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# The Saturating Contact Rate in Marriage- and Epidemic Models

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In this note we show how to derive, by a mechanistic argument, an expression for the saturating contact rate of individual contacts in a population that mixes randomly. The main assumption is that the individual interaction times are typically short as compared to the time-scale of changes in, for example, individual-type, but that the interactions yet make up a considerable fraction of the time-budget of an individual. In special cases an explicit formula for the contact rate is obtained. The result is applied to mathematical epidemiology and marriage models.

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## 1. Introduction

A problem that has been around for a long time in mathematical epidemiology, is that of giving a mechanistic description of the saturation in the number of (re)new(ed) contacts that an individual can make per unit of time, given that the time that an individual has available for these contacts is limited. Of epidemiological importance is of course the number of contacts between infected and susceptible individuals, which determines the possible number of new infections per unit of time [1]. The same problem occurs in marriage models, where one needs to model the number of 'steady relationships' that are established per unit of time. The idea here is that individuals have a number of short lasting contacts per unit of time within a limited time available, and that steady relationships ('marriages') may result from these brief encounters. Frequently a Holling-type argument, borrowed from predator-prey systems, is thought to be the solution to the problem. However, as we explain below, on closer examination the application of the usual Holling argument to epidemic- and marriage models cannot be justified. In this note we give a mechanistically based answer to the 'contact-rate problem' in sections 3 (epidemic models) and 4 (marriage models).

Suppose we have a well-mixed closed population, divided into  $n$  different types of individuals (think e.g. of infected or non-infected males and females), of total density  $N(t)$  at time  $t$ . Suppose furthermore that two individuals can together establish a temporary complex, and that these complexes are formed according to law-of-mass-action kinetics. The rate constants of complex formation and dissociation are allowed to depend on the types of the individuals involved. Our key assumption is that the complexes are of short duration, as compared to the time-scale on which the individuals change their type (where the latter also comprises the

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formation of more permanent relationships), or the various type-densities change by births or deaths.

Instead of 'saturating contact rate' one could also speak of 'the functional response' in the number of individual contacts, but this formulation is traditionally reserved for predator-prey systems. There we can distinguish, for example, two types (prey individuals, and predators that are searching for prey) and one complex (predators that are busy handling prey). The Holling argument then gives an expression for the number of prey caught by a predator, taking into account that a proportion of the predators' available time is spent handling the already caught prey. A prerequisite for the Holling argument is that on the time-scale on which the predator changes from 'searching' to 'busy with prey', the environment of the predators (in this case the density of the prey population) stays constant. This is not the case if interactions also occur between individuals of comparable type (think for example of predators fighting with predators). For those types of individuals the differential equations are no longer linear in the type density itself, but contain quadratic interaction terms. This then makes it impossible to study the problem by following one individual and describing the possible type-changes by a continuous time (semi)-Markov chain (which is one fruitful way of looking at the Holling-type problems). In the case of self interaction, the time-scale on which the density of individuals of a particular type changes is the same as that on which their environment changes. Therefore, the usual Holling-type arguments are not applicable to the description of social interactions such as marriages and contacts between infected and susceptible individuals, where interactions between comparable types are important. Our argument in section 2 serves as a replacement. In section 5 we discuss a slightly more involved Holling argument that does work in our situation. However, we could only deduce this argument from the results of the mathematically correct calculations in the intervening sections.

## 2. Main result

Let  $X_i(t)$  denote the density of free individuals of type  $i$ ,  $i \in \{1, \dots, n\}$ , at time  $t$ . In this paper we assume that complexes are formed between two individuals and we therefore disregard larger groups. Let  $K_{ii}(t)$  denote the density of complexes at time  $t$  involving two  $i$ -type individuals;  $2K_{ij}(t)$  denotes the density of complexes at time  $t$  involving one  $i$ - and one  $j$ -type individual ( $K_{ij} = K_{ji}$ ). There are then  $\frac{1}{2}n(n+1)$  different complexes.

