Threshold quantities for helminth infections

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Abstract. For parasites with a clearly defined life-cycle we give threshold quantities that determine the stability of the parasite-free steady state for autonomous and periodic deterministic systems formulated in terms of mean parasite burdens. We discuss the biological interpretations of the quantities, how to deal with heterogeneity in both parasite and host populations, how to incorporate the effects of periodic discontinuities, and the relation of the threshold quantities to the basic reproduction ratio R_0. Examples from the literature are given. The analysis of the periodic case extends easily to 'micro-parasitic' systems.

Key words: Deterministic epidemic models – Helminths – (Non) autonomous systems – Threshold behaviour – Basic reproduction ratio – Heterogeneity

1. Introduction

Our aim in this paper is to develop a biologically and mathematically rigorous definition of a threshold quantity that determines whether or not an introduced helminth infection will persist in a population of susceptible hosts, both in a constant and in a periodic environment. We will be concerned with the class of deterministic models formulated in terms of mean parasite burdens, which is the most frequently used in applications. We do not consider here models that explicitly take variation in individual parasite burden into account (such as in [10] and [14]). Neither will we consider stochastic models (see, e.g., [3]). Previous authors have often applied the concept of basic

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reproduction ratio R_0, borrowed from 'microparasitic' infections (e.g. viral, bacterial, protozoan) to the invasion problem, see for example [1]. R_0 has then been defined for helminths as the expected number of adult worms that reach reproductive maturity produced by one adult worm during its lifetime, in the absence of density dependent constraints. The calculation of R_0 defined in this way is often based on *ad hoc* methods. A mathematical definition and a frame for calculation, as they have been given for microparasitic diseases [7], are lacking in the case of 'macroparasitic' infections.

Characteristically, helminths do not reproduce within the host, and a rise in parasite level is due to re-infection (see discussion). An additional characteristic of helminths is that they possess a clearly defined life-cycle that contains a number of distinct consecutive parasite stages (e.g., adults lay eggs, eggs hatch to release a larva, and larvae turn into adults). An attempt at a generally applicable theory for R_0 for cyclic infections was made in [17]. In the present paper we give three threshold quantities for cyclic infections, one of which bears a strong resemblance to the threshold quantity derived in that paper.

In Section 2, we define a quantity denoted by Q_0, the basic reproduction quotient, and prove that $Q_0 = 1$ is a threshold determining the stability of the parasite-free steady state of autonomous systems describing the dynamics of a parasite with a given cycle-length. The biological interpretation of Q_0 is the expected number of adult worms that reach reproductive maturity produced by one adult worm during its lifetime, in the absence of density dependent constraints. In Section 6 we show that $Q_0 = R_0$, as defined above, for autonomous systems. In Section 3, we show how these ideas can be extended to allow for heterogeneity in the parasite, and in the various hosts.

The analysis of the autonomous case is straightforward and serves as an introduction to the treatment of the more important problem of defining a threshold quantity for periodic systems. In the context of branching processes, the influence of a periodically varying environment has been discussed in e.g. [13]. In Section 4 we define three different quantities for periodic systems and prove that all have the same threshold behaviour. A mathematical point of view leads to the dominant Floquet multiplier to determine the stability of the trivial steady state after linearisation of the periodic system. A biological point of view leads to a generalisation of the definition of Q_0 from the autonomous case. Finally, as an 'afterthought', we give a quantity P with an 'explicit' formulaic definition (though difficult to evaluate) but with a different biological interpretation than Q_0. If periodicity is neglected, and we return to an autonomous system, then Q_0 and P coincide in value and are equal to what one would call R_0. The fact that none of the three can be identified with the basic reproduction ratio R_0 in the periodic case, because the concept of R_0 does not make sense in a nonautonomous setting, will be discussed in Section 6. There, we also indicate how the analysis of the periodic case extends to *microparasitic* infections in periodic environments.

In Section 5, we extend the ideas from Section 4 to include the influence of periodic discontinuities.

2. The autonomous case

In this section, we assume that there is no heterogeneity in either the parasite or host populations. We assume that the parasite has a life-cycle involving k consecutive stages $1, \ldots, k$, which live in various habitats (hosts, environments), and where the parasite individuals in stage i determine the rate of increase in stage $i + 1$ and stage k determines the inflow of stage 1. We will call this a parasite with cycle-length k. Some transitions $i \to i + 1$ will entail only a physiological change (for example one larval stage to the next, or larva into adult), while other transitions will involve reproduction of some sort in order for one individual of stage i to give rise to many individuals of stage $i + 1$ (for example an adult laying eggs). The term 'habitat' has to be interpreted in a broad sense. For example, in the ruminant/nematode system of Example 2 below, we recognise larvae living in a habitat called 'pasture', and adults living in a habitat called 'sheep'. For the schistosomiasis Example 3 below, miracidia and cercaria live in the habitat 'water', one gives rise to the other in the habitat 'snail', and adults live in humans.

Define $\ell_i > 0$ as the rate of leaving stage i (either due to death or transition to the $i + 1$ stage), and m_i as the rate of giving rise to stage $i + 1$ individuals (or the rate of being transformed into a stage $i + 1$ individual), under optimal conditions (i.e. in the absence of density-dependent constraints). Without loss of generality we assume that certainly the transition from stage k to stage 1 consists of actual reproduction leading to the birth of new parasite individuals. We then regard newborns in stage 1 and remark that the individual's future progress is independent of the environment (the various rates being constants). We can therefore use a simple age-representation when following a newborn through life (see, e.g., [15], Chapter IV). It is then easy to calculate the expected number of stage 1 individuals that will be produced from one newborn stage 1 individual during its entire life, by describing the progress through the life-cycle as a continuous time Markov-chain on $\{1, \ldots, k\}$.

