followed by a long chronic phase of low infectiousness (that increases again in the AIDS stage).

So the four generalizations under consideration pertain to different aspects of the network. Partnership capacity and gender are really individual-level (i-level) characteristics.

In both (i) and (iii), the binding sites of an individual are all (conditionally) independent and identically distributed. These i-level characteristics have different effects at the binding site level: partnership capacity does not influence the dynamics at the binding site level while gender does. On the other hand, (ii) affects binding site characteristics: each binding site has associated with it the type of partnership it can form, and as a consequence an individual can have different types of binding sites. Finally, (iv) has no influence on the network structure itself, and in that sense it is different from the former three.

In Section 2 we consider the influence of (i), (ii), and (iii) on the network model. For each generalization separately, we describe the network dynamics and some key network statistics. Next, in Section 3, we superimpose infection on the network. For the first three generalizations, i.e. the generalizations of the network, we restrict ourselves to an SI infection, which is the simplest compartmental model. The advantage of this is that there are less environmental variables to consider. Finally, we consider (iv).

We will follow the systematic scheme of Chapter 4 that relates the binding site level, i-level, and population level (p-level) to each other:

step 1. Binding site probabilities

step 2. Environmental variables: definition in terms of p-level fractions

step 3. i-level probabilities

step 4. p-level fractions

step 5. Environmental variables in terms of binding site probabilities (combining 2, 3, 4)

Note that, in absence of infection, the feedback from the environmental to the binding site level (and i-level) comes into play in the rate of partner acquisition, i.e. in fractions of free binding sites. The network structure stabilizes in generalizations (i), (ii), and (iii) (as in the original setting Chapter 2) so that we can assume the environment to be constant in the infection-free setting.

In the presence of infection the environment is in general *not* constant. In addition to fractions of free binding sites (that have now associated with them a disease status, i.e. free binding sites that have susceptible or infectious owners), we need to deal with environmental variables that arise from the mean field at distance one assumption. In Section 3 we focus on susceptible binding site probabilities and work out the details for closing the feedback loop by way of the systematic five-step approach. For each generalization, the environmental variables can be expressed in terms of (the history of) susceptible binding site probabilities. As in Chapter 4, also here it is possible to consider infectious binding site probabilities. However, in order to close the system, there is no need to do so (with the exception of (iv)). Therefore, in this chapter, we do not discuss what happens after susceptibility is lost. Yet we want to stress that it is certainly possible to consider the dynamics of infectious individuals.

In Section 4, without working out all details, we explain in some more generality how the infectious disease dynamics on the network are fully described by a set of renewal

equations for the environmental variables. Furthermore, we explain how one can characterize the epidemiological quantities R_0, r, and the endemic steady state via this system of renewal equations. Section 4 is more or less a summary of the essential steps taken in Sections 4.3 and 4.4 of Chapter 4.

The aim of this chapter is mostly to illustrate the flexibility and generality of the binding site framework. The generalizations can be implemented by following these 5 steps that relate the binding-site-, individual-, and population-level to each other. Arguably, the most difficult aspect of this chapter was in deciding on the notation. We tried to make the notation consistent with earlier chapters. We hope that the notation will be clear from the context or at least not too confusing.

Note added in proof. As it turns out, it is dangerous to work from the assumption that generalization (i) is very easy to implement by just averaging over all possible partnership capacities n. While this is true when considering the network structure, this is no longer the case when consider the spread of an infectious disease on the network. We treat this generalization separately in Section 6.2 at the end of this chapter.

2 Network dynamics

2.1 Steady and casual partnerships

An individual is assumed to have n_s steady and n_c casual binding sites. Given that the individual does not die in the period under consideration, all $n_s + n_c$ binding sites are *independent* of one another. Furthermore, all n_s steady (n_c casual) binding sites are identically distributed. Finally, we assume that two individuals in a partnership agree on the nature of their partnership (steady or casual), i.e. binding sites can only connect to binding sites of the same type.

2.1.1 Model formulation

At the binding site level, we have the following dynamics. A steady occupied binding site becomes free at rate $\sigma_s + \mu$ and a steady free binding site becomes occupied at rate $\rho_s F(s)$ while a casual occupied binding site becomes free at rate $\sigma_c + \mu$ and a casual free binding site becomes occupied at rate $\rho_c F(c)$. Here $F(s)$ $\big(F(c)\big)$ is the fraction of free steady (casual) binding sites in the pool of all steady (casual) binding sites. In general we think of $\rho_s \leq \rho_c$, $\sigma_s \leq \sigma_c$, i.e. casual partners are acquired at a higher rate but at the same time also lost at a higher rate than steady partners. As per usual, $F(s)$ and $F(c)$ are yet to be specified.

Let $\varphi(s)(a \mid t_b)$ denote the probability that a steady binding site, given time of birth t_b, is free at age a. The probability $\varphi(s)(a \mid t_b)$ satisfies

$$\frac{d\varphi}{da}(s)(a \mid t_b) = -\rho_s F(s)(a + t_b)\, \varphi(s)(a \mid t_b) + (\sigma_s + \mu)\big(1 - \varphi(s)(a \mid t_b)\big),$$

with birth condition $\varphi(s)(0 \mid t_b) = 1$. Similarly, by replacing s by c we find the probability $\varphi(c)(a \mid t_b)$ for a casual binding site.

The state of an individual is now given by (k, m) where k and m denote the number of steady and casual partners of the individual, respectively, $0 \leq k \leq n_s$, $0 \leq m \leq n_c$. Given that an individual does not die in the period under consideration, we have probabilities $p_{(k,m)}(a \mid t_b)$ that an individual, born at time t_b, has state (k, m) at age a. In terms of binding site probabilities:

$$p_{(k,m)}(a \mid t_b) = \binom{n_s}{k}\binom{n_c}{m}\Big(\varphi(s)^{n-k}\big(1-\varphi(s)\big)^k\varphi(c)^{n-m}\big(1-\varphi(c)\big)^m\Big)(a \mid t_b).$$

We can express p-level fractions $P_{(k,m)}(t)$ in terms of binding site probabilities:

$$P_{(k,m)}(t) = \int_0^\infty \mu e^{-\mu a} p_{(k,m)}(a \mid t-a)da.$$

The feedback conditions are

$$F(s) = \frac{1}{n_s}\sum_{k,m}(n_s - k)P_{(k,m)}, \tag{2.1}$$

$$F(c) = \frac{1}{n_c}\sum_{k,m}(n_c - m)P_{(k,m)}, \tag{2.2}$$

and, as in the original setting, we find that the dynamics of $F(s)$ and $F(c)$ decouple, i.e.

$$\frac{dF(j)}{dt} = \mu - \mu F(j) + (\sigma_j + \mu)\big(1 - F(j)\big) - \rho_j F(j)^2,$$

$j = s, c$. We may assume that $F(s)$ and $F(c)$ are constant (and given by (3.2) with the parameters equipped with subscript s or c where appropriate). We denote these constants by $\bar{F}_s$ and $\bar{F}_c$, respectively. Note that the argument t_b in probabilities φ and $p_{(k,m)}$ no longer matter and, as per usual, we omit these from now on and write $\varphi(\cdot)(a)$ and $p_{(k,m)}(a)$ instead. In terms of binding site probabilities, we find

$$\bar{F}_s = \int_0^\infty \mu e^{-\mu a}\varphi(s)(a)da = \frac{\sigma_s + 2\mu}{\rho_s\bar{F}_s + \sigma_s + 2\mu}$$
$$\bar{F}_c = \int_0^\infty \mu e^{-\mu a}\varphi(c)(a)da = \frac{\sigma_c + 2\mu}{\rho_c\bar{F}_c + \sigma_c + 2\mu}.$$

2.1.2 Network statistics

Note that the mean number of steady partnerships is equal to $\sum_{k,m} kP_{(k,m)} = n_s(1-\bar{F}_s)$ while the mean number of casual partnerships is $\sum_{k,m} mP_{(k,m)} = n_c(1-\bar{F}_c)$. So the probability that a randomly chosen partnership is of type j is equal to

$$\pi_j := \frac{n_j(1-\bar{F}_j)}{n_s(1-\bar{F}_s) + n_c(1-\bar{F}_c)},$$

$j = s, c$, with $\pi_s + \pi_c = 1$. Partnerships of type j have a mean partnership duration of

$$d_P(j) = \frac{1}{\sigma_j + 2\mu}.$$

Mean partnership duration in the population is $\bar{d}_P = \pi_s d_P(s) + \pi_c d_P(c)$. The mean lifetime number of partners $\bar{\theta}$ is the sum of the mean lifetime number of steady and casual partners, i.e. $\bar{\theta} = \theta(s) + \theta(c)$ with

$$\theta(j) = \frac{\rho_j \bar{F}_j (\sigma_j + 2\mu) n_j}{\mu(\rho_j \bar{F}_j + \sigma_j + 2\mu)},$$

$j = s, c$.

We can also find an explicit expression for the concurrency index in the setting of casual and steady partnerships. Consider a randomly chosen partnership, then it is with probability π_s a steady partnership and with $\pi_c = 1 - \pi_s$ a casual partnership. If it is a partnership of type j, then the expected number of additional partners is

$$\frac{\sum_{k,m}(k+m)\ell P_{(k,m)}}{\sum_{k,m} \ell P_{(k,m)}} - 1,$$

where $\ell = k$ if $j = s$ and $\ell = m$ if $j = c$. Therefore we find that

$$\kappa_P = \pi_s \left(\frac{\sum_{k,m}(k+m)kP_{(k,m)}}{\sum_{k,m} kP_{(k,m)}} - 1 \right) + \pi_c \left(\frac{\sum_{k,m}(k+m)mP_{(k,m)}}{\sum_{k,m} mP_{(k,m)}} - 1 \right).$$

We can express κ_P explicitly in terms of model parameters. First of all,

$$\sum_{k,m} \ell^2 P_{(k,m)} = n_j(1 - \bar{F}_j) \left(1 + \frac{2\rho_j \bar{F}_j (n_j - 1)}{2(\rho_j \bar{F}_j + \sigma_j + \mu) + \mu} \right),$$

and $\sum_{k,m} \ell P_{(k,m)} = n_j(1 - \bar{F}_j)$, where $\ell = k$ for $j = s$ and $\ell = m$ for $j = c$. Next,

$$\begin{aligned}
&\sum_{k,m} k\, m P_{(k,m)} = \\
&\sum_{k,m} k\, m \binom{n_s}{k} \binom{n_c}{m} \\
&\quad \int_0^\infty \mu e^{-\mu a} \Big(\varphi(s)^{n_s - k} (1 - \varphi(s))^k \varphi(c)^{n_c - m} (1 - \varphi(c))^m \Big)(a)\, da \\
&= \int_0^\infty \mu e^{-\mu a} n_s \left(1 - \varphi(s)(a)\right) n_c \left(1 - \varphi(c)(a)\right) da \\
&= \frac{n_s \rho_s \bar{F}_s}{\rho_s \bar{F}_s + \sigma_s + 2\mu} \frac{n_c \rho_c \bar{F}_c}{\rho_c \bar{F}_c + \sigma_c + 2\mu} \frac{\rho_c \bar{F}_c + \rho_s \bar{F}_s + \sigma_c + \sigma_s + 4\mu}{\rho_c \bar{F}_c + \rho_s \bar{F}_s + \sigma_c + \sigma_s + 3\mu} \\
&= n_s(1 - \bar{F}_s) n_c (1 - \bar{F}_c) \left(1 + \frac{\mu}{\rho_c \bar{F}_c + \rho_s \bar{F}_s + \sigma_c + \sigma_s + 3\mu} \right).
\end{aligned}$$

Therefore,

$$\kappa_P = \sum_{j=s,c} \pi_j \left\{ \frac{2\rho_j \bar{F}_j (n_j - 1)}{2(\rho_j \bar{F}_j + \sigma_j + \mu) + \mu} + n_{j'}(1 - \bar{F}_{j'}) \left(1 + \frac{\mu}{\rho_c \bar{F}_c + \rho_s \bar{F}_s + \sigma_c + \sigma_s + 3\mu} \right) \right\}.$$

(where j' is the opposite of j so if $j = s$ then $j' = c$ and the other way around). The first term in the $\{\}$-brackets corresponds to the expected number of additional partners of the *same* type as the randomly chosen partnership while the second term corresponds to the expected number of additional partners of the *opposite* type.

2.2 Heterosexual population

We assume that males and females have partnership capacities n_m and n_f, respectively (which is fixed for the entire gender). The sex ratio males : females in the population is assumed to be $1 : x$.

2.2.1 Model formulation

We let g denote the gender of an individual with $g = m$ for men and $g = f$ for women. Furthermore we let g' denote the gender opposite to g (if $g = m$ then $g' = f$ and the other way around). We assume that men and women may have different constant per capita death rates μ_m and μ_f. An occupied binding site of gender g becomes free at rate $\sigma + \mu_{g'}$. A free binding site of gender g becomes occupied at a rate $\rho_g F(g')$. Here $F(g')$ denotes the fraction of binding sites of gender g' in the pool of all binding sites of gender g'. The two parameters ρ_m and ρ_f are related to each other in the following way:

$$\rho_m n_m = \rho_f n_f x. \tag{2.3}$$

Note that the rate at which a free binding site of gender g becomes occupied is dependent on the fraction of free binding sites of gender g' but also on the parameter ρ_g which is not necessarily equal to $\rho_{g'}$. The influence of the sex ratio and the different partnership capacities for men and women are incorporated in these parameters ρ_g. We explain this by considering the limit of a finite population size in Remark 1.

Let $\varphi(g)(a \mid t_b)$ denote the probability that a binding site of gender g, given time of birth t_b, is free at age a and does not die in the period under consideration. The probability $\varphi(g)(a \mid t_b)$ satisfies

$$\frac{d\varphi}{da}(g)(a \mid t_b) = -\rho_g F(g')(a + t_b)\, \varphi(g)(a \mid t_b) - (\sigma + \mu_{g'}) \big(1 - \varphi(g)(a \mid t_b)\big),$$

$\varphi(g)(0 \mid t_b) = 1.$

Now consider an individual of gender g and suppose it does not die in the period under consideration. Then the i-level probability $p_k(g)(a \mid t_b)$ in terms of binding site probabilities is equal to

$$p_k(g)(a \mid t_b) = \binom{n_g}{k}\Big(\varphi(g)^{n_g-k}\big(1-\varphi(g)\big)^k\Big)(a \mid t_b),$$

$0 \leq k \leq n_g$, $g = m, f$. The fraction of individuals of the population of gender g that has k partners is given by

$$P_k(g)(t) = \int_0^\infty \mu_g e^{-\mu_g a} p_k(g)(a \mid t-a)da.$$

The feedback condition for the fractions of free binding sites of gender g are

$$F(g)(t) = \frac{1}{n_g}\sum_k (n_g - k)P_k(g)(t).$$

The dynamics of $F(m)$ and $F(f)$ form a closed system:

$$\begin{aligned}\frac{dF(m)}{dt} &= \mu_m - \mu_m F(m) - \rho_m F(m)F(f) + (\sigma+\mu_f)\big(1-F(m)\big)\\ \frac{dF(f)}{dt} &= \mu_f - \mu_f F(f) - \rho_f F(m)F(f) + (\sigma+\mu_m)\big(1-F(f)\big)\end{aligned} \tag{2.4}$$

From this two-dimensional system we find that $\big(F(m), F(f)\big)$ converges to some $(\bar{F}_m, \bar{F}_f)$ for $t \to \infty$. Actually, we can eliminate one of the two sexes (from our bookkeeping that is) due to consistency between males and females. Indeed, since we are considering a heterosexual population, consistency requires that the total number of partnerships that men have is equal to the total number of partnerships that women have, i.e.

$$\sum_k kP_k(m) = x\sum_k kP_k(f). \tag{2.5}$$

(where x accounts for sex ratio of men and women). by considering the derivative of both left- and right-hand side that

$$\begin{aligned}\frac{d}{dt}\sum_k kP_k(m) &= \rho_m n_m F(m)F(f) - (\sigma+\mu_f)\sum_k kP_k(m) - \mu_m\sum_k kP_k(m),\\ \frac{d}{dt}\sum_k kP_k(f) &= \rho_f n_f F(m)F(f) - (\sigma+\mu_m)\sum_k kP_k(f) - \mu_f\sum_k kP_k(f),\end{aligned}$$

or equivalently

$$n_m(1-F(m)) = xn_f(1-F(f)). \tag{2.6}$$

The rate μ_f represents 'death of partner' while μ_m represents 'death of individual itself' in the ODE for $\sum_k kP_k(m)$ and the other way around for $\sum_k kP_k(f)$. Therefore, using (2.3), we find that if (2.5) holds for some time t_0 then it holds for all $t > t_0$.

We see we can express $F(m)$ in terms of $F(f)$: $F(m) = (n_m - xn_f)/n_m + xn_f/n_m F(f)$. The ODE for $F(f)$ can be written independent of $F(m)$:

$$\begin{aligned}\frac{dF(f)}{dt} &= \mu_f - \mu_f F(f) - \rho_f \left(\frac{n_m - xn_f}{n_m} + \frac{xn_f}{n_m} F(f) \right) F(f) \\ &\quad + (\sigma + \mu_m)\big(1 - F(f)\big).\end{aligned}$$

Hence we see that $F(f)$ converges to a constant $\bar{F}_f$ that we find by putting the right hand side of the ODE equal to zero and solve for $F(f)$:

$$\begin{aligned}\bar{F}_f &= \frac{\sqrt{4x\rho_f n_f n_m(\sigma + \mu_m + \mu_f) + (x\rho_f n_f - (\rho_f + n_f + n_m + \sigma)n_m)^2}}{2x\rho_f n_f} \\ &\quad - \frac{x\rho_f n_f - (\rho_f + n_f + n_m + \sigma)n_m}{2x\rho_f n_f} \\ \bar{F_m} &= \frac{n_m - xn_f}{n_m} + \frac{xn_f}{n_m}\bar{F}_f.\end{aligned}$$

Therefore we may assume that $F(f)$ is equal to this limit $\bar{F}_f$. Moreover, by setting the right hand side of (2.4) equal to zero, we find the $\bar{F}_g$ to satisfy

$$\bar{F}_g = \frac{\sigma + \mu_f + \mu_m}{\rho_g \bar{F}_{g'} + \sigma + \mu_f + \mu_m}. \tag{2.7}$$

Furthermore, we have the identity

$$\bar{F}_g = \int_0^\infty \mu_g e^{-\mu_g a} \varphi(g)(a) da.$$

Remark 1. *The influence of the sex ratio and partnership capacities n_m and n_f are incorporated in ρ_m and ρ_f (as well as any possible influence of population sizes).We explain this by first considering a finite population and then letting population sizes tend to ∞ in an appropriate way.*

Consider a finite population size $N = N_f + N_m$ with N_g denoting the number of individuals of gender g. We allow for $N_m \neq N_f$. Then the sex ratio men : women is $1 : x$ with $x = N_f/N_m$. The population dynamics are described as follows:

$$\begin{aligned}\frac{dN_f}{dt} &= B_f - \mu_f N_f \\ \frac{dN_m}{dt} &= B_m - \mu_m N_m \\ \frac{dN}{dt} &= B_f + B_m - (\mu_f N_f + \mu_m N_m)\end{aligned}$$

The number of binding sites of gender g is $n_g N_g$. Let X_g denote the number of free binding sites in the population, i.e. $X_g = F(g) n_g N_g$. Then the total rate at which new partnerships are formed is $\rho X_m X_f$. The dynamics of X_g are described by the following ODE:

$$\frac{dX_g}{dt} = n_g B_g - \mu_g X_g - \rho X_g X_{g'} + (\sigma + \mu_{g'})(n_g N_g - X_g),$$

where g' denotes the sex opposite to g. The ODE for $F(g) = X_g/(n_g N_g)$, the fraction *of binding sites of gender g in the pool of all binding sites of gender g is then*

$$\frac{dF(g)}{dt} = \frac{n_g B_g}{n_g N_g} - \mu_g F(g) - \rho\, n_{g'} N_{g'} F(f) F(m) + (\sigma + \mu_{g'})\big(1 - F(g)\big), \quad (2.8)$$

with $n_g B_g / n_g N_g = \mu_g$ when population size is stable. Let population sizes N_m and N_f tend to ∞ such that the sex ratio $1 : x$ of men and women does not change. At the same time we let $\rho \to 0$ such that ρN_m converges to a constant $\tilde{\rho}$ (and then, since the sex ratio is maintained in the limit, ρN_f converges to the constant $x\tilde{\rho}$). We let $\rho_f := \tilde{\rho}\, n_m$ and $\rho_m := x\tilde{\rho}\, n_f$. So we find that $\rho\, n_f N_f \to x\tilde{\rho}\, n_f = \rho_m$ and $\rho n_m N_m \to \tilde{\rho}\, n_m = \rho_f$. So we find that ρ_m and ρ_f are related to each other through (2.3)*. Then a male free binding site acquires a partner at rate $\rho_m F(f)$ while a female free binding site acquires a partner at rate $\rho_f F(m)$. We recover* (2.4) *for $F(f)$ and $F(m)$.*

2.2.2 Network statistics

We denote the probability that a randomly chosen individual in the population is male by

$$\pi := \frac{1}{1+x}.$$

Since death rates are gender specific, the life expectancies are as well. The lifespan for individuals of gender g is

$$L(g) = \frac{1}{\mu_g},$$

while the life expectancy in the population is $\bar{L} = \pi L(m) + (1-\pi) L(f)$. Mean partnership duration is equal to

$$d_P = \frac{1}{\sigma + \mu_m + \mu_f}.$$

Mean lifetime number of partners for a newborn individual of gender g is

$$\theta(g) = \frac{\rho_g \bar{F_{g'}} (\sigma + \mu_m + \mu_f) n_g}{\mu_g (\rho_g \bar{F_{g'}} + \sigma + \mu_m + \mu_f)},$$

with g' the gender opposite to g. The mean lifetime number of partners of a randomly chosen newborn individual in the population is $\bar{\theta} = \pi\theta(m) + (1-\pi)\theta(f)$. By using (2.7),

we find that we can rewrite the mean lifetime number of partners $\theta(m)$ and $\theta(f)$ for males and females as

$$\theta(g) = L(g)\frac{1}{d_P}n_g(1-\bar{F}_g).$$

Using consistency condition (2.6), we find that

$$\frac{\theta(m)}{\theta(f)} = x\frac{L(m)}{L(f)}. \tag{2.9}$$

So we see that, in a heterosexual population with a $1:1$ sex ratio, and mean life expectancy for males and females equal to one another, i.e. $L(m) = L(f)$, we obtain $\theta(m) = \theta(f)$ regardless of n_m and n_f. In case either the sex ratio is different or the mean life expectancy is different for males and females in the population, also the mean lifetime number of partners is different for males and females. (But these mean lifetime number of partners are related to each other through relation (2.9).)

Finally, consider the concurrency indices κ_P^m, κ_P^f, and κ_P^{popul} for males, females, and the population as a whole, respectively. Then we obtain

$$\begin{aligned}
\kappa_P^m &= \frac{2\rho_m\bar{F}_f(n_m-1)}{2(\rho_m\bar{F}_f+\sigma+\mu_f)+\mu_m},\\
\kappa_P^f &= \frac{2\rho_f\bar{F}_m(n_f-1)}{2(\rho_f\bar{F}_m+\sigma+\mu_m)+\mu_f},\\
\kappa_P^{\text{popul}} &= \pi\kappa_P^m + (1-\pi)\kappa_P^f.
\end{aligned}$$

3 The spread of infection on the network

In Sections 6.2, 3.2, and 3.3, we superimpose transmission of an SI infection on the network. We make the usual assumptions: individuals are either susceptible or infectious and once infectious they remain so with constant infectiousness for the rest of their lives. Infection has no influence on partnership formation or separation nor on the probability per unit of time of dying. Transmission of infection from an infectious to susceptible individual occurs at a constant rate β. In Section 3.4 we superimpose transmission of an SI_1I_2 infection on the network, we discuss the assumptions in more detail in that subsection.

In this section, not only are there environmental variables in the form of fractions of free binding sites that have susceptible or infectious owners, but also environmental variables concerned with the mean field at distance one assumption. For notational convenience we write $\boldsymbol{E}$ for the vector of environmental variables, which in each subsection will be a vector of different variables.

As in Chapter 4 we start at the susceptible binding site level. By following the systematic five-step approach we end each subsection by expressing the environmental variables in terms of (the history) of susceptible binding site probabilities.

Binding sites in Sections 6.2, 3.2, and 3.3 can be in one of three states:

- 0 - free
- 1 - occupied by a susceptible partner
- 2 - occupied by an infectious partner

In Section 3.4, we need to differentiate between infectious partners that are in either stage 1 or stage 2 of infection, leading to an additional state (but see Section 3.4 for the details).

3.1 Partnership capacity as a random variable

Note added in proof. This generalization is unfortunately much less straightforward than what one would think at first. It is treated separately in Section 6.2.

3.2 Steady and casual binding sites

The rate of transmission can in principle be different in casual and steady partnerships due to e.g. different risk behaviour for each type of partnership. Therefore we assume that there are transmission rates β_s and β_c for steady and casual partnerships, respectively.

Let $F_{\pm}(j)$ denote the fraction of free $\pm$ binding sites of type j, $j = s, c$. The mean field at distance one terms are of the form $\Lambda^j_-(j')$ that are interpreted as the the mean number of infectious partners of type j of a susceptible type j' partner of a susceptible individual, $j, j' = s, c$ (so four of these environmental variables in total). Then we can describe the dynamics of susceptible binding site probabilities of type j with the following system of differential equations:

$$\frac{dx(j)(a \mid t_b)}{da} = M_j\big(\boldsymbol{E}(j)(t_b + a)\big)\, x(j)(a \mid t_b),$$

with $M_j\big(\boldsymbol{E}(j)\big)$ the matrix

$$\begin{pmatrix} -\rho_j \bar{F}_j & \sigma_j + \mu & \sigma_j + \mu \\ \rho_j\big(F_j - F_+(j)\big) & -\big(\beta_s \Lambda^s_-(j) + \beta_c \Lambda^c_-(j) + \sigma_j + \mu\big) & 0 \\ \rho_j F_+(j) & \beta_s \Lambda^s_-(j) + \beta_c \Lambda^c_-(j) & -(\beta_j + \sigma_j + \mu) \end{pmatrix}.$$

An individual is assumed to be susceptible without any partners at birth (and therefore the same applies to all its binding sites). So we have the birth conditions

$$x_0(j)(0 \mid t_b) = 1, \quad x_1(j)(0 \mid t_b) = 0 = x_2(j)(0 \mid t_b).$$

with $j = s, c$. Next, we consider the i-level probability $p_{(-,\boldsymbol{k},\boldsymbol{m})}(a \mid t_b)$ that an individual is in state $(-, \boldsymbol{k}, \boldsymbol{m})$ at age a when born at time t_b, given that it does not die in the period under consideration. Here $\boldsymbol{k} = (k_1, k_2)$ and $\boldsymbol{m} = (m_1, m_2)$ with k_i the number of steady binding sites in state i and m_i the number of casual binding sites in state i, $i = 1, 2$. For

convenience, we let $k_0 = n_s - k_1 - k_2$ and $m_0 = n_c - m_1 - m_2$. From the $x(j)(a \mid t_b)$-probabilities we obtain i-level probabilities $p_{(-,\boldsymbol{k},\boldsymbol{m})}(a \mid t_b)$ by combinatorics:

$$p_{(-,\boldsymbol{k},\boldsymbol{m})}(a \mid t_b) = \frac{n_s!}{k_0!\,k_1!\,k_2!}\frac{n_c!}{m_0!\,m_1!\,m_2!} \Big(\big(x_0^{k_0}\,x_1^{k_1}\,x_2^{k_2}\big)(s)\,\big(x_0^{m_0}\,x_1^{m_1}\,x_2^{m_2}\big)(c)\Big)(a \mid t_b).$$

The i-level probabilities are lifted to p-level fractions $P_{(-,\boldsymbol{k},\boldsymbol{m})}(t)$ using the stable age distribution:

$$P_{(-,\boldsymbol{k},\boldsymbol{m})}(t) = \int_0^\infty \mu e^{-\mu a} p_{(-,\boldsymbol{k},\boldsymbol{m})}(a \mid t-a)da,$$

Taking into account binding site types, we find that the environmental variables are defined as follows:

$$\begin{aligned}
F_+(s)(t) &= \bar{F}_s - F_-(s)(t) = \bar{F}_s - \frac{1}{n_s}\sum_{\boldsymbol{k},\boldsymbol{m}} k_0 P_{(-,\boldsymbol{k},\boldsymbol{m})}(t),\\
F_+(c)(t) &= \bar{F}_c - F_-(c)(t) = \bar{F}_c - \frac{1}{n_c}\sum_{\boldsymbol{k},\boldsymbol{m}} m_0 P_{(-,\boldsymbol{k},\boldsymbol{m})}(t),\\
\Lambda^s_-(s)(t) &= \frac{\sum_{\boldsymbol{k},\boldsymbol{m}} k_1 k_2 P_{(-,\boldsymbol{k},\boldsymbol{m})}(t)}{\sum_{\boldsymbol{k},\boldsymbol{m}} k_1 P_{(-,\boldsymbol{k},\boldsymbol{m})}(t)},\\
\Lambda^s_-(c)(t) &= \frac{\sum_{\boldsymbol{k},\boldsymbol{m}} m_1 k_2 P_{(-,\boldsymbol{k},\boldsymbol{m})}(t)}{\sum_{\boldsymbol{k},\boldsymbol{m}} m_1 P_{(-,\boldsymbol{k},\boldsymbol{m})}(t)},\\
\Lambda^c_-(c)(t) &= \frac{\sum_{\boldsymbol{k},\boldsymbol{m}} m_1 m_2 P_{(-,\boldsymbol{k},\boldsymbol{m})}(t)}{\sum_{\boldsymbol{k},\boldsymbol{m}} m_1 P_{(-,\boldsymbol{k},\boldsymbol{m})}(t)},\\
\Lambda^c_-(s)(t) &= \frac{\sum_{\boldsymbol{k},\boldsymbol{m}} k_1 m_2 P_{(-,\boldsymbol{k},\boldsymbol{m})}(t)}{\sum_{\boldsymbol{k},\boldsymbol{m}} k_1 P_{(-,\boldsymbol{k},\boldsymbol{m})}(t)}.
\end{aligned}$$

Combining the three previous steps, in terms of binding site probabilities we find

$$\begin{aligned}
F_+(s)(t) &= \bar{F}_s - \int_0^\infty \mu e^{-\mu a}\big(\bar{x}(c)^{n_c}\,x_0(s)\,\bar{x}(s)^{n_s-1}\big)(a \mid t-a)da\\
F_+(c)(t) &= \bar{F}_c - \int_0^\infty \mu e^{-\mu a}\big(\bar{x}(s)^{n_s}\,x_0(c)\,\bar{x}(c)^{n_c-1}\big)(a \mid t-a)da
\end{aligned}$$

for the fractions of free binding sites, and

$$\Lambda^s_-(s)(t) = (n_s - 1)\frac{\int_0^\infty \mu e^{-\mu a}\big(\bar{x}(c)^{n_c}\, x_1(s)\, x_2(s)\, \bar{x}(s)^{n_s-2}\big)(a \mid t-a)da}{\int_0^\infty \mu e^{-\mu a}\big(\bar{x}(c)^{n_c}\, x_1(s)\, \bar{x}(s)^{n_s-1}\big)(a \mid t-a)da},$$

$$\Lambda^s_-(c)(t) = n_s\frac{\int_0^\infty \mu e^{-\mu a}\big(x_1(c)\, \bar{x}(c)^{n_c-1}\, x_2(s)\, \bar{x}(s)^{n_s-1}\big)(a \mid t-a)da}{\int_0^\infty \mu e^{-\mu a}\big(\bar{x}(s)^{n_s}\, x_1(c)\, \bar{x}(c)^{n_c-1}\big)(a \mid t-a)da},$$

$$\Lambda^c_-(c)(t) = (n_c - 1)\frac{\int_0^\infty \mu e^{-\mu a}\big(\bar{x}(s)^{n_s}\, x_1(c)\, x_2(c)\, \bar{x}(c)^{n_c-2}\big)(a \mid t-a)da}{\int_0^\infty \mu e^{-\mu a}\big(\bar{x}(s)^{n_s}\, x_1(c)\, \bar{x}(c)^{n_c-1}\big)(a \mid t-a)da},$$

$$\Lambda^c_-(t \mid s) = n_c\frac{\int_0^\infty \mu e^{-\mu a}\big(x_1(s)\, \bar{x}(s)^{n_s-1}\, x_2(c)\, \bar{x}(c)^{n_c-1}\big)(a \mid t-a)da}{\int_0^\infty \mu e^{-\mu a}\big(\bar{x}(c)^{n_c}\, x_1(s)\, \bar{x}(s)^{n_s-1}\big)(a \mid t-a)da}$$

for the mean field at distance one terms.

