Superinfection, Virulence and Density-Dependent Mortality in an Epidemic Model

by

Jaime Mena-Lorca
and
Jorge X. Velasco-Hernandez

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Jaime Mena-Lorca
Instituto de Matemáticas
Universidad Católica de Chile
Chile

Jorge X. Velasco-Hernández[1]
Departamento de Matemáticas
Universidad Autónoma Metropolitana-Iztapalapa
México

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Please send all correspondence to the second author to:

Biometrics Unit
Cornell University
Ithaca, NY 14853-7801
Tel: 607-255-5488
Fax: 607-255-4698
E-mail: jxv1@cornell.edu

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[1] Present address: Biometrics Unit, Cornell University. Ithaca, NY 14853-7801

Superinfection, virulence and density dependent mortality in an epidemic model

Jaime Mena-Lorca
Instituto de Matemáticas,
Universidad Católica de Valparaíso
Casilla 4059, Valparaíso, CHILE

Jorge X. Velasco-Hernandez
Departamento de Matemáticas,
UAM-Iztapalapa
Apdo. Postal 55-534, México, D.F. 09340, MEXICO

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Abstract

A mathematical model of the interaction between two pathogen strains and a single host population is studied. Variable population size, density-dependent mortality, disease-related deaths (virulence) and superinfectivity are incorporated into the model. Results indicate that coexistence of the two strains is possible only in a narrow range of values of virulence and superinfectivity. Global asymptotic stability of the steady-state that gives coexistence of both strains under suitable and biologically feasible constraints is proved.

1 Introduction

Population processes in ecological systems at any given time are the product of coexistence in common habitats. Coexistence, however, is not a permanent phenomenon. During the evolution of the ecological system new

populations will invade the habitat, some will be successful, some will not. At the same time, already established populations will eventually go extinct as a result of the competitive abilities of the new invaders and their own incapacity to adapt to an ever changing situation. Others, however, will remain and reproduce successfully in the new conditions. These processes of invasion, succesfull colonization, extinction and long term persistence of biological species in a given habitat is the main subject of study of this report.

Several authors (*Levins & Culver* [11], *Horn & Mac Arthur* [9], *Hastings* [7], *Cornell & Lawton* [5], *Nee & May* [15], *Hastings* [8]) have noted that the ecological phenomena described in the above paragraph can be chosen as a general paradigm of other biological processes where populations share common resources and coevolve through time. The problem of coexistence of multiple species in a common habitat was first approached in a theoretical setting by *Levins & Culver* [11] who considered a number of populations living in a habitat with a fixed number of available sites, each population able to occupy a sigle site. Populations on each site can go extinct or colonize another site at fixed rates per unit time. They construct a model that follows the dynamics of the proportion of occupied sites resulting from the trade-off of colonization and extinction. This type of model is called a metapopulation model (*Tilman* [18]). The approach exemplified by [11] has evolved immensely since the time of its publication. Nowadays, the concept of metapopulation constitutes one of the foundations of the patch dynamics paradigm which at the present time is one of the basic methodological approaches for the study of complex ecological systems. This paradigm establishes that many biological and ecological phenomena can be viewed as driven by invasion, colonization, extinction and interaction of 'patches'; that the habitat and generaly the environment where biological and ecological phenomena occur are heterogeneous; that this attribute of heterogeneity can be substantially described with the postulation of different patch types; and, finally, that interaction between the state variables that define the biological or ecological phenomena of interest is intertwined with the characteristics and temporal properties of those patches.

One particular example of this statement, which we intend to address here is the problem of coexistence of several closely related types of organisms in the same location. This problem is related to two phenomena.

One is the ecological problem of the coexistence of species in a common environment. In this case the species differ in their competitive abilities, colonization and extinction rates. The interplay of these three factors determines how many and which of the species coexist (*Tilman* [18]). The other is the epidemiological problem of the coexistence of several pathogen strains in the same host population. Several factors may, in principle, play important roles in the determination of the outcome of this interaction. Clearly, besides stable coexistence of both strains, one or both can go extinct or, moreover, the host population can be driven to extinction. Disease-related mortality, density-dependent population regulation and the occurrence of superinfections are determinants of the evolution of this host-pathogen system.

Numerous authors have discused the problem of coexistence in pathogen-host interactions.

Levin & Pimentel [10] analyzed a general *SI* (susceptible-infectious) model where the population in the absence of disease would grow exponentially. Two strains with different virulences compete with each other. The most virulent strain can takeover hosts already infected with the less virulent strain. This phenomena is called superinfection. Superinfection 'ability' can be introduced into epidemiological models as an 'index' which measures the likelihood that a virulent strain will take over a host already infected with a less virulent one. This index was first introduced by *Levin & Pimentel* in reference [10]. Under these assumptions the coexistence of both strains is possible [2]. The stability of this steady-state is only guaranteed for certain range of values of this index. Outside this range one of the boundary equilibria is asymptotically stable.

Bremermann & Thieme [1] postulate a competitive exclusion principle in a epidemiological system where several strains compete for survival in a single host population. The pathogens differ on their virulence. In this model the assumption that virulence is a strictly convex function of the transmission rate (that is, the higher the virulence, the higher the infectivity until stauration occurs and further increments in virulence have no effect on the infectivity rate) implies that the evolution of virulence leads to a transmission rate that maximizes the basic reproductive number of the pathogen [1]. This model describes a *SIR*-type (susceptible-infectious-removed) of epidemic in a population with variable size. The generic outcome of this epidemic system is the competitive exclusion of one of the strains.

Castillo-Chavez et al. [3] find, for a *SIS* two-sex model with variable population size, that competitive exclusion is the norm: the strain with the highest reproductive number persists in both host types.