Let G be the $k \times k$-transition matrix of the Markov process,

$$
G = \begin{pmatrix}
-\ell_1 & 0 & \cdots & 0 & 0 \\
m_1 & -\ell_2 & \cdots & 0 & 0 \\
0 & m_2 & \ddots & 0 & 0 \\
\vdots & \ddots & \ddots & \ddots & \vdots \\
0 & \cdots & 0 & m_{k-1} & -\ell_k
\end{pmatrix},
$$

and let $(0 \cdots 0 \; m_k)$ be the vector of length k, describing the rate of production of stage 1 individuals by individuals in the k different stages. Then Q_0, the expected number of stage 1 parasites produced per stage 1 parasite, is given by [15],

$$
Q_0 = (0 \cdots 0 \; m_k) \int_0^\infty e^{Ga} da \begin{pmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{pmatrix} = -(0 \cdots 0 \; m_k) \, G^{-1} \begin{pmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{pmatrix}.
$$

Direct calculation of this expression leads to

$$Q_0 = \frac{m_k m_1}{\ell_1 \ell_2} \cdots \frac{m_{k-1}}{\ell_k} = \frac{\prod_{i=1}^k m_i}{\prod_{i=1}^k \ell_i} . \tag{2.1}$$

It is clear that Q_0 has threshold value 1. If we define x_i as the mean number of parasite individuals of stage i per (relevant) host ($i \in \{1, \ldots, k\}$), and write $x = (x_1, \ldots, x_k)^T$ for the vector of mean parasite burdens, we can write the associated system of ordinary differential equations, that describes the dynamics of x, as

$$\frac{dx}{dt}(t) = Ax(t), \quad x(0) = x_0 \tag{2.2}$$

with [15]

$$A := G + \begin{pmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{pmatrix} (0 \cdots 0 \; m_k) .$$

One easily shows that $Q_0 < 1$ implies that the trivial steady state $x_i = 0$, $\forall i$ is locally asymptotically stable, whereas this parasite-free state is unstable for $Q_0 > 1$ (see end of section).

Example 1. In [1] (eqn. 16.7–8) the following simple prototype system is given to model the life-cycle of a directly transmitted parasite with two stages, larvae (living in some unspecified habitat) and adults (living in a host).

$$\frac{dx_1}{dt} = -(\mu_2 + \beta N) \, x_1 + s\phi d_2 \lambda N x_2$$

$$\frac{dx_2}{dt} = -(\mu + \mu_1) \, x_2 + d_1 \beta x_1$$

where d_1, d_2 are the respective proportions of individuals that reach maturity as larvae and adults; μ is the death-rate of the host; μ_1 and μ_2 are the death-rates of adults and larvae respectively; N is the constant host density; β is a measure for the rate for contact of the host with infective larvae times the probability that any one contact results in establishment of the parasite; s is the proportion of female worms in the population, ϕ is the probability to mate, and λ is the rate of egg-production.

Equation (2.1) for Q_0 leads to

$$Q_0 = \frac{s\phi\lambda\beta N d_1 d_2}{(\mu + \mu_1) \, (\mu_2 + \beta N)} ,$$

which is equal to the formula given in equation 16.9 for R_0 in [1], with $\phi = 1$. Anderson & May include an explicit time-delay for development to maturity

in both equations, but all that is important for Q_0 and R_0 is the proportion of individuals that live through the development period.

Example 2. In [19], the following model is proposed for the dynamics of nematode infections of ruminants.

$$\frac{dx_1}{dt} = -(\rho + \beta)\, x_1 + q\lambda(r)\, x_2$$

$$\frac{dx_2}{dt} = -\mu(r)\, x_2 + \beta p(r)\, x_1$$

$$\frac{dr}{dt} = \beta x_1 - \sigma r$$

where x_1 is the density of infective larvae on the pasture (i.e. mean number of larvae per 'host'), x_2 is the mean number of adult parasites per host and r is a measure of acquired immunity. The parameters have the following interpretations: ρ is the death rate of larvae on the pasture; β is the per capita rate of ingestion of larvae by ruminants; p is the probability that an ingested larva develops into an adult worm; μ is the death rate of adult worms; λ is the per capita rate of egg-production by adult worms; σ is the rate of loss of immunity and q is the probability that an egg develops into an infective larva.

In the linearised system, we have $r = 0$ and we obtain from (2.1)

$$Q_0 = \frac{\beta\lambda(0)p(0)q}{(\rho + \beta)\mu(0)}$$

which was used as a threshold quantity in [19]. The authors also considered a variant of their model where the state variables were subject to periodic resetting, and in a subsequent paper [20] generalised the system to a model where ρ, β and q were periodic functions of time, see Sections 5 and 4 of the present paper respectively.

Example 3. Anderson & May [1] (p. 564) discussed a model for schistosomiasis with three types of parasite stage (adults, miracidia and cercaria) and three types of 'host' (humans, snails (intermediate host) and water) as a prototype of an indirectly transmitted parasite. The adult worms live in humans, both parasite stages live in water and miracidia give rise to cercaria through infection of snails. We neglect the latency period in snails and only take a death rate of infected snails into account. In a mix of their and our notation their model reads

$$\frac{dx_1}{dt} = -\mu_1 x_1 + \beta_1 x_3$$

$$\frac{dx_2}{dt} = -(\mu_2 + \beta_2 N_2)\, x_2 + \frac{1}{2}\lambda_1 N_1 \phi x_1$$

$$\frac{dx_3}{dt} = -(\mu_5 + \beta_1 N_1)\, x_3 + \frac{\beta_2 \lambda_2 N_2}{\mu_4} x_2$$

where x_1 is the mean number of adults per human host, and x_2 and x_3 are the densities of miracidia and cercaria in water, respectively. The μ_i are the various death rates; β_1 and β_2 are the per capita rates of establishment in human and snail hosts respectively; N_1 and N_2 are the total densities of humans and snails respectively; λ_1 is the per capita fecundity of mature female worms; the factor $\frac{1}{2}$ arises out of an assumption of 1:1 sex ratio of adult worms; ϕ is the probability that a female worm is mated; and finally, λ_2 is the per capita production of cercaria per shedding snail. All terms in the above equation then speak for themselves, except perhaps the production term in the last equation. This term describes the effect of passing through the intermediate host: one miracidium infects a susceptible snail with rate $\beta_2 N_2$ and this snail will generate after infection λ_2 cercaria per unit of time, for a time period of average length $1/\mu_4$ (mean life-time of infected snails).

We calculate Q_0 according to equation (2.1) and find

$$Q_0 = \frac{\beta_1 \beta_2 \lambda_1 \lambda_2 N_1 N_2 \phi}{2\mu_1 \mu_4 (\mu_5 + \beta_1 N_1)\, (\mu_2 + \beta_2 N_2)}$$

which corresponds to equation (20.35) given for R_0 for this model in [1].