3.3 Heterosexual population

We assume there are rates β_m at which an infectious man transmits to his susceptible female partner and β_f at which an infectious woman transmits to her susceptible male partner. Furthermore, we deal with environmental variables concerning $F_\pm(g)$ fractions of free $\pm$ binding sites with owners of gender g, $g = m, f$. The mean field at distance one assumption is expressed in variables $\Lambda_-(g')$ that can be interpreted as the mean number of infectious partners (of gender g) of a susceptible partner (of gender g') of a susceptible individual of gender g, with $g, g' = m, f$ (and g' the gender opposite to gender g).

The dynamics of susceptible binding site probabilities $x(g)(a \mid t_b)$ are described by

$$\frac{dx(g)(a \mid t_b)}{da} = M_g\big(\boldsymbol{E}(g')(t_b + a)\big)\, x(g)(a \mid t_b),$$

with $M_g(\boldsymbol{E}(g'))$ the matrix

$$\begin{pmatrix} -\rho_g \bar{F}_{g'} & \sigma + \mu_{g'} & \sigma + \mu_{g'} \\ \rho_g(\bar{F}_{g'} - F_+(g')) & -(\beta_g \Lambda_-(g') + \sigma + \mu_{g'}) & 0 \\ \rho_g F_+(g') & \beta_g \Lambda_-(g') & -(\beta_{g'} + \sigma + \mu_{g'}) \end{pmatrix}.$$

An individual is assumed to be susceptible without any partners at birth (and therefore the same applies to all its binding sites). So we have the birth conditions

$$x_0(g)(0 \mid t_b) = 1, \quad x_1(g)(0 \mid t_b) = 0 = x_2(g)(0 \mid t_b).$$

From the x-probabilities we obtain i-level probabilities $p_{(-,\boldsymbol{k})}(g)(a \mid t_b)$ by combinatorics:

$$p_{(-,\boldsymbol{k})}(g)(a \mid t_b) = \frac{n_g!}{k_0!\, k_1!\, k_2!}\big({x_0}^{k_0}\, {x_1}^{k_1}\, {x_2}^{k_2}\big)(g)(a \mid t_b),$$

with $k_0 = n_g - k_1 - k_2$. The i-level probabilities are lifted to p-level fractions $P_{(-,\boldsymbol{k})}(g)(t)$ using the stable age distribution:

$$P_{(-,\boldsymbol{k})}(g)(t) = \int_0^\infty \mu_g e^{-\mu_g a} p_{(-,\boldsymbol{k})}(g)(a \mid t-a) da,$$

The environmental variables are defined as follows:

$$F_+(g)(t) = \bar{F}_g - F_-(g)(t) = \bar{F}_g - \frac{1}{n_g} \sum_{\boldsymbol{k}} k_0 P_{(-,\boldsymbol{k})}(g)(t),$$
$$\Lambda_-(g)(t) = \frac{\sum_{\boldsymbol{k}} k_1 k_2 P_{(-,\boldsymbol{k})}(g)(t)}{\sum_{\boldsymbol{k}} k_1 P_{(-,\boldsymbol{k})}(g)(t)}.$$

Combining the three previous steps, in terms of binding site probabilities we obtain

$$F_+(g)(t) = \bar{F}_g - \int_0^\infty \mu_g \, e^{-\mu_g a} \big(x_0 \, \bar{x}^{n_g - 1}\big)(g)(a \mid t-a) da,$$
$$\Lambda_-(g)(t) = (n_g - 1) \frac{\int_0^\infty \mu_g \, e^{-\mu_g a} \big(x_1 \, x_2 \, \bar{x}^{n_g - 2}\big)(g)(a \mid t-a) da}{\int_0^\infty \mu_g \, e^{-\mu_g a} \big(x_1 \, \bar{x}^{n_g - 1}\big)(g)(a \mid t-a) da},$$

for $g = m, f$.

3.4 Multiple stages of infection

In this section we generalize the SI infection without recovery to multiple stages of infection. Consider two stages that we denote by I_1, and I_2 (in principle this can be extended to any number of stages). The usual assumptions apply. We let $-$ correspond with susceptible as usual, while $+$ and $++$ correspond to infectious stages 1 and 2, respectively.

Newly infected individuals are in stage 1 of infection. The rate at which such an infectious individual transmits to a susceptible is β_1. $+$ individuals either die at rate μ or they enter stage 2 of infection I_2 at rate γ. In stage 2 of infection the transmission rate is β_2. Next, individuals in stage 2 may also die at rate μ. A binding site can now be in one of four states

- 0 - free
- 1 - occupied by a susceptible partner
- 2 - occupied by an stage 1 infectious partner
- 3 - occupied by an stage 2 infectious partner

(Note the somewhat unfortunate notation: state 2 corresponds to a stage 1 infectious partner. Moreover, state 3 corresponds to a stage 2 infectious partner and not a recovered partner as was the case in Chapter 4.)

Partner acquisition depends on the fraction F_- of free and susceptible binding sites, the fraction F_+ of free and infectious stage 1 binding sites, and the fraction F_{++} of

free and infectious stage 2 binding sites. These fractions of free binding sites satisfy the consistency relation $\bar{F} = F_- + F_+ + F_{++}$. Furthermore, feedback from the environment is also incorporated in the mean field at distance one assumption. We have environmental variables $\Lambda_-(i)$, $i = +, ++$, which can be interpreted as the mean number of infectious partners in stage i of infection of a susceptible partner of a susceptible individual.

3.4.1 Susceptible

The dynamics of susceptible binding site probabilities x_i are described by:

$$\frac{dx(a \mid t_b)}{da} = M\big(\boldsymbol{E}(t_b + a)\big)\, x(a \mid t_b),$$

with $M(\boldsymbol{E})$ the matrix

$$\begin{pmatrix} -\rho F & \sigma+\mu & \sigma+\mu & \sigma+\mu \\ \rho F_- & -(\star+\sigma+\mu) & 0 & 0 \\ \rho F_+ & \star & -\big(\beta_1+\gamma+\sigma+\mu\big) & 0 \\ \rho(F-F_--F_+) & 0 & \gamma & -(\beta_2+\sigma+\mu) \end{pmatrix},$$

where we abbreviate $\star = \beta_1\Lambda_-(+) + \beta_2\Lambda_-(++)$.

An individual is assumed to be susceptible without any partners at birth (and therefore the same applies to all its binding sites). So we have the birth conditions

$$x_0(0 \mid t_b) = 1, \quad x_1(0 \mid t_b) = 0 = x_2(0 \mid t_b) = x_3(0 \mid t_b).$$

From the x-probabilities we obtain i-level probabilities $p_{(-,\boldsymbol{k})}(a \mid t_b)$, $\boldsymbol{k} = (k_1, k_2, k_3)$, by combinatorics:

$$p_{(-,\boldsymbol{k})}(a \mid n, t_b) = \frac{n!}{k_0!\, k_1!\, k_2!\, k_3} \left(x_0^{k_0}\, x_1^{k_1}\, x_2^{k_2}\, x_3^{k_3}\right)(a \mid t_b), \tag{3.1}$$

with $k_0 = n - k_1 - k_2 - k_3$. The i-level probabilities are lifted to p-level fractions $P_{(-,\boldsymbol{k})}(t)$ using the stable age distribution:

$$P_{(-,\boldsymbol{k})}(t) = \int_0^\infty \mu e^{-\mu a} p_{(-,\boldsymbol{k})}(a \mid t-a) da. \tag{3.2}$$

The environmental variables can be defined in terms of p-level fractions as follows:

$$\begin{aligned} F_-(t) &= \frac{1}{n}\sum_{\boldsymbol{k}} k_0 P_{(-,\boldsymbol{k})}(t), \\ F_+(t) &= \frac{1}{n}\sum_{\boldsymbol{k}} k_0 P_{(+_1,\boldsymbol{k})}(t), \\ \Lambda_-(+)(t) &= \frac{\sum_{\boldsymbol{k}} k_1 k_2 P_{(-,\boldsymbol{k})}(t)}{\sum_{\boldsymbol{k}} k_1 P_{(-,\boldsymbol{k})}(t)}, \\ \Lambda_-(++)(t) &= \frac{\sum_{\boldsymbol{k}} k_1 k_3 P_{(-,\boldsymbol{k})}(t)}{\sum_{\boldsymbol{k}} k_1 P_{(-,\boldsymbol{k})}(t)}. \end{aligned} \tag{3.3}$$

Combining the previous three steps, we can immediately find expressions for F_-, $\Lambda_-(+)$, and $\Lambda_-(++)$ in terms of x:

$$
\begin{aligned}
F_-(t) &= \int_0^\infty \mu e^{-\mu a}\big(x_0 \bar{x}^{n-1}\big)(a \mid t-a)da,\\
\Lambda_-(+) &= (n-1)\frac{\int_0^\infty \mu e^{-\mu a}\big(x_1 x_2 \bar{x}^{n-2}\big)(a \mid t-a)da}{\int_0^\infty \mu e^{-\mu a}\big(x_1 \bar{x}^{n-1}\big)(a \mid t-a)da},\\
\Lambda_-(++) &= (n-1)\frac{\int_0^\infty \mu e^{-\mu a}\big(x_1 x_3 \bar{x}^{n-2}\big)(a \mid t-a)da}{\int_0^\infty \mu e^{-\mu a}\big(x_1 \bar{x}^{n-1}\big)(a \mid t-a)da}.
\end{aligned}
$$

Concerning F_+, we need to turn to stage 1 infectious binding sites (similar to Chapter 4).

3.4.2 After susceptibility is lost: closing the feedback loop for F_+

Consider a binding site that was born at time t_b and infected at age a_+ and remains alive and in stage 1 of infection for the period under consideration. Note that age a_+ for this individual corresponds to calendar time $t_+ = t_b + a_+$. Let $y_i^{\mathrm{e}}(a \mid t_b, a_+)$ denote the probability that the exceptional binding site is in state i at age a and $y_i(a \mid t_b, a_+)$ the same probability for a non-exceptional binding site.

Then, at age a_+, the exceptional binding site is for certain in state 2, while the other $n-1$ binding site states are distributed according to $x(a_+ \mid t_b)/\bar{x}(a_+ \mid t_b)$:

$$
\begin{aligned}
y_0^{\mathrm{e}}(a_+ \mid t_b, a_+) &= 0, \qquad & y_0(a_+ \mid t_b, a_+) &= \frac{x_0}{\bar{x}}(a_+ \mid t_b),\\
y_1^{\mathrm{e}}(a_+ \mid t_b, a_+) &= 0, \qquad & y_1(a_+ \mid t_b, a_+) &= \frac{x_1}{\bar{x}}(a_+ \mid t_b),\\
y_2^{\mathrm{e}}(a_+ \mid t_b, a_+) &= 1, \qquad & y_2(a_+ \mid t_b, a_+) &= \frac{x_2}{\bar{x}}(a_+ \mid t_b),\\
y_3^{\mathrm{e}}(a_+ \mid t_b, a_+) &= 0, \qquad & y_3(a_+ \mid t_b, a_+) &= \frac{x_3}{\bar{x}}(a_+ \mid t_b).
\end{aligned}
$$

The dynamics of stage 1 infectious binding sites are described by:

$$
\frac{dy(a \mid t_b, a_+)}{da} = M_+\big(\boldsymbol{E}(t_b + a)\big)\, y(a \mid t_b, a_+), \tag{3.4}
$$

with $M_+(\boldsymbol{E})$ the matrix

$$
\begin{pmatrix}
-\rho F & \sigma+\mu & \sigma+\mu & \sigma+\mu\\
\rho F_- & -(\star+\sigma+\mu) & 0 & 0\\
\rho F_+ & \star & -(\sigma+\mu+\gamma) & 0\\
\rho(F-F_--F_+) & 0 & \gamma & -(\sigma+\mu)
\end{pmatrix},
$$

where we abbreviate $\star = \beta_1\Lambda_+(+) + \beta_2\Lambda_+(++)$.

Note that there is no rate γ in $M_+(\boldsymbol{E})$ of leaving the system of stage 1 infectious binding sites as we assume that they remain in stage 1 in the period under consideration.

Now the $\Lambda_+(i)$ terms are defined in terms of p-level probabilities $P_{(-,\boldsymbol{k})}$ (and therefore we immediately can express them in terms of susceptible binding site probabilities x). However for what we are after we do not need them, therefore we do not elaborate on the $\Lambda_+(i)$ in this chapter.

The probability $\phi_{(+,\boldsymbol{k})}(t_b, a \mid a_+)$ that an individual, born at time t_b and infected at age a_+, is in state $(+,\boldsymbol{k})$ at age $a \geq a_+$ is given by

$$\begin{aligned}\phi_{(+,\boldsymbol{k})}(a \mid t_b, a_+) = \\ \frac{n!}{k_0!\,k_1!\,k_2!\,k_3!}\left(\frac{k_0}{n}\,y_0^{\mathrm{e}}\,y_0^{k_0-1}y_1^{k_1}y_2^{k_2}y_3^{k_3} + \frac{k_1}{n}\,y_1^{\mathrm{e}}\,y_0^{k_0}y_1^{k_1-1}y_2^{k_2}y_3^{k_3}\right. \\ \left.+\frac{k_2}{n}\,y_2^{\mathrm{e}}\,y_0^{k_0}y_1^{k_1}y_2^{k_2-1}y_3^{k_3} + \frac{k_3}{n}\,y_3^{\mathrm{e}}\,y_0^{k_0}y_1^{k_1}y_2^{k_2}y_3^{k_3-1}\right)(a \mid t_b, a_+),\end{aligned}$$

where the reasoning is the same as in Chapter 4 (combinatorics). A susceptible individual becomes infected if infection is transmitted to this individual through one of its n binding sites. Infection is transmitted at rate β_1 and β_2 from a stage 1 and stage 2 infectious partner, respectively. Therefore, similar to the reasoning in Chapter 4, the contribution to the incidence of individuals of age a_+, born at time t_b and alive for the period under consideration, is given by

$$\beta_1 n x_2 \bar{x}^{n-1}(a_+ \mid t_b) + \beta_2 n x_3 \bar{x}^{n-1}(a_+ \mid t_b).$$

Then, taking into account all possible ages of infection $0 \leq a_+ \leq a$, and the probability that as yet transition to stage 2 of infection did not occur, the probability that an individual, born at time t_b, is in state $(+,\boldsymbol{k})$ at age a is given by

$$\begin{aligned}p_{(+,\boldsymbol{k})}(a \mid t_b) = \\ \int_0^a e^{-\gamma(a-a_+)}\big(\beta_1 x_2 + \beta_2 x_3\big) n \bar{x}^{n-1}(a_+ \mid t_b)\phi_{(+,\boldsymbol{k})}(a \mid t_b, a_+)da_+.\end{aligned}$$

The p-level fractions $P_{(+,\boldsymbol{k})}(t)$ at time t are, in terms of i-level probabilities, equal to

$$P_{(+,\boldsymbol{k})}(n)(t) = \int_0^\infty \mu e^{-\mu a} p_{(+,\boldsymbol{k})}(a \mid t-a)da. \tag{3.5}$$

In this way, the dynamics of infectious binding sites describe the dynamics of stage 1 infectious individuals and the population of such individuals. In particular, combining expression (3.5) for the p-level fractions $P_{(+,\boldsymbol{k})}$ with (3.3), we find that F_+ is defined in terms of infectious (and susceptible) binding sites as follows:

$$\begin{aligned}F_+(t) = \frac{1}{n}\int_0^\infty \mu e^{-\mu a}\int_0^a e^{-\gamma(a-a_+)}\big(\beta_1 x_2 + \beta_2 x_3\big) n \bar{x}^{n-1}(a_+ \mid t-a) \\ \big(y_0^{\mathrm{e}}\,\bar{y}^{n-1} + (n-1)\bar{y}^{\mathrm{e}}\,y_0\,\bar{y}^{n-2}\big)(a \mid t-a, a_+)da_+da.\end{aligned}$$

Since y^{e} and y are probability vectors, they sum to one, i.e. $\bar{y}^{\mathrm{e}}(a \mid t_b, a_+) = 1 = \bar{y}(a \mid t_b, a_+)$. Moreover, with φ_1 given by (4.3) of Chapter 4, since

$$y_0^{\mathrm{e}}(a \mid t_b, a_+) = \varphi_1(a - a_+),$$
$$y_0(a \mid t_b, a_+) = y_0^{\mathrm{e}}(a \mid t_b, a_+) + \frac{x_0}{\bar{x}}(a_+ \mid t_b)\, e^{-(\rho F+\sigma+\mu)(a-a_+)},$$

we can express F_+ in terms of the history of x:

$$F_+(t) = \frac{1}{n}\int_0^\infty \mu e^{-\mu a}\int_0^a e^{-\gamma(a-a_+)}(\beta_1 x_2 + \beta_2 x_3) n\, \bar{x}^{n-1}(a_+ \mid t-a)$$
$$\Big\{\varphi_1(a-a_+) + (n-1)\Big(\varphi_1(a-a_+)$$
$$+ \frac{x_0}{\bar{x}}(a_+ \mid t-a)\, e^{-(\rho F+\sigma+\mu)(a-a_+)}\Big)\Big\} da_+ da.$$

Finally, note that the mean duration of the primary stage of infection is, by the Markov property, equal to $d_A = \frac{1}{\gamma+\mu}$, while the mean duration of the secondary stage of infection is simply $\frac{1}{\mu}$. Then, the mean infectivity of an infectious individual is

$$\frac{\beta_1}{\gamma+\mu} + \frac{\gamma}{\gamma+\mu}\frac{\beta_2}{\mu},$$

where the first and second term correspond to the mean infectivity of an infectious individual in the first and second stage of infection, respectively.

5

4 Renewal equations and the characterization of r, R_0, and the endemic steady state

Here we summarize the general ideas and steps needed to characterize the epidemiological quantities of interest. We do not work out all the details for the four possible generalizations. But really, it all works in the same way as Section 4 of Chapter 4.

For all four different generalizations under consideration, the dynamics of susceptible binding sites were described by a system of the form

$$\frac{dx}{da}(a \mid t_b) = M\big(\boldsymbol{E}(t_b + a)\big)x(a \mid t_b), \tag{4.1}$$

where $M(\boldsymbol{E}(t_b + a))$ is the matrix corresponding to the possible transitions and the rates at which they occur between the states of a susceptible binding site. These rates are dependent on the environmental variables that are captured in the vector $\boldsymbol{E}$. The assumption that individuals are born susceptible without any partners translates into a birth condition

$$x(0 \mid t_b) = \mathbf{1}_B$$

(Note that in case of steady and casual partnerships and a heterosexual population, we needed to consider steady and casual binding site probabilities $x(s)$ and $x(c)$ and male

and female binding site probabilities $x(m)$ and $x(f)$, respectively, but the story is the same otherwise).

Recall that $x(a \mid t_b)$ is completely determined by

$$\boldsymbol{E}|_{[t_b, t_b+a]}$$

via (4.1). Next, via the systematic procedure, we were able to express all environmental variables as a function of the history of x. Therefore, for each generalization, we ended up with a closed system of renewal equations

$$\boldsymbol{E} = G(\boldsymbol{E}). \tag{4.2}$$

Incidentally, this system of equations also fully determines the dynamics of susceptible binding sites, susceptible individuals in states $(-, \ell)$, where ℓ is a vector describing the number of different partners in each of the possible disease states, and the fraction of the population in these states $(-, \ell)$.

The the endemic steady state is characterized as the nontrivial solution to a fixed point problem (4.2) (see Section 4.4 of Chapter 4 on a discussion about existence and uniqueness). The Malthusian parameter r and the basic reproduction ratio R_0 can also be derived from (4.2) similar to Section 4.3. First, one linearizes (4.1) and (4.2) around the disease free steady state. By doing so, one finds a decoupled subsystem (in Chapter 4 these were $\hat{x}_2$, $\hat{F}_+$, and $\hat{\Lambda}_-$). Then one can write a linear system of renewal equations for the environmental variables of the form

$$\tilde{b}(t) = \int_0^\infty \tilde{K}(\tau)\tilde{b}(t-\tau)d\tau \tag{4.3}$$

(in Chapter 4 there are two linear renewal equations (4.28) and (4.29) for $\hat{F}_+$, and $\hat{\Lambda}_-$, respectively).

From (4.3), we can obtain the characteristic equation and deduce threshold parameters r and R_0. We define

$$R_0 = \text{dominant eigenvalue of } \int_0^\infty \tilde{K}(\tau)d\tau. \tag{4.4}$$

Here $\int_0^\infty \tilde{K}(\tau)$ is a matrix whose matrix entries can all be evaluated explicitly. The Malthusian parameter r is defined as the real root (if it exists) of the *characteristic equation*

$$\det\left(I - \int_0^\infty e^{-\lambda\tau}\tilde{K}(\tau)d\tau\right) = 0 \tag{4.5}$$

such that the spectral radius of $\int_0^\infty e^{-\lambda\tau}\tilde{K}(\tau)d\tau$ equals 1. Note that r is necessarily the rightmost solution of the characteristic equation (4.5).

The definition (4.4) for R_0 yields a threshold parameter with threshold value of one for the stability of the disease free steady state of the p-level system. Moreover, this definition

yields the usual interpretation for R_0 as the expected number of secondary cases caused by one typical newly infected case at the beginning of an epidemic. (See Section 4.3 of Chapter 4 for a discussion on R_0 and r.)

Finally, note that it is certainly possible to derive R_0 for the different generalizations using the interpretation. One e.g. finds R_0 for Section 3.3 of a heterosexual population as $\sqrt{R_m R_f}$ where R_g is interpreted as the expected number of secondary cases caused by a typical case of gender g, $g = m, f$. These R_g are then found by considering 'R_0 in the homosexual population setting', but then with the parameters equipped with subscripts m and f where appropriate. This yields the same expression for R_0 as when one would follow the procedure via the renewal equation system described in this section (calculations not shown). The power of the latter approach lies in settings where it is not so straightforward to derive R_0 directly from the interpretation (moreover it can serve as a confirmation of the intuition).

5 Conclusions and Discussion

Note added in proof. In this section we really mean 'the three generalizations (ii), (iii), and (iv)' (and not generalization (i)). See also Section 6 (and the conclusions and discussions in Section 6.3).

In this chapter we considered four generalizations of the original model. The first three of these were concerned with the network model where we looked at (i) partnership capacity as a random variable, (ii) steady and casual partnerships, and (iii) a heterosexual population. The last generalization concerns the infectious disease where we considered (iv) an infection with multiple stages of infection. Network dynamics were described in Section 2 while the spread of infection on the network was described in Section 3.

A key feature of (i)-(iv) is that independence of binding sites is preserved. The systematic approach introduced in Chapter 4 was used to formulate the model for the different generalizations. By following the five steps that connects the binding-site-, i-, and p-level to each other. In essence, the model formulation was nothing more than bookkeeping.

The main purpose of this chapter was to illustrate the generality and flexibility of the binding site formalism by means of working out the bookkeeping for the four generalizations separately. Of course the different generalizations can also be combined. One can consider e.g. a heterosexual population with a two-stage infection (Chapter 7). The systematic approach can still be followed when combining different generalizations. The bookkeeping becomes more involved but the main ingredients do not change.

Concerning the infectious disease, besides generalizing to an infection with multiple stages of infection, also other compartmental models, such as SEIR and SIR, can easily be considered in this framework (as long as individuals, once infected, cannot become susceptible again). In Chapter 4 an SIR infection was considered. What we have not yet investigated are the possibilities in generalizing to a general infectivity function $\mathcal{F}(\tau)$ as in Section 2.5 of Chapter 4.

In Chapter 4 not only the spread of infection on a dynamic network with demography was considered, but also a static network and a dynamic network without demographic

turnover. Also for these two cases of a static network and a dynamic network without demographic turnover, one can implement the generalizations that were considered in this chapter. We considered a dynamic network with demography as that is the main object of study of this thesis, but also because the bookkeeping is most involved in this case.

Other relevant generalizations that are less straightforward were discussed in Section 5 of Chapter 4. These concern the demographic process. In particular, we believe it to be possible to include a disease induced death rate and to consider a general survival function. Unfortunately, due to time limitations, we did not yet have time to explore these further, but it is our believe that the binding site formalism is an excellent starting point for these generalizations. Other possible generalizations and limitations of the binding site formalism are also discussed in Chapter 8.

Finally, what is missing in this chapter is an analysis of the impact that the different generalizations could have on the transmission dynamics, or the application to any epidemiological questions (but see Chapter 7 for an example).

6 Partnership capacity as a random variable

Note added in proof. This section was added to this dissertation at a very late stage explaining the somehow unconventional structure of this chapter.

At first sight, generalizing the binding site formalism of Chapter 4 to partnership capacity as a random variable is straightforward. There does not seem to be more to it than averaging over partnership capacity in the right way. As we will show in Section 6.1, this is more or less true if we consider the network structure itself (but I have learned from experience that it is still easy to get confused). The presence of infection makes life much more complicated, and we discuss this in Section 6.2.

Let N be the random variable denoting partnership capacity. The probability that a randomly chosen individual has partnership capacity n is given by $\pi_n := \mathbb{P}(N = n)$, $n = 1, 2, \ldots$ In particular, the fraction of the population with partnership capacity n is π_n. Partnership capacity does not change throughout the course of an individual's life. Note that the probability that a partner in a randomly chosen partnership has partnership capacity n is

$$\omega_n := \frac{n\pi_n}{\mathbb{E}(N)}, \tag{6.1}$$

where $\mathbb{E}(N) = \sum_n n\pi_n$ is the expected partnership capacity and serves as a normalization factor.