Nowak & May[13] [16] explored the interrelation that exists between virulence and and superinfection in a *constant* host population. Coexistence as function of superinfection, basic reproductive numbers and virulence is a feasible posibility. In this case, competitive exclusion is not the norm but only an alternative outcome of the interaction. This result departs form the pattern established in the models of *Castillo-Chavez et al.* and *Bremermann & Thieme.*

Tilman [18], too, studied an ecological model where several species compete for colonization and permanence in habitat patches. As in the case of *Nowak & May*, *Tilman* also explores the conditions that determine the coexistence of several diferent species but in terms of colonization and extinction rates. *Nowak & May*[13] [16] have shown that their mathematical model for the evolution of virulence and the *Tilman* metapopulation model have equivalent mathematical structures. Therefore, the conclusions that this author obtains on coexistence of multiple species follow those of *Nowak & May.* In particular, the total population size in the *Tilman* case is also constant. In *Tilman*'s case, colonization and extinction rates are analogous to basic reproductive numbers and virulence, respectively. Competitive ability is analogous to superinfection 'ability'.

Castillo-Chavez & Velasco-Hernandez [4] in a two-strain one host epidemic system with superinfection find that in the presence of variable total population size, parameter regions where coexistence of the strains occurs, are relatively narrow when compared with the parameter region where only one of them remains in the system. The parameter region was determined by the susceptibility of individuals to secondary infections (superinfection), and the relative magnitude of the basic reproductive number and virulences of both strains. The presence of windows for coexistence in this system is a consequence of the assumption of variable population size.

In this paper we study the effect on coexistence conditions of variable population, virulence and density-dependent population regulation. We address these factors since in animal populations crowding effects may increase the overall death rate and alter significantly the epidemiological processes taking place in the host population (*Gao, Mena-Lorca & Hethcote* [12]). The interplay between this demographic processes and the presence of a

potentially fatal disease determine the overall conditions for coexistence and competitive exclusion of the two pathogen strains. We show that there exist windows of coexistence that depend on the particular balance between basic reproductive numbers, virulence, and competitive ability of the strains.

The structure of this work is as follows: in the next section we give first a description of our model. Then in section 3 we present the analytical results obtained on local and global stability on the invariant planes of the region where our flow is defined, then in section 4 we present some numerical results and, finally, we give our conclusions.

2 Mathematical model

Let X, Y_1, Y_2 and N represent the densities of susceptible, infected with strain 1, infecteds with strain 2, and total population respectively. In this model it is assumed that disease-independent mortality is a function of population density and that it is shared proportionally by all subpopulations. Model equations stand as follows:

$$\begin{aligned} \dot{X} &= bN - \beta_1 X\frac{Y_1}{N} - \beta_2 X\frac{Y_2}{N} - \theta(N)\frac{X}{N} \\ \dot{Y_1} &= \beta_1 X\frac{Y_1}{N} - \sigma\beta_2 Y_1\frac{Y_2}{N} - \theta(N)\frac{Y_1}{N} - v_1 Y_1, \\ \dot{Y_2} &= \beta_2 X\frac{Y_2}{N} + \sigma\beta_2 Y_1\frac{Y_2}{N} - \theta(N)\frac{Y_2}{N} - v_2 Y_2, \end{aligned} \tag{1}$$

where $\theta(N) = N(u + \frac{r}{K}N)$ and $r = b - u$ is the net growth rate. Disease-related death is represented by v_i which is defined as the extra mortality that the infected population suffers due to the disease. Susceptible organisms are born at rate b, and there is no vertical transmission. Infection by susceptible individuals is acquired by contact with either type of strain (Y_1 or Y_2) at rates $\beta_i\frac{Y_i}{N}$ which give the so-called 'standard incidence' (*Mena-Lorca & Hethcote* [14]). We assume that $\beta_2 > \beta_1$, and $v_2 > v_1$, that is the second strain is more virulent and infectious than the first. Thus, infected individuals with strain 1 may be overtaken by strain 2. This secondary infection can be either enhanced or restricted by the primary infection. This 'susceptibility' is represented in our model by the 'superinfectivity index'

σ. If $0 < \sigma < 1$, infected individuals are more resistant to a secondary infection while $1 < \sigma$ means that secondary infections are facilitated by previous infections with strain 1; $\sigma = 1$ implies that secondary infections are acquired as though infected individuals with strain 1 were completely susceptible.

The equation for the total population is

$$\dot{N} = bN - \theta(N) - v_1 Y_1 - v_2 Y_2 \tag{2}$$

3 Analysis

To analyze model (1-2) we define

$$I_1 = \frac{Y_1}{N}, \quad I_2 = \frac{Y_2}{N}, \quad S = \frac{X}{N},$$

and

$$t = \tau/r, \quad \hat{\beta}_i = \beta_i/r, \quad \tilde{v}_i = v_i/r, \quad \tilde{u} = u/r, \quad \tilde{N} = N/K.$$

Let $\prime = d/d\tau$. We obtain the system

$$\begin{aligned} I_1' &= \left(\tilde{\beta}_1 S - \sigma\tilde{\beta}_2 I_2 - \tilde{u} - \tilde{v}_1 - 1 + \tilde{v}_1 I_1 + \tilde{v}_2 I_2\right) I_1, \\ I_2' &= \left(\tilde{\beta}_2 S + \sigma\tilde{\beta}_2 I_1 - \tilde{u} - \tilde{v}_2 - 1 + \tilde{v}_1 I_1 + \tilde{v}_2 I_2\right) I_2, \\ \tilde{N}' &= \left(1 - \tilde{N} - \tilde{v}_1 I_1 - \tilde{v}_2 I_2\right)\tilde{N}. \end{aligned} \tag{3}$$

From now on we will be working with equations (3). Note that the equations for I_1 and I_2 can be written as Lotka-Volterra competition equations if $\sigma \leq 1$. When $\sigma > 1$, this analogy breakes down since the system becomes one where competition and mutualism act simultaneously. In any case, these susbsystem of equations does not depend on N. Note that because $r = b - u$, then it follows that $\tilde{u} + 1 = b/r$ (cf. 1). However, for clarity of interpretation we do not make this sustitution in (3).