To end this section, we give an alternative way, though for the autonomous case more cumbersome, of deriving expression (2.1) for Q_0. We give this approach in some detail because it paves the way for our treatment of the periodic case in Sections 4 and 5.

System (2.2) describes the linearisation around the trivial steady state of a nonlinear system of differential equations describing the dynamics of the mean parasite loads for the k parasite stages. We rewrite (2.2) as

$$\frac{dx}{dt}(t) = Ax(t) = (M - L)\, x(t), \quad x(0) = x_0 \tag{2.3}$$

where and M and L are the positive matrices

$$
M = \begin{pmatrix}
0 & 0 & \cdots & 0 & m_k \\
m_1 & 0 & \cdots & 0 & 0 \\
0 & m_2 & \ddots & 0 & 0 \\
\vdots & \ddots & \ddots & \ddots & \vdots \\
0 & \cdots & 0 & m_{k-1} & 0
\end{pmatrix}, \quad
L = \begin{pmatrix}
\ell_1 & 0 & \cdots & \cdots & 0 \\
0 & \ell_2 & \cdots & \cdots & 0 \\
\vdots & \ddots & \ddots & & \vdots \\
\vdots & & \ddots & \ddots & \vdots \\
0 & \cdots & \cdots & 0 & \ell_k
\end{pmatrix}.
$$

Let $s(A) := \sup\{\mathrm{Re}\lambda\colon \lambda \in \sigma(A)\ \}$ be the largest real part of the eigenvalues making up the spectrum of A, then, if $s(A) < 0$ the trivial steady state is

locally stable. Define a matrix

$$K = L^{-1}M = \begin{pmatrix} 0 & 0 & \cdots & \cdots & m_k/\ell_1 \\ m_1/\ell_2 & 0 & \cdots & \cdots & 0 \\ 0 & m_2/\ell_3 & \cdots & \cdots & 0 \\ \vdots & \ddots & \ddots & \vdots & \vdots \\ 0 & \cdots & 0 & m_{k-1}/\ell_k & 0 \end{pmatrix}. \qquad (2.4)$$

It is well-known that, under our conditions on M and L, $s(A) < 0 \Leftrightarrow r(K) < 1$, where $r(K)$ is the spectral radius of K (i.e. $r(K) := \sup\{|\lambda|: \lambda \in \sigma(A)\}$). So, if $r(K) < 1$, the trivial steady state (corresponding to absence of the parasite) is locally stable. Observe that if Q_0 is any monotonically increasing function of $r(K)$ with $Q_0 = 1 \Leftrightarrow r(K) = 1$, we have the result that if $Q_0 < 1$, the trivial solution of (2.3) is locally asymptotically stable, and if $Q_0 > 1$ it is unstable.

We define $Q_0 = r(K)^k$, where k is the number of stages in the model life cycle (cycle length). By direct computation from (2.4) this again leads to the expression (2.1) for Q_0. One sees that a biological interpretation of Q_0 is the expected number of adults produced by one adult during its life-time in the absence of density dependent constraints.

Taking $r(K)$ to the power of the cycle-length (see also [11]) not only gives the correct expression (2.1) for Q_0, but also resolves the unfortunate situation that a biologically meaningful quantity in terms of parasite transmission and mortality rates would be different for models of the same system that employ different degrees of simplification. To illustrate this, the model of Roberts & Grenfell [19,20] (see Example 2 above) is a simplification of a more detailed model for nematode parasites (see for example [8]) that takes, among other things, more different consecutive larval stages into account (and has therefore a larger cycle-length). The simplification utilises differences between the time-scales of the various stage-changes in the life-cycle of the parasite. One would want the value of the threshold quantity to be independent of the amount of detail, hence the kth power. Note that the straightforward approach via the age-representation and Markov-chains does not give these problems and automatically leads to (2.1) in all cases.

3. Heterogeneity in the autonomous case

We consider two kinds of heterogeneity: differences within a given host or habitat-type, and differences within a given parasite stage. The former could, for example, be host-age (class) or resistance level, the latter might reflect differences in resistance to control measures. We can deal with both types of heterogeneity in a single formalism.

Remark: We present only the approach via differential equations because the generalisation to periodic systems is then straightforward using the theory of Section 4. One should realise however, that in the autonomous case the approach via Markov chains taken in Section 2 is equally suitable, and perhaps even preferable because it leads to a lower dimensional problem. If we regard again the case where the transition $k \to 1$ involves reproduction and if we can distinguish n_1, say, different types of stage 1 individuals, then instead of a single stage 1 birth-state, we now have n_1 possible birth-states. We then have to calculate, for each given type $s \in \{1, \ldots, n_1\}$, how many stage 1 individuals of type $r \in \{1, \ldots, n_1\}$ are expected to arise if we follow one newborn of type s during its life-cycle. The result is not one number (as in Section 2) but a matrix, and Q_0 will be the spectral radius of that matrix. A detailed example of this analysis can be found in [6], where a different application of the same basic theory is given.

Suppose, for the sake of illustration, that we have two parasite stages (cycle length 2) and that for both stages, we recognise two different *types*. The types of stage 1 parasites will be denoted by (1,1) and (1,2), and *mutatis mutandis* for parasites of stage 2. The cycle length of course remains 2, the life-cycle could just, at least in theory, take a number of different routes of length two. We order the different types lexicographically, i.e. we regard, for this particular case, the map $\pi\colon \{(1, 1), (1, 2), (2, 1), (2, 2)\} \to \{1, 2, 3, 4\}$ where $\pi((i, j)) < \pi((k, l))$ iff either $i < k$ or $i = k$ and $j < l$. The matrices M and L in (2.3) then become

$$M = \begin{pmatrix} 0 & 0 & m_{13} & m_{14} \\ 0 & 0 & m_{23} & m_{24} \\ m_{31} & m_{32} & 0 & 0 \\ m_{41} & m_{42} & 0 & 0 \end{pmatrix}, \qquad L = \begin{pmatrix} \ell_1 & 0 & 0 & 0 \\ 0 & \ell_2 & 0 & 0 \\ 0 & 0 & \ell_3 & 0 \\ 0 & 0 & 0 & \ell_4 \end{pmatrix}, \qquad (3.1)$$

where m_{rs} is the rate of giving rise to type $\pi^{-1}(r)$ individuals by a $\pi^{-1}(s)$ type individual, and ℓ_r is the rate of leaving its current stage for an individual of type $\pi^{-1}(r)$. Since the cycle length has not changed, $Q_0 = r(K)^2$ with $K = L^{-1}M$, but with M and L now given by (3.1).