From the perspective of *binding sites*, ω_n play an important role. This ω_n is the fraction of the total pool of binding sites that have owners with partnership capacity n. Or we can interpret it as the probability that a randomly chosen *binding site* has an owner with partnership capacity n. Indeed, the probability that a randomly chosen individual has partnership capacity n is π_n. Then any of its n binding sites can be chosen, explaining the factor n. Normalization yields (6.1).

This difference between sampling *individuals* and sampling *binding sites* is important to take into account when doing the bookkeeping.

6.1 Network dynamics

6.1.1 Model formulation

Let $\mathcal{F}$ be the fraction of free binding sites in the pool of all binding sites. Let $\varphi(a \mid t_b)$ denote the probability that a binding site is free at age a, given time of birth t_b and its owner not dying in the period under consideration. Then

$$\frac{d\varphi}{da}(a \mid t_b) = -\rho\mathcal{F}(a+t_b)\varphi(a \mid t_b) + (\sigma+\mu)(1-\varphi(a \mid t_b))$$

with birth condition $\varphi(0 \mid t_b) = 1$ (ϵ in Chapter 2 corresponds to $1-\varphi$ and φ_0 in Chapter 4 corresponds to φ with F replaced by $\mathcal{F}$).

Directly from the interpretation it is clear that both φ and $\mathcal{F}$ are independent of partnership capacity. As in Chapter 2, we may assume $\mathcal{F}$ to be constant. In particular, (6.5) shows us that we can set $\mathcal{F}$ equal to $\bar{F}$ (see (3.2) of Chapter 2). Then also φ is independent of time of birth t_b and we may omit t_b as an argument, i.e. write $\varphi(a)$. As before, $\bar{F}$ can be expressed in terms of φ as follows:

$$\bar{F} = \int_0^\infty \mu e^{-\mu a}\varphi(a)da = \frac{\sigma+2\mu}{\rho\bar{F}+\sigma+2\mu}. \tag{6.2}$$

For completeness, we work this out in detail. The additional advantage of this is that we include some concepts that we will use in Section 6.2.

At the individual level, we consider the probability $p_k(n)(a \mid t_b)$ that an individual, given partnership capacity n and time of birth t_b, has k partners at age a, $0 \le k \le n$, given that the individual remains alive in the time under consideration. Then, in terms of binding site probabilities

$$p_k(n)(a \mid t_b) = \binom{n}{k}\big(\varphi^{n-k}(1-\varphi)^k\big)(a \mid t_b). \tag{6.3}$$

Consider the population of individuals with partnership capacity n. Let $P_k(n)$ denote the fraction of this population with k partners. These p-level fractions are obtained from i-level probabilities (6.3) by using the stable age distribution (relation (3.6) of Chapter 2), i.e.

$$P_k(n)(t) = \int_0^\infty \mu e^{-\mu a}p_k(n)(a \mid t-a)da.$$

Let $F(n)$ denote the fraction of binding sites (in the pool of all binding sites) that are free and belong to individuals with partnership capacity n. We define $F(n)$ in terms of p-level fractions by taking both the perspective of individuals and binding sites and show that these two perspectives yield the same definition. First of all, $\pi_n P_k(n)$ is the

probability that an *individual* is in state k and has partnership capacity n. Therefore, the expected number of free binding sites of individuals with partnership capacity n is $\sum_k (n-k)\pi_n P_k(n)$. The pool of all binding sites relative to the population of individuals is $\sum_m m\pi_m$, (suppose we have a total number M of individuals, then the expected total number of binding sites is $\sum_m m\pi_m M$). By dividing by $\sum_m m\pi_m$ we find the fraction $F(n)$. On the other hand, taking the perspective of binding sites, the fraction of free binding sites (in the pool of binding sites) that belong to individuals with partnership capacity n is $\frac{1}{n}\sum_k (n-k)P_k(n)$. Multiplying with the fraction ω_n of binding sites that have owners with partnership capacity n yields $F(n)$. So, in terms of p-level fractions,

$$F(n) = \frac{\pi_n \sum_k (n-k)P_k(n)}{\sum_m m\pi_m} = \omega_n \frac{1}{n}\sum_k (n-k)P_k(n). \tag{6.4}$$

Consistency yields $\mathcal{F} = \sum_n F(n)$. The dynamics of $\mathcal{F}$ decouple:

$$\frac{d\mathcal{F}}{dt} = \mu - (\rho\mathcal{F} + \mu)\mathcal{F} + (\sigma + \mu)(1 - \mathcal{F}) \tag{6.5}$$

(compare with Lemma 1 of Chapter 2) and we find that $\mathcal{F}(t) \to \bar{F}$ as $t \to \infty$, justifying our assumption that $\mathcal{F} = \bar{F}$. Finally, we have the following ODE for $F(n)$:

$$\frac{dF(n)}{dt} = \omega_n\, \mu - (\rho\bar{F} + \mu)F(n) + (\sigma + \mu)\big(\omega_n - F(n)\big),$$

so we find that also $F(n)$ converges to a constant $\bar{F}_n$ where $\bar{F}_n = \omega_n \bar{F}$ (as expected from the interpretation).

Network statistics

We consider some key network statistics (compare to Chapter 2), i.e. mean partnership duration d_P, mean lifetime number of partners $\bar{\theta}$, and the partnership-based concurrency index κ_P. Obviously, the mean partnership duration does not change, so

$$d_P = \frac{1}{\sigma + 2\mu}.$$

The expected lifetime number of partners of an newborn (and therefore single) individual with partnership capacity n is

$$\theta(n) = \frac{\rho\bar{F}(\sigma + 2\mu)n}{\mu(\rho\bar{F} + \sigma + 2\mu)},$$

and we find that the expected lifetime number of partners $\bar{\theta}$ of a randomly chosen newborn individual is

$$\bar{\theta} = \sum_n \pi_n \theta(n) = \frac{\rho\bar{F}(\sigma + 2\mu)}{\mu(\rho\bar{F} + \sigma + 2\mu)}\,\mathbb{E}(N).$$

Finally, consider one of the two partners in randomly chosen partnership in the population, then the expected number of additional partners this individual has is

$$\kappa_P = \text{variance/mean} + \text{mean} - 1 = \frac{2\rho\bar{F}(\mathbb{E}(N)-1)}{2(\rho\bar{F}+\sigma+\mu)+\mu}.$$

6.2 The spread of infection on the network

In this section we consider the spread of infection on the network when partnership capacity is a random variable. Rather than an SI infection as in Section 3, we consider an SIR infection. We focus on all three network cases I, II, and III for the network dynamics (static, dynamic without and with demographic turnover). As in Chapter 4 and the rest of this chapter, we will use our systematic approach that relates binding sites, individuals, and the population to each other to formulate the model. Our main focus, and therefore also what we start with in Section 6.2.1, will be on case III of a dynamic network with demography.

On the i-level, the partnership capacity of an individual needs to be taken into account. On the other hand, a binding site is free or occupied by a partner. A partner can either be susceptible, infectious, or recovered. But partners may have different partnership capacities and this matters! The extent to which it matters depends on the disease status of the partner. An infectious partner can either die, separate, transmit infection, or recover, all for which the partnership capacity of the partner is irrelevant. The same holds true for the transitions of a recovered partner. However, not so for a susceptible partner. Indeed, the expected number of infectious partners of a susceptible partner v of a susceptible individual depends on the partnership capacity of v (as displayed by the explicit dependence on n in (4.12) of Chapter 4 for Λ_-). As a consequence, there are countably infinitely many variables to take into account on the binding site level (unless there is an upper bound on the partnership capacity).

We introduce some variables and assumptions that are used in all three cases I, II, and III of Sections 6.2.1-6.2.3. Let $\chi_1(n)$ be the probability that a binding site is susceptible and occupied by a susceptible partner with partnership capacity n, given that the owner of the binding site does not become infected through one of its other binding sites (and in case III: that the owner does not die in the period under consideration). Then the rate at which the susceptible partner becomes infected depends on the number of infectious partners it has. As usual, with the mean field at distance one assumption, we consider the mean number of infectious partners of all susceptible partners with the same characteristics: let $\Lambda_-(n)$ denote the expected number of infectious partners of a susceptible partner with partnership capacity n of a susceptible individual.

In terms of p-level fractions, $\Lambda_-(n)$ is defined as follows. Consider the population of individuals with partnership capacity n. Let $P_{(d,\boldsymbol{k})}(n)$ denote the fraction of this population that is in state $(d,\boldsymbol{k})$, $d \in \{-,+,*\}$. Then

$$\Lambda_-(n) = \sum_{\boldsymbol{k}} k_2 \frac{k_1 P_{(-,\boldsymbol{k})}(n)}{\sum_{\boldsymbol{m}} m_1 P_{(-,\boldsymbol{m})}(n)} \tag{6.6}$$

(the fraction in this sum is the probability that an individual is in state $(-, \boldsymbol{k})$ at time t, given that it has partnership capacity n and it is a susceptible partner of a susceptible individual).

Finally, as before, we consider probabilities x_i, $i = 0, 1, 2, 3$, and $\bar{x} = \sum_i x_i$, in addition to $\chi_1(n)$. Consistency yields

$$x_1 = \sum_n \chi_1(n). \tag{6.7}$$

In Sections 6.2.1-6.2.3 below we restrict ourselves to consider the dynamics for the variables x_i and $\chi_1(n)$ for the cases III, I, and II, respectively. In Section 6.2.4 we discuss how reductions are possible for cases I and II. Finally, in Section 6.3, we discuss the temptation to average in a different way.

6.2.1 Case III: dynamic with demography

Besides transmission and recovery, we take into account partnership- and demographic changes. In addition to the $\Lambda_-(n)$, we have fractions of free binding sites as environmental variables. Let $\mathcal{F}_d$ denote the fraction of free binding sites belonging to individuals with disease status d in the pool of binding sites, $d \in \{-, +, *\}$. Furthermore, let $F_d(n)$ denote the fraction of binding sites that are free and belong to individuals with partnership capacity n and disease status d. The same reasoning as for defining $F(n)$ by (6.4) yields definitions for the environmental variables in terms of p-level fractions:

$$F_d(n) = \frac{\pi_n \sum_{\boldsymbol{k}} k_0 P_{(d,\boldsymbol{k})}(n)}{\sum_m m\pi_m} = \omega_n \frac{1}{n} \sum_{\boldsymbol{k}} k_0 P_{(d,\boldsymbol{k})}(n), \tag{6.8}$$

with $k_0 = n - k_1 - k_2 - k_3$. Consistency yields

$$\mathcal{F}_d = \sum_n F_d(n), \tag{6.9}$$

and $\mathcal{F}_* = \bar{F} - \mathcal{F}_- - \mathcal{F}_+$.

By assumption, the rate at which a free binding site acquires a partner with disease status d is $\rho\mathcal{F}_d$. The probability that a randomly chosen binding site is free and belongs to an individual with partnership capacity n and disease status d is, by (6.9), equal to $F_d(n)/\mathcal{F}_d$. Therefore, the rate at which a free binding site acquires a susceptible partner with partnership capacity n is $\rho\mathcal{F}_- \cdot F_-(n)/\mathcal{F}_- = \rho F_-(n)$.

The dynamics of $\chi_1(n)$ are described by

$$\begin{aligned}\frac{d\chi_1(n)(a \mid t_b)}{da} &= \rho F_-(n)(a + t_b)\, x_0(a \mid t_b) \\ &\quad - \big(\sigma + \mu + \beta\Lambda_-(n)(a + t_b)\big)\, \chi_1(n)(a \mid t_b).\end{aligned} \tag{6.10}$$

Therefore, using (6.7), by summing over $d\chi_1(n)/da$, we find that

$$\begin{aligned}\frac{dx_1(a \mid t_b)}{da} &= \rho\mathcal{F}_-(a+t_b)\, x_0(a \mid t_b) - (\sigma+\mu)\, x_1(a \mid t_b) \\ &\quad - \beta \sum_n \Lambda_-(n)(a+t_b)\, \chi_1(n)(a \mid t_b). \end{aligned} \tag{6.11}$$

Note that this equation for x_1 still involves $\chi_1(n)$. Finally, the dynamics of x_0, x_2, and x_3 are described by

$$\begin{aligned}\frac{dx_0(a \mid t_b)}{da} &= -\rho\bar{F}\, x_0(a \mid t_b) + (\sigma+\mu)\,(x_1+x_2+x_3)(a \mid t_b) \\ \frac{dx_2(a \mid t_b)}{da} &= \rho\mathcal{F}_+(a+t_b)\, x_0(a \mid t_b) - (\sigma+\mu+\beta+\gamma)\, x_2(a \mid t_b) \\ &\quad + \beta \sum_n \Lambda_-(n)(a+t_b)\, \chi_1(n)(a \mid t_b) \\ \frac{dx_3(a \mid t_b)}{da} &= \rho(\bar{F} - \mathcal{F}_- - \mathcal{F}_+)\, x_0(a \mid t_b) + \gamma\, x_2(a \mid t_b) - (\sigma+\mu)\, x_3(a \mid t_b). \end{aligned} \tag{6.12}$$

Furthermore, we have birth conditions $x_0(0 \mid t_b) = 1$, $\chi_1(n)(0 \mid t_b) = 0 = x_1(0 \mid t_b) = x_2(0 \mid t_b) = x_3(0 \mid t_b)$.

Next, we consider i-level probabilities. Let $p_{(-,\boldsymbol{k})}(n)(a \mid t_b)$ denote the probability that an individual is in state $(-,\boldsymbol{k})$ at age a, given that it has partnership capacity n, time of birth t_b, and it remains alive for the time under consideration. Then combinatorics yield:

$$p_{(-,\boldsymbol{k})}(n)(a \mid t_b) = \frac{n!}{k_0!\, k_1!\, k_2!\, k_3!}\big(x_0^{k_0}\, x_1^{k_1}\, x_2^{k_2}\, x_3^{k_3}\big)(a \mid t_b), \tag{6.13}$$

with $k_0 = n - k_1 - k_2 - k_3$. These probabilities are related to p-level fractions $P_{(-,\boldsymbol{k})}(n)(t)$ as follows:

$$P_{(-,\boldsymbol{k})}(n)(t) = \int_0^\infty \mu e^{-\mu a} p_{(-,\boldsymbol{k})}(n)(a \mid t-a)da. \tag{6.14}$$

Combining (6.13) and (6.14) with definitions (6.6) and (6.8) we can express the environmental variables $F_-(n)$ and $\Lambda_-(n)$ in terms of binding site probabilities:

$$\begin{aligned} F_-(n)(t) &= \omega_n \int_0^\infty \mu e^{-\mu a}\big(x_0 \bar{x}^{n-1}\big)(a \mid t-a)da, \\ \Lambda_-(n)(t) &= (n-1)\frac{\int_0^\infty \mu e^{-\mu a}\big(x_1 x_2 \bar{x}^{n-2}\big)(a \mid t-a)da}{\int_0^\infty \mu e^{-\mu a}\big(x_1 \bar{x}^{n-1}\big)(a \mid t-a)da}. \end{aligned} \tag{6.15}$$

All that is left is to find an expression for $\mathcal{F}_+$ in terms of binding site probabilities. Here we cut some corners (details will be elaborated in a future publication). Similarly to the

susceptible binding site probabilities we additionally need to consider $\Lambda_+(n)$, the probabilities $\tilde{\chi}_1^{\mathrm{e}}(n)$ that the exceptional binding site is infectious and occupied by a susceptible partner with partnership capacity n as well as probabilities $\tilde{\chi}_1(n)$ for non-exceptional binding sites. We claim that, using these probabilities, one can combine the reasoning for the susceptible binding site probabilities of this section and the reasoning for infectious binding site probabilities in Section 4.2.2 of Chapter 4 to obtain

$$F_+(n)(t) = \omega_n \frac{1}{n} \int_0^\infty \mu e^{-\mu a} \int_0^a e^{-\gamma(a-a_+)} \beta n x_2 \bar{x}^{n-1} (a_+ \mid t-a) \Big\{ \varphi_1(a-a_+) + (n-1)\Big(\varphi_1(a-a_+) + \frac{x_0}{\bar{x}} (a_+ \mid t-a)\, e^{-(\rho F+\sigma+\mu)(a-a_+)} \Big) \Big\} da_+ da, \quad (6.16)$$

so

$$\mathcal{F}_+(t) = \sum_n F_+(n)(t), \quad (6.17)$$

with $F_+(n)$ given by (6.16) (compare with (4.19) in Chapter 4). However, note that in (6.16), the x_0, x_2, and $\bar{x}$ satisfy (6.12) which is in general different from (4.7) in Chapter 4

So we have a system of equations (6.10), (6.11), (6.12) with the environmental variables $F_-(n)$, $\Lambda_-(n)$, and $\mathcal{F}_+$ given by (6.15) and (6.17).

6.2.2 Case I: static network

In the static network case, only recovery or transmission can occur and the only environmental variables to consider are the $\Lambda_-(n)$. Directly from the interpretation, we find that $\Lambda_-(n) = (n-1)x_2/\bar{x}$ (alternatively, one can arrive at the same expression by taking the systematic approach via i-level probabilities and p-level fractions). Then

$$\frac{d\chi_1(n)}{dt} = -\beta(n-1)\frac{x_2}{\bar{x}}\chi_1(n). \quad (6.18)$$

The susceptible binding site probabilities x_i are described by

$$\begin{aligned} \frac{dx_1}{dt} &= -\beta \sum_n (n-1)\frac{x_2}{\bar{x}}\, \chi_1(n) \\ \frac{dx_2}{dt} &= \beta \sum_n (n-1)\frac{x_2}{\bar{x}}\, \chi_1(n) - (\beta+\gamma)x_2 \\ \frac{dx_3}{dt} &= \gamma x_2, \end{aligned} \quad (6.19)$$

with 'far past' conditions $x_1(-\infty) = 1$, $\chi_1(n)(-\infty) = \omega_n$, $x_2(-\infty) = 0 = x_3(-\infty)$.

6.2.3 Case II: dynamic network without demography

Case II is the case in between cases I and III. While it is more complicated than case I because one needs to take into account partnership changes (as in case III), it is simpler than case III as we do not need to keep track of age (as in case I).

The dynamics of $\chi_1(n)$ involve both the environmental variable $F_-(n)$ and $\Lambda_-(n)$ (where their interpretation is the same as in Sections 6.2.1 and 6.2.2).

$$\frac{d\chi_1(n)}{dt} = \rho F_-(n)\, x_0 - \big(\sigma + \beta\Lambda_-(n)\big)\chi_1(n), \tag{6.20}$$

with $\chi_1(n)$, $F_-(n)$, and $\Lambda_-(n)$ having the same interpretation as in cases I and III. Similarly, we find that the dynamics of the x-probabilities are governed by

$$\begin{aligned}
\frac{dx_0}{dt} &= -\rho\bar{F}x_0 + \sigma(x_1 + x_2 + x_3)\\
\frac{dx_1}{dt} &= \rho\mathcal{F}_- x_0 - \beta\sum_n \Lambda_-(n)\chi_1(n) - \sigma x_1\\
\frac{dx_2}{dt} &= \rho\mathcal{F}_+ x_0 + \beta\sum_n \Lambda_-(n)\chi_1(n) - (\sigma+\beta+\gamma)x_2\\
\frac{dx_3}{dt} &= \rho(\bar{F} - \mathcal{F}_- - \mathcal{F}_+)\, x_0 + \gamma x_2 - \sigma x_3.
\end{aligned} \tag{6.21}$$

The 'far past' conditions are $x_0(-\infty) = \bar{F}$, $x_1(-\infty) = 1-\bar{F}$, $\chi_1(n)(-\infty) = (1-\bar{F})\omega_n$, and $x_2(-\infty) = 0 = x_3(-\infty)$.

Either directly from the interpretation (as in case I) or by taking the systematic approach (as in case III) we can express the environmental variables $F_-(n)$ and $\Lambda_-(n)$ in terms of x-probabilities:

$$F_-(n) = \omega_n x_0 \bar{x}^{n-1} \tag{6.22}$$

$$\Lambda_-(n) = (n-1)\frac{x_2}{\bar{x}}. \tag{6.23}$$

The environmental variable $\mathcal{F}_+$ can be derived by considering infectious binding site probabilities (similarly to case III). Then one finds that

$$\begin{aligned}
\mathcal{F}_+(t) = \sum_n \omega_n \frac{1}{n}\int_{-\infty}^{t} e^{-\gamma(t-t_+)}\beta n x_2 \bar{x}^{n-1}(t_+)\Big\{&\varphi_1(t-t_+)\\
&+ (n-1)\left(\varphi_1(t-t_+) + \frac{x_0}{\bar{x}}(t_+)e^{-(\rho\bar{F}+\sigma)(t-t_+)}\right)\Big\}dt_+
\end{aligned} \tag{6.24}$$

Alternatively, we can derive an ODE for $\mathcal{F}_+$ (and the fraction of infectious binding sites I). To do so we use the interpretation as for (3.18) and (3.19) in Chapter 4. First of all, free binding sites become occupied at rate $\rho\bar{F}$ and recover at rate γ, so there is a flow $(\rho\bar{F}+\gamma)\mathcal{F}_+$ out of $\mathcal{F}_+$. Furthermore, occupied binding sites can become free again at

rate σ. The fraction occupied binding sites that have infectious owners is equal to $I - \mathcal{F}_+$ where I is the total fraction of binding sites that belong to infectious individuals.

Then there a flow into $\mathcal{F}_+$ of free binding sites whose owners become infected. This term can be interpreted by taking the i-level perspective or the binding-site-level perspective as we will explain now. The probability per unit of time at which a susceptible individual with partnership capacity n becomes infected is $\beta n x_2 \bar{x}^{n-1}$. Then, as the probability that a non-exceptional binding site is free is $x_0/\bar{x}$, the expected number of free binding sites created upon infection of an individual with partnership capacity n is $(n-1)x_0/\bar{x}$. The probability that a randomly chosen individual has partnership capacity n is π_n. So we have an expected number $\pi_n(n-1)x_0/\bar{x}$ of free binding sites (in the pool of all binding sites) upon infection of an individual with partnership capacity n. By dividing this by $\sum_m m\pi_m$, the binding site population relative to the population of individuals (see also the explanation for (6.4)), we obtain the expected fraction of free binding sites. Therefore, by combining these three terms, the flow into $F_+(n)$ is $\pi_n \beta n(n-1)x_0 x_2 \bar{x}^{n-2} / \sum_m m\pi_m$. By summing this rate over n we obtain the flow into $\mathcal{F}_+$ (use consistency (6.17)).

From the binding site level perspective, the expected fraction of free binding sites created upon infection of an individual with partnership capacity n is $\frac{1}{n}(n-1)x_0/\bar{x}$. Next, the fraction of binding sites that belong to individuals with partnership capacity n is ω_n. Combining these factors with the rate $\beta n x_2 \bar{x}^{n-1}$, we find that there is a flow $\beta\omega_n(n-1)x_0 x_2 \bar{x}^{n-2}$ of free susceptible binding sites into $F_+(n)$. By summing over n we find the flow into $\mathcal{F}_+$ (note that it follows from (6.1)) for ω_n that this flow is the same as the flow that we obtain by taking the i-level perspective first).

So we have the following ODE for $\mathcal{F}_+$:

$$\mathcal{F}_+' = \beta \sum_n \omega_n \, (n-1)x_0 x_2 \bar{x}^{n-2} - (\rho\bar{F} + \gamma)\mathcal{F}_+ + \sigma(I - \mathcal{F}_+),$$

with 'far past' $\mathcal{F}_+(-\infty) = 0$. Similarly, we find an ODE for the fraction of infectious binding sites I (we can again take both the i-level and binding site level perspective, but only explain the latter perspective). The probability per unit of time that a susceptible binding site that belongs to an individual with partnership capacity n becomes infected is $\beta n x_2 \bar{x}^{n-1}$. By taking into account the fraction ω_n of binding sites that belong to individuals with partnership capacity n, and summing over all n, we find a flow $\beta \sum_n \omega_n \, n x_2 \bar{x}^{n-1}$ into the fraction of infectious binding sites. Furthermore, there is a rate γ at which an individual, and therefore a binding site, recovers. We find that

$$I' = \beta \sum_n \omega_n \, n x_2 \bar{x}^{n-1} - \gamma I,$$

with 'far past' $I(-\infty) = 0$.

Substituting the expressions (6.22), (6.23), and (6.24) for the environmental variables in (6.21) yields a closed system for the x_i and $\chi_1(n)$, $n = 1, 2, \ldots$ Or, if one prefers, use the ODE for I and $\mathcal{F}_+$ instead of (6.24).

6.2.4 Reduction

Do we really need to deal with an infinite number of variables? The answer turns out to be 'no' in cases I and II. Unfortunately, the answer seems to be 'yes' in case III.

In **case I**, we have a consistency relation between $\chi_1(n)$ and $\bar{x}$ as follows:

$$\chi_1(n) = \omega_n \bar{x}^{n-1} \tag{6.25}$$

(This can be reasoned in exactly the same way as we did for (2.27) in Section 2.5 of Chapter 4. Alternatively, one can consider the derivative of both right- and left-hand side.) From (6.25), we find that

$$\beta \sum_n (n-1) \frac{x_2}{\bar{x}} \chi_1(n) = \beta x_2 \sum_n (n-1) \omega_n \bar{x}^{n-2}.$$

Therefore, we can view the decoupled system

$$\begin{aligned} \frac{dx_2}{dt} &= \beta x_2 \sum_n (n-1) \omega_n \bar{x}^{n-2} - (\beta + \gamma) x_2 \\ \frac{d\bar{x}}{dt} &= -\beta x_2. \end{aligned} \tag{6.26}$$

Note that this can be further reduced to one renewal equation for $\bar{x}$; see (2.30) of Chapter 4.

In **case II**, a consistency condition similar to (6.25) for case I holds. Indeed, consider a binding site with owner u and condition on no transmission occurring through the other binding sites of u. The probability that this binding site is susceptible and has a partner v that is susceptible with partnership capacity n is, by definition, $\chi_1(n)$. On the other hand, the probability that v has partnership capacity n is ω_n. Given partnership capacity n, v is susceptible if it is a collection of n susceptible binding sites. We know v has one susceptible partner u. A randomly chosen binding site is susceptible with probability $\bar{x}$. Individual v has one binding site that is occupied by u, and this binding site is susceptible if it was susceptible when acquiring u. We denote this probability by b. Since binding sites are independent of one another, we find that

$$\chi_1(n) = \omega_n \bar{x}^{n-1} b. \tag{6.27}$$

Next, consider the probability b. Suppose u and v form a partnership at time $t - \tau$. This occurs at rate $\rho x_0 (t-\tau)^2$. Since partnerships dissolve at a constant rate σ, the probability that the partnership duration is longer than τ is $e^{-\sigma\tau}$. Taking this probability into account and integrating over all possible τ, we obtain

$$b(t) = \int_0^\infty e^{-\sigma\tau} \rho x_0 (t-\tau)^2 d\tau = \int_{-\infty}^t e^{-\sigma(t-\tau)} \rho x_0(\tau)^2 d\tau.$$

Differentiating this with respect to t, we obtain an ODE for b, namely $b' = \rho x_0^2 - \sigma b$ with 'far past' condition $b(-\infty) = 1 - F$. (One can also check that the consistency condition (6.27) holds by differentiating the left- and right-hand side of the equality.)

Consistency (6.27) leads to

$$\beta \sum_n \Lambda_-(n)\chi_1(n) = \beta x_2\, b \sum_n (n-1)\omega_n \bar{x}^{n-2}$$

So we are able to write down a decoupled system of six ODE:

$$\begin{aligned}
\frac{dx_0}{dt} &= -\rho \bar{F}\, x_0 + \sigma(\bar{x} - x_0) \\
\frac{dx_2}{dt} &= \rho \mathcal{F}_+\, x_0 + \beta x_2 b \sum_n (n-1)\omega_n \bar{x}^{n-2} - (\sigma + \beta + \gamma)x_2 \\
\frac{d\bar{x}}{dt} &= -\beta x_2 \\
\frac{db}{dt} &= \rho x_0^2 - \sigma b \\
\frac{dI}{dt} &= \beta \sum_n \omega_n x_2 \bar{x}^{n-1} - \gamma I \\
\frac{d\mathcal{F}_+}{dt} &= \beta \sum_n \omega_n (n-1) x_0 x_2 \bar{x}^{n-2} - (\rho \bar{F} + \gamma)\mathcal{F}_+ + \sigma(I - \mathcal{F}_+)
\end{aligned} \tag{6.28}$$

If one prefers, like in Section 3.2.3 of Chapter 4, one can take a different perspective by considering a renewal equation for $\mathcal{F}_+$ where $\mathcal{F}_+$ is given by (6.24). The point here is really that a reduction to a finite number of equations is possible.

Finally, note that case III differs from cases I and II in that we need to take into account both age and time of birth of individuals. In case I and II, age does not play a role and all individuals start off in the same way at time $t = -\infty$. In **case III**, an individual is, given that it was born at time t_b, influenced by the environmental variables at time $t = a + t_b$ at age a. We have not been able to find a consistency relation that allows us to reduce the system and we believe that no such consistency exists. So it seems that we are stuck with an infinite number of variables in case III.

