

Monotonicity of the Number of Passages in Linear Chains and of the Basic Reproduction Number in Epidemic Models

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Abstract. In models for infectious diseases, the basic reproduction number is the crucial parameter which determines the possibility of an outbreak. In simple situations it depends in a monotone way on the infectivity. Non-monotone behavior may occur in diseases where infectivity depends on time since infection and where transmission depends on social structure, as is shown by an example. A typical application is the HIV infection where transmission rates depend on existing pair bonds and infectivity changes drastically over time.

For a class of epidemic models with pair formation models and infectivity depending on time since infection it is shown that the basic reproduction number is a monotone function of infectivity. This observation is a consequence of a general result on a class of cyclic linear reaction chains with tridiagonal structure for which it is shown that the number of passages depends in a monotone way on the rates.

Keywords: *Epidemiology, basic reproduction number, Markov chain, linear chain*

AMS subject classification: 92 D 30, 34 A 30, 35 L 40

1. Introduction

Classical deterministic models for the spread of diseases are based on the so-called Kermack-McKendrick model, actually only a simple case of the class of models proposed by these authors [20]. The simple model distinguishes susceptibles, infecteds and recovered, possibly also exposed individuals. Models of this type have been successfully adapted to many particular diseases, and they provide a valid qualitative description of fundamental phenomena and critical parameters such as the threshold phenomenon [1, 7] and the basic reproduction number [5, 6, 9, 18]. Other diseases, in particular those which do not spread by direct contacts between individuals, require more sophisticated modeling approaches. Starting from the Kermack-McKendrick system, models have been designed that comprise additional features, e.g., for malaria (transmission based on host-vector dynamics), for childhood diseases (age structure of the population

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is an important factor [10, 11]) or for sexually transmitted diseases (essential features are contact distributions, splitting of the population into core and non-core [14, 16]).

Models for infectious diseases have a nonlinear structure which is a direct consequence of the contact process. For a transmission event to occur, a susceptible and an infected must have contact. Since there are two population classes involved, the mathematical description of the contact process is necessarily nonlinear. In the traditional form the nonlinearity is a product of the two densities, similar to chemical mass action law. Only in the last decade it has become widely accepted that a realistic modeling of the contact process (invariant under rescaling) requires nonlinearities of a more complex character (homogenous or asymptotically homogeneous functions [3, 4]).

What has been said about modeling infectious diseases is particularly true for sexually transmitted diseases. For such diseases we can distinguish two large classes of models, those with pair formation and those without. Models without pair formation are similar to the classical models. As a consequence, it is implicitly assumed that in successive sexual contacts of an individual each contact involves a new partner (or rather, that the chance to contact a previous partner is negligibly small). It is further assumed that for a noninfected individual any contact with an infected bears a risk of infection which is independent of partners in previous contacts.

In models with pair formation [2, 8, 15, 17] two individuals may form a pair. Sexual contacts are assumed to occur only within these pairs. Thus, the partners of a pair are mutually faithful. Therefore a pair of two uninfected partners cannot acquire the infection. This effect of "social immunity" slows down the spread of infection within the population. Thus, neglecting the fact that a large part of a population lives in long-lasting pairs, may lead to a gross overestimation of the basic reproduction number and other crucial parameters [8]. Models with pair formation are mathematically more complex (and therefore have met some resistance in the scientific community). Even the description of the uninfected population (which otherwise is a linear system) involves a nonlinear function governing the formation of pairs. On the other hand, any realistic description of a sexually transmitted disease must take social immunity into account, at least in the form of appropriately downscaled infection rates.

We consider a simple model for the transmission of HIV. An essential feature of the HIV infection is variable infectivity. The infectivity of an infected individual changes drastically with time since infection [21, 25, 26]. In the first weeks after infection, infectivity is very high, then it decreases and it may be very low for years until it increases again just before eventually the individual develops AIDS. There are now quite a number of mathematical models which explain this phenomenon of changing infectivity in terms of the dynamics of the immune system and the virus population within one individual [23, 24, 27]. Since the time interval between infection and AIDS may exceed ten years, variable infectivity may have considerable effect on the spread of HIV, in particular on the basic reproduction number.

The goal of the present work is to get insight into how the basic reproduction number R_0 depends on the variable infectivity pattern. Does R_0 depend on infectivity in a monotone way? That is, does R_0 increase when infectivity is increased at some time since infection? At first glance, this question seems simple. Of course increasing infectivity should move R_0 up. However, monotone behaviour is not so evident in

pair formation models. The disease cannot spread outside of pairs, and hence the timing of pair formation, infection, and separation becomes important. A newly infected individual has always an infected partner. If the pair splits, both infected individuals may form new pairs, possibly with uninfected partners, and so on. If the parameters that define formation and splitting of pairs (pair formation rate, separation rate, and mortality) are not affected by the disease, R_0 depends on infectivity in a monotone way. However, if these parameters depend on health status (as is obvious for mortality) then there may be successive partnerships such that the number of secondary cases decreases although infectivity has increased.

We consider the situation where the rates of pair formation and separation are independent of the health status but mortality depends on the presence or absence of the disease. Then we show, with some effort, that R_0 depends monotonely on infectivity. By a somewhat artificial example we show that the naive view is generally wrong; if pair formation and separation rates depend on health status then monotonicity does not hold in general.

In Section 2 we derive the models and useful formulae for the reproduction number. In Section 3 we present the results. In the appendix we prove a general result on non-autonomous linear ordinary differential equations with tridiagonal structure. We show, under an appropriate hypothesis, that the number of passages between two states is a monotone function of certain transition rates. This proof adapts methods from stochastic time-discrete random walks and replaces an earlier proof based on optimal control theory [22].

Acknowledgement. The present proof of Theorem A.1 is based on an idea of Odo Diekmann. The authors thank him and Klaus Dietz for fruitful discussions.