There are 8 feasible equilibria with coordinates $(I_1^*, I_2^*, \tilde{N}^*)$ which can be classified into two subsets, one corresponding to those with total population $\tilde{N} = 0$, and those with $\tilde{N} > 0$. The meaning and relevance of the equilibria with $\tilde{N} = 0$, will be discussed later.

3.1 Feasible equilibria

We look now at equilibria of biological importance, that is, those that are given by positive coordinates and satisfy the bounds imposed by our model. These equilibria we call feasible. The trivial equilibrium $E_{000} = (0, 0, 0)$ and the disease-free equilibrium $E_{00N} = (0, 0, 1)$ always exist. The basic reproductive number for each strain is

$$R_i = \frac{\tilde{\beta}_i}{1 + \tilde{u} + \tilde{v}_i}.$$

The equilibrium points where strain 2 wins over strain 1 are given next. Note that the total population can either persist or go extinct and that both are feasible equilibria if $R_2 > 1$.

$$\begin{aligned} E_{010} &= \Big(0, \frac{(1 + \tilde{v}_2 + \tilde{u})(1 - R_2)}{-\tilde{\beta}_2 + \tilde{v}_2}, 0\Big), \\ E_{01N} &= \Big(0, \frac{(1 + \tilde{v}_2 + \tilde{u})(1 - R_2)}{-\tilde{\beta}_2 + \tilde{v}_2}, 1 - \tilde{v}_2 \frac{(1 + \tilde{v}_2 + \tilde{u})(1 - R_2)}{-\tilde{\beta}_2 + \tilde{v}_2}\Big), \end{aligned}$$

The equilibrium points where strain 1 wins over strain 2 are given next ($\mathcal{R}_1 > 1$ in each case.

$$\begin{aligned} E_{100} &= \Big(\frac{(1 + \tilde{v}_1 + \tilde{u})(1 - R_1)}{-\tilde{\beta}_1 + \tilde{v}_1}, 0, 0\Big), \\ E_{10N} &= \Big(\frac{(1 + \tilde{v}_1 + \tilde{u})(1 - R_1)}{-\tilde{\beta}_1 + \tilde{v}_1}, 0, 1 - \tilde{v}_1 \frac{(1 + \tilde{v}_1 + \tilde{u})(1 - R_1)}{-\tilde{\beta}_1 + \tilde{v}_1}\Big). \end{aligned}$$

Let

$$\Psi_1 = -\tilde{\beta}_1 + \tilde{\beta}_2(1 - \sigma), \ \Psi_2 = \tilde{v}_2 - \tilde{v}_1 - \sigma\tilde{\beta}_2.$$

Then, the coordinates for the equilibria with coexistence of both strains are

$$\begin{aligned} E_{110} &= \Big(\frac{-(1 + \tilde{u})}{\Psi_2} + \frac{\tilde{\beta}_2 - \tilde{v}_2}{\Psi_1}, \frac{1 + \tilde{u}}{\Psi_2} + \frac{-\tilde{\beta}_1 + \tilde{v}_1}{\Psi_1}, 0\Big), \\ E_{11N} &= \Big(\frac{-(1 + \tilde{u})}{\Psi_2} + \frac{\tilde{\beta}_2 - \tilde{v}_2}{\Psi_1}, \frac{1 + \tilde{u}}{\Psi_2} + \frac{-\tilde{\beta}_1 + \tilde{v}_1}{\Psi_1}, \tilde{N}^*\Big). \end{aligned}$$

In the above, $\tilde{N}^* = 1 - \tilde{v}_1 I_1^* - \tilde{v}_2 I_2^*$, with I_1^*, I_2^* representing the first and second components, respectivelly, of E_{11N}. Here again, the total population can either persist of go extinct.

Remark 1: Since we are assuming that $\tilde{\beta}_2 > \tilde{\beta}_1$, Ψ_1 is positive for $\sigma = 0$, that is, when secondary infections do not take place. This expression together with the one for Ψ_2 provides us a threshold value for $\tilde{\beta}_2\sigma$ which can be viewed as the effective infectivity of strain 2 in the presence of superinfectivity. □

Let $\mathcal{V} = \{\tilde{\beta}_2 - \tilde{\beta}_1, \tilde{v}_2 - \tilde{v}_1\}$. From the definitions of Ψ_1 and Ψ_2 we have that both are positive quantities if

$$\min \mathcal{V} > \tilde{\beta}_2\sigma,$$

and that both are negative if

$$\max \mathcal{V} < \tilde{\beta}_2\sigma.$$

These bounds for the 'net infectivity' $\tilde{\beta}_2\sigma$ play an important role in the local stability properties of the endemic states analyzed below.

Nowak & May[16] and *Bremmerman & Thieme*[1] have argued that in many diseases it is reasonable to assume that the infection coefficient β is a nondecreasing bounded function of virulence v. If this assumption is introduced in our model by defining

$$\tilde{\beta}_i = c\tilde{v}_i/(m + \tilde{v}_i).$$

The basic reproductive number for each strain R_i is now a concave function of virulence. This determines the existence of an optimal virulence v^* for which R_i achieves its maximum. Under this particular form of the relationship between infectivity and virulence *Bremmerman & Thieme* [1] and *Nowak & May*[16] found either a competitive exclusion principle (where the strain with optimal virulence subsists in the absence of superinfection), or that coexistence of pathogen strains with virulences greater than the optimal is indeed possible (in the presence of superinfection), respectively.

In this work we present results for this particular form of relationship but our results carry over for cases where $\tilde{v}_1 < \tilde{v}_2$ and $\tilde{\beta}_1 < \tilde{\beta}_2$.