In general, suppose we recognise, for a parasite with cycle length k, n_i different types $(i, 1), \ldots, (i, n_i)$, for stage i. The matrix L then becomes $L = diag(L_1, \ldots, L_k)$, with $L_i = diag(\ell_1, \ldots, \ell_{n_i})$ and

$$M = \begin{pmatrix} 0 & 0 & \cdots & 0 & M_{1k} \\ M_{21} & 0 & \cdots & 0 & 0 \\ 0 & M_{32} & \ddots & 0 & 0 \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & \cdots & 0 & M_{k,k-1} & 0 \end{pmatrix}$$

where each entry 0 is a zero-matrix of appropriate dimension and each M_{rs} is a matrix of dimension $n_i \times n_j$ where $i = \pi^{-1}(r)$ and $j = \pi^{-1}(s)$ (as illustrated in the particular case $k = 2$ above). A cycle is any path $(1, i_1) \to (2, i_2) \to \cdots \to (k, i_k) \to (1, j_1)$, with $i_r \in \{1, \ldots, n_r\}$, $r \in \{1, \ldots, k\}$ and $j_1 \in \{1, \ldots, n_1\}$. The cycle length is still k and $Q_0 = r(K)^k$ where $K = L^{-1}M$ with L and M as given above, i.e.

$$K = \begin{pmatrix} 0 & 0 & \cdots & 0 & K_{1k} \\ K_{21} & 0 & \cdots & 0 & 0 \\ 0 & K_{32} & \ddots & 0 & 0 \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & \cdots & 0 & K_{k,k-1} & 0 \end{pmatrix}$$

where $K_{rs} = L_r^{-1}M_{rs}$.

In the illustration with $k = 2$ above, one can easily verify that $Q_0 = r(K_{12}K_{21}) = r(K_{21}K_{12})$. In general: the kth power of K is a matrix with permutated products of the k matrices K_{rs} on the diagonal, and zero-matrices off-diagonal (a direct generalisation of the non-heterogeneous case), and Q_0 is the spectral radius of the product of the K_{rs}:

$$Q_0 = r\left(\prod_{j=0}^{k-1} K_{i-j,i-j+1}\right)$$

(with indices calculated modulo k).

If instead of (or in addition to) the heterogeneity in parasite types, we distinguish different types of habitat or host, then the formalism remains unchanged and it is a matter of book-keeping to keep track of the various types. The reason for this to work is that each parasite stage is linked to a particular habitat (more than one can live in the same habitat, but any given stage only lives in one habitat). Therefore, we can mimic the effect of having, say, two types of the habitat of stage 1 parasites, and two types of the habitat of stage 2 parasites, by introducing 'mock' parasite types for each habitat type, and acting as if the parasites differed and not the habitats themselves. Any difference in habitat will have its effects on the stages that live in it by affecting 'survival' ℓ and 'reproduction' m, so it is not unnatural to model habitat heterogeneity in this way. This means that the whole formalism above carries over to the case of heterogeneity in habitats.

Examples where heterogeneity can be important are provided by the nematode/ruminant systems. A ruminant population may be infected with several different species of nematode parasite, or the host population itself may consist of 'classes' of animals with different susceptibilities to infection, either due to differences in age or genetic background. Furthermore, the parasite population may exhibit a genetic diversity, with a strain or strains resistant to nematode control procedures. These situations may be modelled by complications of Example 2.

4. The periodic case

In the study of the transmission of helminth infections, periodicity in factors that may influence the dynamics can be explicitly taken into account. Let the matrices M and L below (2.3) now be time-dependent and periodic, with the same period (which we have scaled to 1), i.e. assume that

$$\frac{dx}{dt}(t) = A(t)\, x(t) = \left(M(t) - L(t) \right) x(t), \quad x(0) = x_0 , \tag{4.1}$$

with $M(t+1) = M(t), L(t+1) = L(t), \quad \forall t \geq 0$ and consequently $A(t+1) = A(t)$.

Define $f_i(t) > 0$, $i \in \{1, \ldots, k\}$, as the mean duration of stage i, given that the parasite individual enters stage i at time t (either by birth or transformation). It follows as a special case from Proposition 1 (to be proved in Section 5), that

$$\frac{df_i}{dt}(t) = \ell_i(t)\, f_i(t) - 1, \quad f_i(0) = f_i(1)$$

and

$$f_i(t) = \int_0^\infty e^{-\int_0^a \ell_i(t+z)\,dz}\,da.$$

If we write $F(t) = diag(f_1(t), \ldots, f_k(t))$, a diagonal matrix of the mean stage durations, we can summarise these equations as

$$\frac{dF}{dt}(t) = L(t)\, F(t) - I, \quad F(0) = F(1) . \tag{4.2}$$

Let $\Phi(t)$ be the standard fundamental solution of (4.1), so

$$\frac{d\Phi}{dt}(t) = (M(t) - L(t))\, \Phi(t), \quad \Phi(0) = I . \tag{4.3}$$

This fundamental solution is obtained by solving (4.1) with the k standard unit vectors of $\mathbb{R}^k$ as initial conditions and taking the resulting vectors as columns of Φ. Then, $\Phi(t) \geq 0$ is a positive matrix for all $t \geq 0$, because $\mathbb{R}^k_+$ is positively invariant for (4.3) (we write $M \geq 0$ if all entries m_{ij} of a matrix M are ≥ 0, i.e. if M is *positive*). The solution to (4.1) can then be written as $x(t) = \Phi(t)\, x_0$.