2. The basic reproduction number

We start from a standard pair formation model for a population without age structure (see [17, 19]), i.e. we structure the population by singles and pairs. Every individual can be described by the two characters sex (female, respectively male) and infectious state (uninfected, respectively infected). Then there are four classes of pairs (in a heterosexual population), i.e. the female and the male of a pair may be uninfected or infected. For mathematical convenience we assume symmetry in sex for the parameter functions as well as for the initial conditions. Thus the solution stays symmetric in gender, and we are able to reduce the model to the densities of uninfected singles, the density of infected singles with time since infection a , uninfected pairs, pairs with one infected partner (with time since infection a) and pairs with two infected partners (with time since infection a for the first partner and b for the second). The transitions occur according to Figure 1.

The present work concentrates on the reproduction number. Thus it is not necessary to give the equations of this model in detail, but only to describe the life history of a typical infected person in a situation where only very few other infecteds are present in the population. Although this infected individual is assumed to be infected by another person in the population we will refer to him/her as the primary infected individual. If

we know the life history of the primary infected person, we are able to count the number of secondary cases and to define in this way the reproduction number.

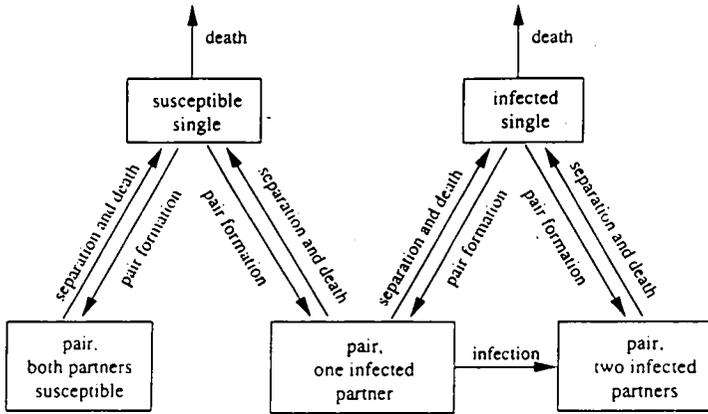


Figure 1: The structure of the model

The first case we consider is that of constant population size in absence of the disease. At the end of the present paragraph we shall introduce also exponential growth of the uninfected population. Let a denote the time since infection of the primary infected individual. At $a = 0$, he/she is just infected and thus is a partner of an infected. Let $z(a, b)$ be the density of pairs of a primary infected person at age of infection a and the infected partner with age of infection $b < a$. (At the onset of an epidemic we can neglect remarriages of already infected partners.) Since we know that for $a = 0$ the primary infected individual has an infected partner, we obtain

$$z(0, b) = \varphi(b), \quad \int_0^\infty \varphi(b) db = 1.$$

$\varphi(b)$ denotes the distribution of the infection time of the partner from whom the primary infected case has been infected. Our aim is to determine the next-generation operator A . The initial situation for the primary infected individual is characterised by $\varphi(b)$. The corresponding quantity for the next generation (with respect to infection) is the density of newly infected secondary cases, structured by age since infection of the primary case. This density is $z(a, 0)$,

$$A[\varphi(\cdot)](a) := z(a, 0).$$

We derive an equation for $z(a, b)$. Pairs of two infected partners split with a rate $\sigma_2(a, b)$, and the primary infected person becomes a single (the density of this state is denoted by $u(a)$). This single forms new pairs with a rate $\rho(a)$, and since we have only very few infecteds in the population, the new partner is assumed to be susceptible. Let $q(a)$ be the density of pairs of the primary infected with a susceptible person. These pairs may either split again with rate $\sigma_1(a)$ or the primary infected may infect his/her partner

with rate $\kappa(a)$. There is only one more process of interest for the definition of R_0 : infected individuals die with a rate $\bar{\mu}(a)$ while uninfected die with rate μ (see Figure 2).

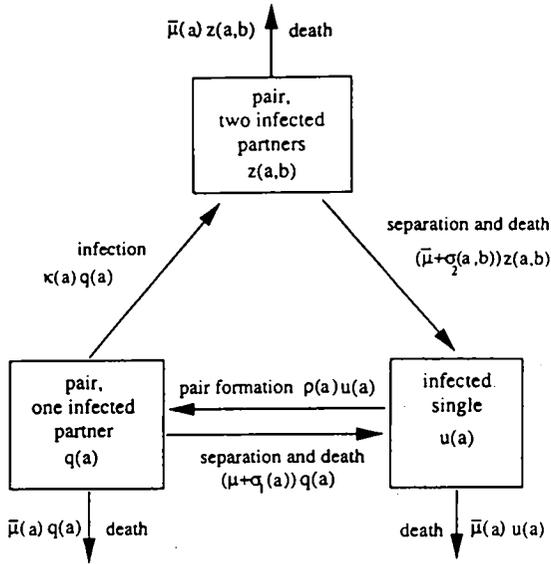


Figure 2: Transitions of the primary infected individual

The equations describing this system read

$$\left. \begin{aligned} \partial_a u &= -(\bar{\mu}(a) + \rho(a))u + (\mu + \sigma_1(a))q + \int_0^\infty (\bar{\mu}(b) + \sigma_2(a, b))z(t, a, b) db \\ \partial_a q &= \rho(a)u - (\mu + \bar{\mu}(a) + \sigma_1(a) + \kappa(a))q \\ (\partial_a + \partial_b)z &= -(\bar{\mu}(a) + \bar{\mu}(b) + \sigma_2(a, b))z \\ u(0) &= 0, q(0) = 0, z(a, 0) = \kappa(a)q(a), z(0, b) = \varphi(b). \end{aligned} \right\}$$