In Figure 1 we have plotted I_1^* and I_2^* as functions of $\tilde{\beta}_2$ and σ where we have defined

$$\tilde{\beta}_i = c\tilde{v}_i/(m + \tilde{v}_i),$$

c and m constants.

Note in the Figure that the region of coexistence is not connected and that it is much smaller than the region where coexistence is impossible (for the given range of parameter values).

Figure 1 about here

We give now conditions for the biological feasibility of several of the equilibria. Equilibria E_{100}, E_{110}, and E_{010} have the third coordinate (total population) equal to zero. We are looking at the asymptotic behavior of solutions of our model and, moreover, we are using *proportions* to perform our analysis. Therefore, these steady-states represent cases where the total population goes extinct but always keeping a positive proportion of infectious individuals. Equilibria E_{100} and E_{010} exist whenever the corresponding basic reproductive ratio R_i is greater than one.

Remark 2: Equilibria E_{10N} and E_{01N} (steady-states with competitive exclusion of one of the strains) are feasible if, again, the corresponding $R_i > 1$ and the third coordinate satisfies $1 - \tilde{v}_i I_i > 0$ which is equivalent to

$$1 < R_i < 1 + \frac{\tilde{\beta}_i - \tilde{v}_i}{\tilde{v}_i(1 + \tilde{v}_i + \tilde{u})}, \tag{4}$$

for each strain, respectively. I_i is the non-zero coordinate of the infectious population that remains in the system. In Figure 2 we show graphically the region determined by (4). □

Figure 2 about here

E_{110} and E_{11N} are feasible when the following conditions are satisfied.

$$\frac{1+\tilde{u}}{\Psi_2} - 1 < \frac{\tilde{\beta}_1 - \tilde{v}_1}{\Psi_1} < \frac{1+\tilde{u}}{\Psi_2} < \frac{\tilde{\beta}_2 - \tilde{v}_2}{\Psi_1} < 1 + \frac{1+\tilde{u}}{\Psi_2}. \tag{5}$$

Note that (5) implies that Ψ_1 and Ψ_2 must have the same sign if R_i are simultaneously greater than 1. Furthermore, E_{11N} requires also that

$$\frac{\tilde{v}_1\tilde{\beta}_2 - \tilde{v}_2\tilde{\beta}_1}{\Psi_1} + \frac{(1+\tilde{u})(\tilde{v}_2 - \tilde{v}_1)}{\Psi_2} < 1. \tag{6}$$

Formula (5) is a set of conditions on the relative distances that both strains must satisfy in their infectivities and virulences. Consider, for example, the central inequalities of (5):

$$\frac{\tilde{\beta}_1 - \tilde{v}_1}{\Psi_1} < \frac{1+\tilde{u}}{\Psi_2} < \frac{\tilde{\beta}_2 - \tilde{v}_2}{\Psi_1}.$$

The first and last terms of this inequality are equivalently expressed as

$$\tilde{\beta}_2 - \tilde{\beta}_1 > \tilde{v}_2 - \tilde{v}_1, \text{ or } \tilde{\beta}_2 - \tilde{\beta}_1 < \tilde{v}_2 - \tilde{v}_1,$$

(depending on the sign of Ψ_1). Therefore, formula (5) states that there must exist *minimum* distances between the phenotypes of both competing strains to achieve coexistence in the same host population. If the final outcome of the interaction is the extinction of the total population, (5) is a necessary and sufficient condition for coexistence. However, if the system is able to persist ($\tilde{N}^* > 0$), then condition (6) is necessary for coexistence. In this case, we can establish the following result.

Lemma 1 *Condition (5) does not hold if and only if Ψ_1 and Ψ_2 are positive and $\Psi_1 < \Psi_2$, or Ψ_1 and Ψ_2 are negative and $\Psi_1 > \Psi_2$, In either case E_{110} and E_{11N} do not exist. However, the equilibria located at the boundary of Ω do exist.*

Define the set

$$\Omega = \left\{(I_1, I_2, \tilde{N}) \in R^3 : \ I_1, I_2, \tilde{N} \geq 0, \ I_1 + I_2 \leq 1, \text{ and } \tilde{N} \leq 1\right\}.$$

Ω is positively invariant for the flow induced by our equations. Within Ω the planes $I_1 = 0$, $I_2 = 0$ and $\tilde{N} = 0$ are invariant sets. Moreover, note that our system is partially uncoupled in the sense that the first two components of the flow can be found independently of the third one. Also note that the coordinates I_1 and I_2 of the equilibrium points in the plane $\tilde{N} = 0$ are the same for the corresponding equilibrium points with third coordinate $\tilde{N} > 0$.

3.2 Local stability

First we consider the stability of the equilibria located at the boundary of Ω.

3.2.1 Stability in the plane $\tilde{N} = 0$

We study now the stability of our model restricted to the plane $\tilde{N} = 0$. Assume that E_{110} is feasible. The Jacobian evaluated at this equilibrium is

$$J = \begin{pmatrix} I_1^*(-\tilde{\beta}_1 + \tilde{v}_1) & I_1^*(-\tilde{\beta}_1 - \sigma\tilde{\beta}_2 + \tilde{v}_2) \\ I_2^*(-\tilde{\beta}_2 + \sigma\tilde{\beta}_2 + \tilde{v}_1) & I_2^*(-\tilde{\beta}_2 + \tilde{v}_2) \end{pmatrix}, \tag{7}$$

where I_1^* and I_2^* are the first and second coordinates of E_{110} respectively.

Then we have that

$$\mathrm{Det}J = I_1^* I_2^* \Psi_1 \Psi_2, \text{ and } \mathrm{Tr}J = I_1^*(-\tilde{\beta}_1 + \tilde{v}_1) + I_2^*(-\tilde{\beta}_2 + \tilde{v}_2) = \frac{1+\tilde{u}}{\Psi_2}(\Psi_1 - \Psi_2).$$

In Table 1 we present the possible local stability outcomes for the equilibrium E_{110} as function of Ψ_i.