The rate constant for the formation of an  $(i, j)$ -complex is denoted by  $r_{ij}$ , the dissociation rate constant by  $s_{ij}$  (we assume  $r_{ij} = r_{ji}$ , and  $s_{ij} = s_{ji}$ ). Type-changes of free individuals of type  $i$  are described by a function  $F_i$ , type-changes by individuals that are part of a complex  $ij$  are described by a function  $G_{ij}$  (describing, for example, infections or marriages). Birth and death of individuals are included in these functions as well. The  $F_i$  and  $G_{ij}$  will, in general, be functions of  $(X_1, \dots, X_n; K_{11}, \dots, K_{nn})$  and we assume that they are Lipschitz continuous in all variables (in many applications they are actually linear). Our main assumption is that the time-scale of type-change is much longer than that of complex formation and dissociation.

We can write down differential equations for the changes in  $X_i$  and  $K_{ij}$ . For  $1 \leq i, j \leq n$  we have

$$\frac{dX_i}{dt} = -X_i \sum_{j=1}^n r_{ij} X_j + 2 \sum_{j=1}^n s_{ij} K_{ij} + F_i, \quad (S1)$$

$$\frac{dK_{ij}}{dt} = \frac{1}{2} r_{ij} X_i X_j - s_{ij} K_{ij} + G_{ij} \quad (S2)$$

In order to correctly apply a time-scale argument, we rewrite (S) as a singular perturbation problem. If the processes of type-change occur with rate constants expressed per unit of  $t$ -

time, then the processes of complex formation and dissociation occur, by assumption, with rate constants ( $r_{ij}$  and  $s_{ij}$ ) expressed per unit of  $\varepsilon t$ -time, for  $\varepsilon \ll 1$ . If we re-scale by writing  $r_{ij} = \rho_{ij}/\varepsilon$  and  $s_{ij} = \sigma_{ij}/\varepsilon$ , then all processes involved in our system are on the same time-scale, and (S) turns into

$$\varepsilon \frac{dX_i}{dt} = -X_i \sum_{j=1}^n \rho_{ij} X_j + 2 \sum_{j=1}^n \sigma_{ij} K_{ij} + \varepsilon F_i, \quad (S_\varepsilon 1)$$

$$\varepsilon \frac{dK_{ij}}{dt} = \frac{1}{2} \rho_{ij} X_i X_j - \sigma_{ij} K_{ij} + \varepsilon G_{ij}. \quad (S_\varepsilon 2)$$

Define  $\theta_{ij} := \frac{\rho_{ij}}{\sigma_{ij}} = \frac{r_{ij}}{s_{ij}}$  and, for  $i \in \{1, \dots, n\}$ , let

$$\xi_i(t) := X_i(t) + 2 \sum_{j=1}^n K_{ij}(t),$$

be the total density of  $i$ -type individuals in the population at time  $t$ . Then  $\sum_{i=1}^n \xi_i(t) = N(t)$ .

**Theorem 1:** For the solution  $X_{\varepsilon i}(t)$ ,  $K_{\varepsilon ij}(t)$  of system  $(S_\varepsilon)$ , we have

$$\lim_{\varepsilon \downarrow 0} X_{\varepsilon i}(t) = X_i^* \quad (2.1)$$

$$\lim_{\varepsilon \downarrow 0} K_{\varepsilon ij}(t) = K_{ij}^*, \quad (2.2)$$

where the convergence is uniform on bounded intervals bounded away from zero. Here  $(X_1^*, \dots, X_n^*)$  is the unique positive solution of the system

$$X_i + X_i \sum_{j=1}^n \theta_{ij} X_j = \xi_i = \text{constant} \quad (2.3)$$

$i \in \{1, \dots, n\}$ , with  $\xi_i \geq 0$  a constant for each  $i$ ,

$$K_{ij}^* = \frac{1}{2} \theta_{ij} X_i^* X_j^* \quad (2.4)$$

and  $\xi_i$  is the solution of

$$\frac{d\xi_i}{dt} = F_i(X_1^*, \dots, X_n^*, K_{11}^*, \dots, K_{nn}^*) + 2 \sum_{j=1}^n G_{ij}(X_1^*, \dots, X_n^*, K_{11}^*, \dots, K_{nn}^*). \quad (2.5)$$