Hence the next generation operator can be expressed in terms of the function q as

$$A[\varphi(\cdot)](a) = z(a, 0) = \kappa(a)q(a).$$

R_0 is the spectral radius of A . Now we assume σ_2 and $\bar{\mu}$ to be constant. Following [13], we define

$$\eta(a) = \int_0^\infty z(a, b) db.$$

Integrating the system above with respect to b we obtain

$$\left. \begin{aligned} \partial_a u &= -(\bar{\mu} + \rho(a))u + (\mu + \sigma_1(a))q + (\bar{\mu} + \sigma_2)\eta(t, a) \\ \partial_a q &= \rho(a)u - (\mu + \bar{\mu} + \sigma_1(a) + \kappa(a))q \\ \partial_a \eta &= \kappa(a)q - (2\bar{\mu} + \sigma_2)\eta \\ u(0) &= 0, q(0) = 0, \eta(0) = 1. \end{aligned} \right\} \quad (1)$$

Here the number of secondary cases does not depend any more on the special shape of φ . Thus, R_0 is equal to $\int_0^\infty A[\varphi(\cdot)](a) da$, i.e. to the number of passages from q to η ,

$$R_0 = \int_0^\infty \kappa(a)q(a) da. \tag{2}$$

Until now we have considered the case where, in the absence of disease, the population remains constant. The system can be easily adapted to an exponentially growing population. Formally, the growth rate $\hat{\lambda}$ enters as an additional mortality (washout effect) [12]. The exponent $\hat{\lambda}$ depends on the present parameters and on the birth rate, which is not specified here. We define

$$B_0 = (e_3 - e_2)e_2^T \tag{3}$$

$$A_0(a) = \begin{pmatrix} -(\bar{\mu} + \rho(a) + \hat{\lambda}) & \mu + \sigma_1(a) & \bar{\mu} + \sigma_2 \\ \rho(a) & -(\bar{\mu} + \mu + \sigma_1(a) + \hat{\lambda}) & 0 \\ 0 & 0 & -(2\bar{\mu} + \sigma_2 + \hat{\lambda}) \end{pmatrix} \tag{4}$$

$$x(a) = (u(a), q(a), \eta(a))^T. \tag{5}$$

Then

$$\left. \begin{aligned} \frac{d}{da}x(a) &= (A_0(a) + \kappa(a)B_0(a))x(a) \\ x(0) &= (0, 0, 1)^T. \end{aligned} \right\} \tag{6}$$

Again, the reproduction number can be written in form (2).

3. Monotonicity results

We investigate the monotonicity of R_0 with respect to the infectivity function $\kappa(a)$. In terms of system (6) we have to investigate whether R_0 , given by (2), depends in a monotone way on the coefficient κ , where $q(a)$ depends on κ implicitly via equations (5) and (6).

Monotonicity of R_0 : We assume that the coefficients $\mu, \bar{\mu}, \rho, \sigma_1, \sigma_2$ are continuous bounded non-negative functions of the age since infection a . These functions and the exponent $\hat{\lambda}$ are fixed. The infectivity $\kappa = \kappa(a)$ is also a non-negative continuous bounded function but subject to variation. We indicate the dependence of R_0 on κ by writing $R_0[\kappa]$.

If two choices of $\kappa(a)$ are comparable, i.e. $\kappa_1(a) \leq \kappa_2(a)$, then one will conjecture that $R_0[\kappa_1] \leq R_0[\kappa_2]$. With some additional hypothesis this conjecture is true. Indeed, we get the following result.

Theorem 3.1. *Let the parameter functions $\mu, \bar{\mu}, \sigma_2, \rho$ be constant, and let $\bar{\mu} > \mu$. Then the reproduction number depends monotonously on κ , i.e. $\kappa_1(a) \leq \kappa_2(a)$ for all $a \geq 0$ implies $R_0[\kappa_1] \leq R_0[\kappa_2]$.*

Proof. The proof follows directly from the representation of the reproduction number (6) and (2) together with Theorem A.1 in Section 4 ■

The claim seems to be obvious, and, at first glance, also to hold in much more general scenarios. It is interesting to note that this theorem is not true any more, if the separation rate σ_2 really depends on the age since infection of both partners, $\sigma_2 = \sigma_2(a, b)$. We sketch the idea of a counter example.

Counter-example for monotonicity of R_0 (in the general case). We assume $\sigma_2(a, b) \equiv 0$ if $|a - b| \leq a_0$ for some $a_0 > 0$, σ_2 strictly positive otherwise. Thus, pairs with two infected partners, whose ages since infection do not differ too much, do not split at all. Other pairs split with a positive rate. If we now increase the infectivity in the age classes $a \leq a_0$, then an infected person is more likely to be "trapped" in a pair with $|a - b| \leq a_0$, i.e. he/she will not contribute to the reproduction number any more. It is possible to choose all other rates in such a manner, that this mechanism decreases R_0 if κ is increased in the interval $[0, a_0)$.

This counterexample shows that it is appropriate to distinguish between the biological infectivity $\kappa(a)$ and the effective infectivity $\kappa(a)q(a)$. While the first describes the infectivity at time since infection a under the condition that an infected person is paired with a susceptible individual, the latter weighs this biological infectivity by the probability to be in a pair with a susceptible individual. In general, the reproduction number does not depend in a monotone way on the (biological) infection rate $\kappa(a)$, but it is a monotone function of the effective infection rate. The latter takes into account social behaviour, in the present case pair formation.

4. Appendix: Monotonicity in systems of ordinary differential equations

Here we show a general theorem on cyclic chains of non-autonomous linear differential equations from which the desired monotonicity result follows.

