Competitive Exclusion In Gonorrhea Models And Other Sexually-Transmitted Diseases

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ABSTRACT

A heterosexually active population is exposed to two competing strains or two distinct sexually-transmitted pathogens. It is assumed that a host cannot be invaded simultaneously by both disease agents and that when symptoms appear, a function of the pathogen or strain virulence, individuals recover. We conclude that in a behaviorally and genetically homogeneous population coexistence is not possible but under very special circumstances. The mathematical qualitatively analysis of our model is complete; that is, we provide a global stability analysis of the stationary states. We conclude this manuscript with two extensions. The first allows for the possibility that a host may face multiple competing strains while the second looks at the effects on coexistence of the host's age-of-infection when two strains compete for the same host.

1. Introduction

The formulation of the first gonorrhea model by Cooke and Yorke (1973) instigated the use of differential equation models to study the transmission dynamics and control of sexually-transmitted diseases (STDs). However, the use of differential equations for models for STDs goes back to Ross who, in 1911, introduced the first differential equation model for the transmission dynamics of vector-transmitted diseases. Ross' modeling work was motivated by his attempts to develop management strategies for the control of malaria, a disease that is transmitted as part of the life cycle of the *Plasmodium* parasite. The life cycle of this parasite requires, at different stages, human and vector hosts for its completion. Humans can only become infected by being bitten by an infected vector (female mosquitoes) and vectors can only become infected by biting infected humans. Ross' contributions to the understanding of the malaria life cycle were rewarded with a Nobel prize in medicine.

Ross made a series of observations that became important components in the modeling of vector- and sexually-transmitted diseases including the fact that the average total rate of contacts between host and vectors must be conserved (Ross, 1911, p.667). This simple conservation law has become the basis for modeling heterogeneous contact structures (Busenberg and Castillo-Chavez, 1989, 1991; Castillo-Chavez and Busenberg, 1991). In this manuscript, the conservation of contacts law takes its simplest form as we are dealing with a gender specific homogeneously mixing population. Ross' contributions were extensive and deserved to be credited in this setting as he explicitly recognized that STDs could be modeled in the same way as vector-transmitted diseases (Ross, 1911, p.678). Furthermore, he was aware

of the role of frequency dependent dynamics and, consequently, he did not restrict his work to situations were the interacting subpopulations did not change (Ross, 1911, p.678; see also Lotka's review of Ross' work, 1923). The assumption that the sizes of interacting populations were constant and not dynamic variables became an important but limiting component in the modeling of sexually-transmitted diseases (Lajmanovich and Yorke, 1976; Hethcote and Yorke, 1984; and references therein). Variable population size significantly affects the qualitative dynamics of epidemic models (Castillo-Chavez et al., 1989a; Huang et al., 1992). In fact, it is a key ingredient in the study of the effects of social dynamics in disease transmission. In the models discussed in this article, the population under consideration does not experience disease induced mortality. Moreover, we assume that the total population size becomes asymptotically constant and, consequently, we implicitly assume that social dynamics does not affect the qualitative dynamics of our model (see Thieme, 1992; Castillo-Chavez and Thieme, 1993). This is a limiting assumption. However, our interest here is on the study of the dynamics of two strains that compete in a two-gender environment.

Biologists have long been concerned with the evolutionary interactions that result from changing host and pathogen populations. Continuous advances in biology and behavior have brought to the forefront of research the importance of their role in disease dynamics (Ewald, 1993). Varying levels of virulence may be due to pathogens' mode of transmission, their ability to survive outside the host, etc. Human behavior may also play a significant role in the evolution of virulence.

Host-vector interactions such as those observed in the myxoma-rabbit system challenge standard views of pathogen evolution while providing a fertile ground for

the study of coevolutionary interactions. If one sees hosts as patches that may be colonized by infectious pathogens the following questions arise: What are the possible outcomes of coevolutionary races where different strains of the same pathogen compete for the same patches/resource? What conditions are needed for a competitive exclusion? What happens if patches change; that is, what happens if a new breed of resistant patches develop? Mathematical models and systematic field studies have begun to yield useful new paradigms for the study of coevolutionary interactions (Anderson and May, 1982, 1991; Beck, 1984; Bremermann and Pickering, 1983; Bremermann and Thieme, 1989; Castillo-Chavez et al., 1988, 1989; Dietz, 1979; Dwyer et al., 1990; Fenner and Myers, 1978; Fenner and Ratcliffe, 1965; Levin, 1983a, 1983b; Levin and Pimentel, 1981; May and Anderson, 1983).

In this manuscript, we provide the global mathematical analysis of a simple but important case. We study a population of humans (the patches) who get exposed to two different strains of the same pathogen (gonorrhea and a strain of partially drug-resistant gonorrhea provide an appropriate system). We asked the question of whether or not coexistence is possible? We found out that coexistence of two competing strains is not possible regardless of initial conditions but in special and unrealistic circumstances. Our results are similar to those obtained by Bremerman and Thieme (1989) for SIR models with variable population size. Here, however, we provide the global analysis of a two-strain and two-sex SIS model while Bremerman and Thieme's model does not include the gender of the host.