**Proof:** We use a standard singular perturbation argument (see, e.g. [8]) for system  $(S_\varepsilon)$ . We start by regarding system  $(S_\varepsilon)$  on the 'fast time-scale' by first substituting  $\tau := t/\varepsilon$ , and then taking the limit  $\varepsilon \downarrow 0$ . The substitution leads to

$$\frac{dX_i}{d\tau} = -X_i \sum_{j=1}^n \rho_{ij} X_j + 2 \sum_{j=1}^n \sigma_{ij} K_{ij} + \varepsilon F_i, \quad (2.6)$$

$$\frac{dK_{ij}}{d\tau} = \frac{1}{2} \rho_{ij} X_i X_j - \sigma_{ij} K_{ij} + \varepsilon G_{ij}, \quad (2.7)$$

and we obtain the following system of equations for the quasi-steady state

$$0 = -X_i \sum_{j=1}^n \rho_{ij} X_j + 2 \sum_{j=1}^n \sigma_{ij} K_{ij}, \quad (S_01)$$

$$0 = \frac{1}{2} \rho_{ij} X_i X_j - \sigma_{ij} K_{ij} \quad (S_02)$$

$1 \leq i, j \leq n$ . Write  $K_{ij} = \frac{1}{2} \theta_{ij} X_i X_j$ , then both  $(S_01)$  and  $(S_02)$  are satisfied. On the fast time-scale we have an additional relation between  $K_{ij}$ ,  $X_i$  and  $X_j$ . On that time scale  $N$  and the  $\xi_i$ 's do not change:

$$\frac{d\xi_i}{d\tau} = \varepsilon F_i + 2\varepsilon \sum_{j=1}^n G_{ij}$$

and therefore we have  $\frac{d\xi_i}{d\tau} = 0$ , which implies that we have to solve  $(S_0)$  within the manifolds  $\xi_i = \text{constant}$ . This leads to the conservation equations  $X_i + 2 \sum_{j=1}^n K_{ij} = \xi_i = \text{constant}$  or

$$X_i + X_i \sum_{j=1}^n \theta_{ij} X_j = \xi_i = \text{constant} \quad (2.8)$$

$i \in \{1, \dots, n\}$ .

In the appendix we show that there is a unique positive solution  $(X_1^*, \dots, X_n^*)$  to system (2.8), and that the corresponding positive solution  $(X_1^*, \dots, X_n^*, K_{11}^*, \dots, K_{nn}^*)$  of  $(S_0)$  is an asymptotically stable steady state of (2.6)-(2.7) at  $\varepsilon = 0$ .

Application of the singular perturbation theorem from [8] now gives that, for  $\varepsilon \downarrow 0$ , the solution to system  $(S_\varepsilon)$  converges to  $(X_1^*, \dots, X_n^*, K_{11}^*, \dots, K_{nn}^*)$  uniformly on intervals bounded away from zero and infinity. Remember that the  $X_i^*$ 's and the  $K_{ij}^*$ 's are functions of time. They change on the 'slow time-scale' because on that time-scale  $N$  and the  $\xi_i$ 's change. We have that  $\xi_i$ , ( $1 \leq i \leq n$ ), is the solution of

$$\frac{d\xi_i}{dt} = F_i(X_1^*, \dots, X_n^*, K_{11}^*, \dots, K_{nn}^*) + 2 \sum_{j=1}^n G_{ij}(X_1^*, \dots, X_n^*, K_{11}^*, \dots, K_{nn}^*), \quad (2.9)$$

which describes the changes in the density of  $i$ -type individuals on the slow time-scale.  $\diamond$

In some special cases one can explicitly solve (2.3) in terms of the  $\xi_i$ .

**Corollary 2:** Let  $\theta_{ij} = \theta$  for all  $1 \leq i, j \leq n$ . Then

$$X_i^* = \frac{-1 + \sqrt{1 + 4\theta N}}{2\theta N} \xi_i \quad (2.10)$$

$$K_{ij}^* = \frac{1 + 2\theta N - \sqrt{1 + 4\theta N}}{2\theta N^2} \xi_i \xi_j \quad (2.11)$$

where  $\xi_i$  is the solution of (2.5),  $1 \leq i, j \leq n$ .