Ψ_1	Ψ_2		$\mathrm{Tr}J$	$\mathrm{Det}J$	Local behavior
+	+	$\Rightarrow$	−	+	asymptotically stable.
−	+	$\Rightarrow$	+	−	saddle
+	−	$\Rightarrow$	+	−	saddle
−	−	$\Rightarrow$	−	+	asymptotically stable

There are no Hopf bifurcations because condition (5) implies that $|\Psi_1 - \Psi_2| \gg 0$.

Figure 3 about here

3.2.2 Stability in the planes $I_1 = 0$ and $I_2 = 0$

In this section we first restrict our analysis to the invariant plane $I_1 = 0$. In this plane we may have up to three non-trivial equilibrium points if $R_2 > 1$ *and* if condition (4) is satisfied. Note that on this plane strain 2 is the only strain that exists. Thus,

1. The trivial equilibrium E_{000} always exists and it is always unstable.
2. If $R_2 < 1$, the point E_{001} exists and is globally asymptotically stable (see Figure 3a).

3. If $R_2 > 1$, then E_{001} still exists but now it is a saddle point. Two new equilibria appear E_{01N} (asymptotically stable) and E_{010} (unstable) if condition (4) is satisfied. Otherwise only E_{010} exists and it is asymptotically stable (see Figure 3b).

Statement 3) above is justified by the following lemma

Lemma 2 *There exists a heteroclinic orbit connecting E_{01N} and E_{010}.*

Proof: Suppose both equilibria are feasible. The existence of a heteroclinic conection between E_{01N} and E_{010} derives from the partial uncoupling of our equations. It is a particular case of a general result associated with the existence of pairs of equilibria with common first and second coordinates. Consider a set parametrically described by $\phi(t) = (0, I_2(t), \tilde{N}(t))$ where $I_2(t) = I_2^*$, a constant equal to the second coordinate of E_{010} or E_{01N}, and $\tilde{N}(t)$ a solution of the equation

$$\tilde{N}' = \tilde{N}(1 - \tilde{N} - \tilde{v}_2 I_2^*).$$

Clearly, $\phi(t)$ is an orbit of our sytem that joins the points E_{010} and E_{01N}.□

By Lemma 2, on the heteroclinic orbit joining E_{010} and E_{01N}, E_{01N} is an atractor. This heteroclinic connection is a subset of the stable manifold of this steady-state. Since $R_2 > 1$ implies the local asymptotic stability endemic equilibrium E_{01N} and also E_{010} is a saddle, then by the Poincare-Bendixon theorem E_{01N} is globally asymptotically stable in the plane $\{(I_1, I_2, \tilde{N}) : I_1 = 0\} \cap \Omega$ (see Figure 4).

Figure 4 about here

For the plane $I_2 = 0$ we have analogous results to those just described. In this case strain 1 is the 'winner' strain while strain 2 is extinct. In Figure 5 to Figure 8 we present representative possible geometries of the flow restricted to the planes $I_1 = 0$ and $I_2 = 0$.

Figures 5 to 8 about here

3.3 Asymptotic behavior and absence of cycles

We now prove the stability of the equilibrium E_{110} restricted to the region $\Omega_{\tilde{N}=0} = \{(I_1, I_2, \tilde{N}) : \tilde{N} = 0\} \cap \Omega$. First we state the following lemma which is a a direct generalization of Lemma 2.

Lemma 3 *Any pair of equilibria with common first and second coordinates is connected by a heteroclinic orbit.*

Theorem 1 *E_{110} is globally asymptotically stable in $\Omega_{\tilde{N}=0}$ if it is locally asymptotically stable in $\Omega_{\tilde{N}=0}$.*

Proof: Assuming that conditions (5) and (6) are satisfied and if conditions in row 1 and row 4 of Table 1 hold, then E_{110} is locally asymptotically stable. The equations for I_1 and I_2 are

$$I_1' = I_1(r_1 - a_{11}I_1 - a_{22}I_2),\ I_2' = I_2(r_2 - a_{21}I_1 - a_{22}I_2),$$

where

$$a_{11} = \tilde{\beta}_1 - \tilde{v}_1,\ a_{12} = \tilde{\beta}_1 + \sigma\tilde{\beta}_2 - \tilde{v}_2,$$
$$a_{21} = \tilde{\beta}_2 - \tilde{v}_2,\ a_{22} = (1-\sigma)\tilde{\beta}_2 - \tilde{v}_1.$$

Therefore, the function

$$V(I_1, I_2) = c_1(I_1 - I_1^* - I_1^* \log\Big(\frac{I_1}{I_1^*}\Big) + c_2(I_2 - I_2^* - I_2^* \log\Big(\frac{I_2}{I_2^*}\Big),$$

is a Lyapunov function for appropriate c_i (*Goh* [6]). Therefore, E_{110} is globally asymptotically stable in $\Omega_{\tilde{N}=0}$ □.

Theorem 2 *1. The equilibrium point E_{11N} is locally asymptotically stable in Ω.*

2. There are no periodic orbits in Ω.

Proof: 1) The Jacobian matrix of (3) at E_{11N} is

$$\begin{pmatrix} J & 0 \\ A & -\tilde{N} \end{pmatrix}, \tag{8}$$

where J is given by (7) and

$$A = (-\tilde{v}_1\tilde{N},\ -\tilde{v}_2\tilde{N}).$$

Thus, the eigenvalues are those of J and $-\tilde{N}$. Therefore, the point is asymptotically stable whenever J is asymptotically stable.