Some generalizations are possible. Hence, we conclude this manuscript with the discussion of possible generalizations. Partial results are stated for a model that considers N-competing strains and for a model involving two competing strains in a

population structured by a strain-dependent age-of-infection. Our results are local but consistent with our global ones. The main conclusion is that in a population that is stratified only by gender and is exposed to two treatable and non-fatal sexually-transmitted pathogens, coexistence is not possible. Therefore, the observed coexistence must be due to behavioral and/or genetical factors, or to geographic isolation (small sexually-interacting networks), or to social dynamics.

This manuscript is organized as follows: Section 2 introduces our model and simplifies it using some recent results on asymptotically autonomous epidemic models (Castillo-Chavez and Thieme, 1993; Thieme, 1993); in Section 3, we compute the necessary thresholds and study the stability of the infection-free state; a principle of competitive exclusion for SIS models with homogeneous mixing is established in Section 4; some extensions and some partial results are given in Section 5; in Section 6 we discuss the consequences of our results and outline our future work.

2. Model Description and Preliminaries

We model a two-sex heterosexually-active population. The disease that guides the modelling is gonorrhea and, consequently, infectives recover after treatment. We further assume that the population is genetically and behaviorally homogeneous except for their gender. Hence, we use a susceptible-infective-susceptible model, that is, a homogeneously mixing two-sex SIS model. We use superscripts m and f to denote the male and female populations, respectively. We think of susceptible hosts as patches that are invaded or colonized by a pathogen. The assumption here is that once a patch has been colonized (infected), it cannot be invaded again. However, patches recover (that is, they get rid of the pathogen) and become again

equally susceptible to infection as the patches' immune system does not remember prior infections (models that incorporate cross-immunity have been developed, see Castillo-Chavez et al., 1988, 1989, and references therein). The infectives are divided into two groups: those infected with strain 1 and those infected with strain 2. The dynamics of the spread of the disease then are governed by

$$\begin{cases} \dot{S}^m = \Lambda^m - B^m - \mu S^m + \sum_{i=1}^{2} \gamma_i^m I_i^m, \\ \dot{I}_i^m = B_i^m - (\mu + \gamma_i^m) I_i^m, \\ \dot{S}^f = \Lambda^f - B^f - \mu S^f + \sum_{i=1}^{2} \gamma_i^f I_i^f, \\ \dot{I}_i^f = B_i^f - \left(\mu + \gamma_i^f\right) I_i^f, \end{cases} \tag{2.1}$$

where

$$B_i^m = c^m S^m \beta_i^f \frac{I_i^f}{T^f}, \qquad B_i^f = c^f S^f \beta_i^m \frac{I_i^m}{T^m},$$

$$B^m = \frac{c^m S^m}{T^f} \sum_{j=1}^{2} \beta_j^f I_j^f, \qquad B^f = \frac{c^f S^f}{T^m} \sum_{j} \beta_j^m I_j^m,$$

with the constraint

$$c^m T^m = c^f T^f. \tag{2.2}$$

Λ^k, $k = m, f$, denote the "recruitment" rates into the sexually active populations; μ is the natural death rate (which includes retirement from sexual activity); γ_i^k denote the rates of recovery (this includes the time that it takes to become symptomatic); c^k gives the average rate of partner acquisition per male or per female; and β_i^k denote the transmission rates of infection. The constraint given by (2.2) indicates that the total average contact rate of females equals the total average contact rate of males.

Since $T^k = S^k + \sum_{i=1}^{2} I_i^k$, (2.1) is equivalent to

$$\begin{cases} \dot{T}^m = \Lambda^m - \mu T^m, \\ \dot{T}^f = \Lambda^f - \mu T^f, \\ \dot{I}_i^m = -(\mu + \gamma_i^m) I_i^m + c^m \beta_i^f \dfrac{\left(T^m - \sum_{j=1}^{2} I_j^m\right) I_i^f}{T^f}, \\ \dot{I}_i^f = -\left(\mu + \gamma_i^f\right) I_i^f + c^f \beta_i^m \dfrac{\left(T^f - \sum_{j=1}^{2} I_j^f\right) I_i^m}{T^m}. \end{cases} \tag{2.3}$$

The equilibrium for T^k is

$$T^m = \frac{\Lambda^m}{\mu}, \qquad T^f = \frac{\Lambda^f}{\mu},$$

which, from the constraint (2.2), leads to

$$c^m \Lambda^m = c^f \Lambda^f.$$

The limiting system of (2.3) is

$$\begin{cases} \dot{I}_i^m = -(\mu + \gamma_i^m) I_i^m + \dfrac{\mu c^m \beta_i^f}{\Lambda^f} \left(\dfrac{\Lambda^m}{\mu} - \sum_{j=1}^{2} I_j^m\right) I_i^f, \\ \dot{I}_i^f = -\left(\mu + \gamma_i^f\right) I_i^f + \dfrac{\mu c^f \beta_i^m}{\Lambda^m} \left(\dfrac{\Lambda^f}{\mu} - \sum_{j=1}^{2} I_j^f\right) I_i^m. \end{cases} \tag{2.4}$$

The dynamics of (2.3) or (2.1) can be qualitatively determined by those of (2.4), (Castillo-Chavez and Thieme, 1993; Thieme, 1993). We will investigate (2.4) hereafter.