6.3 Dangerous assumptions

It's very tempting to assume that we can average over the $\Lambda_-(n)$. In other words, one could make the assumption that a binding site in state 1, i.e. in a partnership with a susceptible partner, loses its susceptible partner due to transmission to this partner at a rate $\beta\tilde{\Lambda}_-$ where, in terms of p-level fractions,

$$\tilde{\Lambda}_- = \sum_n \omega_n \Lambda_-(n) = \sum_n \omega_n \sum_{\boldsymbol{k}} k_2 \frac{k_1 P_{(-,\boldsymbol{k})}(n)}{\sum_{\boldsymbol{m}} m_1 P_{(-,\boldsymbol{m})}(n)}. \tag{6.29}$$

It also seems reasonable to ignore the partnership capacity of a susceptible partner altogether. One can instead let $\tilde{\Lambda}_-$ be the mean number of infectious partners of a randomly

chosen susceptible partner of a susceptible individual (and this is exactly the assumption that is made in [76]). In terms of p-level fractions this is

$$\tilde{\Lambda}_- = \sum_{\boldsymbol{k}} k_2 \frac{k_1 \mathcal{P}_{(-,\boldsymbol{k})}}{\sum_{\boldsymbol{m}} m_1 \mathcal{P}_{(-,\boldsymbol{m})}} = \frac{\sum_{\boldsymbol{k},n} \omega_n k_1 k_2 P_{(-,\boldsymbol{k})}(n)}{\sum_{\boldsymbol{m},n} \omega_n m_1 P_{(-,\boldsymbol{m})}(n)}. \tag{6.30}$$

Making an assumption of this kind would lead to the term $-\beta\tilde{\Lambda}_- \, x_1$ in the ODE for x_1 (rather than $-\beta \sum_n \Lambda_-(n)\chi_1(n)$). And why wouldn't we? This would eliminate the need of binding site probabilities $\chi_1(n)$, i.e. the need to keep track of the partnership capacity of susceptible partners.

In the setting of a static network, i.e. case I, there is a good reason not to do so. The reduced system (6.26) was shown to capture the appropriate large population limit of a stochastic Markovian SIR epidemic on a static configuration network [83, 84, 89]. Assuming the existence of a $\tilde{\Lambda}_-$ of the form (6.29) or (6.30) would yield different systems. (Note that, in case I, in terms of x probabilities, (6.29) would lead to $\tilde{\Lambda}_- = x_2/\bar{x} \sum_n \omega_n(n-1)$ while (6.30) would lead to $\tilde{\Lambda}_- = x_2 \sum_n \pi_n n(n-1)\bar{x}^{n-2}/\sum_n \pi_n n \bar{x}^{n-1}$)

In case II, no such proof exists (and we posed it as one of the open problems in Chapter 4), while in case III, we *know* that the mean field at distance one assumption ignores certain correlations between the states of partners in the case of a fixed partnership capacity for the entire population (see Appendix B of Chapter 3). So, especially in case III, why not make it easier on ourselves? Incidentally, in their slightly different but related network model called the 'dormant contacts' model [50], the authors make the assumption that the rate at which a susceptible partner becomes infected is $\beta\tilde{\Lambda}_-$ with $\tilde{\Lambda}_-$ of the form (6.30).

One big argument against doing this is the inconsistency that this creates with case I of a static network. It seems unlikely that, with this inconsistency, assuming one environmental variable Λ_- for case II would result in a system of equations that is the large population limit of a stochastic process as (6.26) is for case I (especially since we would like to recover case I in the limit of $\sigma \to 0$, $\rho \to 0$ of case II).

On the other hand, we can also accept that an approximation is made. In the end, any model is an approximation of reality anyway. Besides, such an assumption comes with the huge advantage that, in case III, we do not need to deal with an infinite number of equations for the $\chi_1(n)$. Rather, we would be able to formulate a system of renewal equations for environmental variables $\mathcal{F}_-$, $\mathcal{F}_+$, and Λ_-, and apply the techniques that we described in Section 4 to characterize the endemic steady state.

When it comes to R_0, things are less difficult. Even if the nonlinear system contains an infinite number of equations, R_0 is still a simple weighted average of the form $\sum_n \omega_n \tilde{R}_0(n)$, where $\tilde{R}_0(n)$ is the basic reproduction ratio in the case that n is fixed for the entire population (calculations not shown). In fact, different nonlinear systems may very well lead to the same linear system when linearizing in the disease free steady state. Therefore, even if model descriptions are different, the epidemic threshold parameter R_0 might still coincide. Whether we let the mean field at distance one assumption manifest itself in probabilities $\chi_1(n)$ and environmental variables $\Lambda_-(n)$ as in Sections 6.2.1-6.2.3

or in one environmental variables of the form (6.29) or (6.30), the resulting systems have the same expression for R_0 associated to them (calculations not shown).

All in all, this endeavour makes clear how subtle the mean field at distance one assumption is. We should be aware that first taking into account the partnership capacity of a susceptible partner in $\Lambda_-(n)$ is distinctively different from assuming that we can average over all partnership capacities of susceptible partners in $\tilde{\Lambda}_-$. It certainly shows that there is a need to better understand how 'good' each of the different approximations are. Especially in case III we need to ask ourselves how much we gain from assuming environmental variables of the form (6.6) rather than assuming one variable $\tilde{\Lambda}_-$ of the form (6.29) or (6.30). Trying to answer such a question is certainly nontrivial and it's likely that much will depend on the assumptions for the partnership capacity distribution (π_n).

Part II

Epidemiological questions

Chapter 6

Concurrency can drive an HIV epidemic by moving R_0 across the epidemic threshold

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Abstract

Objective
To investigate whether concurrency can drive an HIV epidemic by moving R_0 across the epidemic threshold.

Design and methods
We use a mathematical framework for a dynamic partnership network and the spread of a one-stage infection to study how concurrency is related to the basic reproduction number R_0. Two concurrency indices were used to measure the level of concurrency. The model allows varying the level of concurrency in the population while other key network properties such as partnership duration and lifetime number of partners are kept fixed. In this way the effect of concurrency on R_0 is investigated as an isolated phenomenon.

Results
We find that an increase in concurrency is associated with an increase of R_0. For plausible parameter sets for MSM populations, R_0 is always above the epidemic threshold of 1. For scenarios that are plausible for sub-Saharan African populations, we show that increasing the level of concurrency can lead to R_0 crossing the epidemic threshold. This occurs already at low levels of concurrency. Only a slight shift of the network structure from a purely monogamous population to one where individuals are allowed to have at most 2 partners is enough for this to happen.

Conclusions
Concurrency can be a driver of an HIV epidemic in sub-Saharan Africa for low levels of concurrency while it is not decisive in MSM populations. A small increase in the level of concurrency can lead to R_0 crossing the epidemic threshold in a sub-Saharan African setting.

1 Introduction

In the past there has been much discussion on the role of concurrent partnerships in driving the HIV epidemic in heterosexual sub-Saharan African (SSA) populations. Establishing conclusive evidence of the role of concurrency in empirical investigations is difficult [11, 12, 23]. One of the reasons is the fact that concurrency cannot be studied as an isolated phenomenon, but is connected to sexual behavior in all its complexity and is interwoven with many other network structural properties [29]. More specifically, when the distribution of partnerships over a population or the duration of partnerships change, it will also change the fraction of concurrent partnerships that are observed at any time or accumulated over a longer time period.

On the other hand, mathematical models consistently show the impact of concurrency on incidence and prevalence of HIV [18, 21, 35, 43, 108]. Watts and May [18] were one of the first to use a mathematical model to investigate the influence of concurrency on HIV dynamics. The authors used an intuitive notion of concurrency and focused on the dynamics over time for $R_0 > 1$. They found that concurrency could lead to a very fast initial spread compared to a monogamous population. Others have mainly used simulation models to investigate the relation between concurrency and initial growth rate or endemic situations [21, 35, 43, 108]. In such models it is inherently difficult to control for different sexual behavior properties. Also, earlier modeling results have been refuted, because they used unrealistic parameter values and neglected demographic flow through the population [13].

In [30] it was suggested that for a factor to be considered a driver of HIV one needs to show that this factor can drive the basic reproduction number R_0 across the threshold value of 1, while all other factors remain unchanged. Using a flexible mathematical model in which different sexual behavior properties can easily be kept fixed, we investigated whether concurrency can be a driver of HIV in this way.

Here we focused on a model of a one-stage infection (Susceptible-Infected) without recovery [109, 110]. In this model, formation and separation of partnerships is dynamic, and demographic flow through the sexually active population is incorporated. It allows a change in the concurrency level in a population while other key parameters describing the contact network are kept fixed. One of the central notions of the model that distinguishes it from earlier approaches is the so-called 'partnership capacity', a number n that denotes the maximum number of partners that an individual can have at any time. Pair-formation models for monogamous populations implicitly take $n = 1$. Infection can then be transmitted in a partnership between an infectious and susceptible individual. The model does not assume any disease-related mortality. For this model it is possible to derive an explicit expression for the basic reproduction number R_0. This has the advantage that R_0 can easily be studied as functions of infection and sexual behavior and parameters.

We investigated how R_0 depends on concurrency when duration of partnerships and lifetime number of partners are kept constant. The parameter choices are based on estimates from existing literature. We used a measure for concurrency that allows us to compare populations with different levels of concurrency. The concurrency measure was

then varied by varying partnership capacity n only. Our aim was not to provide a realistic estimate of how HIV transmission depends on concurrency in specific populations, but to provide a proof of principle that concurrency alone can be a driving factor of HIV transmission by moving the reproduction number across the threshold value of 1.

2 Methods

The method used in this paper is as follows; we have a model for the spread of infection in a concurrent partnership network where sexually active lifespan $1/\mu$, mean partnership duration d_P, mean lifetime number of partners θ, and transmission rate β are kept fixed. Concurrency is purely a network characteristic and can be measured using concurrency indices. The basic reproduction number R_0 can be calculated for this model. The relation between concurrency and R_0 is then investigated for six scenarios. The different aspects of our method are explained below (a more detailed description is given in Appendix A).

2.1 Partnership network

In Chapter 3 a model was introduced for a dynamic partnership network with demographic flow. In this model we consider a population in which we do not distinguish between gender and all individuals have the same characteristics, i.e. the population is homogeneous. The model generalizes earlier pair-formation models to a situation where concurrent partnerships are possible. This is done by introducing a maximum number of partners an individual can have simultaneously. This number n is called the partnership capacity. Monogamous individuals then have partnership capacity $n = 1$. One may think of an individual as having n 'binding sites' for partners that are either free or occupied by a partner. The crucial (but also limiting) assumption is that these binding sites behave independently of one another as far as partnership formation and separation is concerned.

2.2 Concurrency

Concurrency is related to many other sexual behavior characteristics. The most straightforward of these are partnership duration and lifetime number of partners. Indeed, the longer the duration of a partnership, the more overlap there can be with other partnerships and the more partners an individual has, the more it can have at the same time. Therefore, in order to be able to study the effect of concurrency on infection dynamics, these quantities need to be kept fixed when varying the level of concurrency.

Our simple model has only four parameters. We can fix sexually active lifespan $1/\mu$, mean partnership duration d_P, and mean lifetime number of partners θ. Then the level of concurrency is varied by varying partnership capacity n. This parameter is a theoretical construct that does not have any measurable variable associated with it. Therefore, for fixed network properties $1/\mu$, d_P, and θ, we quantified concurrency in terms of concurrency indices.

Various ways of quantifying concurrency in a population have been suggested, both in theoretical context [65] and Chapter 2 and for practical use [32, 34]. Here we use the partnership-based concurrency index κ_P introduced in Chapter 2 and compare it to the point prevalence of concurrency as suggested by UNAIDS [32] that we denote here by κ_U. The point prevalence of concurrency is the fraction of the population with two or more partners while the partnership-based concurrency index κ_P can be interpreted as follows: choose a partnership at random and consider one of the two individuals in this partnership. In the model, κ_P can be computed explicitly (Chapter 2).

2.3 Infectious disease dynamics

In the partnership network we considered the spread of an infection without recovery as described in Chapter 3. We assumed that infection does not impact partnership formation or separation nor does it impact the demographic process. An infectious individual transmits infection to its susceptible partner at rate β. A susceptible individual becomes infectious at the very instant that it gets infected and stays infectious with the same level of infectiousness for the rest of its sexual lifetime. For this model we characterized the basic reproduction number R_0 (Chapter 3) that we can evaluate numerically for given values of model parameters $1/\mu$, d_P, θ, n, and β.

2.4 Definition of scenarios

To study the impact of concurrency in different types of populations we defined a number of scenarios. These descriptions are caricatures only. The model considers a homogeneous population. Therefore it is fully determined by sexually active lifespan $1/\mu$, mean partnership duration d_P, mean lifetime number of partners θ, partnership capacity n, and transmission rate β.

We kept $1/\mu = 40$ years [111] and $\beta = 0.12$ per year [112, 113] fixed throughout this investigation. A scenario is defined by one set of parameter values for the partnership duration d_P and lifetime number of partners θ (Table 1). For each scenario we considered populations with different concurrency levels by varying partnership capacity n. The scenarios are based on estimates from literature as follows.

We defined four scenarios representing sexual behavior in SSA. Because of the large discrepancies between male and female sexual behavior as reported in the literature, we considered separate scenarios based on male and female respondents in SSA heterosexual populations. Furthermore, we also defined distinct scenarios based on spousal versus non-spousal partnerships. Here SSA 1 and SSA 2 represent heterosexual SSA women in their spousal and non-spousal behavior while SSA 3 and SSA 4 represent the spousal and non-spousal behavior of heterosexual SSA men (for order of magnitude of these values we used [15, 34, 56, 114, 115]). Finally, we defined two scenarios meaning to represent sexual behavior of men having sex with men (MSM) populations in their steady and casual partnerships, denoted by MSM 1 and MSM 2, respectively [54, 116]. The six scenarios are presented in Table 1. The parameter value estimates are explained in more detail in the Supplemental Digital Content.

Scenario	d_P (years)	θ
SSA 1 (women spousal)	10	2
SSA 2 (women non-spousal)	2.4	4.5
SSA 3 (men spousal)	5	3
SSA 4 (men non-spousal)	1.7	6
MSM 1	1.5	45
MSM 2	0.083	135

Table 1: The six scenarios. Six scenarios defined by mean partnership duration d_P and mean lifetime number of partners θ. Scenarios SSA 1-4 represent caricatures of spousal and non-spousal behavior of males and females in sub-Saharan Africa and MSM 1 and 2 represent caricatures of sexual behavior of MSM populations.

Although the parameter choices are based on estimates from published literature, these scenarios are not meant to represent the complexity of sexual behavior in populations nor did we aim to make precise/detailed quantitative statements for those populations. We chose parameters such that their orders of magnitude are within a plausible range. Our aim was to show that R_0 can cross the threshold value of 1 when only the level of concurrency is increased.

In the section below, we first studied the structure of the sexual network. In particular we computed degree distributions and concurrency indices. We then studied the dependency of R_0 on model parameters and concurrency indices.

3 Results

3.1 Sexual network and concurrency

First we considered the network by considering degree distributions (where the degree of an individual is the number of partners it has) for different values of partnership duration d_P and lifetime number of partners θ and for partnership capacities $n = 3$ and $n = 6$; see Fig. 1.

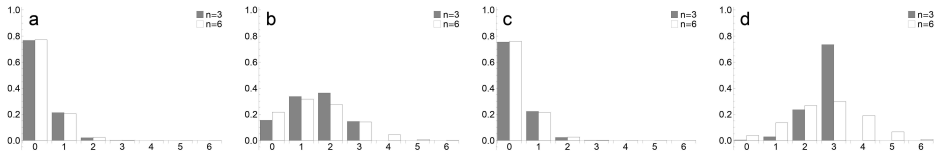

Figure 1: Degree distributions for different parameter values. d_P denotes mean partnership duration and θ mean lifetime number of partners. The parameter values for (a) and (c) correspond to scenarios SSA 4 and SSA 2, respectively (see also Table 1) (a) $d_P = 1.7$ years, $\theta = 6$ (SSA 4) (b) $d_P = 10$ years, $\theta = 6$ (c) $d_P = 2.4$ years, $\theta = 4.5$ (SSA 2) (d) $d_P = 2.4$ years, $\theta = 45$.

The degree distribution may look very similar for different partnership capacities (Fig. 1a, c). Note however that they are never equal. There is always a non-zero fraction

of the population with the maximum number of n partners. For instance, in a population with $n = 6$ there is always a small fraction of the population with 6 partners, while for $n = 3$ no individual has more than 3 partners (by definition of n). That small fraction with many concurrent partners plays an important role for transmission. Therefore a shift of n to larger values can have a significant impact even if the degree distribution seems hardly affected. We see that when n increases the degree mean does not change (degree mean is equal to the product $\theta d_P \mu$ which is independent of n), while the variance does (Table 2). However, the variance is almost always smaller than the mean, i.e. the degree distribution is under-dispersed. Compared to observed degree distributions (see e.g. [108]) the means in Table 2 are either lower or higher. We expect the variance in real populations to be larger than the mean.

Parameter values	n	**mean**	**variance**
$d_P = 1.7$ years, $\theta = 6$ (SSA 4)	3	0.26	0.23
	6	0.26	0.25
$d_P = 10$ years, $\theta = 6$	3	1.5	0.85
	6	1.5	1.32
$d_P = 2.4$ years, $\theta = 4.5$ (SSA 2)	3	0.27	0.25
	6	0.27	0.29
$d_P = 2.4$ years, $\theta = 45$	3	2.7	0.28
	6	2.7	1.59

Table 2: Mean and variance for different parameter values. Sexual network characteristics captured by the mean and variance for different parameter value combinations of mean partnership duration d_P, mean lifetime number of partners θ and partnership capacity n. The first and third set of parameter values correspond to scenarios SSA 4 and SSA 2, respectively (indicated between brackets; see also Table 1 for the scenarios).

We next studied how the concurrency indices κ_P and κ_U depend on the parameters of the sexual network (Fig. 2). Intuitively concurrency measures should increase as a function of partnership duration d_P (when keeping n and θ fixed) and as a function of θ (when keeping n and d_P fixed). Indeed, the longer partnership durations are or the higher the lifetime numbers of partners, the more overlap there has to be in order to 'fit' all partnerships into an individual's life. We found that this indeed holds for κ_P and κ_U. Using its explicit expression (see Chapter 2 and Supplementary Digital Contents for details) we see that κ_P is strictly increasing in d_P and θ (Fig. 2a,b). Numerical investigation of κ_U showed that also this is strictly increasing in d_P and θ (Fig. 2 c,d).

We also expect, for fixed partnership duration d_P and lifetime number of partners θ, an increase in n yields an increase in the concurrency indices. Indeed, the larger the maximum number n of simultaneous partnerships individuals may have, the more concurrent partnerships there may be in the population. We immediately find that this is the case for κ_P (using its explicit expression; see Chapter 2 and Supplementary Digital Contents for details). However, this is not necessarily the case for κ_U as we find in Fig. 2 c,d. Here we see that κ_U may decrease when n increases. The reason for this, perhaps counter-intuitive, result becomes clear when looking at the changes in degree distribution with increasing n

for those situations (see Fig. 1d). With increasing partnership capacity some individuals will have more partners, but at the expense of a larger proportion of single individuals in the population. The index κ_U is sensitive only to the latter, not to the former. So it could be that the fraction of the population that has more than one partner decreases while the total number of overlapping partnerships increases. We concluded that κ_U is not useful for our analysis and from here on focus on κ_P.

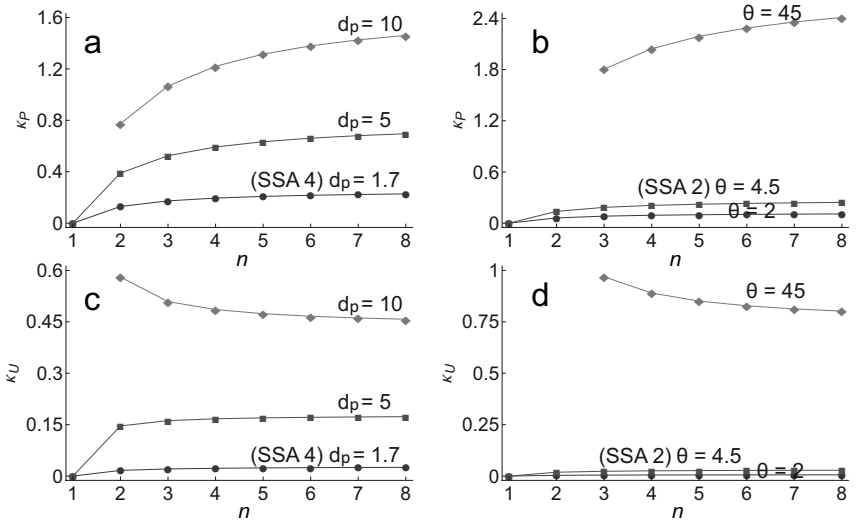

Figure 2: Concurrency indices κ_P and κ_U as functions of partnership capacity n for different values of mean partnership duration d_P and mean lifetime number of partners θ. (a) $\theta = 6$ (b) $d_P = 2.4$ years (c) $\theta = 6$ (d) $d_P = 2.4$ years.

3.2 R_0 as function of partnership capacity n

In the same way as we did for κ_P and κ_U in the previous section we also studied R_0. Using the explicit expression for R_0 (see Chapter 3 and Appendix A for details), we found that R_0 is increasing in n. Therefore we can immediately conclude that the concurrency index κ_P is always positively correlated to R_0 when varying n only. In what follows we studied this in more detail, in particular we were interested in R_0 for the six scenarios.

3.3 Impact of concurrency on R_0

We considered how κ_P and R_0 are related for the six scenarios (Table 1). The results are presented in Fig. 3.

We see that an increase in n alone yields an increase in both κ_P and R_0. We also find that the MSM scenarios yield relatively large R_0-values compared to the SSA scenarios (Fig 3 a). In particular, for the smallest n, R_0 is already larger than 1. It also does not seem to be very sensitive to changes in the concurrency level. Note that MSM 1 yields

larger values for R_0 than MSM 2. Even though the lifetime number of partners in MSM 1 is much smaller, the mean partnership duration in MSM 2 is much shorter. Therefore, the probability of transmission within a partnership is also much smaller in MSM 2.

Next, we considered the SSA scenarios in Fig. 3 b. For all four SSA scenarios we found that R_0 crosses the threshold value of 1 when concurrency is increased by increasing n. This shows that it is possible that a population where at first no epidemic outbreak is possible can change into a population where an epidemic outbreak is possible when more partnerships are concurrent (while all other sexual behavior remains unchanged). So we see that concurrency can be a driver of HIV for these SSA scenarios. The crossing of the epidemic threshold occurs already at low levels of concurrency (between $n = 1$ and $n = 2$ so for small values of n).

The sensitivity analysis in Appendix C show that whether or not R_0 crosses the threshold value of 1 depends on the parameter values. It is certainly not always the case.

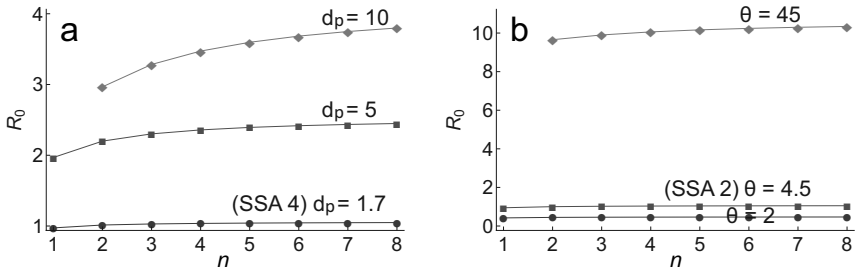

Figure 3: The impact of concurrency on R_0 by varying partnership capacity n for the six scenarios. The six scenarios are presented in Table 1. Numbers at each point reflect the corresponding partnership capacity number n. (a) MSM scenarios (b) SSA scenarios.

4 Discussion and conclusion

Using a model for a dynamic sexual network and the transmission of infection we analyzed the association between concurrency and R_0. We found that, for parameter sets that are plausible for MSM populations, R_0 is always above 1. Therefore, concurrency is not a driver of HIV in these MSM populations in the sense that in these populations other factors like the lifetime number of partners are more important in determining R_0. We also see that concurrency does not really have an effect on the two MSM scenarios, supporting our conclusion that it is not a driver in these MSM populations. However, for parameter sets that are plausible for SSA populations, we found that an increase of the level of concurrency in a population can drive the basic reproduction number from below to above the threshold of 1. Only a slight shift of the network structure from a purely monogamous population to one where individuals have at most 2 partners is required for this to happen.

Furthermore, we showed that two widely used concurrency indices have different

properties. In particular, while the partnership-based concurrency index κ_P is always increasing with increasing partnership capacity n, this is not necessarily the case for the point-prevalence of concurrency κ_U. The latter can possibly decrease with increasing n, leading to some doubt about the usefulness of κ_U in measuring the impact of concurrency on transmission of infection.

The level of concurrency as measured by the index κ_P is closely related to other network properties such as the lifetime number of partners and partnership duration. By defining a model in which all parameters except for the partnership capacity n can be kept at a fixed value we were able to study the impact of changing concurrency levels without changing lifetime numbers of partners and partnership duration. As the network is dynamic, the number of partners at age a are changing due to partnership formation and separation over the course of an individual's life, even if lifetime number of partners is defined as a constant parameter.

In all scenarios we used the same estimate for the transmission rate β. However, it is expected that the transmission rate is higher in MSM populations than in heterosexual populations due higher risk in sexual practices and higher rates of sexual acts within partnerships; see e.g. [117] for estimated per-act probabilities for different exposure routes. A larger transmission rate β for MSM scenarios would also yield a larger R_0 and support our conclusion that concurrency is not decisive for the epidemic in those populations.

Our results also illustrate that that the value of R_0 is not merely determined by κ_P but other parameters (partnership duration d_P, lifetime number of partners θ and transmission rate β) play an important role as well (compare e.g. scenarios SSA 2 and SSA 4 to MSM 2 in Fig. 3, which all have similar κ_P-values but different R_0-values).

Finally, we have only investigated whether concurrency can lead to R_0 crossing the threshold value 1 and therefore allowing for an epidemic outbreak. In other words, we have only investigated the impact of concurrency on the beginning of an epidemic, not its impact on a mature epidemic that has reached its endemic state. The role of concurrency for persistence of HIV in an endemic state could be different and has to be investigated in a different way. Preliminary numerical investigations with our model have shown that concurrency is also positively correlated with endemic prevalence for the sub-Saharan African scenarios. However, this has to be investigated further and is outside the scope of this paper.

Our modeling approach has a number of limitations that have to be kept in mind. First, we considered a partnership network in a homogeneous population with only one type of individuals and one type of partnerships. The model at present neglects all population heterogeneity and differences between men and women. However, our framework can be generalized to a two-sex population with asymmetry between men and women in partnership capacity. Furthermore, our framework can be modified to allow for two (or multiple) types of partnerships. By distinguishing different types of partnerships, e.g. spousal and non-spousal, it is possible to take different partnership dissolution rates into account. See Chapter 2 for a more detailed description on various generalizations of the model.

Next, we do not take any disease-related mortality into account. In the case of disease-related mortality, an infectious individual has a shorter life expectancy and less secondary

cases may occur than in the case without disease mortality, i.e. the R_0 will be smaller. This means that, with the addition of disease mortality, R_0 will then cross the threshold value at somewhat higher levels of concurrency than shown in Fig. 3. The addition of disease-related mortality will not change the mechanism demonstrated in this paper.

The most important limiting assumption however is that partnerships are considered to be independent of each other. In other words, whether an individual already has a partner or not has no influence on his propensity to acquire another partner. Secondly, infection does not influence partnership dynamics nor does it lead to increased mortality. Finally, we assumed that infectivity is constant throughout the infectious period, thereby neglecting the possibility of high transmission rates during early HIV infection.

While these are serious limitations when one wants to make quantitative prediction in a real population, our aim here was to establish the possible role of concurrency as a factor in driving the basic reproduction R_0 across the threshold value of 1 without changing other network properties. We conclude that not only is this possible in a dynamic sexual network, but also that for parameter sets that are plausible for heterosexual SSA populations, crossing the threshold occurs for a shift of concurrency from monogamous to very low levels of concurrency.

Acknowledgements

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Author contributions

Both authors contributed to the study design, discussion of the results and manuscript draft. KYL conducted the numerical investigation. Both authors have read and approved the text as submitted to AIDS.

A Model

In this appendix we provide details for the partnership network model, the concurrency indices, the infection model, and the parametrization of the model.

Partnership model

The partnership model that we considered here is introduced in Chapter 2. In this network, concurrent partnerships are possible. This generalizes earlier pair-formation models where only monogamy was allowed. We introduced partnership capacity n as the

maximum number of partners an individual can have simultaneously (in the case of a monogamous population $n = 1$). An individual then has a dynamically varying number of simultaneous partners between 0 and n. One may think of an individual as having n 'binding sites' for partners. An individual with k partners, $0 \leq k \leq n$, then has k binding sites occupied and $n - k$ binding sites free. These binding sites behave independently of one another as far as partnership formation and separation is concerned. An individual with k partners, $k = 0, \ldots, n$, acquires a new partner at rate $\rho F(n-k)$ where $n-k$ is the number of free binding sites the individual has and F denotes the fraction of free binding site in the population. Partnerships dissolve with a constant rate $\sigma + 2\mu$, i.e. partnership duration is exponentially distributed. Here σ corresponds to 'separation' and 2μ to 'death of either partner'. We do not differentiate between the sexual behavior of individuals in this model. They all follow the same process regarding their sexual behavior.