**Proof:** Let  $X := \sum_{i=1}^n X_i$ , and  $K := \sum_{ij} K_{ij}$ . Then system (2.3) can be written as

$$X + \theta X^2 = N. \quad (2.12)$$

Its unique positive solution is

$$X^* = \frac{-1 + \sqrt{1 + 4\theta N}}{2\theta}.$$

From the relation  $K^* = \frac{1}{2}\theta X^{*2}$  we then obtain

$$K^* = \frac{1 + 2\theta N - \sqrt{1 + 4\theta N}}{4\theta}.$$

We express  $K_{ij}^*$  in terms of  $K^*$ . If we substitute (2.4) in the definition of  $\xi_i$ , then we can write  $X_i^*$  as

$$X_i^* = \frac{\xi_i}{1 + \theta X^*} = \frac{\xi_i}{N} X^*$$

where, in the last equality, we have used equation (2.12). Then

$$K_{ij}^* = \frac{\xi_i \xi_j}{N^2} K^*.$$

◇

The following special case was suggested by sexual activity models in the AIDS-literature.

**Corollary 3:** Let  $\theta_{ij} = \alpha_i \alpha_j$  and define  $A := \sum_{j=1}^n \alpha_j X_j^*$ . Then

$$X_i^* = \frac{\xi_i}{1 + \alpha_i A}$$

$$K_{ij}^* = \frac{\alpha_i \alpha_j}{(1 + \alpha_i A)(1 + \alpha_j A)} \xi_i \xi_j$$

where  $A$  is the unique positive solution of

$$A = \sum_{j=1}^n \frac{\alpha_j \xi_j}{1 + \alpha_j A} \tag{2.13}$$

and where  $\xi_i$  is the solution of (2.5).

**Proof:** From (2.3) we obtain  $X_i + \alpha_i X_i A = \xi_i$  which gives

$$X_i^* = \frac{\xi_i}{1 + \alpha_i A}$$

from which the result follows by using (2.4). Substituting  $X_i^*$  in the defining relation for  $A$  gives (2.13), which can easily be seen to have a unique positive solution.

◇

### 3. Application to mathematical epidemiology

In non-pair formation models for sexually transmitted diseases it has been argued (see e.g. [7]) that the number of new cases of the infection arising per unit of time, should be written as

$$\beta C(N) S \frac{I}{N}$$



where  $\beta$  is the probability per unit of time of transmitting the infection between two individuals taking part in a contact;  $C(N)$  is the 'unknown' probability for an individual to take part in a contact;  $S$  and  $I$  are the densities of the non-infected and infected populations, respectively. Some reasonable demands on  $C(N)$  are that it should be a non-decreasing function of  $N$  and that  $C(N)/N$  should be a non-increasing function of  $N$ . Furthermore, the function should behave linearly in  $N$ , for small  $N$ , and it should be independent of  $N$ , for  $N$  large. Of course, many functional forms can, and have been, suggested that have these properties, but a mechanistically derived form was lacking.

Let  $X_1$  and  $X_2$  denote the densities of susceptible and infected *singles*, respectively. The infection process constitutes a change from  $K_{12} \rightarrow K_{22}$ , which we assume to happen with some probability per unit of time  $\beta$ . If we now write  $S := X_1 + 2K_{11} + 2K_{12}$  and  $I := N - S$  for  $\xi_1$  and  $\xi_2$ , respectively, then the number of new cases of the disease appearing per unit of time is

$$\beta K_{12}^* = \beta \frac{1 + 2\theta N - \sqrt{1 + 4\theta N}}{2\theta N^2} SI,$$

if we regard the simplest case where the disease has no influence on the propensity to form complexes and the time spent in a complex. We find therefore the following expression for  $C(N)$  in the simplest case

$$C(N) = \frac{1 + 2\theta N - \sqrt{1 + 4\theta N}}{2\theta N}.$$

This expression has the four properties mentioned above. If we multiply both the numerator and the denominator by  $1 + 2\theta N + \sqrt{1 + 4\theta N}$  to obtain

$$C(N) = \frac{2\theta N}{1 + 2\theta N + \sqrt{1 + 4\theta N}},$$

then we see that, for  $N$  small,  $C(N) \sim 2\theta N$ , whereas for  $N$  large,  $C(N) \sim 1$ . Furthermore,  $C(N)$  is non-decreasing and  $C(N)/N$  is non-increasing.