Set $\sigma_i^k = (\mu + \gamma_i^k)$, $a_i^m = \dfrac{\mu c^m \beta_i^f}{\Lambda^f}$, $a_i^f = \dfrac{\mu c^f \beta_i^m}{\Lambda^m}$, and $p^k = \dfrac{\Lambda^k}{\mu}$. System (2.4) can be rewritten as

$$\begin{aligned} \dot{I}_i^m &= -\sigma_i^m I_i^m + a_i^m \left(p^m - \sum_{j=1}^{2} I_j^m \right) I_i^f, \\ \dot{I}_i^f &= -\sigma_i^f I_i^f + a_i^f \left(p^f - \sum_{j=1}^{2} I_j^f \right) I_i^m. \end{aligned} \tag{2.5}$$

Define a subset of R_+^4 by

$$\Omega = \left\{ \left(I_1^m, I_1^f, I_2^m, I_2^f\right) \in \mathrm{R}_+^4; \quad \sum_{j=1}^{2} I_j^m \le p^m, \quad \sum_{j=1}^{2} I_j^f \le p^f \right\}.$$

Then, clearly, the flow generated by (2.5) is positively invariant on Ω.

Under a usual order, such a flow is not monotone. However, we can introduce a special order so that the flow generated by (2.5) becomes monotone.

Definition 2.1. *Let* $x = (x_1, x_2, x_3, x_4)^T \in \mathrm{R}^4$ *and* $K = \left\{x \in \mathrm{R}^4; x_1, x_2 \ge 0, x_3, x_4 \le 0\right\}$. *A type* K *order, denoted by* " $\le_K$ ", *is defined in such a way that*

$$x^0 \le_K x^1 \qquad \text{if and only if} \quad x^1 - x^0 \in K. \tag{2.6}$$

Using this order, we can show that the flow generated by (2.5) is monotone.

Theorem 2.2. *Let* $I = \left(I_1^m, I_1^f, I_2^m, I_2^f\right)^T$ *and let* $I(t, I_0)$ *be a solution of (2.5) with* $I(0, I_0) = I_0$. *Then*

$$I\left(t, I_0^a\right) \le_K I\left(t, I_0^b\right), \quad t \ge 0,$$

if $I_0^a, I_0^b \in \Omega$ *and* $I_0^a \le_K I_0^b$.

Proof. Let $Q = \mathrm{diag}(q_i)$ with $q_1 = q_2 = 1$, $q_3 = q_4 = -1$. The matrix $QJ(I)Q$ has nonnegative off-diagonal elements for every $I \in \Omega$, where $J(I)$ is the Jacobian

matrix of (2.5) evaluated at I. It follows from Lemma 2.1 in Smith (1988) that the flow $I(t, I_0)$ preserves a type K order on Ω, that is, the flow is monotone under a type K order.

The flow generated by (2.5) has many remarkable properties under the defined type K order. More details will be given in the following sections.

3. Thresholds

The concept of a threshold condition is one of the most important concepts in mathematical epidemiology. It determines whether an epidemic spreads or dies out in a population; that is, it addresses the question of invasion. Thresholds are usually characterized by the reproductive number (Diekmann et al., 1990; Heesterbeek, 1992) which usually determines the stability of the infection-free equilibrium of the epidemiological system, which is $\left(S^k > 0, I_i^k = 0\right)$ for (2.1) or (2.5).

We compute the reproductive number from the linearization of the model (2.5) around the infection-free equilibrium, that is, from the system

$$\begin{cases} \dot{I}_i^m = -\sigma_i^m I_i^m + a_i^m p^m I_i^f, \\ \dot{I}_i^f = -\sigma_i^f I_i^f + a_i^f p^f I_i^m. \end{cases} \tag{3.1}$$

Equations in (3.1) are decoupled. If

$$\sigma_i^m \sigma_i^f > a_i^m a_i^f p^m p^f, \qquad i = 1, 2,$$

the infection-free equilibrium is stable. If there exists an i, $1 \leq i \leq 2$, such that

$$\sigma_i^m \sigma_i^f < a_i^m a_i^f p^m p^f,$$

then the infection-free equilibrium is unstable.

We define the reproductive number, R_i, of the ith subgroup by

$$R_i = \frac{a_i^m a_i^f p^m p^f}{\sigma_i^m \sigma_i^f} = \frac{c^m c^f \beta_i^m \beta_i^f}{\left(\mu + \gamma_i^m\right)\left(\mu + \gamma_i^f\right)}. \tag{3.2}$$

Then, if $R_i < 1$, $\left(I_i^m, I_i^f\right) \to (0,0)$. Hence, if $R_i < 1$, for $i = 1$ and 2, the infection-free equilibrium is stable and the disease in the population goes extinct. However, if there exists at least one subgroup such that $R_i > 1$, then $\left(I_i^m, I_i^f\right) \not\to (0,0)$; that is, the disease spreads in the population. In fact, the infection-free equilibrium is globally stable if $R_i \leq 1$.

The following lemma is needed to show the global stability of the infection-free equilibrium and in the next sections.