We assume that the partnership process, although dynamic, is in equilibrium. Then the fraction of free binding sites F is constant and it can be expressed (see Chapter 2) as a function of the model parameters μ, ρ, and σ:

$$F = \frac{\sqrt{(\sigma + 2\mu)(4\rho + \sigma + 2\mu)} - (\sigma + 2\mu)}{2\rho}.$$

The partnership network is fully characterized by the four parameters μ, ρ, σ, and n.

In the following we summarize some results obtained in Chapter 2 that we have used in this paper.

The partnership model allows us to determine the lifespan, mean partnership duration and mean lifetime number of partners as functions of the model parameters μ, ρ, σ, and n. The mean lifetime of an individual is

$$1/\mu$$

and mean partnership duration is

$$d_P = 1/(\sigma + 2\mu).$$

The mean lifetime number of partners is given by

$$\theta = \rho F(\sigma + 2\mu)n/\mu(\rho F + \sigma + 2\mu).$$

Note that we find the restriction

$$\theta d_P = \frac{n}{\mu} \frac{\rho F}{\rho F + \sigma + 2\mu} < n/\mu,$$

on the parameters μ, d_P, θ, and n. This restriction can be easily interpreted: an individual with lifetime $1/\mu$ and n binding sites can only 'fit' θ partners with a mean partnership duration d_P in its life.

Since we assume the partnership process to be in equilibrium, the population has a stable degree distribution $P = (P_k)$ (the probability that a randomly chosen individual

has k partners is given by P_k). A schematic diagram representing the flow between the different degrees is presented in Figure A.1.

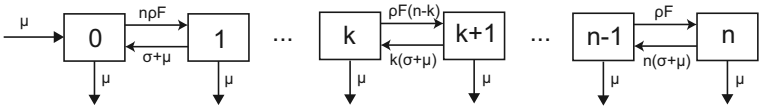

Figure A.1: Flowchart representing the transitions between the different number of partners an individual with partnership capacity n can have. Note that an individual enters the population without any partners (hence the arrow entering 0 with rate μ) and an individual leave the population with a constant rate μ (hence the arrows leaving all k with rate μ).

The degree P_k given by

$$P_k = \binom{n}{k}\mu\left(\frac{\rho F}{\rho F+\sigma+\mu}\right)^n \sum_{j=0}^{n-k}\sum_{i=0}^{k}\binom{n-k}{j}\binom{k}{i}(-1)^i \left(\frac{\sigma+\mu}{\rho F}\right)^j \frac{1}{\mu+(\rho F+\sigma+\mu)(n-k-j+i)}. \tag{A.1}$$

Note that we can write P_k as a function of d_P, θ, μ, and n by substituting $\sigma+\mu = 1/d_P-\mu$ and $\rho F = \theta\mu/(n-d_P\theta\mu)$.

This partnership model allows for an impression of the typical life course of an individual with respect to partnership dynamics. For fixed μ, this life course is determined by the parameters ρ, σ, and n, or equivalently, by the compound parameters θ, d_P, and n.

In the following we considered μ to be a given and fixed parameter, we did not further discuss the dependence on life expectancy. Furthermore, we used the compound parameters d_P, θ, and n for our investigation.

Concurrency indices

In this section we provide the expressions for the partnership-based concurrency index κ_P and the point prevalence of concurrency κ_U that we use in the main text. We express these indices as a function of sexually active lifespan $1/\mu$, mean partnership duration d_P, mean lifetime number of partners θ, and partnership capacity n.

The partnership-based concurrency index κ_P has the following interpretation. Choose a partnership from the population and consider one of the two individuals in this partnership. Then κ_P is the expected number of other partners of this individual, i.e. variance/mean+mean-1 (where variance and mean are with respect to (P_k)) (Chapter 2). Expressed in terms of the parameters d_P, θ, and n this is given by

$$\kappa_P(d_P,\theta,n) = \frac{2\theta\mu d_P(n-1)}{\theta {d_P}^2+\mu n(2\mu-d_P)}. \tag{A.2}$$

The point prevalence of concurrency, i.e. the fraction of the population with two or more partners, has the following expression in our setting. Denote this measure for concurrency by κ_U, then

$$\kappa_U(d_P, \theta, n) = \sum_{k=2}^{n} P_k(d_P, \theta, n) = 1 - P_0(d_P, \theta, n) - P_1(d_P, \theta, n),$$

where P_k is given by (A.1). This index measures the *proportion of individuals* that have concurrent partnerships at a given time. It does not take into account the *number of concurrent partnerships* these individuals have.

Note that $\kappa_P(d_P, \theta, 1) = \kappa_U(d_P, \theta, 1) = 0$ for all d_P and θ, i.e. both concurrency indices are equal to zero when no concurrency present (recall that $n = 1$ corresponds to a monogamous population).

Infection model

The infection model is described in detail in Chapter 3. In this model, the spread of an SI infection on the partnership network is considered, i.e. an individual is either susceptible or infectious, and once infected it remains so with the same level of infectiousness for the rest of its sexual lifetime. The main assumptions in this model were that infection did not have an impact on the partnership formation or separation nor on the probability per unit of time of dying of leaving the sexually active population. The transmission rate from an infectious individual to its susceptible partner is denoted by β (see also Figure A.2).

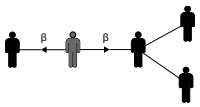

Figure A.2: Infection is transmitted from an infectious individual to a susceptible partner at a rate β. In this example, the infectious individual has two susceptible partners to whom he can transmit.

The state of an individual is now characterized by its infection status (susceptible or infectious), its number of susceptible partners and number of infectious partners. The full individual state should also include information about partners of partners which is not included in the model description. Therefore, we defined an approximation termed the 'mean field at distance one' assumption: properties concerning partners of partners can be obtained by averaging over the population in an appropriate way. The state of an individual can now change through both partnership dynamics and transmission of infection.

For this infection model we characterized R_0 as the dominant eigenvalue of a 3×3 next generation matrix and we derived an explicit expression for R_0 and (an implicit expression for the exponential growth rate r); see Chapter 3. These expressions are quite long, but can be manipulated symbolically using *Mathematica*. In particular, R_0 can be evaluated numerically for given values of d_P, θ, n, and β.

B Parameterization of the model

We chose parameter ranges for model parameters based on published sexual-behavior studies. The parameters of the model are the sexually active lifespan $1/\mu$, partnership duration d_P, lifetime number of partners θ, and the transmission rate β. These were then used to study the impact of different parameter sets on infectious disease transmission by means of numerical investigation. An overview of the parameters of the model is given in Table B.1 on p. 204.

Sexually active lifespan

We took the average length of a sexually active life to be 40 years based on a life expectancy of around 56 years [111] and assuming the start of the sexually active life to be at 16. Note that although an exponentially distributed age distribution might be reasonable for populations in SSA, this is not the case for men who have sex with men (MSM) populations. However, to enable comparison between those populations in terms of sexual behavior parameters, we took $1/\mu = 40$ years to be fixed throughout the paper.

Partnership duration

Partnership duration varies between types of partnerships and between populations. Information about partnership duration can be obtained by asking respondents about start and end dates of their partnerships. If a partnership is still ongoing at the moment of the survey, the information about duration will be censored, which has to be taken into account for estimating the duration. For heterosexual populations in SSA information on partnership duration is scarce. We used published estimates from the Rakai Study [114] and from a study among STI (sexually transmitted infection) clinic attenders in Malawi [56]. For MSM populations we used estimates from [54]. In the model partnership duration is exponentially distributed with parameter $1/d_P$. We therefore used only means of distributions observed in the above studies (compare Table 1).

Lifetime number of partners

Questions about the lifetime number of partners (or number of partners in some fixed time period, e.g. in the past year) are included in almost every survey on sexual behavior. In a survey, respondents typically report the number of partners they have had up to moment of the survey, so this number depends on the sexually active age of the participant.

In most studies, the reported lifetime numbers of partners are low in heterosexual populations (often less than ten [15, 34] with the majority of respondents reporting less than 5 lifetime partners. Men typically report more partners than women [15, 34, 115, 116]. In MSM populations the reported lifetime numbers of partners are significantly higher [54, 116]. For example, in [116], the median number of reported lifetime partners of an MSM population in the US is 45 with range 0-9005.

Transmission rate

One of the few studies providing estimates of HIV transmission rates [112] is based on an empirical study in a heterosexual population in SSA [112]. In [111], we find estimates $\beta_1 = 2.76$ years^{-1} for the transmission rate in the primary stage, $d_a = 0.24$ years for the duration of the primary stage, and $\beta_2 = 0.106$ years^{-1} for the transmission rate in the asymptomatic stage.

We used those estimates for quantifying the transmission rate β in our model by choosing β as a weighted average of the estimates β_1, d_a, and β_2 when taking into account survival probabilities in both stages. The total infectivity of a newly infected individual in the SI model is β/μ. For a model with two infection stages, infectivity in the first stage is $\beta_1 d_a$, while infectivity in the second stage is $\beta_2(1/\mu - d_a)$. Therefore we chose β such that it satisfied $\beta/\mu = \beta_1 d_a + \beta_2(1/\mu - d_a)$, and we obtained $\beta = 0.12$ years^{-1}.

Parameter	
n	partnership capacity
$1/\mu$	sexually active lifespan (years)
d_P	partnership duration (years)
θ	lifetime number of partners
β	transmission rate (years^{-1})

Table B.1: Overview of parameters of the model

C Sensitivity analysis

We provide the sensitivity analysis performed for the (κ_P, R_0)-curves for the six scenarios (Fig. 3). We conducted a sensitivity analysis with respect to the parameters β, θ and d_P. First we focused on the transmission rate β. We investigated this as follows. A random sample of values for β was drawn from the interval $(0.106, 0.20)$, where 0.106 is the estimate for the transmission rate in the asymptomatic phase in [112] and 0.20 is the value for the transmission rate in the constant infection model of [21]. The (κ_P, R_0)-curves using a random sample of β in this interval were considered. In this way we obtained upper- and lower bounds for R_0 yielding a range of outcomes for each scenario; see Fig. C.1.

Similarly, sensitivity analysis was performed for the parameters d_P and θ. We consider a 25% interval around the values for d_P and for θ, i.e. intervals of the form $d_P * (0.75, 1.25)$ and $\theta * (0.75, 1.25)$. Again we took random samples of values from these two intervals and plotted the (κ_P, R_0)-curves. From these curves we took the curves with the lowest and highest values of R_0 and we obtained a range of outcomes for each scenario; see Fig. C.2.

Note that for each pair of (d_P, θ) values, a different value of κ_P is obtained (κ_P is a function of d_P, θ, and n; recall expression (A.2) for κ_P). Therefore, if we consider a parameter-value combination (d_P, θ) close to one of the six scenarios, a change in the R_0-values occurs (y-axis) as well as a change in the κ_P-values (x-axis). For the

same partnership capacity n, the κ_P-values of the upper- and lower bound of R_0 do not necessarily match up with the κ_P-values of our six scenarios.

Results in Figs. C.1 and C.2 show that whether or not R_0 crosses the threshold value of 1 depends on the parameter values. It is certainly not always the case.

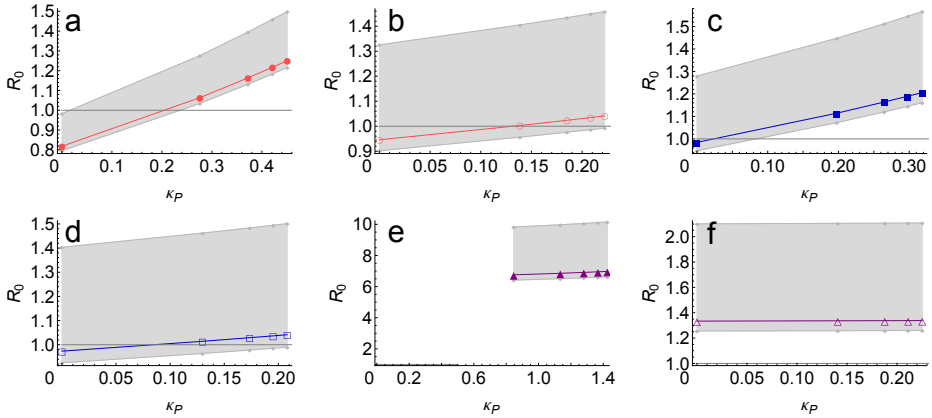

Figure C.1: Sensitivity of transmission rate β for the six scenarios (see also Table 1 in the main text). (a) SSA 1 (b) SSA 2 (c) SSA 3 (d) SSA 4 (e) MSM 1 (f) MSM 2.

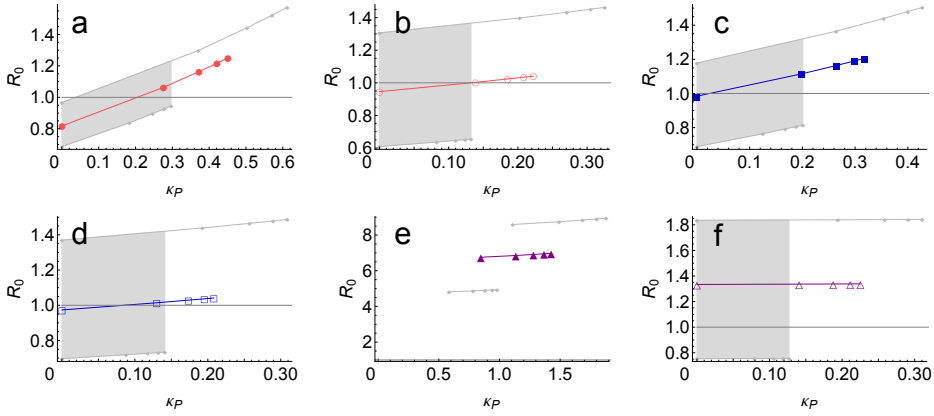

Figure C.2: Sensitivity of partnership duration d_P and lifetime number of partners θ for the six scenarios (see also Table 1 in the main text). (a) SSA 1 (b) SSA 2 (c) SSA 3 (d) SSA 4 (e) MSM 1 (f) MSM 2.

Chapter 7

Gender asymmetry in concurrent partnerships and HIV prevalence

K.Y. Leung
K.A. Powers
M.E.E. Kretzschmar

In review

Abstract

The structure of the sexual network of a population plays an essential role in the transmission of HIV. Concurrent partnerships are important in determining this network structure. Men and women may differ in their concurrent behavior, e.g. in the case of polygyny where women are monogamous while men may have concurrent partnerships. This form of concurrency was found to be negatively associated with HIV prevalence in an empirical study by Reniers and Watkins [24], which motivated this study. Besides formal polygyny, gender asymmetry in concurrent partnerships is often found. Here we investigated how gender asymmetry in concurrency, and in particular polygyny, can affect the disease dynamics in the population. We used a model for a dynamic network where partnerships can be formed and broken over time and individuals can enter and leave the population due to demographic turnover. Individuals in the population may have multiple partners at a time and the maximum possible number of simultaneous partnerships varied for men and women. We considered the gender asymmetric scenario of polygynous unions where women are monogamous but men may not be, the symmetric scenario where men and women may have the same number of simultaneous partnerships, and scenarios in between. For these scenarios the epidemic and endemic phases of the disease in the population were considered by means of R_0, the relative contribution of the acute phase to R_0, and the endemic prevalence. We found that gender asymmetry in concurrent partnerships is associated with lower levels of all three epidemiological quantities, especially in the polygynous case when women have at most one partner at a time.

1 Introduction

Sexual behavior plays an essential role in the transmission of HIV and other sexually transmitted infections (STIs) in a population. There is large diversity in sexual behavior leading to varying risks of acquiring or transmitting infection. Some behavior predominantly influences transmissability and susceptibility, such as condom use. Other behavior, such as concurrency, influences the population network structure.

Whether or not concurrent partnerships are driving HIV epidemics in sub-Saharan Africa has been much debated for a long time (e.g. [10–14, 17, 20, 24, 29, 30, 118]). In the setting of serial monogamy, a newly infected individual is typically still in a partnership only with his/her infector during this acute phase. On the other hand, when partnerships overlap in time, newly infected individuals can transmit infection to their susceptible partners while in the acute phase of HIV, i.e. the elevated infectiousness in the first few week/months immediately after infection. It has been hypothesized that this could potentially enhance the spread of HIV in the population.

Some forms of concurrency such as polygyny (men may have multiple partners at a time while women are monogamous) naturally lead to gender asymmetry in concurrent behavior. An ecological study of 34 countries in sub-Saharan Africa [24] suggested that this form of concurrency is negatively correlated with HIV prevalence in the population. This motivated our study. Polygyny is an extreme form of gender asymmetry in concurrent partnerships. Besides formal polygynous unions, men are often found to report more concurrent partners than women do [20, 34, 119]. It is not straightforward what the effect of such differences in men and women could be on the population-level HIV transmission or acquisition risks. How does gender asymmetry in concurrent partnerships, and in particular polygyny, affect the HIV disease dynamics in the population?

We studied how gender asymmetry affects the beginning of an epidemic by studying the basic reproduction number R_0 and the relative contribution of the acute stage of HIV to R_0. As most HIV epidemics in sub-Saharan Africa are now endemic, our main aim was to study the endemic prevalence. How does gender asymmetry affect the population prevalence; are more asymmetric populations associated with lower levels of HIV prevalence (as found in [24])? As a secondary outcome we were interested in the HIV prevalence among women compared to men. In this study we used a mathematical model for the spread of HIV on a dynamic sexual network for a heterosexual population. To parametrize the model we used existing data on sexual behavior from a study population in Malawi and published estimates of HIV infectivity parameters. Different scenarios in the maximum number of simultaneous partners with this set of baseline parameter values were investigated.

2 Methods

2.1 Model

Previously, a model of a dynamic network for a homosexual population and the spread of a one-stage infection without recovery was introduced (Chapters 2 and 3). In the current paper, we extended this to a heterosexual population with a 1:1 sex ratio and two infectious stages. Concurrent partnerships are modeled by allowing each individual a maximum number of partners it can have simultaneously; we call this number the individual's partnership capacity. We assume that there are two partnership capacities n_m and n_f for men and women in the population, respectively. Newly infected individuals are in the acute stage of infection and then progress to the chronic stage. The time spent in the acute stage is assumed to be exponentially distributed. The transmission rate in the acute stage of infection is associated with a higher level of infectiousness than the chronic phase. An infectious individual remains infectious for the rest of his or her sexually active life.

The network structure is stable over time which leads to stable degree distributions for men and women (here the degree of an individual is the given by the number of partners that he or she has). However, the network is dynamic in time due to individuals forming new partnerships and separating from existing partners during the course of their life. Furthermore, there is demographic flow due to individuals entering and leaving the population. Infection is assumed to have no impact on partnership formation or separation nor the mortality.

The model is deterministic in nature. It is fully characterized by a set of parameters that can be distinguished between sexual behavior and infection parameters. Individuals are characterized by sex-specific parameters; see Table 1. We assumed that the infection parameters do not depend on gender [120–122].

By fixing all parameters except for the partnership capacities n_f and n_m, concurrency in the population is varied by varying n_f and n_m. Concurrency was measured using the partnership-based concurrency index [35] and Chapters 2 and 6. It measures the mean number of additional partners of an individual in a randomly chosen partnership. Here we distinguish between concurrency indices κ_P^m and κ_P^f for men and women, respectively, and the concurrency index κ_P^{popul} for the population as a whole. A more detailed and technical description of the model can be found in Appendix A.

2.2 Parametrization of the model

Throughout this study we kept mean partnership duration d_P, sexually active lifespan $\bar{L}$, and mean lifetime number of partners $\bar{\theta}$ in the population fixed.

Mean partnership duration was based on self-reported data collected in a study of acute HIV detection strategies and longitudinal HIV viral dynamics at an STI clinic in Lilongwe, Malawi. Sampling strategies and study procedures have been described previously [56, 123–125]. As our model assumes a constant partnership dissolution rate, we

calculated the slope of a linear curve fitted to the reported duration of steady partnerships (in days) on the x-axis and the $-\ln$(partnership survival) on the y-axis, see Appendix B. We estimated a weighted mean partnership duration d_P of 3.92 years as the inverse of this slope.

Mathematical models of heterosexual HIV transmission in sub-Saharan African settings commonly assume a sexually active population between the ages of 15 and 49 years [126], corresponding to an average sexually active lifespan $\bar{L}$ of 35 years. Differences in the duration of sexual activity by sex are not well defined. Given the uncertainty in sexual lifespans for men and women, we modeled three scenarios: one in which both men and women had a mean sexual lifespan of $L_f = L_m = 35$ years; one in which the sexually active lifespan was $L_f = 33$ years for women and $L_m = 37$ years for men; and one in which the sexually active lifespan was $L_m = 33$ years for men and $L_f = 37$ years for women.

The mean lifetime number of partners $\bar{\theta}$ for the $L_f = L_m$ scenario was then gauged such that endemic HIV prevalence in the population was around 13%, corresponding to [127] (see Section 3.3 for more details). This leads to a mean lifetime number of partners $\bar{\theta} = 3.5$. This choice was motivated by our interest in qualitative behavior rather than trying to make any quantitative predictions about disease prevalence.

Infection is characterized by the transmission rates β_1, β_2 and duration of the acute phase d_A (Table 1). We let $\beta_1 = 2.76$/year, $d_A = 2.9$ months, and $\beta_2 = 0.106$/year [112]. In Appendix C.3 we conducted sensitivity analysis using infectivity parameter estimates from a different, more recently, published study [128]. In [128] a much lower transmission rate for the acute stage of infection was estimated but a higher transmission rate for the chronic stage of infection (and therefore yielding a comparable total infectivity).

Parameter values are summarized in Table 1. Variation around these values were addressed in the sensitivity analysis in Appendix C.

Parameter	**Description**	**Estimate**
n_m	partnership capacity for men	varied (see Table 2)
n_f	partnership capacity for women	varied (see Table 2)
d_P	mean partnership duration	3.92 years
L_f	sexually active lifespan for women	varied (see Table 2)
L_m	sexually active lifespan for men	varied (see Table 2)
$\bar{L} = \frac{1}{2}(L_f + L_m)$	sexually active lifespan	35 years
θ_f	mean lifetime number of partners for women	varied (see Table 2)
θ_m	mean lifetime number of partners for men	varied (see Table 2)
$\bar{\theta} = \frac{1}{2}(\theta_f + \theta_m)$	mean lifetime number of partners	3.5
β_1	transmission rate acute phase	2.76/year
d_A	duration acute phase	2.9 months
β_2	transmission rate chronic phase	0.106/year

Table 1: Model parameters and baseline parameter values.

2.3 Scenarios

We focused on gender asymmetry in the maximum number of partners men and women may have simultaneously, i.e. in partnership capacities n_f and n_m. Mean partnership capacity was fixed at $\bar{n} = (n_f+n_m)/2 = 4$. The extremes are the asymmetric polygynous situation $(n_f, n_m) = (1, 7)$ (i.e. women are monogamous) and the symmetric situation $(n_f, n_m) = (4, 4)$. Furthermore, we considered $L_f < L_m$, $L_m = L_f$, and $L_f > L_m$. Note that, since infection parameters are gender independent, asymmetry in the opposite direction ($(n_f, n_m) = (7, 1)$, etcetera) is automatically included by switching the role of males and females in the results.

Together, gender asymmetry in partnership capacities and sexually active lifespans give rise to twelve different scenarios; these are summarized in Table 2. These scenarios were used to investigate the effect of asymmetry in the population on the infection dynamics. In particular we were interested in R_0, the relative contribution of the acute phase to R_0, and the endemic prevalence.

	$L_f = 33$ years $L_m = 37$ years	$L_f = 35$ years $L_m = 35$ years	$L_f = 37$ years, $L_m = 33$ years
$(n_f, n_m) = (1, 7)$	A1	A2	A3
$(n_f, n_m) = (2, 6)$	B1	B2	B3
$(n_f, n_m) = (3, 5)$	C1	C2	C3
$(n_f, n_m) = (4, 4)$	D1	D2	D3

Table 2: The twelve different scenarios. Corresponding lifetime number of partners are $\theta_f = 3.3$ and $\theta_m = 3.7$ for $L_f = 33$ years, $L_m = 37$ years, $\theta_f = 3.5 = \theta_m$ for $L_f = 35 = L_m$ years, and $\theta_f = 3.7$ and $\theta_m = 3.3$ for $L_f = 37$ years, $L_m = 33$ years.

3 Results

Both network structure, R_0, and the relative contribution of the acute phase to R_0 lead to very similar results for the three different sexually active lifespan cases $L_f < L_m$, $L_f = L_m$, and $L_f > L_m$. Therefore, in both Sections 3.1 and 3.2, we focused on the sexually active lifespan case $L_f = L_m$, i.e. scenarios A2, B2, C2, and D2. In Section 3.3 all twelve scenarios of Table 2 are considered.

3.1 Network structure

The degree distributions for scenarios A2, B2, C2, and D2 were considered. The parameter values associated with these scenarios lead to very small fractions of men with more than two partners across all scenarios. the key difference is in the degree distributions for women: in A2, women are monogamous and can have either zero or one partner, which is distinctly different from scenarios B2, C2, and D2, where there are fractions of women with more than one partner at a time. As the overall degree distributions (across women

and men) are very similar across scenarios B2, C2, and D2, we show only scenarios A2 and D2 in Fig 1.

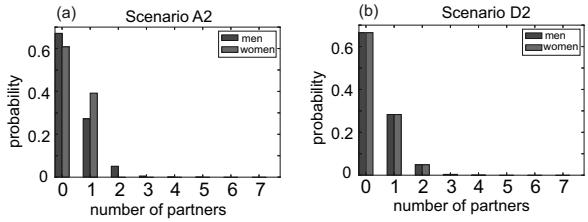

Figure 1: Degree distributions. The degree distributions for (a) scenario A2 and (b) scenario D2 calculated from the model parameters.

In Fig. 2 networks for scenarios A2 and D2 were visualized by simulating cross-sections of the networks using degree distributions of Fig. 1. Network structure is significantly different in the two scenarios A2 and D2. In scenario D2, longer 'chains' of partnerships can be found, e.g. a chain consisting of six individuals. This is absent in scenario A2 where women have at most one partner at a time. Note that the networks in Fig. 2 are only snapshots of one randomly chosen point in time as they are evolving in time with partnership formation and dissolution as well as individuals entering and leaving the sexually active population. Furthermore, single individuals are omitted from the network figures to better show the partnerships. Finally, although partnership capacity choices in principle allow for much larger connected components, the chosen parameter values are such that this is rarely the case; there is only a very small fraction of the population with more than two partners (Fig. 1).

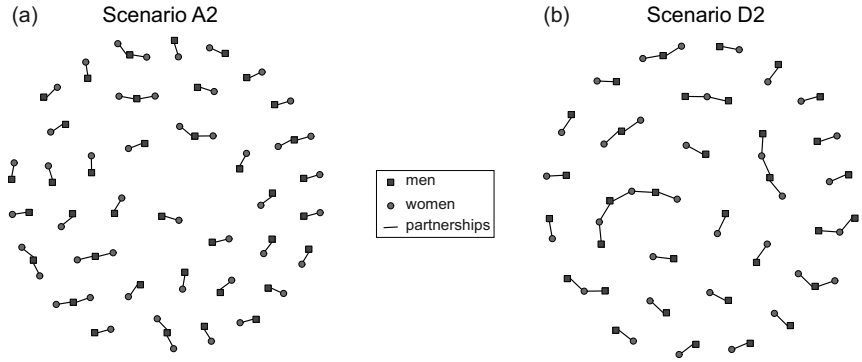

Figure 2: Simulated configuration networks. The networks are shown at one point in time for a population size of 100 individuals from given degree distributions for scenarios A2 and D2. In (a) and (b) networks for scenarios A2 and D2, respectively, are simulated. At any point in time, a large part of the population is single. In network A2 there are 62 single males and 54 single females while in network D2 there are 67 single males and females. These single individuals are not displayed in the two figures.

Next, we considered the level of concurrency for the scenarios A2, B2, C2, and D2. We measured the level of concurrency with the partnership-based concurrency index (cf. [35] and Chapters 2 and 6, see also Appendix A). The results are presented in Fig. 3.

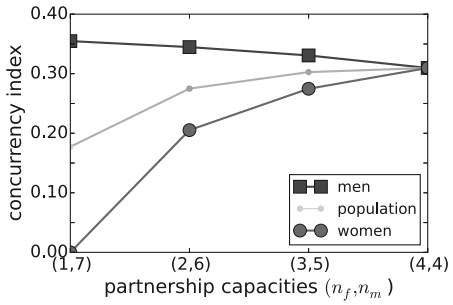

Figure 3: The partnership-based concurrency index. The concurrency index κ_P^m for men, κ_P^f for women, and κ_P^{popul} for the population, in the four scenarios for scenarios A2, B2, C2, and D2.

Note that female concurrency is zero for $n_f = 1$ (monogamy) and it increases for $n_f = 2, 3, 4$. Male concurrency is highest in the most asymmetric scenario A2 and decreases with more symmetric scenarios. Similar to the case for women, this is caused by a decrease in the maximum number of simultaneous partners ($n_m = 7, 6, 5, 4$). Moreover, the decrease in male concurrency is less than the increase in female concurrency. Therefore, the overall population-level concurrency index κ_P^{popul} increases with increasing gender symmetry.