The stability of the trivial steady state of periodic systems is determined by a quantity related to Φ. To be more precise, we can write

$$\Phi(t + 1) = \Phi(t)E$$

where E is a constant (i.e. independent of t) $k \times k$ matrix whose eigenvalues are uniquely determined by $A(t)$ (see e.g. [5], [9] for standard results in this direction). Setting $t = 0$, we find that $E = \Phi(1)$, and moreover that $E \geq 0$, in our setting. The dominant eigenvalue of E (the dominant characteristic, or Floquet, multiplier) determines the stability of the trivial steady state;

essentially it describes the asymptotic behaviour of the discrete sequence $x(0) \to x(1) \to x(2) \to \cdots$. Therefore, from a mathematical point of view, a sensible threshold quantity for system (4.1) is the dominant eigenvalue $\lambda_d(E)$ of E.

Although $\lambda_d(E)$ is probably also the 'easiest' threshold quantity to calculate numerically, it is not very satisfying that $\lambda_d(E)$ is defined in an implicit way, making it less suitable for the development of meaningful approximating expressions. Before we show how to derive an alternative threshold quantity for the periodic case with the same interpretation as Q_0, let us first examine the relation between Q_0 and $\lambda_d(E)$ in the autonomous case.

The fundamental solution of (2.3) is given by $\Phi(t) = e^{tA}$, so one could write $E = \Phi(1) = e^A$ in the autonomous case. By the Spectral Mapping Theorem (see e.g., [21]) the spectra of E and A are related as $\sigma(E) = exp(\sigma(A))$.

Lemma 1. *In the autonomous case $\lambda_d(E) < 1 \Leftrightarrow Q_0 < 1$, where $Q_0 = r(K)^k$.*

Proof: We have the relation $Q_0 < 1 \Leftrightarrow s(A) < 0$ (see Section 2). If $\mu \in \sigma(A)$ is the eigenvalue with largest real part, i.e. $s(A) = \mathrm{Re}\mu$, then the eigenvalue λ of E with largest absolute value, is $\lambda = e^\mu$. By the positivity of E, the spectral radius $r(E) = \lambda_d(E)$, which implies that $\lambda_d(E) \in \mathbb{R}$. Therefore, $s(A) < 0 \Leftrightarrow \lambda_d(E) < 1$. $\qquad\qquad\square$

We turn to the definition of Q_0 for the nonautonomous case. We start by multiplying equation (4.2) from the right with matrix $\Phi(t)$, and equation (4.3) from the left by $F(t)$, and adding the results

$$F\frac{d\Phi}{dt} + \frac{dF}{dt}\Phi = FM\Phi + (LF - FL)\,\Phi - \Phi.$$

Now note that $LF = FL$ because both L and F are diagonal matrices, and integrate the above expression over t from 0 to 1, to obtain

$$\Phi(1) - I = F_0^{-1} \int_0^1 \left[F(t)\,M(t)\,\Phi(t) - \Phi(t) \right] dt \qquad (4.4)$$

where we have used $\Phi(0) = I$ and $F(0) = F(1) = F_0$. We now rewrite (4.4) as

$$\Phi(1) - I = F_0^{-1}C(\mathscr{K} - I) \qquad (4.5)$$

where

$$C := \int_0^1 \Phi(t)\,dt$$

(note that C is a positive matrix) and

$$\mathscr{K} := C^{-1} \int_0^1 F(t)\,M(t)\,\Phi(t)\,dt\ . \qquad (4.6)$$

Define $Q_0 = r(\mathscr{K})^k$, the spectral radius of $\mathscr{K}$ raised to the power k.

Lemma 2. *In the autonomous case $\mathscr{K}$ is similar to K, $\mathscr{K} \sim K$, where K is given by (2.4).*

Proof: If L is a constant matrix, then solving (4.2) leads to $F = L^{-1}$. If M is also constant, then from (4.6) we find $\mathscr{K} = C^{-1}L^{-1}MC = C^{-1}KC$ and the result follows.   □

As a result of the previous lemma, the spectrum of $\mathscr{K}$ is equal to the spectrum of K and therefore $r(\mathscr{K}) = r(K)$ in the autonomous case.

In the nonautonomous case, we have the following elementary relation between the spectra of E and the matrix on the right-hand side of (4.5).

Lemma 3. $\lambda \in \sigma(E) \Leftrightarrow \lambda - 1 \in \sigma(F_0^{-1}C(\mathscr{K} - I))$.

Proof: Let ξ be the eigenvector of $E = \Phi(1)$ corresponding to eigenvalue λ. Then (4.5) leads to $(\lambda - 1)\xi = F_0^{-1}C(\mathscr{K} - I)\xi$ and we conclude that ξ is also an eigenvector of $F_0^{-1}C(\mathscr{K} - I)$, but with eigenvalue $\lambda - 1$. We have $\lambda \in \sigma(E) \Leftrightarrow \lambda - 1 \in \sigma(F_0^{-1}C(\mathscr{K} - I))$.   □

For the proof of the main threshold result in Theorem 1 we use the following lemma.

Lemma 4. *Let A be a real $n \times n$ matrix with $a_{ij} \geqq 0$, $i \neq j$. Then $s(A) < 0 \Leftrightarrow \det A \neq 0$ and $A^{-1} \leqq 0$.*

Proof:

$\Rightarrow$ First of all $s(A) < 0 \Rightarrow \det A \neq 0$ because $\det A = 0$ implies $0 \in \sigma(A)$ which contradicts $s(A) < 0$. Then for A we have by assumption $a_{ij} \geqq 0$, $i \neq j$, and hence: $e^{tA} \geqq 0$ for all $t \geqq 0$ (see e.g. [4] Theorem 3.12). So, as $\det A \neq 0$ and all eigenvalues have negative real parts we have $\int_0^\infty e^{tA}dt \geqq 0$ $\Rightarrow -A^{-1} \geqq 0 \Rightarrow A^{-1} \leqq 0$.