Lemma 3.1. *Let* $E_1 = \left(I_1^m, I_1^f, 0, 0\right)^T$ *and* $E_2 = \left(0, 0, I_2^m, I_2^f\right)^T$ *be equilibria of (2.5), where* $I_i^m, I_i^f > 0$, *if* $R_i > 1$, *and* $I_i^m = I_i^f = 0$, *if* $R_i \leq 1$. *Let* $\xi^1 = \left(p^m, p^f, 0, 0\right)^T$ *and* $\xi^2 = \left(0, 0, p^m, p^f\right)^T$. *Then*

$$\lim_{t \to \infty} I\left(t, \xi^i\right) = E_i, \qquad i = 1, 2.$$

Proof. Notice that the subset

$$U := \left\{ I \in \Omega; \quad I_2^m = I_2^f = 0 \right\} \subseteq \Omega$$

is positively invariant under the flow $I(t, \cdot)$ and that $\xi^1 \in U$. It follows that

$$I\left(t, \xi^1\right) \in U, \quad t \geq 0.$$

That is, $I_2^m = I_2^f = 0$, $t \geq 0$, and I_1^m and I_1^f satisfy the following equations

$$\begin{cases} \dot{I}_1^m = -\sigma_1^m I_1^m + a_1^m \left(p^m - I_1^m\right) I_1^f, \\ \dot{I}_1^f = -\sigma_1^f I_1^f + a_1^f \left(p^f - I_1^f\right) I_1^m, \end{cases} \tag{3.3}$$

with the initial condition

$$I_1^m(0) = p^m, \qquad I_2^f(0) = p^f. \tag{3.4}$$

System (3.3) is a special case of the equations in Lajmanovich and Yorke (1976). Hence it follows that the solutions of (3.3) with the initial condition (3.4) approach a unique equilibrium, that is,

$$\lim_{t\to\infty} I\left(t, \xi^1\right) = E_1.$$

Similarly, we can show that

$$\lim_{t\to\infty} I\left(t, \xi^2\right) = E_2.$$

The proof is complete.

Assume $R_i \leq 1$. Since for any $I = \left(I_1^m, I_1^f, I_2^m, I_2^f\right)^T \in \Omega$,

$$0 \leq I_i^m \leq p^m, \quad 0 \leq I_i^f \leq p^f, \quad i = 1, 2,$$

which implies that

$$\xi^2 \leq_K I \leq_K \xi^1. \tag{3.5}$$

It follows immediately from Theorem 2.2 and Lemma 3.1 that

$$0 = E_2 = \lim_{t\to\infty} I\left(t, \xi^2\right) \leq_K \lim_{t\to\infty} I\left(t, I_0\right) \leq_K \lim_{t\to\infty} I\left(t, \xi^1\right) = E_1 = 0.$$

In summary:

Theorem 3.2. *Let the reproductive number R_i for each group be defined in (3.2). Then, if $R_i \leq 1$, $i = 1, 2$, the epidemic goes extinct regardless of the initial levels of infection . If $R_i > 1$ for $i = 1$, or 2, the epidemic spreads in the population.*

4. Endemic Equilibrium

The model investigated in this paper is decomposable. Hence, there exist two types of endemic equilibria, one of which consists of one nonzero pair $\left(I_i^m, I_i^f\right)$ and the other pair being zero (boundary equilibria), and a second for which coexistence is possible. We call the first type of endemic equilibria winner equilibria, and the second coexistence equilibria.

4.1. The Winner Equilibrium.

A winner equilibrium exists whenever the epidemic spreads in the population:

Theorem 4.1.1. *Assume that $R_i > 1$, $i = 1, 2$. Then the nontrivial equilibrium $\left(S^k > 0, I_i^k > 0, I_j^k = 0, j \neq i\right)$ exists.*

Proof. We need to solve

$$\begin{cases} \sigma_i^m I_i^m = a_i^m \left(p^m - I_i^m\right) I_i^f, \\ \sigma_i^f I_i^f = a_i^f \left(p^f - I_i^f\right) I_i^m, \end{cases} \tag{4.1.1}$$

for I_i^k, $0 < I_i^k < p^k$. A straightforward algebraic manipulation leads to

$$\begin{aligned} I_i^m &= \frac{a_i^m a_i^f p^m p^f - \sigma_i^m \sigma_i^f}{a_i^f \left(\sigma_i^m + a_i^m p^f\right)} = \frac{(R_i - 1)\sigma_i^m \sigma_i^f}{a_i^f \left(\sigma_i^m + a_i^m p^f\right)}, \\ I_i^f &= \frac{a_i^m a_i^f p^m p^f - \sigma_i^m \sigma_i^f}{a_i^m \left(\sigma_i^f + a_i^f p^m\right)} = \frac{(R_i - 1)\sigma_i^m \sigma_i^f}{a_i^m \left(\sigma_i^f + a_i^f p^m\right)}. \end{aligned}$$

Hence, $I_i^k > 0$ if and only if $R_i > 1$.

We may think of these equilibria as the result of competition for resources between two populations of pathogens. It is not surprising to see that the reproductive number determines the stability of these equilibria under the assumption of homogeneous mixing.