2) Suppose that there is a periodic orbit of (3) inside Ω. The existence of the heteroclinic orbit connecting E_{110} and $E_{11\tilde{N}}$ (Lemma 3), forces the projection of the periodic orbit onto the invariant plane $\Omega_{\tilde{N}=0}$ to be either a periodic solution or a finite union of solution trajectories traversed in one sense (these are solution trajectories because the partial uncoupling of our differential equations). But this contradicts Theorem 1. Furthermore, homoclinic orbits cannot exists around $E_{11\tilde{N}}$ for the same reason. This ends the proof of the theorem. □

Finally we present the proof of the global stability of $E_{11\tilde{N}}$.

Theorem 3 *Suppose $E_{11\tilde{N}}$ is locally asypmtotically stable. Then, $E_{11\tilde{N}}$ is globally asymptotically stable.*

Proof: By Theorem 1, E_{110} is globally asymptotically stable in $\Omega_{\tilde{N}=0}$. Let $V(I_1, I_2)$ be the Lyapunov function define above. Define the *Lyapunov* cylinder

$$\mathcal{C}_\epsilon = \{(I_1, I_2, \tilde{N}) \in \Omega : \ V(I_1, I_2) = \epsilon\}.$$

For any $\epsilon > 0$ such that $\mathcal{C}_\epsilon \subset \Omega$, let $\phi(t) \in \Omega$ be the flow of (3) such that $\phi(t_0) = (\phi_1(t_0), \phi_2(t_0), \phi_3(t_0))$ is on $\mathcal{C}_\epsilon$. So for $t > t_0$ it follows that $V(\phi^*(t)) < V(\phi^*(t_0))$ where $\phi^*(t)$ is the projection of ϕ onto $\Omega_{\tilde{N}=0}$. Therefore, $\phi(t)$ is in the interior of $\mathcal{C}_\epsilon$ for $t > t_0$.

Choose a neighborhood of radius δ, B_δ of $E_{11\tilde{N}}$ such that this point is stable and attractive. Then the projection of B_δ onto $\Omega_{\tilde{N}=0}$ is too a neighborhood of E_{110}. Choose ϵ such that the level curve $V(I_1, I_2) = \epsilon$ is completely contained in the projection of B_δ. Consider now the cylinder $\mathcal{C}_\epsilon$. Any orbit starting on this cylinder must go inside it as we have shown above. Moreover, by continuity of the flow the component $\phi_3(t)$ must simultaneously follow the direction imposed by the heteroclinic orbit γ (Lemma 3). Therefore for every $\phi(t_0) \in \Omega$ there exists a t such that $\phi(t) \in B_\delta$, $t > t_0$. The conclusion of the theorem follows. □

4 Conclusions

The environment where populations interact is a dynamic entity. In the study of infectious diseases, the role of the environment is played by the host

population. In this paper we have explored the implication upon epidemiological steady-states of variable host population size. As in previous published results [13] we have found that competitive exclusion and coexistence are outcomes that depend on the relative competitive ability of the strains and the similarity (in terms of virulence) that this strains must posses in order to guarantee coexistence. However, a changing host population alters significantly the patterns of coexistence that may develop during the course of this interaction. Previous results [4] have shown that the introduccion of variable population size through constant immigration rates, which it is arguable the simplest way of introducing variable population size into our system, affects the range of values of superinfection for which coexistence of two pathogen strain is possible. In this case windows of coexistence appear bounded by values of the superinfection coefficient σ contrary to the outcome of competition when the host population is assumed constant (where coexistence is guaranteed for large values of superinfection) [4].

The introduction of more realistic forms of variable population, changes dramaticaly the above results. In this paper we have shown that the parameter region where coexistence is possible when density dependent mortality is introduced into the model is disconnected and much reduced in size compared with the same parameter ranges in the cases of constant population size and constant recruitment. In Figures 8a and 8b we show the regions of coexistence for these last cases. The reader should compare them with Figure 1. Finally, in figure 9 we present a graph that shows the coexistence equilibrium point as a function of the superinfection index. In this case, for $\sigma > 1$ competitive exclusion of the first strain is more likely, whereas for $\sigma < 1$ competitive exclusion of the second strain eventually occurs.

Variable population size introduces a whole range of conditions that determine coexistence. Our results indicate that, at least for the case of density dependent mortality, coexistence is a rather special outcome of the interaction bewteen competing strains. In particular cannot be to similar (limiting similarity principle, see Remark 1 and inequality (5)) but also cannot be too disimilar (Figure 1). The boundaries of the regions that allow coexistence are function of several parameters and are impossible to determine them in a meaningful way. Figure 1 shows them as functions of $\tilde{v}_2$ and σ only. Other combinations of parameters are possible but they do not change our general conclusions.

As inequalities (5) and (6) show, non-trivial equilibrium point may ex-

ists even when R_i are not strictly greater than 1. This is a consequence of the presence of the superinfection coefficient σ. In fact, coexistence regions can be seen as functions of σ and R_i, the reproductive numbers of each strain.

Finally we point out that the results that we have obtained with the density-dependence function $\theta(N) = N(u+rN/K)$ are immediately generalizable to $\theta(N)$ a convex non-decreasing function of N with the properties described in Pugliese [17]. This kind of function allows for the partial decoupling of (1) into a system analogous to (3). Thus, our treatment of $\theta(N)$ as logistic density-dependent term involves no loss of generality. Moreover, including n strains and $\theta(N)$ as described allows the partial decoupling and the existence of heteroclinic connections (cf. lemma 3).

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FIGURE CAPTIONS

Figure 1a: We show the regions of coexistence, $I_i > 0$, as function of $\tilde{v}_2$ and σ. Parameter values are $\tilde{v}_1 = 0.5$, $u = 0.01$, $c = 5$, $m = 1$ and $\tilde{\beta}_i = c\tilde{v}_i / m + \tilde{v}_i$. The parameters $\tilde{v}_2$ and σ were varied in the intervals [0,10] and [0.51,10] respectively. Note the disconnected nature of the region of coexistence.