**Remark:** If we equate 'time-scale of the infection process' with the length of the infectious period, and 'time-scale of the complex' with the inverse of the dissociation rate constant, then for most infectious diseases in many different populations our assumption that the infection processes and the formation of complexes are on two different time-scales, is reasonable. This not only applies to sexually transmitted diseases. For example, regard influenza or measles where contacts are often on the scale of minutes or hours, whereas the infectious period is on the scale of days. The problem with the present approach for these non-sexually transmitted diseases however, is that complexes in these cases may sometimes consist of more than two individuals. In order to describe the contact process for these cases more realistically, the approach in Theorem 1 should then in theory be generalised to allow for larger complexes. The problem is that such a generalisation immediately leads to an almost limitless proliferation of rate constants. Moreover, one should be very careful about what one considers to be complexes in this generalisation, and which variability in contacts one could better take care of by extending the number of individual types. For example, classmates in school, fellow passengers on a commuter train, and colleagues at work are not met randomly, but over and over again. This means that, if these contacts would be important transmission risks, your schoolclass, the commuter train you take, and the place where you work, all should be made part of your individual type. In a certain sense (to be discussed more fully in section 5) our present model is the simplest mechanistical model that can account for the fact that individuals have limited time-budgets for their social interactions, as well as variability among types.

#### 4. Application to marriage models

The calculations in this paper can also be applied to marriage models. In that case, one would let  $X_1$  and  $X_2$  be single females and males, respectively. The complexes would signify the brief encounters between singles, for example in a bar, in a theatre, on the street, etcetera. "Brief" should here be interpreted as short relative to the time-scale of 'steady partnerships' between two individuals (for convenience called: marriages). One introduces a new group within the population, the *married couples*. The saturating contact rate then determines, in randomly mixing population (a well-stirred society), the possible number of new marriages formed per unit of time.

To illustrate the use of the approach in section 2, we will now derive a well-known simple marriage model, based on our mechanistic principles. Let the index '1' refer to female individuals, and '2' to male individuals. The longer lasting relationships are the married couples ( $p$ ), that are assumed to be exclusively heterosexual; the shorter lasting encounters are the complexes  $K_{11}, K_{12}(= K_{21})$ , and  $K_{22}$ . The idea is that a considerable fraction of the time that an individual has available to find "the one-and-only", is wasted by brief encounters with both sexes. We want to determine  $K_{12}^*$ .

Let  $\mu$  denote the per capita death rate,  $b$  the constant birth rate,  $\gamma$  the probability per unit of time for a complex consisting of a male and a female to get married, and  $\alpha$  the divorce rate for married couples. The other parameters are as in section 2.

System ( $S$ ) now reads

$$\begin{aligned}\frac{dX_1}{dt} &= -r_{11}X_1^2 - r_{12}X_1X_2 + 2s_{11}K_{11} + 2s_{12}K_{12} + b - \mu X_1 + 2\mu K_{11} + \mu K_{12} + (\mu + \alpha)p \\ \frac{dX_2}{dt} &= -r_{12}X_2X_1 - r_{22}X_2^2 + 2s_{22}K_{22} + 2s_{12}K_{12} + b - \mu X_2 + 2\mu K_{22} + \mu K_{12} + (\mu + \alpha)p \\ \frac{dK_{11}}{dt} &= \frac{1}{2}r_{11}X_1^2 - s_{11}K_{11} - 2\mu K_{11} \\ \frac{dK_{12}}{dt} &= \frac{1}{2}r_{12}X_1X_2 - s_{12}K_{12} - 2\mu K_{12} - \gamma K_{12} \\ \frac{dK_{22}}{dt} &= \frac{1}{2}r_{22}X_2^2 - s_{22}K_{22} - 2\mu K_{22} \\ \frac{dp}{dt} &= \gamma K_{12} - (2\mu + \alpha)p.\end{aligned}$$