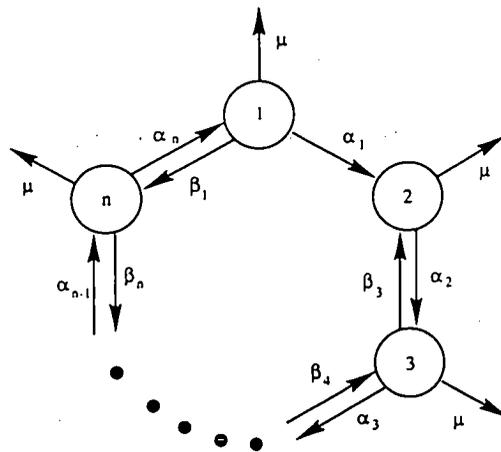


Figure 3: The structure of the system

Problem (P): We consider a linear, time-dependent system of differential equations with cyclic structure (see Figure 3)

$$\left. \begin{aligned} \dot{z}_1 &= -(\mu(t) + \alpha_1(t) + \beta_1(t))z_1 + \alpha_n(t)z_n \\ \dot{z}_2 &= -(\mu(t) + \alpha_2(t))z_2 + \alpha_1(t)z_1 + \beta_3(t)z_3 \\ \dot{z}_3 &= -(\mu(t) + \alpha_3(t) + \beta_3(t))z_3 + \alpha_2(t)z_2 + \beta_4(t)z_4 \\ &\vdots \\ \dot{z}_{n-1} &= -(\mu(t) + \alpha_{n-1}(t) + \beta_{n-1}(t))z_{n-1} + \alpha_{n-2}(t)z_{n-2} + \beta_n(t)z_n \\ \dot{z}_n &= -(\mu(t) + \alpha_n(t) + \beta_n(t))z_n + \alpha_{n-1}(t)z_{n-1} + \beta_1(t)z_1 \end{aligned} \right\}$$

and initial condition

$$z_j(0) = x_j^0 \geq 0 \quad (j = 1, \dots, n).$$

Formally, we define $\beta_2 = 0$. Then, we introduce $\xi_j = \alpha_j + \beta_j$, the matrix

$$A(t) = \begin{pmatrix} -\xi_1 & \beta_2 & 0 & 0 & \cdots & 0 & 0 & \alpha_n \\ \alpha_1 & -\xi_2 & \beta_3 & 0 & \cdots & 0 & 0 & 0 \\ 0 & \alpha_2 & -\xi_3 & \beta_4 & \cdots & 0 & 0 & 0 \\ & & & & \vdots & & & \\ 0 & 0 & 0 & 0 & \cdots & \alpha_{n-2} & -\xi_{n-1} & \beta_n \\ \beta_1 & 0 & 0 & 0 & \cdots & 0 & \alpha_{n-1} & -\xi_n \end{pmatrix}$$

and the vectors $z = (z_1, \dots, z_n)^T$ and $x^0 = (x_1^0, \dots, x_n^0)^T$. The system reads

$$\left. \begin{aligned} \dot{z}(t) &= (A(t) - \mu(t)I)z(t) \\ z(0) &= x^0. \end{aligned} \right\}$$

We assume that

$$\alpha_j, \beta_j, \mu \in C^0(\mathbb{R}_+) \quad \text{with } \alpha_j(t), \beta_j(t) \geq 0 \text{ and } \mu(t) \geq \underline{\mu} > 0$$

and ask whether the integral

$$\int_0^\infty \alpha_1(t)z_1(t) dt$$

depends monotonously on the parameter functions α_j and β_j . Note that always $\beta_2 = 0$.

We can shift the mortality μ from the differential equations into the integral. Let

$$x_j(t) = e^{\int_0^t \mu(\tau) d\tau} z_j(t) \quad \text{and} \quad x(t) = e^{\int_0^t \mu(\tau) d\tau} z(t).$$

Then

$$\left. \begin{aligned} \dot{x}(t) &= A(t)x(t) \\ x(0) &= x^0 \end{aligned} \right\}$$

and

$$\int_0^\infty \alpha_1(t)z_1(t) dt = \int_0^\infty \alpha_1(t)x_1(t)e^{-\int_0^t \mu(\tau) d\tau} dt.$$

Now we formulate our central theorem that establishes the monotone dependency of this integral on the parameter functions α_j and β_j .

Theorem A.1. Consider the system defined in Problem (P) in two copies. For the first copy, assume the parameter functions $(\alpha_j, \beta_j) = (\bar{\alpha}_j, \bar{\beta}_j)$ which correspond to the matrix \bar{A} and the solution $x_j = \bar{x}_j$, while in the second copy the parameter functions are $(\alpha_j, \beta_j) = (\tilde{\alpha}_j, \tilde{\beta}_j)$ with matrix \tilde{A} and solution $x_j = \tilde{x}_j$. The initial conditions are for both copies the same, $\bar{x}_j(0) = \tilde{x}_j(0) = x_j^0$, i.e.

$$\left. \begin{aligned} \dot{\bar{x}} &= \bar{A} \bar{x} \\ \bar{x}(0) &= x^0 \end{aligned} \right\} \quad \text{and} \quad \left. \begin{aligned} \dot{\tilde{x}} &= \tilde{A} \tilde{x} \\ \tilde{x}(0) &= x^0 \end{aligned} \right\}.$$

Furthermore, assume

$$\bar{\alpha}_j(t) \geq \tilde{\alpha}_j(t) \quad \text{and} \quad \bar{\beta}_j(t) \leq \tilde{\beta}_j(t). \tag{7}$$

Then

$$\int_0^\infty \bar{\alpha}_1(t) \bar{x}_1(t) e^{-\int_0^t \mu(\tau) d\tau} dt \geq \int_0^\infty \tilde{\alpha}_1(t) \tilde{x}_1(t) e^{-\int_0^t \mu(\tau) d\tau} dt, \tag{8}$$

i.e. this integral depends monotonously on the parameter functions α_i and β_i .

Remark A.2. For such monotonicity assertions as stated above to hold it seems to be necessary that the network has the described cyclic topology. Otherwise, one can construct situations where one particle “overtakes” another particle. This mechanism destroys the monotonicity. From similar reasons, also $\beta_2 \equiv 0$ is required.

We will prove this theorem step by step in the following propositions.