Theorem 4.1.2. *Let $R_i > 1$, $i = 1, 2$, and assume $R_1 \neq R_2$. If $R_i > R_j$, then the nontrivial equilibrium $\left(S^{k*} > 0, I_i^{k*} > 0, I_j^k = 0, j \neq i\right)$ is globally stable and the other equilibrium $\left(S^{k*} > 0, I_j^{k*} > 0, I_i^k = 0\right)$ is unstable.*

Proof. Without loss of generality, we assume $R_1 > R_2$ and show that the equilibrium $(S^{k*} > 0, I_1^k = 0, I_2^{k*} > 0)$ is unstable.

The Jacobian, J, of (2.5) at this equilibrium has the form

$$J = \begin{pmatrix} A_{11} & 0 \\ B_{21} & A_{22} \end{pmatrix},$$

where

$$A_{ii} = \begin{pmatrix} -\sigma_i^m - \delta_{2i} a_2^m I_2^{f*} & a_i^m \left(p^m - I_2^{m*}\right) \\ a_i^f \left(p^f - I_2^{f*}\right) & -\sigma_i^f - \delta_{2i} a_2^f I_2^{m*} \end{pmatrix}, \qquad B_{21} = \begin{pmatrix} -a_2^m I_2^{f*} & 0 \\ 0 & -a_2^f I_2^{m*} \end{pmatrix},$$

with δ_{ij} being the Kronecker delta function.

The eigenvalues of J consist of the eigenvalues of A_{ii}, $i = 1, 2$. All of the elements on the diagonal are negative, hence, whether all of the eigenvalues have a negative real part or some of them have a positive real part is determined by the signs of the determinants $\det A_{ii}$.

The winner equilibrium satisfies

$$\begin{cases} p^m - I_2^{m*} = \dfrac{\sigma_2^m I_2^{m*}}{a_2^m I_2^{f*}}, \\ p^f - I_2^{f*} = \dfrac{\sigma_2^f I_2^{f*}}{a_2^f I_2^{m*}}. \end{cases}$$

Hence,

$$\begin{aligned} \det\left(A_{11}\right) =& \sigma_1^m \sigma_1^f - a_1^m a_1^f \left(p^m - I_2^{m*}\right)\left(p^f - I_2^{f*}\right) = a_1^m a_1^f \left(\frac{\sigma_1^m \sigma_1^f}{a_1^m a_1^f} - \frac{\sigma_2^m \sigma_2^f}{a_2^m a_2^f}\right) \\ =& p^m p^f \left(\frac{1}{R_1} - \frac{1}{R_2}\right) < 0, \end{aligned}$$

which implies that the equilibrium $\left(S^k > 0, I_1^k = 0, I_2^{k*} > 0\right)$ is unstable.

Next, we show that the equilibrium $\left(S^k > 0, I_1^{k*} > 0, I_2^k = 0\right)$ is globally stable.

As it is shown above, the matrix

$$A_{11} = \begin{pmatrix} -\sigma_1^m & a_1^m\left(p^m - I_2^{m*}\right) \\ a_1^f\left(p^f - I_2^{f*}\right) & -\sigma_1^f \end{pmatrix}$$

is unstable. Moreover since the off-diagonal elements of A_{11} are positive, there is a positive eigenvalue λ of A_{11} with a strictly positive eigenvector $(\eta_1, \eta_2)^T$. In addition from (4.1.1), there is $\epsilon > 0$ such that

$$\begin{aligned} G_1^m &:= \sigma_1^m \eta_1 + a_1^m\left(p^m - (I_2^{m*} + \epsilon)\right)\eta_2 > 0, \\ G_1^f &:= a_1^f\left(p^f - (I_2^{f*} + \epsilon)\right)\eta_1 - \sigma_1^f \eta_2 > 0, \\ G_2^m &:= -\sigma_2^m I_2^{m*}(1+\epsilon) + a_2^m\left(p^m - I_2^{m*}(1+\epsilon)\right)I_2^{f*} < 0, \\ G_2^f &:= -\sigma_2^f I_2^{f*}(1+\epsilon) + a_2^f\left(p^f - I_2^{f*}(1+\epsilon)\right)I_2^{m*} < 0. \end{aligned} \tag{4.1.2}$$

Let τ be a positive real number and let $I^\tau = \left(I_1^{m\tau}, I_1^{f\tau}, I_2^{m\tau}, I_2^{f\tau}\right)^T$, where

$$I_1^{m\tau} = \tau\eta_1, \quad I_1^{f\tau} = \tau\eta_2, \quad I_2^{m\tau} = I_2^{m*}(1+\epsilon), \quad I_2^{f\tau} = I_2^{f*}(1+\epsilon).$$

¿From (4.1.2) it follows that

$$\begin{aligned} \lim_{\tau\to 0+} \frac{1}{\tau}\dot{I}_1^{k\tau} &= G_1^k > 0, \\ \lim_{\tau\to 0+} \dot{I}_2^{k\tau} &= G_2^k < 0, \end{aligned}$$

and, hence, there is $\tau^* > 0$ such that for all $\tau \in (0, \tau^*]$,

$$\dot{I}_1^{k\tau} > 0, \quad \dot{I}_2^{k\tau} < 0,$$

which implies that $I(t, I^\tau)$ is type K monotone; that is, $I_1^k(t, I^\tau)$ are increasing and $I_2^k(t, I^\tau)$ are decreasing.