If we carry through our time-scale argument from section 2, we can collapse the above system into a standard system of three differential equations describing heterosexual pair formation in a two-sex population (see for example [3]). In the process we get a specific form of the marriage function. Define  $x := X_1 + 2K_{11} + 2K_{12}$ , and  $y := X_2 + 2K_{22} + 2K_{12}$  as the total density of females and males that are not members of a married couple, respectively. Then we arrive at

$$\begin{aligned}\frac{dx}{dt} &= b - \mu x + (\mu + \alpha)p - \gamma K_{12}^* \\ \frac{dy}{dt} &= b - \mu y + (\mu + \alpha)p - \gamma K_{12}^* \\ \frac{dp}{dt} &= \gamma K_{12}^* - (2\mu + \alpha)p.\end{aligned}$$

Here

$$K_{12}^* = \frac{1}{2} \frac{r_{12}}{s_{12}} X_1^* X_2^*$$

and  $(X_1^*, X_2^*)$  is the unique positive solution, in terms of  $x$  and  $y$ , of the system

$$\begin{aligned} X_1 + \theta_{11}X_1^2 + \theta_{12}X_1X_2 &= x \\ X_2 + \theta_{22}X_2^2 + \theta_{12}X_1X_2 &= y. \end{aligned}$$

This system reduces to an equation in one unknown of degree 4, and can therefore be solved explicitly. In the not unreasonable special case that  $x = y =: z$  (equal sex-ratio in the population) and  $\theta_{11} = \theta_{22} =: \theta$ , we easily obtain the unique positive solution

$$X_1^* = X_2^* = \frac{-1 + \sqrt{1 + 4\zeta z}}{2\zeta},$$

where  $\zeta := \theta + \theta_{12}$ .

### 5. Encore: Holling squared

In the introduction we argued that the usual Holling argument could not be applied to the 'contact rate problem' because *both* individuals that are involved in a contact are time-limited. However, we can adapt the Holling argument to this situation, and we christen this adaptation "Holling squared".

For convenience only, we regard the easiest case with only one type of single individual. This is not a restriction on the method, it is similar for the general setting of Theorem 1. Let  $Z$  denote the number of (re)new(ed) contacts in time interval  $T$  by a given individual. Let  $Y = Z/T$ . With  $\tau = s^{-1}$  we denote the mean contact duration, with  $r$  we denote the complex formation rate constant among singles. We let  $N$  be the density of individuals, and  $K$  and  $X$  the density of complexes and singles, respectively. We have  $K = \frac{1}{2}NY\tau$ , and  $X + 2K = N$ . The usual Holling argument would be

$$Z = rX(T - Z\tau) \Rightarrow Y = rX(1 - Y\tau) \Rightarrow Y = \frac{rX}{1 + \theta X}$$

with  $\theta = r\tau$ . In our case however, the singles are time limited, and the available singles are given by

$$X = N\left(\frac{T - Z\tau}{T}\right) \Rightarrow X = n(1 - Y\tau).$$

Inserting this in the equation for  $Y$  above, we find

$$Y = rN(1 - Y\tau)^2$$

which leads, with  $K = \frac{1}{2}NY\tau$ , to

$$K = \frac{1}{2}\theta X^2$$

and this is exactly the condition found in Theorem 1, for this particular special case. This shows that the Holling squared leads to the same saturating contact rate expression as Theorem 1. Analogously one shows that the general case of Holling squared leads to the conditions (2.3)-(2.4).

The fact that the equilibrium conditions are the same for both the heuristic Holling squared and the rigorous mechanistic Theorem 1, raises an important point. In the Holling argument one does not use the fact that  $\tau$  comes from any particular probability distribution. This suggests that, in the general approach, we can replace the exponential distribution by an arbitrary distribution and take for our parameter  $s$ , the inverse of the mean duration of the complex time period.