Proposition A.3. Inequality (8) holds for general \bar{x} and \tilde{x} if and only if

$$\int_0^T \bar{\alpha}_1(t) \bar{x}_1(t) e^{-\int_0^t \mu(\tau) d\tau} dt \geq \int_0^T \tilde{\alpha}_1(t) \tilde{x}_1(t) e^{-\int_0^t \mu(\tau) d\tau} dt \tag{9}$$

holds for all coordinate vectors $x^0 = e_{j_0}$ ($j_0 = 1, \dots, n$) and all $T > 0$.

Proof. The proof is evident because of the linear structure of the problem, since the e_{j_0} ($j_0 = 1, \dots, n$) generate \mathbb{R}_+^n and since T is arbitrarily chosen ■

In the next propositions we return to the notations of Problem (P). First we discretise the system with an Euler scheme and obtain a special representation of the approximation of the solution and of integrals (9). Using this representation, the desired monotonicity will be proven.

Proposition A.4. Let $T > 0$ and

$$h < h_0 := \max \left\{ \alpha_j(t) + \beta_j(t) \mid t \in [0, T] \text{ and } j = 1, \dots, n \right\}.$$

Define N as the greatest integer with $Nh < T$, and for $i = 0, \dots, N$ and $j = 1, \dots, n$ let

$$t_i = hi, \quad \alpha_j^i = \alpha_j(t_i), \quad \beta_j^i = \beta_j(t_i), \quad m^i = e^{-\int_0^{t_i} \mu(\tau) d\tau}, \quad A^i = A(t_i).$$

Define the Euler approximation scheme for the solution x by

$$\left. \begin{aligned} B^i &= I + hA^i = ((b_{j,j'}^i))_{j,j'=1,\dots,n} \\ x^0 &= x(0) \\ x^{i+1} &= B^i x^i \quad (i = 0, \dots, N-1). \end{aligned} \right\} \quad (10)$$

Let x_j^i be the j 'th component of the vector x^i . The integrals (9) are monotone in the parameter functions, if the sum

$$\Sigma := \sum_{i=0}^{N-1} h\alpha_1^i x_1^i m^i \quad (11)$$

is monotone for all $h < h_0$ and $T > 0$.

Proof. Since the parameter functions are assumed to be smooth, the Euler approximations converge to the solution for $h \rightarrow 0$, and also the sum Σ tends to the corresponding integral. Hence, if this sum depends monotonously on the parameter functions, then also the integral ■

We consider a sequence that mimics a non-stationary, time discrete random walk with n states. The states are represented by the numbers j or, equivalently, by the unit vectors e_j . Since the network is cyclic, the index j is always to be taken as $j \bmod n$. The transition probability in the i 'th time step for $j \mapsto j+1 \bmod n$ is given by $h\alpha_j^i$, and $h\beta_j^i$ for $j \mapsto j-1 \bmod n$. The superscript i denotes the time step. Note that the following construction only *mimics* the stochastic process, it is fully deterministic. For every state $j = 1, \dots, n$ and every time step $i = 0, \dots, N-1$ we define a variable $\theta_j^i \in [0, 1]$. In a stochastic formulation, the variables θ_j^i would be random variables which are uniformly distributed in $[0, 1]$. Assume that the particle is in state j in time step i . Then the deterministic rule

if $\theta_j^i \in [0, h\beta_j^i) = [0, b_{j,j-1}^i)$, then jump to state $(j-1) \bmod n$

if $\theta_j^i \in [h\beta_j^i, 1 - h\alpha_j^i) = [b_{j,j-1}^i, b_{j,j-1}^i + b_{j,j}^i)$, then stay in state j

if $\theta_j^i \in [1 - h\alpha_j^i, 1) = [b_{j,j-1}^i + b_{j,j}^i, 1)$

$= [b_{j,j-1}^i + b_{j,j}^i, b_{j,j-1}^i + b_{j,j}^i + b_{j,j+1}^i)$, then jump to state $(j+1) \bmod n$

follows. In the following, the indices j, j', j'' always denote numbers mod n , in particular $j \pm 1 \equiv (j \pm 1) \bmod n$. Define the abbreviations $u_j^i = b_{j,j}^i$ and $v_j^i = b_{j,j-1}^i + b_{j,j}^i$.

Definition A.5. Let

$$\theta^i = (\theta_1^i, \dots, \theta_n^i) \in [0, 1]^n =: \Pi \quad (i = 0, \dots, N-1)$$

and $\vartheta = (\vartheta^0, \vartheta^1, \dots, \vartheta^{N-1}) \in \Pi^N$. With each $\vartheta \in \Pi^N$ associate a sequence

$$y[\vartheta] = (y^0[\vartheta], \dots, y^N[\vartheta]) \quad (y^i \in \{e_1, \dots, e_n\} \quad (i = 0, \dots, N))$$

given by the following recursive definition $y^0[\vartheta] = e_{j_0}$ and

$$y^{i+1}[\vartheta] = \sum_{j=1}^n (e_j^T y^i[\vartheta]) \left(e_{j-1} \chi_{[0, u_j^i)}(\theta_j^i) + e_j \chi_{[u_j^i, v_j^i)}(\theta_j^i) + e_{j+1} \chi_{[v_j^i, 1)}(\theta_j^i) \right).$$

The sequences $y[\vartheta]$ have the same distribution as the original stochastic jump process, in particular, the "mean value" $\int_{\vartheta \in \Pi^N} y[\vartheta] d\vartheta$ satisfies equation (10).