$\Leftarrow$ By assumption there exists $\theta > 0$ such that $A + \theta I \geqq 0$ where I is the identity matrix. We can now deduce from the Perron-Frobenius Theorem (see e.g. [16]) that $s(A)$ is an eigenvalue with nonnegative eigenvector. So $Ax = s(A)x$ for some vector $x \geqq 0$. Applying A^{-1} to both sides we find $x = s(A)A^{-1}x$. But $A^{-1}x \leqq 0$, $x \geqq 0$ and $x \neq 0$ (because x is an eigenvector), hence $s(A) < 0$.   □

Theorem 1. *In the periodic case $\lambda_d(E) < 1 \Leftrightarrow Q_0 < 1$, where $Q_0 = r(\mathscr{K})^k$.*

Proof: Since $E \geqq 0$, we have $r(E) < 1 \Leftrightarrow s(E) < 1 \Leftrightarrow s(E - I) < 0$. This leads to the following chain of inferences: $s(E - I) < 0 \Leftrightarrow s(F_0^{-1}C(\mathscr{K} - I)) < 0$ (by (4.5)) $\Leftrightarrow (F_0^{-1}C(\mathscr{K} - I))^{-1} \leqq 0$, by Lemma 4. Then

$$(F_0^{-1}C(\mathscr{K} - I))^{-1} \leqq 0 \Leftrightarrow (\mathscr{K} - I)^{-1}C^{-1}F_0 \leqq 0 \Leftrightarrow (\mathscr{K} - I)^{-1} \leqq 0$$

and by invoking Lemma 4 once more $(\mathscr{K} - I)^{-1} \leqq 0 \Leftrightarrow s(\mathscr{K} - I) < 0 \Leftrightarrow s(\mathscr{K}) < 1$ and finally $s(\mathscr{K}) < 1 \Leftrightarrow r(\mathscr{K}) < 1$. This ends the proof of Theorem 1.   □

In the autonomous case, $\mathscr{K} = L^{-1}M$, and Q_0 is equal to the expression (2.1) given in Section 2, or alternatively the product of the k f_i's and the k m_i's. In the periodic case the biological interpretation of Q_0 is the same as in the autonomous case. Save for a normalisation, $\mathscr{K}$ is, in analogy to models in demography, the integral over the reproduction function FM, i.e. the product of fertility M with life expectancy (stage duration) F, and the spectral radius of $\mathscr{K}$ or some power of it, is the threshold quantity for growth or decline of the parasite population. $Q_0 < 1$ implies that the average number of stage i parasite individuals per (relevant) host decreases to zero, for all $i \in \{1, \ldots, k\}$. $Q_0 > 1$ implies that average parasite burdens for all stages will increase, which, under certain conditions of homogeneous mixing, can be described as an epidemic in the host populations involved.

The threshold quantity $\lambda_d(E)$ is probably easier to calculate in applications. For this calculation, remember that $E = \Phi(1)$ where Φ is the standard fundamental matrix solution to (4.1). Numerically, the idea would be to solve system (4.1) k times over one period starting with the consecutive standard unit vectors in $\mathbb{R}^k$. The resulting numerical solutions written as column-vectors then make up the matrix E.

The components e_{ij} of E can be interpreted as measures for the mean parasite burdens for the various stages at the end of one period, if we start the period with unit-vector distributions. Therefore, if $\lambda_d(E) > 1$, and an epidemic develops, $\lambda_d(E)$ is likely to be a very large number indeed. One only has to look at the sheep/nematode examples we discussed before where larvae live on a pasture, to appreciate that, in an epidemic situation, the number of larvae living on the pasture at the end of a period can be very large. In the case $k = 2$ above, this will cause ψ to be very large, and therefore $\lambda_d(E)$. For example, in Roberts & Heesterbeek (in prep.) we present calculations for a model concerning the nematode *Trichostrongylus colubriformis* in sheep in New Zealand, where we find that for a set of realistic parameter choices, $Q_0 \approx 8$ while $\lambda_d(E) \approx 6 \times 10^{16}$. This shows that, whereas Q_0 and $\lambda_d(E)$ have the same threshold behaviour, their values can differ widely. In a sense $\lambda_d(E)$ has an interpretation on the population level, whereas Q_0 has an interpretation on the individual level.

To end this Section, we introduce a third threshold quantity for the same system. This is not an option from a numerical point of view, because its calculation requires calculating $\lambda_d(E)$ as a first step. However, it might be useful in generating meaningful approximating expressions. In addition, it is interesting from a biological point of view because it has an interpretation different from Q_0 and has previously been used in the literature.

Regard the following generalisation of (2.1),

$$P = \prod_{i=1}^{k} \frac{\int_0^1 f_{i+1}(t)\, m_i(t)\, x_i(t)\, dt}{\int_0^1 x_i(t)\, dt}, \qquad (4.7)$$

where $x(t)$ is the solution of (4.1) with initial condition $x(0) = \xi_d$, the eigenvector corresponding to the dominant eigenvalue of E. Then P has the same threshold behaviour as $\lambda_d(E)$ and Q_0.

Theorem 2. *In the periodic case* $\lambda_d(E) < 1 \Leftrightarrow P < 1$, *where P is given by* (4.7).

Proof: We first prove that $\lambda_d(E) = 1$ implies $P = 1$, next that $\lambda_d(E) < 1 \Rightarrow P < 1$, and $\lambda_d(E) > 1 \Rightarrow P > 1$, and finally (trivially from the previous) that $P < 1 \Rightarrow \lambda_d(E) < 1$.

(1) Let ξ_d be the eigenvector of E corresponding to $\lambda_d(E) = 1$. From (4.6)

$$\mathscr{K}\xi_d = \xi_d \Rightarrow \int_0^1 F(t)M(t)\Phi(t)\xi_d\,dt = \int_0^1 \Phi(t)\xi_d\,dt.$$

But $\Phi(t)\xi_d = x(t)$ if we solve (4.1) with $x_0 = \xi_d$ and we obtain the series of equalities

$$\int_0^1 f_{i+1}(t)m_i(t)x_i(t)\,dt = \int_0^1 x_{i+1}(t)\,dt, \quad i \in \{1, \ldots, k\}$$

with $k + 1 \equiv 1 \bmod k$. All k equalities are fulfilled and this implies $P = 1$.

(2) Let ξ_d be the eigenvector of E corresponding to $\lambda_d(E)$, and assume that $\lambda_d(E) < 1$, we show that this implies $P < 1$ (the case $\lambda_d(E) > 1 \Rightarrow P > 1$ is completely analogous). From (4.5) we obtain

$$\alpha\xi_d = F_0^{-1}C(\mathscr{K} - I)\xi_d$$

where $\alpha := \lambda_d(E) - 1 < 0$, by assumption. This leads to

$$F_0^{-1}C\mathscr{K}\xi_d \leqq F_0^{-1}C\xi_d \tag{4.8}$$

with strict inequality in at least one component.