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## Appendix

In this appendix we prove that the system

$$\frac{dX_i}{d\tau} = -X_i \sum_{j=1}^n \rho_{ij} X_j + 2 \sum_{j=1}^n \sigma_{ij} K_{ij}, \quad (A1)$$

$$\frac{dK_{ij}}{d\tau} = \frac{1}{2} \rho_{ij} X_i X_j - \sigma_{ij} K_{ij}, \quad (A2)$$

together with the conservation equations

$$X_i + 2 \sum_{j=1}^n K_{ij} = \xi_i, \quad 1 \leq i \leq n, \quad (A3)$$

has a unique asymptotically stable positive equilibrium.

We first prove existence of positive solutions  $(X_1^*, \dots, X_n^*)$  to system (2.3). Solutions to (2.3) correspond to equilibria of (A1-A3) by letting  $K_{ij}^* = \frac{1}{2} \theta_{ij} X_i^* X_j^*$ . For given  $\xi_1, \dots, \xi_n > 0$  and  $\theta_{ij} \geq 0$ ,  $(i, j \in \{1, \dots, n\})$  define the map  $A : \mathbb{R}^n \rightarrow \mathbb{R}^n$  acting on a vector  $X = (X_1, \dots, X_n)^T$  by

$$(X_1, \dots, X_n) \mapsto \left( \frac{\xi_1}{1 + a_1(X)}, \dots, \frac{\xi_n}{1 + a_n(X)} \right),$$

where  $a_i(X) := \sum_{j=1}^n \theta_{ij} X_j$ . Note that positive fixed points of  $A$  correspond to positive solutions to system (2.3). The operator  $A$  is continuous and maps the bounded, convex and closed set  $\Lambda := \{X \in \mathbb{R}^n : 0 \leq X_i \leq \xi_i\}$  into itself. Therefore, there exists at least one  $X^* \in \Lambda$  with  $AX^* = X^*$ , by the Brouwer fixed point theorem (see, e.g. [2]).

**Lemma A1:** *The solutions to system (2.3) are isolated.*

**Proof:** Define a map  $F : \mathbb{R}^n \rightarrow \mathbb{R}^n$  acting on a vector  $X = (X_1, \dots, X_n)^T$  by

$$(X_1, \dots, X_n) \mapsto (X_1(1 + a_1(X)) - \xi_1, \dots, X_n(1 + a_n(X)) - \xi_n),$$

with  $a_i(X) := \sum_{j=1}^n \theta_{ij} X_j$ . Then  $F$  is differentiable and a solution to (2.3) corresponds to a zero of  $F$ . Let  $X \geq 0$  satisfy  $F(X) = 0$ , and regard the derivative  $D := DF(X)$  of the map  $F$  at the point  $X$  in  $\mathbb{R}^n$ :

$$D = (d_{ij})_{1 \leq i, j \leq n} = \begin{pmatrix} 1 + \theta_{11}X_1 + a_1(X) & \theta_{12}X_1 & \cdots & \theta_{1n}X_1 \\ \theta_{12}X_2 & 1 + \theta_{22}X_2 + a_2(X) & & \vdots \\ \vdots & & \ddots & \vdots \\ \theta_{1n}X_n & \cdots & \cdots & 1 + \theta_{nn}X_n + a_n(X) \end{pmatrix}.$$

Regard the transpose  $D^T$  of  $D$ . Note that for  $D^T$  we have

$$d_{ii} > \sum_{j \neq i} d_{ij}. \quad (\text{A4})$$

It is elementary that such a matrix is non-singular by the following well-known argument. Suppose to the contrary that there exists a non-trivial solution  $z$  of  $D^T z = 0$ . Let  $k$  be one of the indices with maximal  $|z_k|$  and consider the  $k$ 'th equation of  $D^T z = 0$ . Rearranging this equation and taking absolute values leads to the estimate

$$d_{kk}|z_k| \leq \sum_{j \neq k} d_{kj}|z_j| \leq |z_k| \sum_{j \neq k} d_{kj}$$

which is a contradiction to (A4).