Lemma A.6. *The variable x^i can be represented as*

$$x^i = \int_{\vartheta \in \Pi^N} y^i[\vartheta] d\vartheta \quad (i = 0, \dots, N). \quad (12)$$

Proof. The proof uses induction. For $i = 0$, $y^i[\vartheta]$ does not depend on ϑ , thus

$$\int_{\vartheta \in \Pi^N} y^0[\vartheta] d\vartheta = \int_{\vartheta \in \Pi^N} x^0 d\vartheta = x^0.$$

Assume that (12) has been proven for $i = 0, \dots, l-1 < N$. We show that the representation is also valid for $i = l$. Still, j and $j \pm 1$ are taken mod n ,

$$\begin{aligned} & \int_{\vartheta \in \Pi^N} y^l[\vartheta] d\vartheta \\ &= \int_{(\theta^0, \dots, \theta^{l-1}) \in \Pi^l} y^l[\vartheta] d(\theta^0, \dots, \theta^{l-1}) \\ &= \int_{(\theta^0, \dots, \theta^{l-2}) \in \Pi^{l-1}} \int_{(\theta_1^{l-1}, \dots, \theta_n^{l-1}) \in \Pi} y^l[\vartheta] d(\theta_1^{l-1}, \dots, \theta_n^{l-1}) d(\theta^0, \dots, \theta^{l-2}) \\ &= \int_{(\theta^0, \dots, \theta^{l-2}) \in \Pi^{l-1}} \int_{(\theta_1^{l-1}, \dots, \theta_n^{l-1}) \in \Pi} \sum_{j=1}^n e_j^T y^{l-1}[\vartheta] \\ & \quad \times \left(e_{j-1} \chi_{[0, u_j^{l-1})}(\theta_j^{l-1}) + e_j \chi_{[u_j^{l-1}, v_j^{l-1})}(\theta_j^{l-1}) + e_{j+1} \chi_{[v_j^{l-1}, 1]}(\theta_j^{l-1}) \right) \\ & \quad \times d(\theta_1^{l-1}, \dots, \theta_n^{l-1}) d(\theta^0, \dots, \theta^{l-2}) \\ &= \int_{(\theta^0, \dots, \theta^{l-2}) \in \Pi^{l-1}} \sum_{j=1}^n \left(b_{j,j-1}^{l-1} e_{j-1} + b_{j,j}^{l-1} e_j + b_{j,j+1}^{l-1} e_{j+1} \right) e_j^T y^{l-1}[\vartheta] d(\theta^0, \dots, \theta^{l-2}) \\ &= \int_{(\theta^0, \dots, \theta^{l-2}) \in \Pi^{l-1}} B^{l-1} y^{l-1}[\vartheta] d(\theta^0, \dots, \theta^{l-2}) \\ &= B^{l-1} \int_{\vartheta \in \Pi^N} y^{l-1}[\vartheta] d\vartheta \\ &= B^{l-1} x^{l-1} \\ &= x^l \end{aligned}$$

and the statement is proven \blacksquare

The following lemma says that the sum Σ defined in (11) can be interpreted as the number of passages from state 1 to state 2 weighted by m^i .

Lemma A.7. *The sum Σ can be represented in terms of the sequences $y[\vartheta]$ as*

$$\Sigma = \int_{\vartheta \in \Pi^N} \sum_{i=0}^{N-1} m^i (e_1^T y^i[\vartheta]) (e_2^T y^{i+1}[\vartheta]) d\vartheta. \quad (13)$$

Proof. The sum Σ can be written as

$$\begin{aligned}\Sigma &= \sum_{i=0}^{N-1} h \alpha_1^i x_1^i m^i \\ &= \sum_{i=0}^{N-1} b_{j,j+1}^i (e_j^T x^i) m^i \Big|_{j=1} \\ &= \sum_{i=0}^{N-1} m^i \int_{(\theta^0, \dots, \theta^{i-1}) \in \Pi^i} b_{j,j+1}^i (e_j^T y^i[\vartheta]) d(\theta^0, \dots, \theta^{i-1}) \Big|_{j=1}.\end{aligned}$$

Furthermore, we obtain

$$\begin{aligned}b_{j,j+1}^i (e_j^T y^i[\vartheta]) &= e_{j+1}^T \left(\sum_{j',j''=1}^n e_{j''} b_{j',j''}^i (e_{j'}^T y^i[\vartheta]) \right) (e_j^T y^i[\vartheta]) \\ &= e_{j+1}^T \left(\sum_{j''=1}^n e_{j''} b_{j,j''}^i (e_{j''}^T y^i[\vartheta]) \right) (e_j^T y^i[\vartheta]) \\ &= (e_{j+1}^T B^i y^i[\vartheta]) (e_j^T y^i[\vartheta]) \\ &= e_{j+1}^T \left(\int_{\theta^i \in \Pi} y^{i+1}[\vartheta] d\theta^i \right) (e_j^T y^i[\vartheta]),\end{aligned}$$

and thus

$$\begin{aligned}\Sigma &= \sum_{i=0}^{N-1} m^i \int_{(\theta^0, \dots, \theta^i) \in \Pi^i} (e_j^T y^i[\vartheta]) (e_{j+1}^T y^{i+1}[\vartheta]) d(\theta^0, \dots, \theta^i) \Big|_{j=1} \\ &= \int_{\vartheta \in \Pi^N} \sum_{i=0}^{N-1} m^i (e_1^T y^i[\vartheta]) (e_2^T y^{i+1}[\vartheta]) d\vartheta.\end{aligned}$$

Thus the statement is proven ■

Now we go back to the two copies of our original system, $\dot{\bar{x}} = \bar{A}\bar{x}$ and $\dot{\tilde{x}} = \tilde{A}\tilde{x}$, $\bar{x}(0) = \tilde{x}(0) = e_{j_0}$. We will refer to the system with “bar” as system 1 and to that with “tilde” as system 2. All the variables occurring in Remark A.2 and Lemma A.7 now are used with bar or tilde. From (7) we have $\bar{\alpha}_j^i \geq \tilde{\alpha}_j^i$ and $\bar{\beta}_j^i \leq \tilde{\beta}_j^i$.