The fact that the set $\left\{I \in \mathrm{R}^4; I_1^m = I_1^f = 0\right\}$ is positively invariant under the flow $I(t,\cdot)$ implies that for all $I \in \Omega$ with $I_1^m(0) + I_1^f(0) > 0$, $I_1^m(t, I_0) > 0$ and $I_1^f(t, I_0) > 0$ for all $t > 0$, where $I_0 = \left(I_1^m(0), I_1^f(0), I_2^m(0), I_2^f(0)\right)^T$. Hence, we have from (3.5), that for each $I \in \Omega$ with $I_1^m(0) + I_1^f(0) > 0$,

$$E_2 = \lim_{t\to\infty} I\left(t, \xi^2\right) \leq_K \omega(I),$$

where $\omega(I)$ is the omega limit set of I. From the definition of type K order and the definition of E_2, we have that for any $\tilde{I} = \left(\tilde{I}_1^m, \tilde{I}_1^f, \tilde{I}_2^m, \tilde{I}_2^f\right)^T \in \omega(I)$,

$$\tilde{I}_2^m \leq I_2^{m*}, \quad \tilde{I}_2^f \leq I_2^{f*}.$$

Therefore, for sufficiently large t_1,

$$I_2^k(t_1, I_0) \leq I_2^{k*}(1+\epsilon).$$

On the other hand, since $I_1^k(t_1, I_0) > 0$, if $I_1^m(0) + I_1^f(0) > 0$, τ can chosen so small that

$$\tau\eta_i \leq I_1^k(t_1, I_0),$$

which yields

$$I^\tau \leq_K I(t_1, I_0) \leq_K \xi^1.$$

Hence

$$I(t, I^\tau) \leq_K I\left(t, I(t_1, I_0)\right) = I(t + t_1, I_0) \leq_K I(t, \xi^1).$$

Moreover, since $I(t, I^\tau)$ is type K monotone,

$$\lim_{t\to\infty} I(t, I^\tau) = E^* = \left(e_1^*, e_2^*, e_3^*, e_4^*\right)^T,$$

where E^* is an equilibrium with $e_i^* \geq \tau\eta_i > 0$, $i = 1, 2$. Hence, it follows that $E^* = E_1$ (see Theorem 4.2.1 below), and

$$\lim_{t\to\infty} I(t, I_0) = E_1.$$

The proof of Theorem 4.1.2 is complete.

4.2. The Coexistence Equilibrium.

Coexistence of two viral strains can occur mathematically provided a very special relationship between the parameters takes place. This relationship is not robust and, consequently, it is of no biological significance. We include it here for mathematical completeness.

Theorem 4.2.1. *Let $R_1 > 1$ and $R_2 > 1$ be the reproductive numbers for groups 1 and 2 respectively. Then there exists a coexistence equilibrium $\left(S^k > 0, I_i^k > 0, i = 1, 2\right)$ if and only if*

$$R_1 = R_2. \tag{4.2.1}$$

Furthermore, if (4.2.1) is satisfied then there exists a continuum of equilibria explicitly given by

$$\begin{cases} I_i^m = \dfrac{p^m a_i^m \left(R\sigma_j^m + p^f a_j^m\right)\alpha}{R\left(\sigma_1^m\sigma_2^m + p^f\sigma_i^m a_j^m + \left(\sigma_i^m a_j^m - \sigma_j^m a_i^m\right)\alpha\right)}, & i = 1, \text{ or } 2, \\ I_i^f = \alpha, & \\ I_j^m = \dfrac{p^m a_j^m\left(p^f\sigma_i^m(R-1) - \left(R\sigma_i + p^f a_i^m\right)\alpha\right)}{R\left(\sigma_1^m\sigma_2^m + p^f\sigma_i^m a_j^m + \left(\sigma_i^m a_j^m - \sigma_j^m a_i^m\right)\alpha\right)}, & j \neq i, \\ I_j^f = \dfrac{p^f\sigma_1^m\sigma_2^m(R-1) - \left(R\sigma_1^m\sigma_2^m + p^f\sigma_j^m a_i^m\right)\alpha}{R\sigma_1^m\sigma_2^m + p^f\sigma_i^m a_j^m}, & \end{cases} \tag{4.2.2}$$

where

$$0 \leq \alpha \leq \frac{p^f \sigma_i^m (R-1)}{(R\sigma_i^m + p^f a_i^m)}. \tag{4.2.3}$$

Proof. Suppose that such an equilibrium exists. Then

$$\begin{cases} \sigma_i^m I_i^m = a_i^m \left(p^m - \sum_{l=1}^{2} I_l^m \right) I_i^f, \\ \sigma_i^f I_i^f = a_i^f \left(p^f - \sum_{l=1}^{2} I_l^f \right) I_i^m. \end{cases}$$

Hence

$$\left(p^m - \sum_{l=1}^{2} I_l^m \right) \left(p^f \sum_{l=1}^{2} I_l^f \right) \frac{R_i}{p^m p^f} = 1,$$

holds for $i = 1, 2$. This shows that (4.2.1) is necessary for the existence of a coexistence equilibrium.