From (4.8) we obtain

$$\int_0^1 F(t)M(t)\Phi(t)\xi_d\,dt \leqq \int_0^1 \Phi(t)\xi_d\,dt$$

which leads to

$$\int_0^1 f_{i+1}(t)m_i(t)x_i(t)\,dt \leqq \int_0^1 x_{i+1}(t)\,dt, \quad i \in \{1, \ldots, k\}$$

with at least one i for which the inequality is strict. This implies that $P < 1$.

(3) From (1) it follows that $P \neq 1 \Rightarrow \lambda_d(E) \neq 1$. (2) gives $\lambda_d(E) < 1 \Rightarrow P < 1$. Assume $P < 1$ then $\lambda_d(E) \neq 1$, so suppose $\lambda_d(E) > 1$. This leads to a contradiction with (2), which proves that $\lambda_d(E) < 1$. $\square$

Looking carefully at (4.7) we arrive at the following biological interpretation of P. P is the expected number of years of adult life that is produced per

year of adult life. In the autonomous case, the interpretations of P and Q_0 (as the expected number of adult individuals produced per adult individual during its life-time) coincide because the various mean stage durations are constant in time. Indeed, $P = Q_0$ of course in the autonomous case. In the nonautonomous case however, where life-expectancy depends on the time of birth of a parasite individual, the interpretations of P and Q_0 do not coincide and P and Q_0 can have different values.

If fluctuations in f and m are sufficiently small, then one could, by expanding $f_i(t)$ and $m_i(t)$ in their respective Taylor-series around $t = 0$, crudely approximate P by

$$P \approx \prod_{i=1}^{k} \left(f_{i+1}(0)m_i(0) + [f'_{i+1}(0)m_i(0) + f_{i+1}(0)m'_i(0)] \frac{\int_0^1 tx_i(t)\,dt}{\int_0^1 x_i(t)\,dt} \right). \quad (4.9)$$

If f and m are constant, then (4.9) is exact and equal to (2.1). With nonconstant f and m (4.9) could be useful if one knows the values of f and m (and their derivatives) at the beginning of the season ($t = 0$). In that case, the only unknown in (4.9) is the quotient of integrals in the last term. This quotient however, can be interpreted as the approximate time that the epidemic peaks for parasites of stage i (if the epidemic is sufficiently well behaved within one season), and this information might be obtainable from data.

In [18] and [20], P was taken as the threshold property for the non-autonomous periodic version of the ruminant/nematode system described in Example 2 of Section 2. These authors considered a model for nematode infections of ruminants with seasonal transmission, and analysed the system described as Example 2 above, but with p, β and q periodic functions of time. They showed, *inter alia*, that $P = 1$ (which they incautiously referred to as R_0, see Section 6) is a bifurcation point for the stability of their system.

Finally, we remark that adding heterogeneity in the periodic case is a straightforward generalisation of the ideas in Section 3.

5. The influence of periodic discontinuities

In many practical applications there are, apart from the continuous 'environmentally caused' periodic perturbations treated in Section 4, additional discontinuous 'man caused' perturbations that affect the mean duration of various parasite stages. For example, in the sheep/nematode system discussed in Section 2, the sheep are removed from the pasture after one year and replaced by lambs. The effect is an immediate reduction of the adult parasite population to practically zero. One could envisage that systems where new hosts are born at specific times of the year might also be better represented by equations with periodic discontinuities, than by equations with periodic functions such as those discussed in Section 4.

In general, suppose that at regular intervals, the parasite population density in a given stage is reduced by a factor d. We derive a differential equation for the mean stage duration f as a function of time.

Proposition 1. *Consider an individual that enters a certain stage at time t. Define $\ell(t)$ as the time-dependent rate of leaving that stage, and $f(t)$ as the expected stage duration. Every time t equals an integer value, let $0 \leqq d \leqq 1$ be the probability that the individual remains in the same stage. Then $f(t)$ satisfies the following differential equation*

$$\frac{df}{dt}(t) = \ell(t)f(t) - 1, \quad df(n-) = f(n+), \quad n \in \mathbb{N} .$$

Proof: Define $\zeta(a, t)$ to be the probability that an individual entering the stage at time t, remains there to age a. Then $\zeta(a, t)$ is given by

$$\zeta(a, t) = e^{-\int_0^a \ell(t+x)\,dx} = e^{-\int_t^{t+a} \ell(x)\,dx}.$$

We obtain $f(t)$ by calculating the average over all possible stage durations

$$f(t) = \int_0^\infty a\,d_a(1 - \zeta(a, t))$$

where $1 - \zeta(a, t)$ is the probability of no longer being in the given stage at age a, if one entered (age 0) at time t. After partial integration we find for the case $d = 1$ (no periodic discontinuities) $f(t) = \int_0^\infty \zeta(a, t)\,da$. In general, let n be the smallest integer larger than t, then $f(t)$ is calculated as

$$f(t) = \int_0^{n-t} \zeta(a, t)\,da + \sum_{i=0}^\infty d^{i+1} \int_{n-t+i}^{n-t+i+1} \zeta(a, t)\,da.$$

We rewrite this as

$$f(t) = \int_0^{n-t} \zeta(a, t)\,da + \sum_{i=0}^\infty d^{i+1} \int_0^1 e^{-\int_t^{v+n+i} \ell(x)\,dx}\,dv$$

and differentiate with respect to t. Then,

$$\frac{df}{dt}(t) = -e^{-\int_t^n \ell(x)\,dx} - \int_0^{n-t} (\ell(t+a) - \ell(t))\,e^{-\int_0^a \ell(t+x)\,dx}\,da$$

$$+ \sum_{i=0}^\infty d^{i+1} \int_0^1 \ell(t)\,e^{-\int_t^{v+n+i} \ell(x)\,dx}\,dv$$

which after some rewriting becomes

$$\frac{df}{dt}(t) = \ell(t)\left[\int_0^{n-t} \zeta(a, t)\,da + \sum_{i=0}^\infty d^{i+1} \int_0^1 e^{-\int_t^{v+n+i} \ell(x)\,dx}\,dv \right]$$

$$- e^{-\int_t^n \ell(x)\,dx} + \int_0^{n-t} de^{-\int_0^a \ell(t+x)\,dx}$$

and finally

$$\frac{df}{dt}(t) = \ell(t)f(t) - 1.$$ □

If $d = 1$, it is clear from the proof that if $\ell(\cdot)$ is a periodic function, then $f(\cdot)$ is periodic with the same period.