In the next proposition we consider the sequence $y[\vartheta]$ for a fixed $\vartheta \in \Pi^N$. We define a counter $C(i)$ depending on time step i . This variable counts the signed passages that a particle undergoes (signed does mean that the counter is decreased if a particle steps back). Whereas $C(i) \bmod n$ gives information on the state in particular, $C(i)$ itself contains informations on the signed number of full cycles the particle has performed. In the present case, due to $\beta_2 = 0$, there are no full cycles backward.

We show, for any given time step i , that the number of passages from state 1 to state 2 in system 2 does not exceed the number of passages between these two states in system 1.

Proposition A.8. Let $\bar{\alpha}_j^i \geq \tilde{\alpha}_j^i$, $\bar{\beta}_j^i \leq \tilde{\beta}_j^i$ and $\vartheta \in \Pi^N$ fixed. Define $\bar{C}(i)$ as a counter that is increased at a passage $e_j \rightarrow e_{j+1}$ and decreased at a passage $e_j \rightarrow e_{j-1}$,

$$\bar{C}(0) = j_0, \quad \bar{C}(i+1) = \begin{cases} \bar{C}(i) + 1 & \text{for } \bar{y}^i[\vartheta] = e_j, \bar{y}^{i+1}[\vartheta] = e_{j+1} \\ \bar{C}(i) & \text{for } \bar{y}^i[\vartheta] = e_j, \bar{y}^{i+1}[\vartheta] = e_j \\ \bar{C}(i) - 1 & \text{for } \bar{y}^i[\vartheta] = e_j, \bar{y}^{i+1}[\vartheta] = e_{j-1} \end{cases}$$

(hence, $\bar{y}^i[\vartheta] = e_{\bar{C}(i) \bmod n}$). Let $\tilde{C}(i)$ be the same counter for system 2. Then $\bar{C}(i) \geq \tilde{C}(i)$ for $i = 0, \dots, N$.

Proof. Assume $\bar{C}(l) < \tilde{C}(l)$ for some $l \in \{1, \dots, N\}$. Without restriction, let l be the first number with this property, i.e. $\bar{C}(l-1) = \tilde{C}(l-1)$. Thus at time $l-1$ both sequences $\bar{y}[\vartheta]$ and $\tilde{y}[\vartheta]$ are in the same state, $\bar{y}^{l-1}[\vartheta] = \tilde{y}^{l-1}[\vartheta] = e_j$, and in the next step either \bar{y} steps back while $\tilde{y}[\vartheta]$ stays or steps forward, or \bar{y} steps back or stays and $\tilde{y}[\vartheta]$ steps forward.

Since $\bar{\alpha}_j^i \geq \tilde{\alpha}_j^i$ and $\bar{\beta}_j^i \leq \tilde{\beta}_j^i$, we obtain

$$\begin{aligned} \bar{b}_{j,j-1}^{l-1} &= h\bar{\beta}_j^{l-1} \leq h\tilde{\beta}_j^{l-1} = \tilde{b}_{j,j-1}^{l-1} \\ \bar{b}_{j,j-1}^{l-1} + \bar{b}_{j,j}^{l-1} &= 1 - h\bar{\alpha}_j^{l-1} \leq 1 - h\tilde{\alpha}_j^{l-1} = \tilde{b}_{j,j-1}^{l-1} + \tilde{b}_{j,j}^{l-1}. \end{aligned} \tag{14}$$

Case 1: $\bar{y}^l[\vartheta] = e_{j-1}$ and $\tilde{y}^l[\vartheta] \in \{e_j, e_{j+1}\}$. Hence $\theta_j^i < \bar{b}_{j,j-1}^{l-1}$ and $\theta_j^i \geq \tilde{b}_{j,j-1}^{l-1}$. These inequalities contradict (14).

Case 2: $\bar{y}^l[\vartheta] \in \{e_{j-1}, e_j\}$ and $\tilde{y}^l[\vartheta] = e_{j+1}$. Hence $\theta_j^i < \bar{b}_{j,j-1}^{l-1} + \bar{b}_{j,j}^{l-1}$ and $\theta_j^i \geq \tilde{b}_{j,j-1}^{l-1} + \tilde{b}_{j,j}^{l-1}$. Also these inequalities contradict (14) ■

From this proposition we get the monotonicity of Σ .

Proposition A.9. Let $\bar{\alpha}_j^i \geq \tilde{\alpha}_j^i$ and $\bar{\beta}_j^i \leq \tilde{\beta}_j^i$. Then

$$\sum_{i=0}^{N-1} m^i (e_1^T \bar{y}^i[\vartheta]) (e_2^T \bar{y}^{i+1}[\vartheta]) \geq \sum_{i=0}^{N-1} m^i (e_1^T \tilde{y}^i[\vartheta]) (e_2^T \tilde{y}^{i+1}[\vartheta]).$$

Proof. For system 1, passages from e_1 to e_2 occur, if

$$\exists \omega \in \mathbb{N}: \quad \omega \bmod n = 1, \quad \bar{C}(i) = \omega, \quad \bar{C}(i+1) = \omega + 1.$$

Now we inspect those time steps \bar{k}_l or \tilde{k}_l , respectively, where the system changes from state 1 to state 2, in other words, when the counter \bar{C} or \tilde{C} changes from ω to $\omega + 1$, where $\omega \bmod n = 1$, i.e. $\omega = ln + 1$. For system 1 and system 2 let \bar{L} and \tilde{L} , respectively, the number of these passages. Since $\bar{C}(i) \geq \tilde{C}(i)$, and since $\bar{C}(\bar{k}_l)$ and $\tilde{C}(\tilde{k}_l)$ are strictly monotone in l , we have $\bar{k}_l \leq \tilde{k}_l$ for $l = 0, \dots, \min\{\bar{L}, \tilde{L}\} = \tilde{L}$. Thus

$$\sum_{i=0}^{N-1} m^i (e_1^T \bar{y}^i[\vartheta]) (e_2^T \bar{y}^{i+1}[\vartheta]) = \sum_{i=0}^{\bar{L}} m^{\bar{k}_i} \leq \sum_{i=0}^{\tilde{L}} m^{\tilde{k}_i} = \sum_{i=0}^{N-1} m^i (e_1^T \tilde{y}^i[\vartheta]) (e_2^T \tilde{y}^{i+1}[\vartheta])$$

and the statement is proven ■

Proof of Theorem A.1. The proof is now an immediate consequence of Proposition A.9 and Lemma A.7 ■