3.2 R_0 and the contribution of the acute phase to R_0

The beginning of the epidemic was studied by considering R_0 and the relative contribution of the acute phase to R_0 for scenarios A2, B2, C2, and D2 in Fig. 4.

R_0 increases with increasing symmetry in the population. In all four scenarios R_0 is above the epidemic threshold value one. In the most asymmetric scenario A2 there is only a small contribution of the acute phase to R_0. The acute phase does play a significant role in the other three scenarios with a contribution of up to 13% to R_0. This makes sense since R_0 averages over secondary cases caused by men and women in the population, the relative contribution of the acute phase becomes very small, if it is small for women which is the case when women are monogamous. More importantly, adding an acute stage with high infectivity to the infection model does not change model behaviour qualitatively: R_0 is increasing with population-level concurrency (combine Fig. 3 with Fig. 4), consistent with earlier findings (Chapter 6).

Compared to women being monogamous ($n_f = 1$), allowing for some possibility of forming concurrent partnerships ($n_f = 2$) for women greatly changes the contribution of the acute phase to R_0 while the difference is much smaller between scenarios B2, C2,

and D2 (compare with the increase in population concurrency in Fig. 3). The relative contribution of the acute phase to R_0 is somewhat insensitive to model parameter values; see also Fig. C.3 in Appendix C.

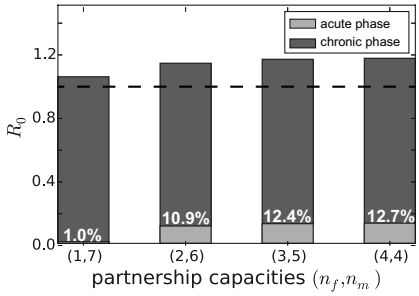

Figure 4: The basic reproduction ratio R_0. R_0 in the four scenarios A2, B2, C2, and D2 . The light and dark green indicate the fraction of R_0 that is caused in the acute and chronic phase of infection, respectively, while the height of the bar is given by R_0.

3.3 Endemic prevalence

In Fig. 5 population HIV prevalence was considered as a function of the sexually active lifespan scenarios.

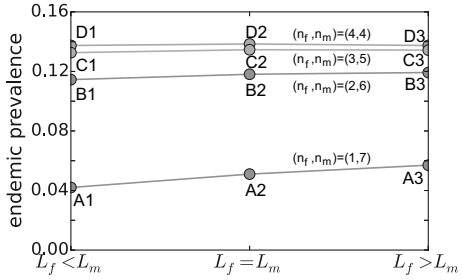

Figure 5: Endemic prevalence in the population. The endemic prevalence in the population for the twelve different scenarios plotted as a function of sexually active lifespan with partnership capacities fixed. The corresponding scenario (see Table 2) is denoted for each point in the graph.

Gender asymmetry in sexually active lifespans seems not to matter much for the endemic prevalence in the population. There is not much variation between the three different sexually active lifespans in Fig. 5 (compare e.g. scenarios B1, B2, and B3). On the other hand, prevalence clearly increases with more symmetry in partnership capacities (compare e.g. scenarios A2 and D2). We investigated this further by considering endemic prevalence separately for men and women as a function of partnership capacity in Fig. 6.

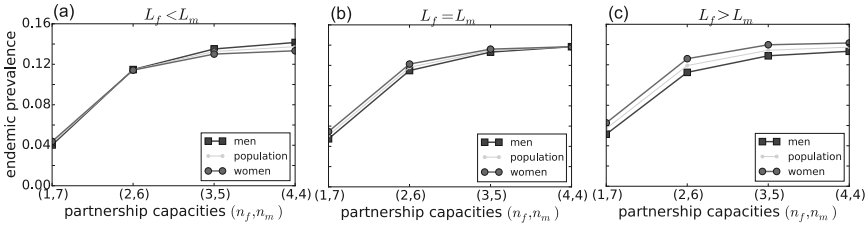

Figure 6: Endemic prevalence in the population. The endemic prevalence as a function of different partnership capacity combinations with sexually active lifespans (a) $L_f < L_m$, (b) $L_f = L_m$ and (c) $L_f > L_m$.

The fact that endemic prevalence is in a reasonable range [127] is a consequence of our parameter value choice for $\bar{\theta}$ (recall Section 2.2: we *gauged* $\bar{\theta}$ to an endemic disease prevalence of around 13% in the population for the scenarios B2 and C2; see Fig. 6). Our interest was in the qualitative behavior, in particular we were interested in comparing the endemic prevalences of scenarios A2, B2, C2, and D2 relative to each other (see Section 2). Qualitatively, gender asymmetry in partnership capacity is associated with lower endemic prevalence in the population.

Next, there is also gender asymmetry in disease prevalence. In Fig. 6(b) and (c) female prevalence is higher than male prevalence for all four partnership capacity combinations. This difference is larger in Fig. 6(c). However, in Fig 6(a) for $(n_f, n_m) = (3, 5)$, and $(4, 4)$, female prevalence is slightly lower than male prevalence. Sensitivity analysis shows that this is a general result for partnership capacity combination $(n_f, n_m) = (4, 4)$ and $L_m > L_f$ (Fig. C.5 in Appendix C). On the other hand, the same analysis shows that for $(n_f, n_m) = (1, 7)$, female prevalence is always larger than male prevalence regardless of gender differences in sexually active lifespans (so $(n_f, n_m) = (2, 6), (3, 5)$ lie somewhere in between). While disease prevalence differs only slightly in Fig. 6, these differences are greatly enhanced by greater gender asymmetry in sexually active lifespans (Fig. C.5 in Appendix C).

Finally, from these results, we conclude that the epidemiological quantities R_0, the relative contribution of the acute phase to R_0, and the endemic prevalence are increasing with increasing concurrency in the population (combine Fig. 3 with either Fig. 4, or Fig. 6). However, note that the level of concurrency in the population is varied by gender asymmetry in partnership capacities.

Moreover, when sampling sexual behavior parameter value combinations around the baseline parameter values using the Latin Hypercube Sampling method in Appendix C a very strong correlation between population-level concurrency and R_0 and population disease prevalence appears (see Figs. C.2 and C.4 in Appendix C for the details). This suggests that, although all sexual behavior parameters separately have an impact on prevalence, the combination of these parameters in the concurrency index κ_P^{popul} yields a much stronger correlation. This effect is much less strong when considering the relative contribution of the acute phase to R_0, which seems in general not very sensitive to model

parameters (Fig. C.3 in Appendix C).

4 Discussion

In this study we investigated the effect of gender asymmetry in the maximum number of partners an individual can have simultaneously, the so-called partnership capacity, on HIV disease dynamics. Our study is mainly qualitative in nature and can not be used to make any quantitative statements (we have e.g. chosen the expected lifetime number of partners to be such that the endemic prevalence is around the estimated 13% for Malawi in 2010 [127]). Motivated by the findings of [24], we were especially interested in the extreme case of polygynous unions, i.e. $(n_f, n_m) = (1, 7)$. We found that all three epidemiological outcomes R_0, the relative contribution of the acute phase to R_0, and endemic prevalence are much lower than in more gender symmetric cases. The epidemiological outcomes were also lower in the other two gender asymmetric scenarios $(n_f, n_m) = (2, 6), (3, 5)$ compared to the symmetric scenario $(n_f, n_m) = (4, 4)$. However, the differences are much smaller than for the polygynous setting $(n_f, n_m) = (1, 7)$. Our sensitivity analysis in Appendix C shows that, *qualitatively*, our conclusions do not depend on the parameter values (Fig. C.1 in Appendix C).

We also investigated the influence of gender asymmetry in sexually active lifespans L_f and L_m for women and men, respectively. Women tend to enter the sexually active population at a younger age than men [129]. At the same time, men tend to remain sexually active at older ages when women are no longer so [129]. Since it is not clear how these effects together exactly influence mean times that men and women spent in the sexually active population, we considered three different cases (but see [130] for an estimation of sexually active lifespans for a US heterosexual population). More empirical information on sexually active lifespans is needed to better understand this.

Nevertheless, gender asymmetry in sexually active lifespans did not change our findings about gender asymmetry in partnership capacities and the association with the epidemiological quantities under consideration. Additionally, we found that in case of gender symmetric sexually active lifespans ($L_f = L_m$) or longer sexually active lifespans for women than men ($L_f > L_m$), endemic prevalence among women is slightly higher than among men. This difference is slightly larger the more gender asymmetry in partnership capacity there is (and these differences are enhanced by different parameter value choices, see Fig. C.5 in Appendix C). HIV prevalence data indeed shows that more women than men are living with HIV in sub-Saharan Africa, e.g. in Malawi [9, 127]. Our study suggests that this difference could in some part be explained by gender asymmetry in concurrent partners (the infection parameters in our study did not depend on gender at all).

We mainly focused on gender asymmetry in partnership capacities leading to gender asymmetry in concurrent partnerships while keeping other key parameters fixed. Note, however, that different network properties are usually dependent on each other. This is also the case here where there is dependence between e.g. lifetime number of partners and sexually active lifespans (compare sexually active lifespans and the corresponding lifetime number of partners values in Table 2). We found that any of the sexual behavior

parameters, such as lifetime number of partners and partnership duration correlate positively with the epidemic quantities. In particular, there is a strong correlation between population-level concurrency index κ_P^{popul} and R_0 as well as population disease prevalence (Appendix C).

Sexual network structure and gender asymmetry in concurrency were also addressed in the recent modeling study of [131]. In particular, they used an agent-based modelling approach to investigate gender-symmetric and -asymmetric concurrency levels. Concurrency was an input parameter in their model (which also influenced mean number of partnerships). In our study the levels of concurrency in the population were determined by sexual behavior parameters that were kept constant throughout different scenarios. As a consequence, gender asymmetry led to a different (lower) level of overall concurrency in the population compared to gender symmetry. Therefore, results from our study are not directly comparable with [131]. However, consistent with our findings, [131] found that higher levels of concurrency are associated with higher disease prevalence.

In Fig. 4 the R_0 values were smaller than published estimates of R_0 for HIV epidemics in SSA [132, 133] (but, compared to [112], whose infection parameter estimates we have used in this study, it is reasonably close to their estimate of 1.09 for serially monogamous populations). Another result worth mentioning is the relative contribution of the acute phase to R_0. This is very low in the most asymmetric scenario. We believe that this is a consequence of our homogeneous model population, leading to lower values of R_0 and lower relative contributions of the acute phase to R_0 than in more heterogeneous (and therefore more realistic) populations.

Our model framework can be generalized to allow for more heterogeneity in the population (see also Chapter 2). In particular, we can modify the model to include variability between individuals of the same gender by allowing for a distribution over a range of partnership capacities rather than just one partnership capacity for the entire gender. In reality, populations where *all* women are monogamous probably do not exist, and we should account for some fraction of non-monogamous women. We can further generalize to include multiple types of partnerships. Then e.g. spousal and non-spousal relationships can be distinguished, each with their own partner acquisition and dissolution rates. We expect that allowing more heterogeneity in the population can matter greatly for the HIV infection dynamics, with a lot depending on the ways heterogeneity is included. Further research is needed to better understand this.

In this study we studied gender differences in numbers of concurrent partners and sexually active lifespans. There are of course many factors that can play a role in determining disease dynamics. For example, age mixing (where young women tend to form partnerships with older men) has been proposed as an explanation in creating the difference in HIV prevalence in men and women [134–136]. But note that there are also longitudinal studies finding no increase in HIV acquisition among young women with older partners in South Africa [137–139]. In our model, partner acquisition (or separation) does not depend on the age of individuals at all. Another aspect not included in our model is change in sexual behavior due to the infection, e.g. in separation or acquisition of partners due to (suspected) HIV status of oneself or partners (but see [131] where this is addressed). Obviously these factors may also be of influence although it is not immediately clear what

their influences are.

Another weakness of the model is that we do not include any disease-related mortality. This causes the infectious period of an infectious individual to be shorter. As a consequence, he/she remains in the sexually active population for a shorter time, therefore also causing less secondary cases than if there is no disease-related mortality. This could then lead to lower levels of disease prevalence. However, assuming that disease-related mortality affects both genders in the same way, we believe that it will not influence the mechanisms demonstrated in this paper.

In conclusion, we find that gender asymmetry in expected numbers of concurrent partnerships can have a large effect on both the epidemic and the endemic state of HIV transmission dynamics. It can also create gender differences in endemic prevalence. Higher levels of gender asymmetry in concurrency are correlated with lower R_0 values and lower endemic prevalences in a population.

Acknowledgements

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A Model and parameters

In this supporting information details and calculations are given for the model used in the main text. Section A.1 describes the network model and Section A.2 described the infection model.

A.1 Network

In Chapter 2 a dynamic partnership network model for a homosexual population was introduced. In this paper we generalized this network model to consider a heterosexual population of men and women. The network is dynamic in two ways: individuals enter and leave the sexually active population and partnerships can be formed and broken over time. We allow for concurrent partnerships in the network in the following way. Each individual in the population has a maximum number of simultaneous partners; we call this number the individual's partnership capacity. In this paper we will assume that there are two partnership capacities n_m and n_f for men and women. Furthermore, we assume the population sex ratio to be $1:1$.

The network model is fully characterized by six parameters n_f, n_m, μ_m, μ_f, σ and ρ_f. Here n_f and n_m are the partnership capacities for women and men, μ_f and μ_m are the death rates for women and men, σ is the separation rate of partnerships, and finally ρ_f is a parameter concerned with acquisition of new partners. (In this model, the rate a female free binding site becomes occupied is $\rho_f F_m$ where F_m denotes the fraction of free male binding sites, with F_m constant and a function of the other model parameters;

see Chapter 2. The rate a male free binding site becomes occupied is $\rho_m F_f$, where F_f denotes the fraction of free female binding sites, and $\rho_m := \rho_f n_f/n_m$. Consistency requires that the total number of partnerships that men have must equal the total number of partnerships that women have, this translates into $n_m(1 - F_m) = n_f(1 - F_f)$, see also Chapter 2 for calculating the mean number of partnerships in the population). Note that, if we let $\mu_m \neq \mu_f$, i.e. different death rates for men and women, then also the sexually active lifespans for men and women are different ($L_m \neq L_f$).

Although the network is dynamic in time, the structure is stable. We have stable degree distributions $(P_k^m)_k$ and $(P_k^f)_k$ for men and women where the degree of an individual is given by the number of partners he/she has. The network model allows us to express these degree distributions as functions of the model parameters.

Rather than the model parameters, we focus on the following network statistics: L_f and L_m, the sexually active lifespans for women and men, d_P, the mean partnership duration, and $\bar{\theta}$, the mean lifetime number of partners for a randomly chosen individual. Since we assume a 1:1 sex ratio, $\bar{\theta} = \frac{1}{2}(\theta_m + \theta_f)$ is simply the average of mean lifetime number of partners for men and women.

These network statistics can be expressed as functions of the parameters. The determination of these statistics goes in exactly the same way as in Chapter 2 of a homosexual population, only here we need to equip the model parameters with subscripts f and m when appropriate. Therefore, we refer to Chapter 2 for details and only give the resulting expressions here. Gender specific sexually active lifespans are given by

$$L_f = \frac{1}{\mu_f}, \qquad L_m = \frac{1}{\mu_m},$$

while the sexually active lifespan $\bar{L}$ of a random individual in the population is obtained by simply taking the average $\bar{L} = \frac{1}{2}(L_m + L_f)$. Mean partnership duration is independent of gender and is given by

$$d_P = \frac{1}{\sigma + \mu_f + \mu_m}.$$

Finally, the mean lifetime number of partners for men and women are given by

$$\theta_f = \frac{\rho_f F_m(\sigma + \mu_f + \mu_m)n_f}{\mu_f(\rho_f F_m + \sigma + \mu_f + \mu_m)},$$
$$\theta_m = \frac{\rho_m F_f(\sigma + \mu_f + \mu_m)n_m}{\mu_m(\rho_m F_f + \sigma + \mu_f + \mu_m)}.$$

Consistency requires that $\frac{\theta_m}{\theta_f} = \frac{L_m}{L_f}$. If we furthermore use $\bar{\theta} = \frac{1}{2}(\theta_m + \theta_f)$, then we find that

$$\theta_f = \bar{\theta}/\bar{L}\, L_f, \qquad \theta_m = \bar{\theta}/\bar{L}\, L_m. \tag{A.1}$$

Then we can express the model parameters σ, μ_m, μ_f, and ρ_f in terms of the network statistics $\bar{L}$, L_f, $\bar{\theta}$, d_P (see Appendix F in Chapter 2 for the details in case of a homosexual

population). So by fixing $\bar{L}$, L_f, $\bar{\theta}$, d_P, all but two parameters of the model are fixed. The two parameters left to vary with are the partnership capacities n_f and n_m.

Finally, we measure concurrency in the population with the partnership-based concurrency index κ_P that was introduced in Chapter 2. In the context of a heterosexual population we will have separate measures κ_P^m and κ_P^f for male and female concurrency, and a measure κ_P^{popul} for the concurrency in the population as a whole. Here the partnership-based concurrency index can be interpreted as follows: choose a partnership at random from the population and consider one of the two individuals in this partnership. Then the partnership-based concurrency index describes the number of other partners of that individual. In the case of κ_P^f and κ_P^m, we choose the female and male individual, respectively, while in the case of κ_P^{popul}, we choose the individual at random. The partnership-based concurrency index can be expressed explicitly in terms of the model parameters. Similar to (5.2) of Chapter 2, we find in terms of the model parameters:

$$\kappa_P^m = \frac{2\rho_m F_f (n_m - 1)}{2(\rho_m F_f + \sigma + \mu_f) + \mu_m},$$
$$\kappa_P^f = \frac{2\rho_f F_m (n_f - 1)}{2(\rho_f F_m + \sigma + \mu_m) + \mu_f},$$

and, since the sex ratio in the population is $1:1$, for the population as a whole we have

$$\kappa_P^{\text{popul}} = \frac{1}{2}\kappa_P^m + \frac{1}{2}\kappa_P^f.$$

A.2 Infection

In Chapter 3 a one-stage infection without recovery is considered. In this paper we generalized this to two stages I_1 and I_2 of infection. A newly infected individual is always in the first stage I_1 of infection, and there is a constant rate (α_f and α_m for women and men, respectively) at which it progresses to the second stage I_2 of infection. We will denote the transmission rate of an infectious individual in the first and second stage by β_1 and β_2, respectively. At any point in time there is also the constant rate μ_f and μ_m for women and men, respectively, of dying.

In the model, individuals enter the sexually active population as susceptibles without any partners. Once infectious, individuals remain so until leaving the sexually active population. Furthermore, infection does not influence partnership dynamics, nor does it affect the probability per unit of time of dying.

We let d_A denote the duration of the first stage. We assumed that the mean duration of the first stage of infection is the same for both men and women. This d_A can be expressed as a function of the model parameters:

$$d_A = \frac{1}{\alpha_m + \mu_m} = \frac{1}{\alpha_f + \mu_f}.$$

By fixing d_A, μ_m, and μ_f, also $\alpha_m = 1/d_A - \mu_m$ and $\alpha_f = d_A - \mu_f$ are fixed. Therefore, there are three more parameters involved with the infection model, namely β_1, d_A, and β_2.

B Partnership duration estimate

Mean partnership duration was based on self-reported data collected in a study of acute HIV detection strategies and longitudinal HIV viral dynamics at an STI clinic in Lilongwe, Malawi; see also Section 2.2.

Mean steady partnership duration reported by women: $1/0.0008 * 365 = 3.42$ years
Mean steady partnership duration reported by men: $1/0.0006 * 365 = 4.57$ years

Mean partnership duration d_P was the weighted average mean of the mean partnership duration reported by men and women:

$$d_P = 3.42 * 0.569 + 457 * 0.431 = 3.92 \text{ years}$$

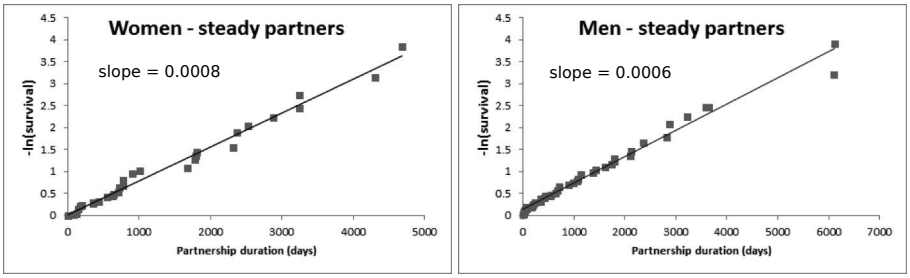

Figure B.1: The plots represent $-\ln$(survival) vs. partnership duration in days, such that the slope of a straight line through the points represents the (assumed constant) hazard of dissolution.

C Sensitivity analysis

In this supporting information the sensitivity of our findings to model parameters was considered. We performed a sensitivity analysis on all sexual behavior parameters at once by sampling different parameter value combinations around the baseline parameter values using a Latin hypercube sampling method in Section C.1. In Section C.2 we looked at only partnership duration and mean lifetime number of partners while keeping the other model parameter values fixed. Finally the infection parameters of the baseline setting of Table 1 in the main text were compared to other, more recently published, estimates of the same parameters in Section C.3.

Our main focus was on partnership capacity cases $(n_f, n_m) = (1, 7)$ and $(n_f, n_m) = (4, 4)$ and for convenience we referred to them as cases A and D, respectively.

C.1 Latin hypercube sampling

To study the sensitivity of model outcomes to sexual behavior parameters d_P, $\bar{\theta}$, L_m, and L_f we used a Latin hypercube sampling (LHS) method [140]. In short, LHS is a random sampling method that generates a representative sample of parameter value combinations.

It simultaneously varies the values of all four sexual behavior parameters. In that way LHS covers the parameter space of all possible combinations in a better way than random sampling.

In the LHS, parameter values for the four sexual behavior parameters were sampled. We considered a $\pm 20\%$ deviation from the baseline value $\bar{L} = 35$ years for L_m and L_f (this then automatically included $L_m < L_f$ and $L_m > L_f$). Finally, we considered a $\pm 20\%$ deviation from the baseline value $\bar{\theta} = 3.5$. (Parameter values $L_m, L_f, \bar{\theta}$ together determined θ_m and θ_f). We assumed that parameters L_m, L_f, $\bar{\theta}$, and d_P were uniformly distributed in these intervals. The LHS method then generates a sample of parameter value combinations from the multi-dimensional uniform distribution; see Table C.1 for an overview. A sample size of 500 parameter value combinations were considered for the two partnership capacity cases A ($(n_f, n_m) = (1, 7)$) and D ($(n_f, n_m) = (4, 4)$). Note that the scenarios of the main text (Table 2) also specified the sexually active lifespans whereas here in the sensitivity analysis the sexually active lifespan parameters L_m, L_f, and $\bar{L}$ are also varied. Therefore, we use letters A and D to refer to the two different partnership capacity combinations.

Parameter	**Description**	**Sampling interval**
d_P	mean partnership duration (years)	$(0.8 * 3.92, 1.2 * 3.92)$ $= (3.12, 4.70)$
L_m	mean male sexually active lifespan (years)	$(0.8 * 35, 1.2 * 35)$ $= (28, 42)$
L_f	mean female sexually active lifespan (years)	$(0.8 * 35, 1.2 * 35)$ $= (28, 42)$
$\bar{\theta}$	mean lifetime number of partners	$(0.8 * 3.5, 1.2 * 3.5)$ $= (2.8, 4.2)$

Table C.1: Sampling intervals for the parameters d_P, L_m, L_f, and $\bar{\theta}$. Parameters were assumed to be uniformly distributed in these intervals. LHS samples from all four intervals simultaneously.

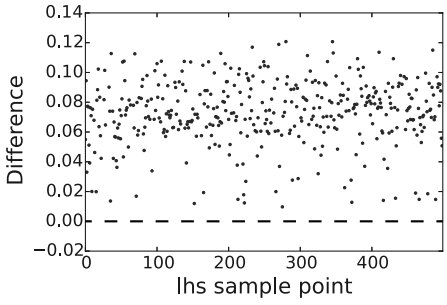

Figure C.1: The difference in endemic prevalence in the gender symmetric partnership capacity case A and the gender asymmetric case D. Parameter value combinations for which $R_0 < 1$ in case A are omitted.

All 500 parameter value combinations obtained through LHS yield a higher endemic prevalence in case A compared to case D (Fig. C.1). This supports our main finding that gender asymmetry in partnership capacity is associated with lower levels of endemic prevalence.

We investigated the correlation between different sexual behavior parameters (θ_m, θ_f, $\bar{\theta}$, L_m, L_f, $\bar{L}$, $L_f/L_m = \theta_f/\theta_m$, d_P, κ_P^{popul}) and the three epidemic quantities R_0, the contribution of the acute phase to R_0, and total endemic prevalence in the population.

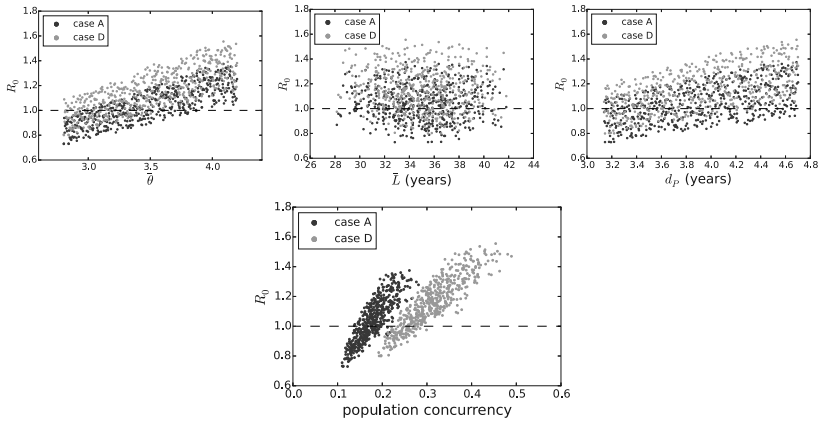

Figure C.2: R_0 as a function of sexual behavior parameters for cases A (dark orange) and D (light orange) for the LHS parameter value combinations. Dashed line represents the epidemic threshold value of one.

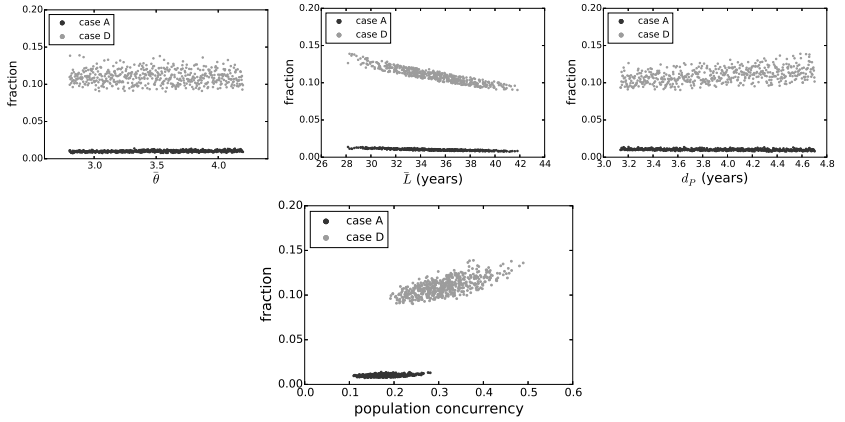

Figure C.3: The relative contribution of the acute phase to R_0 as a function of sexual behavior parameters for cases A (dark orange) and D (light orange) for the LHS parameter value combinations.

Since a large range of parameter values are considered, the epidemic quantities R_0 and endemic prevalence are quite sensitive (Figs. C.2, C.4). The LHS sample of parameter values yields a range of R_0 values from $\sim$0.7 to $\sim$1.6 and endemic prevalences from 0 to $\sim$40%. In a way this is to be expected as the population is homogeneous and all individuals of the same gender are described by the same parameters. Note that the contribution of the acute phase is somewhat less sensitive to the parameters in case A of asymmetric partnership capacities (Fig. C.3).

Lifetime number of partners ($\bar{\theta}$, θ_f, and θ_m) and partnership duration d_P are clearly positively correlated to R_0 and the endemic prevalence. The strongest correlation can be found in population concurrency (Figs. C.2 and C.4).

The relative contribution of the acute phase to R_0 does not really exhibit strong correlation with any of the sexual behavior parameters (Fig. C.3). A slightly negative correlation with sexually active lifespan ($\bar{L}, L_m, L_f$) and a slight positive correlation with partnership duration d_P and partnership concurrency in the population is found. This is to be expected: the longer mean lifetime is, the likelier it is that partnerships do not overlap. On the other hand, the longer partnership duration and larger partnership concurrency are, the likelier it is that partnerships do overlap (or are closer together in time) and in those settings more secondary cases can be caused in the acute phase.