Figure 1b: We show the regions of coexistence, $I_i > 0$, as function of $\tilde{v}_2$ and σ. Parameter values are $\tilde{v}_1 = 0.5$, $u = 0.01$, $c = 5$, $m = 1$ and $\tilde{\beta}_i = c\tilde{v}_i / m + \tilde{v}_i$. The parameters v_2 and σ were varied in the intervals [0,2] and [0.51,10] respectively to show more clearly the regions of coexistence.

Figure 2: We show the region of feasibility of the equilibrium E_{01N}. The line $R_2 = 1$ is shown together with the curves defined by $\dfrac{\tilde{v}_2(\tilde{v}_2 + \tilde{u})}{\tilde{v}_2 - 1} = \tilde{\beta}_2$.

Figure 3a: The figure shows the global stability of the equilibrium E_{00N} in the invariant plane $I_1 = 0$ when $R_2 < 1$.

Figure 3b: The figure shows the global stability of the equilibrium E_{010} in the invariant plane $I_1 = 0$ when $R_2 > 1 + \dfrac{\tilde{\beta}_2 - \tilde{v}_2}{\tilde{v}_2(1 + \tilde{v}_2 + \tilde{u})}$.

Figure 4: The figure shows the global stability of the equilibrium E_{01N} in the invariant plane $I_1 = 0$ with $1 < R_2 < 1 + \dfrac{\tilde{\beta}_2 - \tilde{v}_2}{\tilde{v}_2(1 + \tilde{v}_2 + \tilde{u})}$.

Figure 5: The figure shows the global stability on the planes $I_i = 0$ when $R_i < 1$.

Figure 6: The figure shows the global stability on the planes $I_i = 0$ when $1 < R_i < 1 + \dfrac{\tilde{\beta}_i - \tilde{v}_i}{\tilde{v}_i(1 + \tilde{v}_i + \tilde{u})}$.

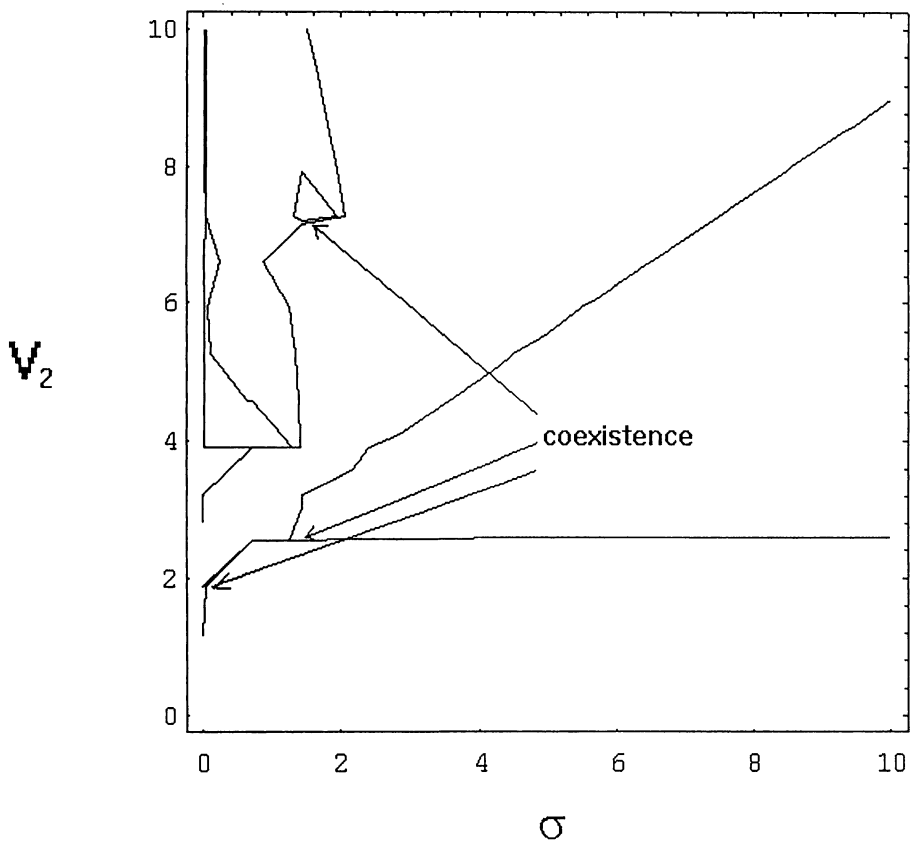
Figure 7a: The figure shows the global stability on the planes $I_i = 0$ when $R_1 < 1$ and $1 < R_2 < 1 + \frac{\tilde{\beta}_2 - \tilde{v}_2}{\tilde{v}_2(1 + \tilde{v}_2 + \tilde{u})}$. Analogous geometries are obtained when the indices are replaced with 1 in the previous inequalities.

Figure 7b: The figure shows the global stability on the planes $I_i = 0$ when $R_1 < 1$ and $R_2 > 1 + \frac{\tilde{\beta}_2 - \tilde{v}_2}{\tilde{v}_2(1 + \tilde{v}_2 + \tilde{u})}$. Analogous geometries are obtained when the indices are replaced with 1 in the previous inequalities.

Figure 8a: We show the regions of coexistence, $I_i > 0$, for the constant population size model of Nowak and May [11] as function of $\tilde{v}_2$ and σ. Parameter values are $\tilde{v}_1 = 0.5$, $u = 0.01$, $c = 5$, $m = 1$ and $\tilde{\beta}_i = c\tilde{v}_i / m + \tilde{v}_i$. The parameters $\tilde{v}_2$ and σ were varied in the intervals [0,10] and [0.51,10] respectively. The region of coexistence is connected and the lower boundary is largely independent of σ.