The durations of the k parasite stages are independent, and therefore the differential equation for the diagonal matrix of mean stage durations is given by

$$\frac{dF}{dt}(t) = L(t)\,F(t) - I, \qquad DF(n-) = F(n+) \tag{5.1}$$

where $D = diag(d_1, \ldots, d_k)$ is the matrix containing the various resetting factors $0 \leqq d_i \leqq 1$, for all $i \in \{1, \ldots, k\}$. Note that D and $F(0)$ commute because both are diagonal.

It is easy to show that equation (4.4) for $\Phi(1)$ is, under periodic resetting, replaced by

$$D\Phi(1) - I = F_0^{-1}\int_0^1 \left(F(t)M(t)\,\Phi(t) - \Phi(t)\right)dt$$

and Q_0 is defined as in Section 4, as the kth power of the spectral radius of $\mathscr{K}$. The solution of (4.1) with resetting is $x(t) = \Phi(t)x_0$, for $0 \leqq t < 1$, with $x(1+) = Dx(1-) = D\Phi(1)x_0$. So the dynamics of the map $x(0) \to x(1)$ are determined by $D\Phi(1)$ and the appropriate threshold quantity is

$$Q_0 = r(\mathscr{K})^k$$

where $\mathscr{K}$ is the matrix defined by (4.6), taking into account that the matrix F is now the solution of (5.1).

In [19], Roberts & Grenfell introduced periodic resetting into the autonomous equations for the ruminant/nematode system of Example 2, and determined the threshold quantity to be P as defined by (4.7). This analysis was extended to the periodic case in [20] (see also [18]). We have demonstrated in Theorem 1 and 2 that P and Q_0 are equally valid as threshold quantities for this system.

6. Discussion

The rigorous mathematical definition of R_0 for micro-organisms is based on the assumption that the infection develops as an autonomous process within the host [7]; one assumes multiplication of the parasite within the host is so fast that additional reinfections play no part, the environment is constant. One then regards generations of infected hosts and determines, given a heterogeneous population, a positive operator that describes the next generation in terms of the present generation and defines R_0 as the dominant eigenvalue of this (next-generation) operator. The fact that we may assume autonomy

within the host once infection has occured, justifies the use of an age-repre-
sentation for the development of the infection within the host and one can
meaningfully discuss the infectiousness of the host-individual as a function of
the time elapsed since infection took place. To keep track of the infectious
'output' of an infected host, one need only to know the age-of-infection. The
interpretation given to R_0 is then the expected number of newly infected hosts
caused by a typical infected host during its entire period of infectivity in an
ideal population consisting of susceptibles only.

For helminth infections, the picture is very different. The infective output
depends largely on how many parasites are present in the host and because
reproduction within the host is rare (it is possible for some intermediate stages
of helminths), the rise in parasite levels within a host is purely due to frequent
re-infection. Because the infection has to 'pass through' the environment to
increase the infectiousness of a host individual, and the environment is as
a rule not constant, one can realistically not make the assumption that
a helminth infection develops as an autonomous process within the host. It
makes no sense therefore for these infections to define a threshold quantity in
terms of a next generation operator as in the micro-parasite case above. An
age-representation is not possible, and the quantities $\lambda_d(E)$ and Q_0 (and to
a lesser extent P) defined in Section 4 could be used instead.

Of course, if one assumes from the outset that the environment is constant,
the life-cycle of the helminth is an autonomous process (i.e. if all rates that
determine births, deaths or transitions of one stage to the next are constants),
and then an approach very similar to the microparasite case can be meaning-
ful. In contrast to the variable environment case, where the expected stage-
durations depend on the time of 'birth' into those stages, if the physiological
development and reproduction are autonomous, then all parasites in a given
stage of the life-cycle have the same expected stage-duration and are thus born
equal. It therefore makes sense to regard an age-representation and to define
a threshold quantity in that setting. In analogy to the microparasite-case, one
could then call this quantity R_0. Essentially, one then has $R_0 = Q_0 = P$. In the
above sense is the concept of R_0 from [7] meaningful for helminth infections.

In the case that we do not regard mean parasite burdens but the more
general models that take variation in parasite burden into account, see e.g.
[10], [14], there does not yet exist a theory of threshold quantities. However,
see Barbour [2] for an approach for stochastic models.

For the same reason that the generation based reproduction ratio R_0 is
not meaningful for nonautonomous helminth systems, it is not meaningful for
nonautonomous microparasite systems. However, the approach that we have
taken in Section 4 can easily be applied to microparasitic infections in
heterogeneous host populations as well. Suppose there are k different groups
of individuals. We then consider the vector x in (4.1) as describing the
population density of the infecteds in the k groups, A to be the matrix of
transmission rates between the various groups and (4.1) to describe the
linearised real-time development of the epidemic (where the susceptible
population density is in a demographic, possibly periodic, steady state

in the absence of infection). The quantities $\lambda_d(E)$, Q_0 and P then indicate whether an introduction of the microparasite in a virgin population will result in an epidemic.

Of course, after having defined the thresholds $\lambda_d(E)$ and Q_0 in a rigorous way, thereby reducing the original difficulty of numerically solving the full nonlinear periodic system considerably, the main problem is to find useful approximations to these quantities to make calculations more practical. In Roberts and Heesterbeek (in prep.), we will combine calculation of Q_0 and $\lambda_d(E)$ from data with the evaluation of various control-strategies involving chemotherapy for sheep/parasitic nematode systems. In systems like that all elements touched upon in the present paper are of importance and should ideally be taken into account when evaluating optimal control methods. Indeed, the probabilities of eggs and larvae maturing into larvae and adults respectively, are influenced by a periodic environment; there are differences in nematode resistance between adult sheep and lambs; there are varying degrees of resistance to chemical treatment in the nematode species; and finally, periodic man-induced discontinuities by removal of sheep strongly influence the adult worm population. In reviewing various control strategies, the quantity Q_0 might prove to be more useful than $\lambda_d(E)$ because of the very large values the latter quantity can take in an epidemic situation. Finally, P might be the best candidate for which to find approximating expressions.

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