We then assume that (4.2.1) is satisfied and solve the following system

$$\begin{cases} \sigma_1^m I_1^m = a_1^m \Big(p^m - \big(I_1^m + I_2^m \big) \Big) I_1^f, \\ \sigma_1^f I_1^f = a_1^f \Big(p^f - \big(I_1^f + I_2^f \big) \Big) I_1^m, \\ \sigma_2^m I_2^m = a_2^m \Big(p^m - \big(I_1^m + I_2^m \big) \Big) I_2^f, \\ \sigma_2^f I_2^f = a_2^f \Big(p^f - \big(I_1^f + I_2^f \big) \Big) I_2^m, \end{cases} \tag{4.2.4}$$

for I_i^k and I_j^k, with $0 < I_1^m + I_2^m < p^m$ and $0 < I_1^f + I_2^f < p^f$.

¿From $(4.2.4)_1$ and $(4.2.4)_3$,

$$I_j^m = \frac{\sigma_i^m a_j^m I_j^f}{\sigma_j^m a_i^m I_i^f} I_i^m.$$

¿From (4.2.4) we obtain

$$\begin{cases} I_1^m = \dfrac{\sigma_2^m a_1^m p^m I_1^f}{\sigma_1^m \sigma_2^m + \sigma_2^m a_1^m I_1^f + \sigma_1^m a_2^m I_2^f}, \\ I_2^m = \dfrac{\sigma_1^m a_2^m p^m I_2^f}{\sigma_1^m \sigma_2^m + \sigma_2^m a_1^m I_1^f + \sigma_1^m a_2^m I_2^f}. \end{cases} \tag{4.2.5}$$

Substituting (4.2.5) into $(4.2.4)_2$, using (3.2), and after some straightforward algebraic manipulations we arrive at

$$\sum_{i=1}^{2} \frac{p^f a_i^m + R\sigma_i^m}{\sigma_i^m} I_i^f = p^f (R-1).$$

Choosing $I_i^f = \alpha \geq 0$ (satisfying (4.2.3)) leads to (4.2.2).

Remark. System (4.2.4) is equivalent to

$$\begin{cases} \sigma_i^m I_i^m = a_i^m \left(p^m - \sum_{j=1}^{2} I_j^m \right) I_i^f, \\ R \left(p^m - \sum_{j=1}^{2} I_j^m \right) \left(p^f - \sum_{j=1}^{2} I_j^f \right) = p^m p^f; \end{cases}$$

that is, the system (4.2.4) is undetermined (there are three equations for four variables). Hence, solutions can be obtained by choosing $I_i^f = \alpha$ arbitrarily.

It is not difficult to see that this continuum is stable. Because these equilibria are a continuum and the flow generated by (2.5) is type K monotone, then all equilibrium points have the same stability. Consider either of the two end points for α, that is $\alpha = 0$ or $\alpha = \dfrac{\sigma_i p^f (R-1)}{(R\sigma_i^m + p^f a_i^m)}$. Then from the proof of Theorem 4.1.2 we see that an eigenvalue of A_{11} and A_{22} equals zero while the other three have negative real parts. Hence, each equilibrium is stable and so is the continuum. We summarize our results on the next theorem.

Theorem 4.2.2. *Let the reproductive numbers for the two groups be R_1 and R_2, respectively, and assume that $R_1 = R_2 > 1$. Then every equilibrium on the continuum parameterized by (4.2.3) is stable.*

5. Extensions

It is possible to provide extensions of the results of this manuscript to more general situations including the case in which a two-sex host population is exposed to any number of strains. Age-of-infection has become an important variable in recent epidemiological studies (see Thieme and Castillo-Chavez 1989, 1993). We also extend our two-strain model to the situation in which the hosts' age of infection depends on the the infective strain. We find out that realistic coexistence is not possible in these more elaborate situations.

5.1. The Multi-strain Model.

Assume there are N different viral strains spreading in a heterosexually-active and homogeneously mixing population. The infected males and females are divided into N groups based on the infectious viral strain that they have acquired. We assume that susceptibles that become infected acquire the viral strain of their infectors and that individuals cannot carry two or more strains simultaneously. Then the model can be described, as in Section 2, by the following system of equations:

$$\begin{cases} \dot{S}^m = \Lambda^m - B^m - \mu S^m + \sum_{i=1}^{N} \gamma_i^m I_i^m, \\ \dot{I}_i^m = B_i^m - (\mu + \gamma_i^m) I_i^m, \\ \dot{S}^f = \Lambda^f - B^f - \mu S^f + \sum_{i=1}^{N} \gamma_i^f I_i^f, \\ \dot{I}_i^f = B_i^f - \left(\mu + \gamma_i^f\right) I_i^f, \end{cases}$$

where

$$B_i^m = c^m S^m \beta_i^f \frac{I_i^f}{T^f}, \qquad B_i^f = c^f S^f \beta_i^m \frac{I_i^m}{T^m},$$

$$B^m = \frac{c^m S^m}{T^f} \sum_{j=1}^{N} \beta_j^f I_j^f, \qquad B^f = \frac{c^f S^f}{T^m} \sum_{j=1}^{N} \beta_j^m I_j^m,$$

with the constraint

$$c^m T^m = c^f T^f.$$

The reproductive number of each group is also given by (3.2). If $R_i \leq 0$ for all i, the epidemic dies out or the disease cannot invade while if there exists one $R_i > 1$ then the epidemic spreads. Mathematically, there are two types of endemic equilibria if $R_i > 1$. If all the reproductive numbers are distinct, one viral strain wins; that is, there is only one stable winner equilibrium, the viral strain with the largest reproductive number. If two or more groups have the same reproductive number then mathematical coexistence occurs. We have a continuum of endemic equilibria which can be computed explicitly. The stability of this continuum cannot be settled with the arguments provided in Section 4. Fortunately, this situation is of less biological interest.