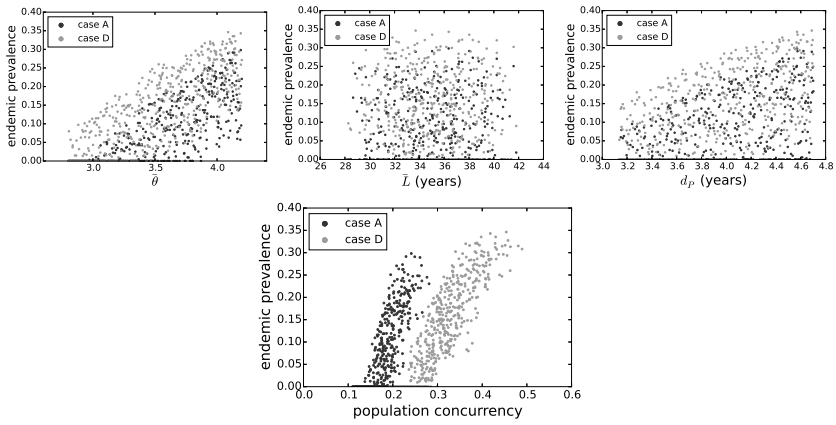

Figure C.4: The endemic prevalence in the population as a function of sexual behavior parameters for cases A (dark orange) and D (light orange) for the LHS parameter value combinations.

Next, let I_f and I_m denote female and male endemic prevalence, respectively. In Fig. C.5, we see that the asymmetric partnership capacity case A yields $I_f > I_m$ regardless of the difference in sexually active lifespans. In the symmetric partnership capacity case D, disease prevalence among women is lower than among men in the case that the male sexually active lifespan are longer than the female sexually active lifespans and the other way around (i.e. $L_m > L_f$ is correlated with $I_m > I_f$ and $L_m < L_f$ is correlated with $I_m < I_f$). This corresponds with our observations in the main text (compare with Fig. C.5 in the main text). Furthermore, in case D, the magnitude of endemic prevalence

difference is strongly correlated to the magnitude in sexually active lifespan differences (much less so in case A where the points are more spread out).

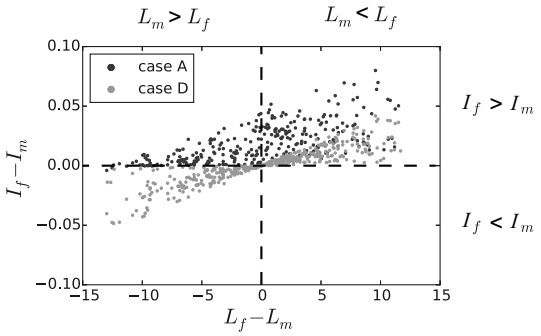

Figure C.5: Gender difference in endemic prevalence $I_f - I_m$ as a function of gender difference in sexually active lifespans $L_f - L_m$. The points for which $R_0 < 1$, i.e. with endemic prevalence $I_f = I_m = 0$ are not displayed.

C.2 Partnership duration d_P and lifetime number of partners $\bar{\theta}$

Since our mean partnership duration of 3.92 years in the baseline setting is likely an underestimation of 'true' partnership durations in a population, we considered d_P in the much larger interval $(1/2 * 3.92, 3 * 3.92) = (1.96, 11.8)$ in Fig. C.6. All other parameter values were chosen as in the baseline setting with a sexually active lifespan of $\bar{L} = L_m = L_f = 35$ years.

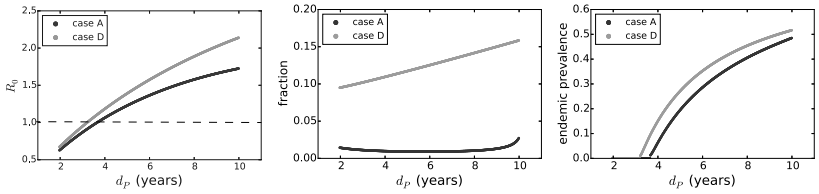

Figure C.6: Sensitivity of R_0, the relative contribution of the acute phase to R_0, and endemic prevalence to partnership duration d_P with d_P in the interval (1.96, 11.8).

Next, we consider lifetime number of partners $\bar{\theta}$ in Fig. C.7. We varied $\bar{\theta}$ in the interval $(0.5, 8.5)$. All other parameter values were chosen as in the baseline setting with a sexually active lifespan of $\bar{L} = L_f = L_m = 35$ years. Note that $\bar{\theta} = (\theta_f + \theta_m)/2$, so the larger θ_m would be, the smaller θ_f in order to maintain an average $\bar{\theta}$.

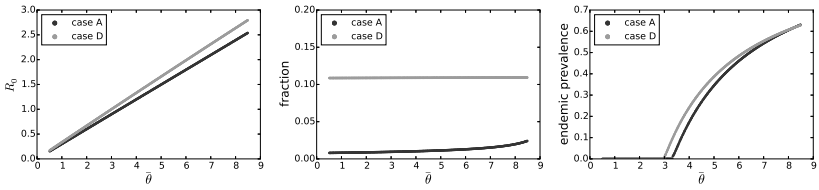

Figure C.7: Sensitivity of R_0, the relative contribution of the acute phase to R_0, and endemic prevalence to lifetime number of partners $\bar{\theta}$ with $\bar{\theta}$ in the interval (0.5,8.5).

As expected, all three epidemic quantities are all positively correlated to d_P and $\bar{\theta}$. Regardless of the parameter value for d_P or $\bar{\theta}$, the endemic prevalence in the asymmetric partnership capacity case A is always below that of case D (but they are much closer together when $\bar{\theta}$ is larger). The relative contribution of the acute phase is not very sensitive to $\bar{\theta}$. This makes sense as an increase in the contribution of the acute phase to the number of secondary cases caused by one sex are to some extent balanced out by a decrease of the opposite sex ($\bar{\theta} = 1/2(\theta_f + \theta_m)$ is the population mean lifetime number of partners).

C.3 Infection parameters

In [128] estimates for the HIV infection parameters were found using the same data set that [112] used. Estimates of $\tilde{\beta}_1 = 0.62$/year, $\tilde{d}_A = 1.7$ months, and $\tilde{beta}_2 = 0.12$/year were given. In particular, infectiousness in the acute phase is much lower in these estimates than in [112]. These infection parameter values were compared to the baseline infection parameter values $\beta_1 = 2.76$/years, $d_A = 2.9$ months, and $\beta_2 = 0.106$/years (see also Table 1 in the main text). We compared the resulting R_0, contribution of the acute phase to R_0, and the endemic prevalence for both sets of infection parameters in Figs. C.8, and C.9. Sexual behavior parameters are kept at the baseline values of Table 1 in the main text. In this section we will refer to the [112] estimates as the baseline infection parameter values and the [128] as the alternative infection parameter values.

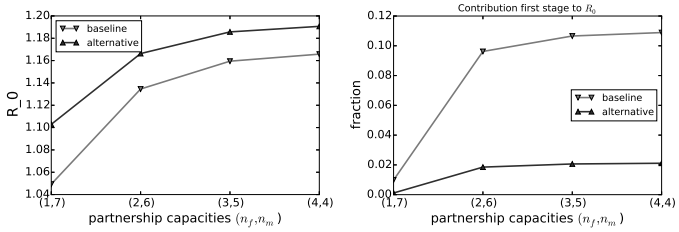

Figure C.8: Sensitivity of R_0 and the relative contribution of the acute phase to R_0 to the infection parameters

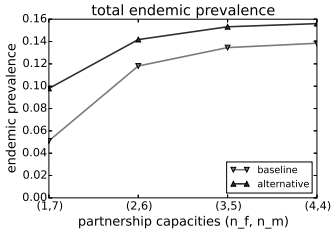

Figure C.9: Sensitivity of the endemic equilibrium to the infection parameters

Qualitatively the results are the same. With increasing symmetry in the population (from the most asymmetric partnership capacity case A to the most symmetric case D also the three epidemiological quantities under consideration increase. However, quantitatively, we do find a difference. Especially in the contribution of the acute phase to R_0 (Fig. C.8).

Both the endemic prevalence and R_0 are higher in the baseline setting than with the alternative infection parameters (Fig. C.9) whereas the contribution of the first stage of infection to R_0 is much lower in the case of alternative infection parameters compared to the baseline infection parameters (Fig. C.8,). Note that in the baseline setting, both the transmission rate β_1 in the acute stage and the duration of the acute phase are (much) larger than in the alternative setting. So, since the network structure is the same in both cases, we would expect that the relative contribution of the first stage of infection to R_0 to be much larger for the baseline values than for the alternative values.

Part III

To conclude

Chapter 8

Conclusion and discussion

In Part I we developed a mathematical framework for the spread of infectious diseases on networks, the so-called binding site formalism. The binding site models are amenable to mathematical analysis but also general and flexible so that several meaningful generalizations can be considered. In Part II, taking the models of Part I, we studied epidemiological questions related to concurrent partnerships and the impact on disease dynamics. Although not unrelated, the questions and challenges were quite different in the two parts. In this discussion chapter we also discuss them separately with certain overlapping themes.

Model formulation and analysis

This thesis started with Chapters 2 and 3. Motivated by the debate on the role of concurrent partnerships in HIV epidemics, we aimed to develop simple models for infectious disease spread on dynamic networks. This started with the development of a dynamic network model that incorporates both partnership changes and demographic changes (Chapter 2). We considered measures for concurrency and characterized several network characteristics such as mean lifetime number of partners and sexually active lifespan. The ideas were developed for comparing populations with different levels of concurrency (which were used in Chapters 6 and 7). Next, in Chapter 3, an SI infection was superimposed on the dynamic network. We made the mean field at distance one assumption. This approximation allowed us to close the system. We characterized R_0 by considering the infectious binding site perspective and proved that it indeed yielded a threshold parameter with threshold value one for the stability of the disease free steady state of the population-level (p-level) system.

In both Chapters 2 and 3 the individual-level (i-level) perspective was taken. On the i-level, we dealt with a continuous time Markov chain where the interaction *between* individuals was captured by environmental variables that were defined on the p-level. The p-level was obtained by averaging over individuals in the population. Implicitly we also used the binding-site level in our description and analysis. This binding-site level was first considered by Volz, Miller, and co-workers. They considered static configuration networks and dynamic configuration networks without demography in their so-called edge-based compartmental models [50, 79, 92–94] (see also Chapter 4). In their model formulation the focus was on the binding site and i-level. In the work by Lindquist et al. [76] and Chapters 2 and 3, the focus was on the i-level and p-level.

In Chapter 4, the binding site level and the relation between (1) binding sites, (2) individuals, and (3) the population was made explicit. We developed a class of binding site models for infectious disease epidemiology that is amenable to analysis. Three time scales of the disease relative to partnership- and demographic changes were covered, translating into networks that are (I) static, (II) dynamic without demographic turnover, and (III) dynamic with demographic turnover. Via a systematic procedure the three levels (1), (2), and (3) are related to each other. The binding site model description leads to only a few equations that determine the dynamics on all three levels.

We considered the three different cases I, II, and III for the network dynamics, for-

mulated the model under these time scale assumptions, and analyzed the corresponding equations. The epidemiological quantities R_0, r, the final size, and the endemic equilibrium were characterized. When it came to R_0, in cases I and II, we used the 'standard' perspective of an *infectious* case. In case III, we used a susceptible perspective instead (the infectious perspective of case III is covered in Chapter 3). We did this by considering 'reproduction opportunities'. This did not matter for R_0 (Chapter 4). It led to a huge simplification compared to Chapter 3 (but, without Chapter 3, there would not have been a Chapter 4). In particular, R_0 and r are easily defined from the equations that describe the model. This way, we can relate R_0 and r to the stability of the disease free steady state of the p-level system. Moreover, R_0 can easily be interpreted from the equations. Even if one is not so familiar with the concept of R_0, by algebraic manipulation of the equations, one can simply derive an epidemic threshold value *with the right interpretation*. As a bonus, it provides a double check: does the quantity that is derived purely from the interpretation on the i-level coincide with the quantity that is derived purely from the equations that determine the stability of the disease free steady state of the p-level system?

I believe that the binding site formalism of Chapter 4 is an important addition to the toolbox of mathematical modelling of infectious disease dynamics. It provides a way to deal with the spread of infection on *dynamic* networks. Moreover, we also relate binding sites, individuals, and the population to each other in a precise way. The binding sites are the essential building blocks of the framework and these allow for an understanding of the disease dynamics. However, the binding sites are merely a tool, it is the *individuals* that matter. Our framework relates binding sites to individuals, and in this way the processes taking place on the i-level are clear. Finally, from the point of view of epidemiology, what we are really interested in are the p-level disease dynamics and how these dependent on i-level behaviour. By relating the three levels to each other, the framework can be used to study epidemiological questions relating to disease spread on networks (which is exactly what we did in Part II).

Mean field at distance one assumption

One of the main points of discussion of Part I is the mean field at distance one assumption. The binding site model formulation includes only information about partners of an individual and none about partners of partners. For that the mean field at distance one assumption is needed. The idea is that, for the partners of a partner v of an individual u, one can average over the population of individuals that share the essential characteristics of v and u.

As discussed in Chapters 3 and 4, this assumption is an approximation in case the network is dynamic with demographic turnover. In this setting, the age of individuals causes correlations between the states of two partners that are not taken into account in the mean field at distance one assumption; see Appendix B of Chapter 3. Note however that the mean field at distance one assumption is exact in the static network case [83, 84, 89]. In the dynamic network case without demography it remains an open problem (but our conjecture is that it is also exact in this case). It is *this* assumption, even if it may be an approximation, that enables us to close the system.

In Chapters 3 and 4 we relied on wishful thinking, hoping that the mean field at distance one assumption was not too bad of an approximation. But of course it is relevant to ask how far from the truth it is. In order to investigate this we would need a description of the network as a whole: who is connected to whom and what are the disease states of each of the individuals. Therefore, the way to investigate the mean field at distance one assumption seems to be via simulation studies that allow us to keep track of the network at any point in time. How close to the truth is the mean field at distance one assumption? Can we identify parameter value ranges where it performs better or worse? Ideally we would like to develop some sort of intuition for it. (Immediately this raises the next question: how do we rigorously define 'not too far from the truth'?)

Since the mean field at distance one assumption is an approximation in the case of a dynamic network with demography, one can rightfully make a different assumption to close the system. One could for example approximate triples with pairs in the network and in this way close the system; this leads to so-called pair approximation models e.g. [141–145, and references therein]. We have not tried to assess which approximation performs better and certainly this deserves further investigation. However, since the mean field at distance one assumption is proven to be exact in the static network case, we believe this to be a natural assumption for the other two time scale cases as well.

Note added in proof. Things are no longer so straightforward when we allow for partnership capacity to vary in the population. See Section 6.2 of Chapter 5 for a discussion.

The infectious disease

As we already pointed out in the introduction of this thesis: often times compartmental models are used to describe the infectious disease under consideration. With the exception of Section 2.5 in Chapter 4, also in this thesis, we restricted ourselves to compartmental models.

In reality, the course of an infectious life of an individual will, as a rule, not be very accurately represented by a simple compartmental model. In compartmental models such as SIR (Susceptible-Infectious-Recovered), infected individuals are infectious with a constant level of infectiousness until they leave the I-compartment for the R-compartment, which occurs with a constant probability per unit of time. Once in the R-compartment, they immediately stop being infectious. More natural and general would be to consider an infectivity profile as a (continuous) function of age since infection [8, 57, 60].

It is certainly possible to approximate a general infectivity profile by considering more involved compartmental models by discretizing (e.g. Fig. 2 in [107]). Suppose that infectiousness varies greatly as a function of age since infection, then one can include multiple 'I' stages, each with a different transmission rate associated to it. The compartmental model could then be of the form $SI_1 \cdots I_kR$, with k any finite number. A downside of this approach is that the system of ODE generally grows with the number of compartments that one has. The advantage of an ODE system is then counteracted by the need of a large number of equations.

Alternatively, if one is willing to move away from ODE systems, then one can try to formulate infectious disease models using a general infectivity profile function. One may

end up with renewal equations (Section 2.5 of Chapter 4) that are more abstract than ODE, but allow for greater generality. In fact, making the problem more abstract can actually simplify it (using the interpretation it was much easier to derive the renewal equation in Section 2.5 of Chapter 4). Especially in case one is interested in studying e.g. the effect of the infectivity profile on transmission dynamics it could certainly pay to try to use a more general infectivity function.

But, as always, it depends very much on the context and the question at hand whether a simplifying assumption is too simple or whether more sophistication is just unnecessarily complicating matters.

Systematic model formulation: generalizations and limitations

The binding site formalism naturally leads to a small number of equations that fully determine the dynamics of binding sites, individuals, and the population. This system of equations enables us to characterize population-level epidemiological quantities, such as R_0, r, the final size, and the endemic equilibrium. The binding site model formulation forces one to be precise about assumptions. We need to specify how the binding site, i-, and p-level are related to each other. The environmental variables force us to make precise how the p-level influences the binding site and i-level. This is also one of the attractive points of the binding site models: it is very clear what the assumptions are.

The systematic procedure to formulate the binding site models lead to an intuitively clear, understandable, and easy tools for modelling the spread of infectious diseases on networks (both static and dynamic). The flexibility and generalizability makes this class of models attractive to study mathematically as well as to use in studying epidemiological questions.

But of course there is the other side of the coin as well. One of the aims of this thesis was to develop a class of models that is amenable to analysis. This desire comes with its limitations. An important and limiting assumption is that binding sites of an individual are conditionally independent entities. As far as partnership formation and separation is concerned, the state of one binding site of an individual does not influence the other binding sites.

On the other hand, it is exactly this independence assumption that enables us to consider several meaningful generalizations. As long as independence of binding sites in the partnership dynamics is maintained, a generalization is easily implemented in the current framework. Actually, the only issue is in doing the bookkeeping correctly. When it comes to the mathematics, this does not lead to any more complex or different problems than Chapter 4. In particular, the characterization of the different epidemiological quantities of interest do not change.

In Chapter 5 several meaningful generalizations were considered. The main purpose of this chapter was to show how these generalizations are implemented, and what the bookkeeping entails. It also serves to demonstrate the power of the toolbox developed in Chapter 4. We worked out the bookkeeping for a few generalizations that are rather straightforward. Time limitations unfortunately did not allow me to investigate other possible generalizations (as discussed in Section 5 of Chapter 4). However, it is my

belief that, although perhaps less straightforward than the generalizations of Chapter 5, our framework does provide a way of dealing with other generalizations. Exactly this flexibility of our binding site formalism is one of its strengths.

Note added in proof. As it turns out, implementing a seemingly straightforward generalization is more involved than what one would think (see Section 6.2 of Chapter 5). One can rightfully question the generality and flexibility of the formalism. However, it is the same binding site formalism that exposes the subtleties involved. So in that sense, the systematic approach of our formalism is also powerful in helping us understand the possibilities and subtleties of modelling infectious disease spread on configuration-like networks (and ideally prevents us from falling into pitfalls).

In the current framework it is not clear how to relax the independence assumption in some way, if possible. One of the limitations of the models is formed by the mass-action assumption for partnership formation: any two free binding sites can be joined together to form a partnership between their owners. It is imaginable that the rate at which an individual acquires a new partner depends on the number of partners it already has. (But to understand how this dependence 'works' is a challenge in itself.) On the binding site level this translates into 'the rate at which a free binding site acquires a partner is dependent on the number of partners the owner has'. An example would be to distinguish between the rate at which a single individual acquires a partner compared to a non-single individual, see [142] for such a network model using moment closure approximations. More research is needed to understand whether it is possible to extend the current binding site model formulation to include a proportionate mixing assumption for partners (in a way that analytical tractability of the model remains).

A different consequence of the configuration-network-construction is that the binding site models in this thesis are free from any clustering. In reality, networks contain loops. It is quite likely that two individuals with a common friend are themselves friends (leading to triangles in the network). Such loops not only exist in friendship networks but also in sexual networks (see [115] for an example of a real-life sexual network and [146] for an example of a 'romantic' network of adolescents in a high school), and these will influence the disease dynamics in a population. On the one hand, one may wonder whether there are general clustering patterns or rules in real-life networks: what, if any, are the mechanisms causing clustering in networks? This question lies more in the area of sociology (and is outside the scope of this thesis). On the other hand, from the modelling point of view, the challenge is in incorporating clustering in network models and to study the impact on disease dynamics [58]. This problem has been investigated for several different static network cases, e.g. [147–150]. One way to model short loops in static networks is when individuals are placed on a lattice, but this is rather restrictive. If we allow for some random contacts between individuals on the lattice, then longer range connections are added and we arrive at the small-world model [39, 41, 42]. Unfortunately, not much heterogeneity in the degree of individuals is possible. In the context of epidemic modelling, a special form of, less restrictive, clustering is considered by household models [77, 151] which contain two levels of mixing. In these models, individuals belong to small non-overlapping groups and contacts outside the group with the general population

are based on the random mixing assumption. These are some possible starting points for investigating the possibility of incorporating clustering in dynamic binding site models.

In the current framework, we make assumptions about the demographic process that are mathematically very convenient (and therefore also prevailing in literature): we assume that the individual's age is exponentially distributed. However, in many populations there is not a constant probability per unit of time of dying. So we would like to consider more general survival functions. I believe that this is possible using the current framework as a starting point. When considering a general survival function, the i-level is then related to the p-level in a different way. Moreover, we need to take into account the age of partners, which, I hope, can be done by averaging in the right way.

Related to this, in the current framework, the demographic process is assumed not to be influenced by the infectious disease in any way. When it comes to infectious diseases such as HIV we know infection can greatly impact the demography of a population. So disease-related mortality is certainly very relevant. The addition of disease-related mortality leads to an age distribution that is no longer stationary. Rather, the survival of an individual will depend on its disease status. Although we can not immediately include any disease-related mortality in the current framework, it does provide us with a way to do so. In particular, I believe that this can be done by focussing on *infectious* binding site probabilities (Section 5 of Chapter 4).

Not only did we assume that infection does not change the demographic process, we also assumed it not to influence the partnership dynamics in any way. We justified this simplification for ourselves by reasoning that individuals may not be aware of their own disease state or the disease state of their (potential) partners and therefore no behavioural changes arise in the presence of disease. But, when individuals are aware of the risk of transmission of infection, they may very well change their behaviour, by e.g. condom use (which changes infectiousness). Other behavioural changes may fundamentally impact network structure. In the context of HIV, serosorting has been identified as such a form: individuals seek partners with the same HIV status as themselves [24, 152]. As such changes may have important consequences for the transmission dynamics we would like to be able to capture that in epidemic models [153–156]. In the current framework, any such behavioural changes are ignored. I believe the binding site model formulation to form an excellent starting point for exploring the possibility of analytically tractable models for infectious disease dynamics on networks incorporating behavioural changes.

Despite the limitations that come with the binding site models as they are described in this thesis, I believe their use to go beyond mathematical interest. The simplicity of the models limits the number of parameters. At the same time these models do capture some essential features regarding partnership dynamics, concurrent partnerships, and demographic turnover. Moreover, the binding site models serve as excellent jumping-off points for more complex models that incorporate some of the aspects that are described in this section. Furthermore, as illustrated by Part II of this thesis, they can be used to study epidemiological questions, and in this way enhance our understanding of how different network mechanisms impact disease dynamics in a population.

Epidemiological questions

In Chapter 6 we used the simplest setting of a homosexual population and an SI infection to study whether concurrency can drive an HIV epidemic by moving the epidemic threshold value from below to above one. Concurrency was measured using the partnership-based concurrency index (Chapter 2). We considered populations that differed in the level of concurrency but were the same in other key aspects, viz. the transmission rate, mean lifetime number of partners, mean partnership duration, and sexually active lifespan. One parameter in the model was left: the partnership capacity n corresponding to the maximum number of simultaneous partnerships an individual can have. We found that the partnership-based concurrency index was positively associated with R_0 and that an increase of the concurrency index could move R_0 across the epidemic threshold value of one.

In Chapter 7 we investigated how gender asymmetry in concurrent partnerships impacts transmission dynamics. In particular, this included the situation of traditional polygyny where men may have multiple wives but women are monogamous. We considered a heterosexual population and a two-stage SI_1I_2 infection. Gender asymmetry in concurrent partnerships was controlled by considering gender asymmetry in partnership capacities for men and women. As in Chapter 6, we compared populations that were the same in many respects, e.g. mean partnership duration. We found that gender asymmetry in partnership capacity is associated with lower levels of R_0 and the relative contribution of the acute stage to R_0 as well as lower levels of the endemic disease prevalence.

In both Chapters 6 and 7 the simple models of Part I were used. The advantage was that only few parameters were needed. Based on literature, ballpark estimates of parameter values were made, and different scenarios were considered to gain understanding of the impact of different mechanisms on transmission dynamics. We did not mean to represent or model the complexity of sexual behaviour in any population. Neither did we aim to make any quantitative statements. Rather we aimed to, by isolating it from other network properties, understand how one specific feature *could* impact transmission dynamics.

The two modelling studies in Part II left us with some qualitative conclusions. First, concurrency can drive HIV epidemics by moving R_0 from below to above the epidemic threshold value of one. Secondly, gender asymmetry in concurrent partnerships is associated with lower disease prevalence in the population. Especially polygyny is associated with much lower disease prevalence in the population (thus supporting the empirical findings of [24]). Our findings provide some important qualitative insights in the role concurrent partnerships can play in the disease dynamics in a population.

Moreover, the two modelling studies forced us to think more carefully about how to formulate questions related to concurrency and infectious disease dynamics mathematically as well as how to answer these questions. In this way, our studies also contribute to the methodological toolbox of using mathematical models in infectious disease epidemiology. We carefully defined different scenarios by fixing key network characteristics. This enabled us to compare populations with each other and draw epidemiological conclusions.

Comparing populations, isolating network characteristics

At first sight it seems to be an easy task: to understand the impact of one phenomenon, we isolate it, and then see how transmission dynamics are affected. Question answered. But, in fact, this is, in my opinion, one of the most difficult challenges in infectious disease epidemiology. Isolating one phenomenon is not easy: often times it is closely related to many other relevant aspects.

In our case, the focus was on concurrency. Therefore, we wanted to compare populations with different levels of concurrency with one another. As concurrency is really a network property, it is also related to many other network characteristics. Intuitively, this is easy to understand. Suppose we increase mean lifetime number of partners while keeping mean partnership duration and sexually active lifespan fixed. Then we would expect there also to be more overlap in partnerships of an individual, translating into more concurrency. However, when lifetime number of partners of an individual increases, not surprisingly, also more secondary cases are, on average, caused by one infectious individual. This would lead to an increased R_0 which, through mean lifetime number of partners, is positively correlated to concurrency. But would we then conclude that concurrency is driving HIV transmission dynamics?

So, we wanted to isolate concurrency. In Chapter 6, where we considered the simplest model possible, we did so by fixing certain key characteristics of the network:

- sexually active lifespan (the longer an infectious individual is alive and sexually active, the more transmissions can occur)
- mean lifetime number of partners (the more partners an infectious individual has, the more transmissions can occur)
- mean partnership duration (the longer partnership duration, the larger the probability that infection is transmitted in that partnership)

Truly isolating a network characteristic from the network while keeping all else equal is never possible. In our simple model, fixing the above network properties, leaves only one parameter free, namely the partnership capacity for individuals. But then there are still differences between the populations with different partnership capacities, e.g. the fraction of the population that is single is different for these populations. Differences of some sort are unavoidable. A huge advantage of a simple model is of course that there are only few quantities that one has to take into account to fix almost all model parameters.

Things already become more complicated in Chapter 7 when we also take into account gender. In order to study gender asymmetry in partnership capacity we e.g. chose to keep the mean partnership capacity in the population fixed and consider different distributions for the partnership capacity for men and women.

As we have already mentioned in every chapter of this thesis, including this one: the simple model allows for several meaningful generalizations without adding much complexity to the mathematics. From the point of view of comparing different populations more complexity is added. A more involved model will inevitably come with more parameters and therefore more freedom to choose which quantities to keep fixed and which

not. To a large extent this depends on the question of interest. But, there is not one straightforward way to compare populations with each other and it matters what choices are made. The methods of Part II to define scenarios ensure that this stays as transparent as possible.

So, the challenge does not just lie in the development (and analysis) of a mathematical framework for the spread of an infectious disease on a network, which was the main focus of Part I. But, equally nontrivial, one needs to decide how to use a model to answer epidemiological questions.

Limitations and perspectives for public health

In Part II we were very precise and careful in formulating our epidemiological questions and drawing conclusions. In this way, the two studies of Chapters 6 and 7 contribute to a better understanding of HIV epidemics in sub-Saharan Africa and the role concurrent partnerships can play. In large part this was also due to the study designs. These methods could also be applicable in addressing other epidemiological questions.

I am the first to admit that the models in this thesis are very simple. While there are many benefits to simple, analytically tractable, models, there are also limitations to their use. A consequence of simple models is of course that they are far from describing any real population. There are so many factors involved in human behaviour that are simply ignored in our models. Of course the binding site models developed here were never meant to describe reality in its fullest. Rather they were meant to gain qualitative understanding. By means of Part II we did obtain some valuable epidemiological insights.

Moreover, these simple models form the starting point for more complicated models and several meaningful generalizations related to e.g. partnership type can easily be included. There are other generalizations that I believe can be incorporated in the model (Section **Systematic model formulation**). By many people this may be considered to be too much work to be worth the effort. And even then, there are limitations to what the binding site framework can handle. In such cases individual-based simulation models can be the outcome for which I believe the binding site models of this thesis to be good jumping-off points for simulation models.