References

- [1] Bailey, N.: *The Mathematical Theory of Infectious Diseases and its Applications*. London: Charles Griffin & Co. Ltd 1975.
- [2] Blythe, S., Castillo-Chavez, C., Palmer, J. and M. Cheng: *Toward a unified theory of sexual mixing and pair formation*. *Math. Biosc.* 107 (1991), 376 – 405.
- [3] Busenberg, S. N. and K. P. Haderler: *Demography and epidemics*. *Math. Biosc.* 101 (1990), 63 – 74.
- [4] Diekmann, O., De Jong, M., De Koeijer, A. and P. Reijnders: *The force of infection in populations of varying size: a modelling problem*. *J. Biol. Syst.* 3 (1995), 519 – 529.
- [5] Diekmann, O., Dietz, K. and J. Heesterbeek: *The basic reproduction ratio for sexually transmitted diseases*. Part I: *Theoretical considerations*. *Math. Biosc.* 107 (1991), 325 – 339.
- [6] Diekmann, O., Heesterbeek, J. and J. Metz: *On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations*. *J. Math. Biol.* 28 (1990), 365 – 382.
- [7] Dietz, K.: *Transmission and control of arbovirus diseases*. In: *Epidemiology* (ed.: K. Cooke). Philadelphia: SIAM 1975, pp. 104 – 121.
- [8] Dietz, K. and K. P. Haderler: *Epidemiological models for sexually transmitted diseases*. *J. Math. Biol.* 26 (1988), 1 – 25.
- [9] Dietz, K., Heesterbeek, J. and D. Tudor: *The basic reproduction ratio for sexually transmitted diseases*. Part 2: *Effects of variable HIV infectivity*. *Math. Biosc.* 117 (1993), 35 – 47.
- [10] Dietz, K. and D. Schenzle: *Proportionate mixing models for age-dependent infection transmission*. *J. Math. Biol.* 22 (1985), 117 – 120.
- [11] Greenhalgh G.: *Vaccination campaigns for common childhood diseases*. *Math. Biosc.* 100 (1990), 201 – 240.
- [12] Haderler, K. P.: *Periodic solutions of homogeneous equations*. *J. Diff. Equ.* 95 (1992), 183 – 202.
- [13] Haderler, K. P.: *Structured population models for HIV infection. Pair formation and non-constant infectivity*. In: *AIDS Epidemiology: Methodological Issues* (eds.: N. P. Jewell et al.). Boston: Birkhäuser 1992, pp. 156 - 173.
- [14] Haderler, K. P. and C. Castillo-Chavez: *A core group model for disease transmission*. *Math. Biosc.* 128 (1995), 41 – 55.
- [15] Haderler, K. P. and K. Ngoma: *Homogeneous models for sexually transmitted diseases*. *Rocky Mountain J. Math.* 20 (1990), 967 – 985.
- [16] Haderler, K. P. and P. van den Driessche: *Backward bifurcation in epidemic control*. *Math. Biosc.* 146 (1997), 15 – 35.
- [17] Haderler, K. P., Waldstätter, R. and A. Wörz-Busekros: *Models for pair formation in bisexual populations*. *J. Math. Biol.* 26 (1988), 635 – 649.
- [18] Hethcote, H. W.: *Qualitative analysis of communicable disease models*. *Math. Biosc.* 28 (1976), 335 – 356.
- [19] Kendall, D.: *Stochastic processes and population growth*. *Royal Stat. Soc. (Ser. B2)* 11 (1949), 230 – 264.
- [20] Kermack, W. and A. McKendrick: *A contribution to the mathematical theory of epidemics*. *Proc. Roy. Soc. (Ser. A)* 115 (1927), 700 – 721; reprinted in: *Applicable Mathematics of*

Nonphysical Phenomena (eds.: G. Oliveira-Pinto and B. W. Conolly). Chichester: Ellis Horwood 1982, pp. 222 - 247.

- [21] Kretzschmar, M. and K. Dietz: *The effect of pair formation and variable infectivity on the spread of an infection without recovery*. Math. Biosc. 148 (1998), 83 - 113.
- [22] Müller, J. and K. P. Hadeler: *Variable infectivity in sexually transmitted diseases*. Dynamik, Analysis, effiziente Simulation und Ergodentheorie (DANSE), Preprint 2/97, Tübingen 1997.
- [23] Novak, M., Anderson, R., McLean, A., Wolfs, T., Goudsmit, J. and R. May: *Antigenic diversity threshold and the development of AIDS*. Science 254 (1991), 963 - 969.
- [24] Novak, M. and R. May: *Mathematical biology of HIV-infection: Antigenic variation and diversity threshold*. Math. Biosc. 106 (1991), 1 - 21.
- [25] Pantaleo, G., Graziosi, C. and A. Fauci: *The immunopathogenesis of human immunodeficiency virus infection*. N. Engl. J. Med. 328 (1993), 327 - 335.
- [26] Stilianakis, N., Dietz, K. and D. Schenzle: *On the antigenic diversity threshold models for AIDS*. Math. Biosc. 121 (1994), 235 - 247.
- [27] Stilianakis, N., Schenzle, D. and K. Dietz: *Analysis of a model for the pathogenesis of AIDS*. Math. Biosc. 145 (1997), 27 - 46.

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