5.2. The Infection-age Structured Model.

If the ages of infection, as a function of the strain, are included in the process, then the dynamics of disease spread are governed by a system of first order partial differential equations with complex boundary conditions (integral equations). In this section, for simplicity, we only formulate a model for a two-sex population that is exposed to only two strains. Suceptibles are divided by gender while infectives are stratified by gender, strain, and age-of-infection. The system is given by the

following set of equations:

$$\begin{cases} \dot{S}^m(t) = \Lambda^m - B^m(t) - \mu S^m(t) + \sum_{i=1}^{2} \int_0^\infty \gamma_i^m(\tau) I_i^m(t,\tau) d\tau, \\ \partial_t I_i^m(t,\tau) + \partial_\tau I_i^m(t,\tau) = -\left(\mu + \gamma_i^m(\tau)\right) I_i^m(t,\tau), \\ I_i^m(t,0) = B_i^m(t), \\ \dot{S}^f(t) = \Lambda^f - B^f(t) - \mu S^f(t) + \sum_{i=1}^{2} \int_0^\infty \gamma_i^f(\tau) I_i^f(t,\tau) d\tau, \\ \partial_t I_i^f(t,\tau) + \partial_\tau I_i^f(t,\tau) = -\left(\mu + \gamma_i^f(\tau)\right) I_i^f(t,\tau), \\ I_i^f(t,0) = B_i^f(t), \end{cases}$$

where

$$B_i^m(t) = \frac{c^m S^m(t)}{T^f(t)} \int_0^\infty \beta_i^f(\tau) I_i^f(t,\tau) d\tau, \quad B_i^f(t) = \frac{c^f S^f(t)}{T^m(t)} \int_0^\infty \beta_i^m(\tau) I_i^m(t,\tau) d\tau,$$

and

$$B^k(t) = \sum_{i=1}^{2} B_i^k(t), \quad T^k(t) = S^k(t) + \sum_{i=1}^{2} \int_0^\infty I_i^k(t,\tau) d\tau,$$

with the constraint

$$c^m T^m(t) = c^f T^f(t).$$

The reproductive number for each group is given by

$$R_i = c^m c^f \int_0^\infty \beta_i^m(\tau) e^{-\mu\tau - \int_0^\tau \gamma_i^m(u)du} d\tau \int_0^\infty \beta_i^f(\tau) e^{-\mu\tau - \int_0^\tau \gamma_i^f(u)du} d\tau.$$

Existence, stability, and coexistence can be handled as before. We again observe the existence of a continuum of equilibria if $R_1 = R_2$, which is of less biological interest. The argument that we used to settle the stability of this continuum does not seem to work in this case.

6. Discussion

An important principle in theoretical biology is that of competitive exclusion which states that *no two species can forever occupy the same ecological niche.* Clarifications on the meaning of competitive exclusion and niche have been central to theoretical ecology (Butler et al., 1983; Levin, 1970; May 1975; Maynard Smiths, 1974). Sexually-transmitted diseases like gonorrhea have incredibly high incidences throughout the world providing the necessary environment and opportunities for the evolution of new strains (see Hethcote and Yorke, 1984, and references therein). The coexistence of gonorrhea strains is becoming an increasingly serious problem. Understanding the mechanisms that lead to coexistence or competitive exclusion is central to the development of disease management strategies as well as to our increase understanding of STD-dynamics.

In this article, we have set up a very simple situation in which two strains or possibly more compete for the same resource. Lack of genetical and behavioral heterogeneity in a heterosexually mixing host leads to competitive exclusion. However, as it is indicated above, coexistence has been observed in many situations and, hence, it is important to determine the type of mechanisms that lead to coexistence. For example, a large proportion of women are asymptomatic to gonorrhea and, hence, a potential reservoir for the pathogen. Is this sufficient for coexistence? Heterogeneity in human behavior is central to the spread of gonorrhea as Hethcote and Yorke (1984) convincingly illustrated through their introduction of the core group concept. Research driven by HIV/AIDS dynamics (see, e.g., the volume edited by Castillo-Chavez, 1989) has shown the importance of social networks and social dynamics for the spread of STDs. Behavioral and geographical isolation may

play a central role in maintaining pathogen heterogeneity. As it has been shown in ecological systems, homogeneity leads to competitive exclusion while heterogeneity may, in its various manifestations, lead to coexistence. This seems to be the pattern for STDs and, consequently, we need to conduct further research to understand the *type* of heterogeneities that lead to coexistence.

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