We can apply the inverse function theorem to  $F$  at  $X$ . This asserts that  $F$  is a homeomorphism in some neighbourhood of  $X$ . The zeros of  $F$  are therefore isolated.  $\diamond$

We now consider system (A1-A3). Let  $m = \frac{1}{2}n(n+1)$ , and write  $c = (c_1, \dots, c_m)$  for  $(X_1, \dots, X_n, K_{11}, \dots, K_{nn})$  (where we order the components of the latter lexicographically, starting with the  $X_i$ 's). We are only concerned with  $c$ 's in the positive cone of  $\mathbb{R}^m$ . Let  $c^* = (c_1^*, \dots, c_m^*)$  be a given positive equilibrium of (A1-A3) and define  $H_{c^*} : \mathbb{R}^m \rightarrow \mathbb{R}$  as

$$H_{c^*}(c) = \sum_{i=1}^m (c_i \ln \frac{c_i}{c_i^*} - c_i + c_i^*).$$

In [6], it is shown that  $H_{c^*}$  is a Lyapunov function for closed mass-action chemical reaction systems, of which (A1-A3) is an example. Specifically, the following holds: 1)  $H_{c^*}(c) \geq 0$  for all positive  $c \in \mathbb{R}^m$ , and  $H_{c^*}(c) = 0 \Leftrightarrow c = c^*$ ; 2)  $\frac{dH_{c^*}}{dt}(c) \leq 0$  for all positive  $c \in \mathbb{R}^m$ , and  $\frac{dH_{c^*}}{dt}(c) = 0 \Leftrightarrow dc/dt = 0$ ; 3)  $\frac{\partial H_{c^*}}{\partial c_i} = \ln \frac{c_i}{c_i^*}$ . The Lyapunov function  $H_{c^*}$  assures that in the case of a unique positive equilibrium  $c^*$ , this equilibrium is asymptotically stable. What remains to be shown is that we indeed have a unique positive equilibrium  $c^*$  of (A1-A3).

**Lemma A2:** *There exists only one positive equilibrium  $c^*$  to (A1-A3).*

**Proof:** By lemma A1, the equilibria are isolated. So assume, without loss of generality, that there are two,  $r, s \in \mathbb{R}^m$ , with  $r \neq s$ . Construct the Lyapunov function  $H_r$  based on the equilibrium  $r$ . Then  $H_r(s) =: h_s > 0$ . The graph of the function  $H_r(c_1, \dots, c_m)$  in  $\mathbb{R}^{m+1}$  has a single zero for  $c = r$ , and in every coordinate direction  $i$ ,  $H_r$  strictly decreases when  $c_i < r_i$  and strictly increases for  $c_i > r_i$ . This implies that levelsets of fixed values of  $H_r$  have dimension  $m - 1$ . Regard the levelset  $\{c \in \mathbb{R}^m : H_r(c) = h_s\}$ . Because this set is of dimension less than  $m$ , it follows that in every neighbourhood of  $s$  there is a point  $z \in \mathbb{R}^m$  such that  $H_r(z) < h_s$ . But  $H_r$  decreases along the trajectories of system (A1-A3), so the equilibrium  $s$  cannot be stable. Now construct the Lyapunov function  $H_s$  based on the equilibrium  $s$ . By the theorem of Lyapunov it follows that  $s$  is stable, and we have found a contradiction.  $\diamond$

**Remark:** For completeness we mention that the claim in [6] that the function  $H_{c^*}$  is also a Lyapunov function for open mass-action chemical reaction systems, was proved false in [4]. Furthermore, there is an alternative way to show asymptotic stability of the equilibrium of (A1-A3). In [5], a general theory for mass-action kinetics is developed. One can show that our system (A1-A3) is, in the terminology of [5], so-called *complex-balanced*, and therefore *quasi-thermodynamic*. According to Lemma 4c in [5], this is sufficient to assure asymptotic stability of the unique equilibrium.