The advantage of simulation models is of course that they are much more flexible in dealing with e.g. dependencies. No mean field at distance one assumption of any kind needs to be made. Rather, a computer can keep track of all individuals and partnerships at all time. A pitfall of simulation models is that, because they are more flexible to deal with more complicated situations, it is very tempting to try and include many features that are observed in real populations. The overview can easily lost. Some implicit assumptions may be made that one is not aware of. Even if this does not happen, it may be disadvantageous to include as many features as possible. No one will argue that there are not many different aspects that can contribute to transmission dynamics. Infinitely more important is to understand what features are *essential*.

I believe that simple models, even if they may seem way too simple from an applied perspective, are important. They allow for an understanding of the essential features, precisely because one may only be able to include the essential features in the model

(e.g. Chapters 6 and 7). This is not to say that simulation models are redundant and only simple mathematical models are needed. Not at all! Both the top-down approach of simple models and the bottom-up approach of simulation models are important and complement each other. In the ideal world these two approached meet somewhere in between (see also the preface of [157]).

With any model, one can always come up with an aspect that is not captured (which is probably not too difficult) due to the complexity of life. But this is exactly what models should be for! If we want to know how reality is, then we look at reality. But *because* reality is so complex, we use models to simplify. In any scientific discipline, we need to make assumptions when trying to answer a question [64].

So, are the models used in Part II too simple to teach us anything about concurrency and HIV transmission dynamics? Although we did gain more qualitative insights, the, perhaps rather unsatisfying, answer is: 'more research is needed'. However, even though the studies in this thesis did not provide any answers, our studies are of relevance in different way. We used mathematical models in exactly the way that I believe that they can play an important role in infectious disease epidemiology. Simple mathematical models can serve as initial investigations of a question. It forces us to define the question at hand in a precise and rigorous way. They can serve as proof of concepts (rather than serving as proof for a real world phenomenon, for that empirical evidence will always be needed).

In Chapter 6 we show that, yes, concurrency can drive an HIV epidemic (which in our definition meant that concurrency can move R_0 above the epidemic threshold value of one when other parameters are kept constant). But in what way does this reflect reality? It is hard to say as there are no two populations that differ only in concurrency while all other network properties are equal. The advantage of mathematical modelling is that we can create a theoretical setting in which such questions can be explored. The approach of a mathematical modelling study is that it also forces us to be precise about the question we ask and the underlying assumptions we make about e.g. network dynamics.

From a public health perspective the relevant issue is not whether something is theoretically possible. Rather, one wants to know whether something is actually happening (*is* concurrency driving HIV epidemics in sub-Saharan Africa?). Mathematical modelling studies alone can never answer this. Empirical studies are and will always be necessary.

On the other hand, mathematical modelling allows us to do thought experiments when real experiments are not possible. In this way we can isolate features to some extent to understand their impact on transmission dynamics. And this is what we did in Part II. I think it is important for mathematical modellers to appreciate the difficulties that come with empirical studies and keep in mind the limitations and possibilities (of both models and empirical work). We should always keep in mind the available data. While it is all nice and well to develop a model that has parameters such as the 'partner acquisition rate' or the 'separation rate', these are generally not parameters that can be observed. Rather, we expressed 'mean lifetime number of partners' and 'mean partnership duration' in terms of model parameters and used estimates for such network statistics.

Finally, our focus was on concurrent partnerships and the relation with HIV transmission dynamics. We can use the models and techniques employed in this thesis more broadly to investigate other epidemiological questions. However, one should keep in mind

that infectious disease epidemiology covers a wide range of disciplines from very theoretical mathematics to the practical public health policy. From the theoretical side we can always investigate how transmission dynamics are influenced if we vary some theoretical parameter in the model, and this may very well lead to interesting theoretical results. But, while mathematical modelling has proven to be an important tool in understanding infectious disease epidemiology, this does not mean that all mathematical modelling studies are of relevance to the field. One can not expect mathematical modelling results to have an impact in infectious disease epidemiology or public health without strong feedback and collaborations with people from this field, especially when it comes to control or intervention strategies.

To conclude

The main challenges in Part I were different from the ones in Part II. In Part I our focus was on model formulation and mathematical analysis while in Part II we tried to gain some understanding of real-life phenomena. In many respects it is easier to remain in the very theoretical context and study questions that are mostly of mathematical interest.

Trying to take into account reality and all its complexity is very challenging. When are models simple enough so that they are still amenable to analysis but not too simple so that they have no relevance for the questions at hand? This depends very much on the context and the question at hand. The art of modelling lies in balancing simplicity and reality.

The balance in this thesis has mostly been in favour of simplicity (which is not to say easy). This has lead to a lot of enjoyable mathematics, a lot of subtle modelling issues and R_0-calculations and -interpretations from different points of views. More importantly, it has lead the development of a class of models that enrich the mathematical modelling toolbox for understanding infectious disease dynamics.

Despite (or because?) the simplicity of the models that we used we were also able to address several epidemiological questions related to concurrent partnerships and infectious disease spread. This led to qualitative insights and a better understanding of the role of concurrent partnerships in HIV epidemics in sub-Saharan African populations.

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Samenvatting

Een soa (seksueel overdraagbare aandoening) oplopen? Nee hoor, mijn beide partners zijn monogaam. Of toch niet? Zonder je het te realiseren zou je wel eens deel uit kunnen maken van een groot seksueel netwerk. Via een partner van je partner kun je zo een soa oplopen. Hoe beïnvloedt het hebben van meerdere partners tegelijkertijd de verspreiding van een soa over een seksueel netwerk? Het antwoord op deze vraag lijkt simpel: via eventuele partners van partners kan een soa zich snel over een netwerk verspreiden. Maar is dat ook echt zo? In dit hoofstuk gaan we in op de rol van wiskunde bij het onderzoeken van deze vraag en bespreken we dit proefschrift.

Seksuele netwerken

De motivatie voor dit proefschrift is de hiv-epidemie in Afrika bezuiden de Sahara. Hiv is een soa die aids veroorzaakt. De voornaamste manieren waarop besmetting met hiv ontstaat zijn onbeschermd seksueel contact, bloedcontact (bijvoorbeeld via injectienaalden), en moeder-op-kind besmetting bij geboorte of borstvoeding. Hoewel er medicijnen bestaan die het virus relatief lang onder controle kunnen houden, bestaat er tot nu toe geen geneesmiddel. Het grootste percentage hiv-geïnfecteerden bevindt zich in Afrika ten zuiden van de Sahara. De verspreiding van hiv is in een groot deel van de wereld vooral een probleem bij specifieke risicogroepen zoals prostituees, mannen die seks hebben met mannen, en injecterende drugsgebruikers. In Afrika bezuiden de Sahara daarentegen is het virus wijdverspreid onder de heteroseksuele bevolking. Kan het hebben van meerdere partners tegelijkertijd de hiv-epidemie in deze regio aandrijven? De meningen hierover verschillen! [10–17] In dit proefschrift wilden we deze vraag onderzoeken met behulp van wiskundige modellen.

Zoals de term ‘seksueel overdraagbare aandoening’ al aangeeft, verspreiden soa’s zoals hiv zich voornamelijk via seksueel contact. Het is dus belangrijk om de seksuele contactpatronen in een samenleving te begrijpen. De meeste mensen gaan relaties aan en hebben dan meerdere seksuele contacten met hun partner. Dit soort contactpatronen kunnen we weergeven als een netwerk van mensen waarbij de seksuele relaties de verbindingen tussen mensen vormen. Het netwerk verandert in de loop van de tijd omdat mensen relaties verbreken en nieuwe relaties aangaan. Bovendien zijn er demografische veranderingen door mensen die seksueel actief of inactief worden. Een soa kan zich verspreiden via ‘gevaarlijke verbintenissen’ tussen twee mensen waarvan de één de soa heeft en de ander niet. Op welke manier dragen verschillende eigenschappen van een seksueel

netwerk, zoals het hebben van meerdere partners tegelijkertijd, bij aan de verspreiding van de soa?

Als we van alle seksuele relaties in een bevolking op de hoogte zouden zijn, dan weten we in theorie hoe het seksuele netwerk eruit ziet. In de praktijk is het erg lastig om hier achter te komen en vaak zelfs onmogelijk. Bovendien verandert het netwerk ook nog eens in de loop van de tijd. Een netwerk wordt al snel te ingewikkeld. Nog moeilijker wordt het om de invloed van het netwerk op de verspreiding van soa's te bepalen.

Modellen

Omdat de werkelijkheid zo complex is gebruiken wetenschappers van allerlei disciplines modellen om hun onderzoeksvragen te beantwoorden. Deze modellen kunnen heel verschillende vormen aannemen: een muis als model voor een mens om ons immuunsysteem beter te begrijpen, cellen in een reageerbuis als model voor levende cellen in een plant, een groep studenten als model voor de samenleving in psychologische experimenten, etcetera. De voorbeelden die ik hier opnoem hebben voornamelijk betrekking op experimenteel onderzoek. Soms is het niet mogelijk om experimenten uit te voeren in de gecontroleerde omgeving van een laboratorium. Denk hierbij maar aan klimaatverandering of zwaartekrachtgolven. In het geval van de verspreiding van soa's, waar dit proefschrift om draait, is het bijvoorbeeld niet verantwoord om met mensen te experimenteren. In zulke gevallen kunnen theoretische modellen, zoals wiskundige modellen in de infectieziektenepidemiologie, een belangrijke rol spelen. Ondanks het feit dat we geen echte experimenten met mensen kunnen doen, lenen wiskundige modellen zich uitstekend voor gedachtenexperimenten. Hoe verspreidt een soa zich in een aanvankelijk soa-vrije bevolking als één individu met een soa de populatie binnenkomt? Deze en andere vragen kunnen we bestuderen met behulp van wiskundige modellen.

Hoe ziet een wiskundig model eruit? Om de werkelijkheid te begrijpen moeten we vereenvoudigingen bekijken met behulp van modellen. Modellen bevatten alleen de belangrijkste eigenschappen en niet alle details, alleen de belangrijkste eigenschappen. In het geval van wiskundige modellen vertalen we een model naar een wiskundige formulering (Deel I van dit proefschrift). Maar hoe bepalen we welke eigenschappen belangrijk zijn? En hoe kunnen we een wiskundig model gebruiken om een onderzoeksvraag te beantwoorden?

Deze vertaling van de werkelijkheid naar een model is naar mijn mening een van de grote uitdagingen van het wiskundig modelleren. Welke elementen je in je model wilt opnemen hangt sterk af van de onderzoeksvraag. Maar ook het stellen van de juiste vraag is vaak niet eenvoudig. Stel je voor dat je de snelste route van Utrecht naar Stockholm wilt vinden. Om deze vraag te beantwoorden moeten we hem eerst preciezer maken: welke vervoersmiddelen willen we bijvoorbeeld gebruiken? Daarnaast moeten we ook bedenken wat we bedoelen met 'de snelste'. Welke criteria vallen hieronder? En hoe zwaar weegt elk criterium? Stel je voor dat we een route voor de fiets zoeken. Dan zijn bijvoorbeeld afstand, de kwaliteit van het wegdek, 'bergen en heuvels' belangrijke criteria. Maar telt afstand net zo zwaar mee als de kwaliteit van het wegdek?

Een andere component is de modelformulering. Aan de ene kant is het duidelijk wat we nodig hebben: een plattegrond om van Utrecht naar Stockholm te fietsen. We moeten dus weten waar de fietspaden liggen. Maar de plattegrond moet meer bevatten. We willen bijvoorbeeld ook weten waar de bergen en heuvels zijn. Aan de andere kant kan het toevoegen van teveel details het model onnodig moeilijk maken. Het toevoegen van bijvoorbeeld brievenbussen heeft voor onze onderzoeksvraag niet veel nut. Stel dat alle brievenbussen zich om een of andere reden langs de snelste route bevinden. Dan kan dit onterecht het idee geven dat deze in het algemeen belangrijk zijn voor het bepalen voor de snelste route.

Stel je voor dat we een geschikt model hebben geformuleerd; de kaart is in orde. Dan volgt de uitdaging om de snelste route te bepalen. In de context van wiskundige modellen in de infectieziektenepidemiologie gaat het hier vaak om de wiskundige analyse van het model, bijvoorbeeld het bepalen van het zogeheten basis reproductiegetal R_0. Dit is een epidemiologische grootheid waarmee we iets over de stabiliteit van de ziektevrije toestand van een populatie kunnen zeggen (meer hierover onder het kopje **Infectieziektenepidemiologie en R_0**).

Daarna moeten we een vertaalslag maken van het model en de modelresultaten naar de werkelijkheid. Stel je voor dat degene die van Utrecht naar Stockholm wil fietsen een Amerikaan is die geen idee heeft hoe lang een kilometer is, dan willen we de afstanden van kilometers naar mijlen vertalen. In de context van wiskundige modellen in de infectieziektenepidemiologie gaat dit bijvoorbeeld om de vertaling van R_0 als wiskundig begrip naar een biologische interpretatie. Voor veel modellen in de infectieziektenepidemiologie geldt dat R_0 gekarakteriseerd kan worden als de dominante eigenwaarde van een bepaalde matrix. Deze matrix is niet uniek vastgelegd. De keuze van de matrix bepaalt hoe we R_0 kunnen interpreteren. In het bijzonder bestaat een belangrijk deel van de interpretatie uit de definitie van 'reproductie' (zie ook **Infectieziektenepidemiologie en R_0**).

We moeten niet vergeten dat het uiteindelijke doel van het model is om de onderzoeksvraag te beantwoorden: wat is de snelste fietsroute van Utrecht naar Stockholm? We moeten bij het onderzoek dus de juiste context in ogenschouw te nemen: wat voor persoon gaat de route fietsen? Gaat het om iemand die uit Nederland komt en totaal niet gewend is aan heuvels? In dat geval is een vlakke route die qua afstand langer is mogelijk sneller dan een route met veel heuvels. Dit is dan een belangrijke onderliggende aanname in het onderzoek die we maken als we praten over de snelste route. In de context van mijn proefschrift (zie Deel II) bekijken we bijvoorbeeld hoe een verandering in het aantal relaties die in de tijd overlappen gerelateerd is aan R_0. Maar dit doen we onder de aanname dat bepaalde andere grootheden, zoals de gemiddelde relatieduur en het gemiddelde aantal partners in een leven, constant blijven.

Infectieziektenepidemiologie en R_0

Het gebruik van wiskundige modellen in de infectieziektenepidemiologie is erg nuttig om inzichten te krijgen in de verspreiding van infectieziekten in een populatie. Deze inzichten kunnen ons helpen in het ontwikkelen van bijvoorbeeld preventiemaatregelen

of vaccinatiestrategieën. Voorbeelden van bijdragen van wiskundige modellen aan de infectieziektenepidemiolgie worden bijvoorbeeld in [6] besproken.

Een belangrijk inzicht dat werd verkregen met behulp van wiskundige modellen kwam in 1911 in de context van malaria. De arts Ronald Ross ontdekte dat mensen besmet raakten met malaria via muggen die de malariaparasiet met zich meedragen. Voor zijn werk aan malaria kreeg hij later de Nobelprijs. Zelf vond hij zijn wiskundige bijdrage erg belangrijk. Hij beweerde, op basis van zijn wiskundige modellen, dat het niet noodzakelijk is om *alle* muggen uit te roeien om een malaria-epidemie in een gebied te stoppen. Zijn modellen leidden tot het inzicht dat het voldoende is om het aantal muggen beneden een bepaalde kritische waarde te krijgen. Met dit laatste was Ross een van de eersten die het concept van het basis reproductiegetal R_0 gebruikte in deze context.

Tot op de dag van vandaag is R_0 een van de belangrijkste begrippen in de infectieziektenepidemiologie. Dit begrip heb ik al een paar keer eerder in dit hoofdstuk genoemd en wil ik hier wat gedetailleerder bespreken. Stel je voor dat we een volledig vatbare populatie hebben. In deze populatie wordt een pas-geïnfecteerd individu geïntroduceerd. Zal de ziekte zich dan verspreiden over de populatie of stopt de verspreiding na enkele besmettingen? We kunnen R_0 interpreteren als het gemiddelde aantal nieuwe besmettingen veroorzaakt door één pas-geïnfecteerd individu. Als R_0 groter is dan één dan ontstaat er een epidemie (in zogenaamde 'deterministische' modellen waar toevallige gebeurtenissen worden verwaarloosd) en als R_0 kleiner is dan één gebeurt dit niet. Het geeft ons een idee van de ernst van de infectieziekte op populatieniveau. Verder kan het inzichten opleveren over belangrijke mechanismen in de verspreiding van de ziekte en dus ook wat we kunnen doen om een epidemie te voorkomen. Het is dan ook niet verwonderlijk dat veel van de wiskundige analyse van modellen in de infectieziektenepidemiologie zich hiermee bezig houdt (zo ook Hoofstukken 3 en 4 van dit proefschrift).

Door het perspectief van een pas-geïnfecteerd individu in een volledig vatbare populatie aan te nemen kan er vaak een uitdrukking voor R_0 worden gevonden met behulp van de biologische interpretatie. Dit is dikwijls de manier waarop R_0 wordt bepaald voor modellen in de infectieziektenepidemiologie. Zo ook in Hoofdstuk 3. Door slim gebruik te maken van de bouwstenen waaruit een pas-geïnfecteerd individu in het model uit bestaat (zogenaamde 'bindingsplaatsen') konden berekeningen verder vereenvoudigd worden waardoor uiteindelijk een expliciete uitdrukking voor R_0 gevonden kon worden (als de dominante eigenwaarde van een 2×2 matrix). Het mooie van Hoofdstuk 4 is dat, door een ander perspectief te gebruiken, R_0 voor hetzelfde model nog veel eenvoudiger te bepalen was. In plaats van het perspectief van een pas-geïnfecteerd individu keken we vanuit het perspectief van een 'gevaarlijke verbintenis' tussen een vatbaar en een geïnfecteerd individu. Hierdoor kregen we de uitdrukking voor R_0 min of meer cadeau!

Dit proefschrift

In dit proefschrift bestuderen we twee epidemiologische vragen die gerelateerd zijn aan de invloed van het hebben van meerdere partners tegelijkertijd op de verspreiding van een soa over een netwerk. Om die vragen te onderzoeken wilden we wiskundige model-

len gebruiken voor de verspreiding van soa's over dynamisch seksuele netwerken. Het overgrote deel van dit proefschrift bestaat dan ook uit de ontwikkeling en de wiskundige analyse van modellen. Hieronder beschrijven we kort waar elk hoofdstuk van dit proefschrift over gaat. Deze beschrijving is wat technischer dan het voorgaande en gaat wat meer in op de wiskundige details van het proefschrift.

Deel I: wiskundige modellen

In **Hoofdstuk 2** formuleren we een netwerkmodel. Dit model vormt de basis voor de rest van het onderzoek. In dit model bekijken we een populatie waarvan de individuen meerdere partners tegelijkertijd hebben. Het maximum aantal partners wordt bepaald door een zogenaamde partnercapciteit n, met $n = 1, 2, 3, \ldots$, en we zeggen dat een individu n 'bindingsplaatsen' voor partners heeft. Individuen kunnen nieuwe relaties aangaan en van partners scheiden. Bovenop deze dynamica is er ook nog het demografische proces: de populatie groeit door individuen die seksueel actief worden en krimpt door individuen die seksueel inactief worden. Op individu-niveau wordt het model beschreven door een Markovketen waarbij de toestand van een individu het aantal partners van het individu is. Er is een afhankelijkheid van de populatie via de fractie van vrije bindingsplaatsen in de populatie. Dit bepaalt de kans per eenheid van tijd dat een vrije bindingsplaats bezet raakt (en dus een individu een nieuwe relatie vormt).

In **Hoofdstuk 3** kijken we naar de verspreiding van een infectieziekte over het netwerk uit Hoofdstuk 2. Individuen zijn ofwel vatbaar ofwel besmettelijk ('Susceptible' of 'Infectious', vandaar de titel van het hoofdstuk), en wanneer een individu eenmaal besmet is blijft hij/zij dat. Elke relatie tussen een vatbaar en een besmettelijk individu is 'gevaarlijk': binnen zulke relaties is er een kans op besmetting. De toestand van een individu wordt nu beschreven door (i) de ziektetoestand van het individu (vatbaar of geïnfecteerd), (ii) het aantal vatbare partners, en (iii) het aantal besmettelijke partners. Naast de modelformulering bestaat een groot deel van dit hoofdstuk uit de bepaling van R_0. Hiervoor gebruiken we de interpretatie door te kijken naar 'besmettelijke bindingsplaatsen'. Hoewel het stelsel van differentiaalvergelijkingen dat het model op populatieniveau beschrijft hoogdimensionaal is (van orde n^2, waarbij n de partnercapaciteit is), slagen we erin om een expliciete uitdrukking voor R_0 te vinden. Vervolgens bewijzen we dat deze R_0, met behulp van de interpretatie afgeleide uitdrukking op het niveau van bindingsplaatsen, daadwerkelijk de stabiliteit van de ziektevrije toestand van het populatiemodel bepaalt.

In **Hoofdstuk 4** ontwikkelen we een klasse van modellen voor de verspreiding van infectieziekten over netwerken. We maken hier expliciet gebruik van de bindingsplaatsen als bouwstenen voor individuen. Een belangrijke aanname hier (net als in Hoofdstukken 2 en 3) is dat de bindingsplaatsen van een individu (conditioneel) onafhankelijk zijn. Hierdoor kunnen drie verschillende niveaus worden onderscheiden: (1) bindingsplaatsen, (2) individuen, en (3) de populatie. Op niveaus (1) en (2) hebben we wederom een beschrijving in termen van Markovketens waar er afhankelijkheid van de populatie is via omgevingsvariabelen. Deze omgevingsvariabelen zijn op populatieniveau gedefinieerd, waar het model deterministisch is. Door de drie niveaus met elkaar te verbinden verkrij-

gen we een gesloten systeem van maar enkele vergelijkingen dat de dynamica op alle drie de niveaus beschrijft. In Hoofdstuk 3 wordt het model op populatieniveau beschreven met behulp van gewone differentiaalvergelijkingen. In Hoofdstuk 4 is onze beschrijving in termen van de omgevingsvariabelen, wat tot een aantal renewalvergelijkingen leidt. Een van de mooie resultaten van dit hoofdstuk is de afleiding van R_0. In Hoofdstuk 3 is dit vrij veel werk. Met behulp van de modelformulering van Hoofdstuk 4 is de bepaling van R_0 vrij eenvoudig (het volgt min of meer direct uit het stelsel renewalvergelijkingen).

De kracht van Hoofdstuk 4 is de ontwikkeling van het formalisme. Het biedt een systematische manier om modellen voor de verspreiding van infectieziekten over netwerken te formuleren. Aan de andere kant is het formalisme ook zo flexibel dat verschillende betekenisvolle generalisaties kunnen worden beschouwd. De grootste 'moeilijkheid' is hier het doen van de boekhouding.

In **Hoofdstuk 5** worden een aantal voorbeelden van generalisaties uitgewerkt om de flexibiliteit en kracht van het formalisme van Hoofdstuk 4 te illustreren. We behandelen hierin de volgende situaties:

- heteroseksuele bevolking,
- variabele partnercapaciteit in de bevolking,
- vaste en losse relaties,
- meerdere infectiestadia.

Deel II: epidemiologische vragen

Kan het gelijktijdig onderhouden van meerdere relaties (*concurrency*) een hiv-epidemie aandrijven? In **Hoofdstuk 6** werken we uit wat we precies met deze vraag bedoelen. Als we de seksueel actieve levensduur, de verwachte relatieduur, en het verwachte aantal partners in een leven gelijk houden, kan concurrency dan de parameter R_0 voorbij de epidemische drempelwaarde van één schuiven? In Hoofdstuk 6 laten we zien dat dit inderdaad mogelijk is. Concurrency wordt in dit hoofdstuk gemeten met behulp van een van de maten ontwikkeld in Hoofdstuk 2. Deze maat geeft een indicatie voor het verwachte aantal partners van een partner van een individu.

In **Hoofdstuk 7** bestuderen we asymmetrie tussen mannen en vrouwen in concurrency en het effect ervan op de prevalentie van hiv in de bevolking. Een van de belangrijkste motivaties voor dit onderzoek was een artikel [24] waarin data werd gebruikt om de correlatie tussen polygyny (een vorm van polygamie waarin mannen meerdere vrouwen kunnen hebben maar vrouwen monogaam zijn) en hiv-prevalentie te onderzoeken. In Hoofdstuk 7 gebruiken we onze wiskundige modellen om dit te bestuderen. We onderzoeken de asymmetrie in concurrency tussen mannen en vrouwen via de partnercapaciteit. We vinden onder andere dat een grotere asymmetrie tussen mannen en vrouwen gerelateerd is aan een lagere endemische prevalentie (in overeenstemming met [24]).

In dit tweede deel van het proefschrift hebben we met behulp van de modellen van Deel I bepaalde epidemiologische vragen onderzocht. We proberen met ons onderzoek vooral kwalitatieve inzichten te krijgen (wat voor invloed kunnen bepaalde mechanismen

hebben op de verspreiding van soa's?). Let wel, modellen zijn altijd een versimpeling van de werkelijkheid. In de twee hoofdstukken van Deel II geven we dan ook niet *de* antwoorden (vaak bestaat zoiets ook niet). We hebben laten zien welke rol concurrency kán spelen. Dit betekent niet dat in de concrete situatie van Afrika bezuiden de Sahara het daadwerkelijk het geval is.

Conclusie

De grote uitdagingen in Deel I waren anders dan in Deel II. In Deel I lag onze focus bij de modelformulering en wiskundige analyse terwijl we in Deel II geprobeerd hebben meer (kwalitatief) inzicht te krijgen in de invloed van relatiestructuren op de verspreiding van hiv. In veel opzichten is het wiskundige gedeelte een stuk gemakkelijker. De lezer zal al wel gemerkt hebben dat de focus van zowel dit hoofdstuk als het gehele proefschrift bij het modelleren en de wiskunde lag. De belangrijkste bijdrage van dit proefschrift is dan ook de ontwikkeling van een klasse van modellen voor de verspreiding van infectieziekten op dynamische netwerken. Deze klasse van modellen leveren, naar mijn mening, belangrijk nieuw gereedschap op voor het beter begrijpen van infectieziektendynamica.

Er is nog veel meer te vertellen over dit proefschrift en het vakgebied dan wat ik heb beschreven in dit korte hoofdstuk (daar is de rest van dit proefschrift en overige bestaande literatuur voor). Een van de dingen die ik hier wel nog wil noemen is het belang van niet-wiskundige modellen. Behalve de relatief eenvoudige wiskundige modellen die in dit proefschrift worden gebruikt, zou je bijvoorbeeld ook simulatiemodellen kunnen gebruiken. Een voordeel van simulatiemodellen is vaak dat het eenvoudiger is om complexere situaties te bestuderen. Een nadeel is dat het soms gemakkelijk is om onderliggende aannames over het hoofd te zien. Een andere belangrijke aanpak is het empirisch onderzoek. Zulk onderzoek is essentieel als we de werkelijkheid beter willen begrijpen. Via vragenlijsten werd bijvoorbeeld onderzocht hoe seksuele relatiepatronen eruit zien in Likoma Island in Malawi [115] (dit is overigens ook een van de weinige studies waarin het seksueel netwerk van een populatie op meerdere tijdstippen in kaart is gebracht).

In dit hoofdstuk heb ik hopelijk een beter idee gegeven waar mijn promotieonderzoek over ging. Hopelijk heeft deze samenvatting een aantal mensen gemotiveerd om (een deel van) het proefschrift te lezen.

Naschrift. De wetenschap verschilt niet veel van het dagelijks leven in de zin dat er vaak dingen anders gaan dan gehoopt. Zo ook hier. Dit resulteerde in de eindfase van het schrijven van dit proefschrift een ander Hoofdstuk 5 (vooral Sectie 6 van dat hoofdstuk). De kracht en flexibiliteit van ons formalisme zou je hierdoor best in twijfel mogen trekken. Ik geloof er nog steeds in. Maar het formalisme heeft wel een andere toevoeging gekregen juist doordat het zelf duidelijk maakt waar de subtiliteiten liggen (zij het op het nippertje).

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Curriculum Vitae

Ka Yin Leung was born on 11 March 1988 in Amersfoort. She attended the high school 't Atrium and participated in Junior College Utrecht which replaced the regular programme in physics, biology, mathematics, and chemistry in the last two years of high school. Afterwards she started her studies in mathematics at Utrecht University. She was awarded the Kartini prize by the Royal Holland Society of Sciences and Humanities for her first year academic performances. During her master's programme she discovered the subject of mathematical biology and infectious disease epidemiology in particular. This made her decide to pursue her master's research project in that area with Odo Diekmann and Mirjam Kretzschmar as supervisors, who later became her PhD supervisors. Her master's thesis was awarded a prize for most socially relevant research by the Faculty of Science of Utrecht University. She graduated cum laude in 2011, after which she held a one year research position at the University Medical Center Utrecht, extending the research of her master's thesis. In 2012 she obtained an NWO subsidy for her PhD research proposal on the impact of concurrent partnerships on the spread of infectious diseases, which resulted in this thesis. During her PhD period she was active in the Utrecht Center for Infection Dynamics journal club. She had the opportunity to attend several summer schools, workshops, and conferences. She was part of the Young Scientist Summer Program 2013 at the International Institute for Applied System Analysis in Austria and was a long-term visitor at the Mathematical Biosciences Institute in the USA. In the fall of 2016 she will start a postdoc at Stockholm University.