Figure 8b: We show the regions of coexistence, $I_i > 0$, for the constant recruitment model with bN replaced with Λ, and (N) replaced by $\tilde{u}N$, as function of $\tilde{v}_2$ and σ. Parameter values are $\tilde{v}_1 = 0.5$, $u = 0.01$, $c = 5$, $m = 1$ and $\tilde{\beta}_i = c\tilde{v}_i / m + \tilde{v}_i$. The parameters v_2 and σ were varied in the intervals [0,2] and [0.51,10] respectively to show more clearly the regions of coexistence. In this case the region of coexistence is still connected but the lower boundary is and increasing function of the superinfection index.

Figure 9: The graph shows the location of the coexistence equilibrium as the superinfection index changes. Parameter values for this case are $\beta_1 = 5$, $\beta_2 = 3$, $v_1 = 0.04$, $v_2 = 0.01$, $u = 1.0$. Note that increased susceptibility shifts the equilibrium towards competiting exclusion of the first strain, whereas increased resistence shifts it toward competitive exclusion of the second strain.



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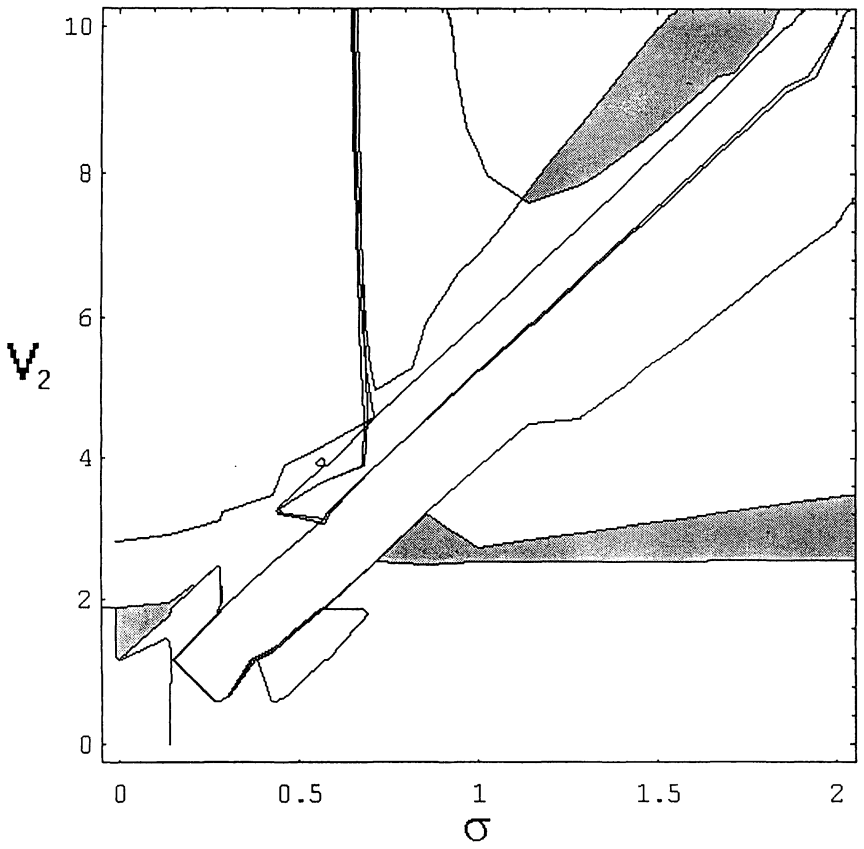

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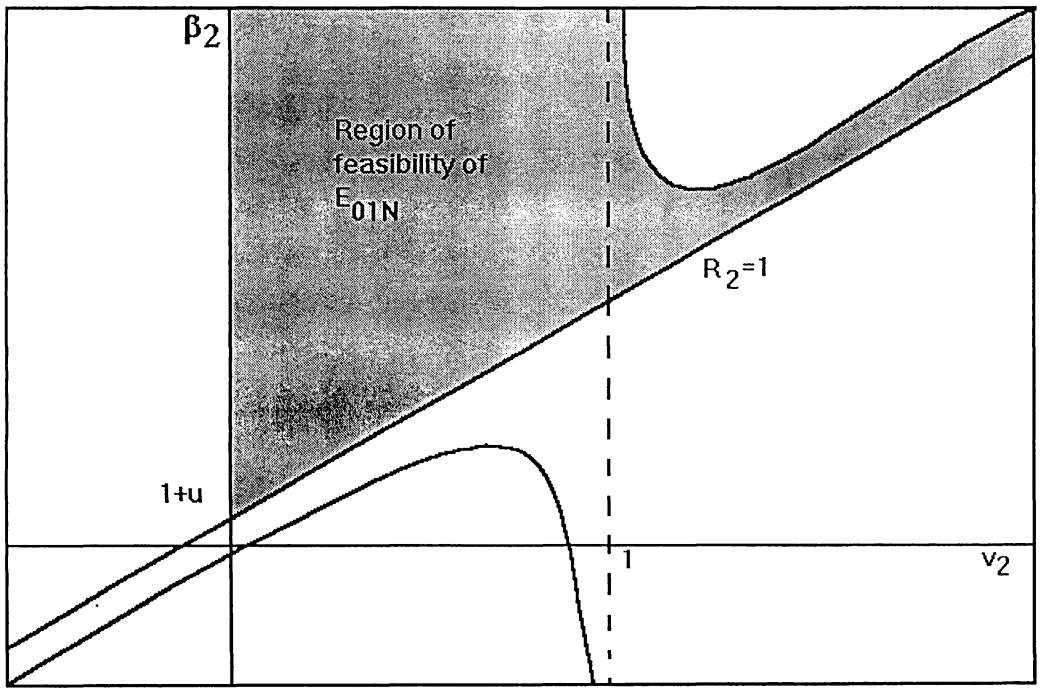
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feasibility of
E01N
R2=1
1+u
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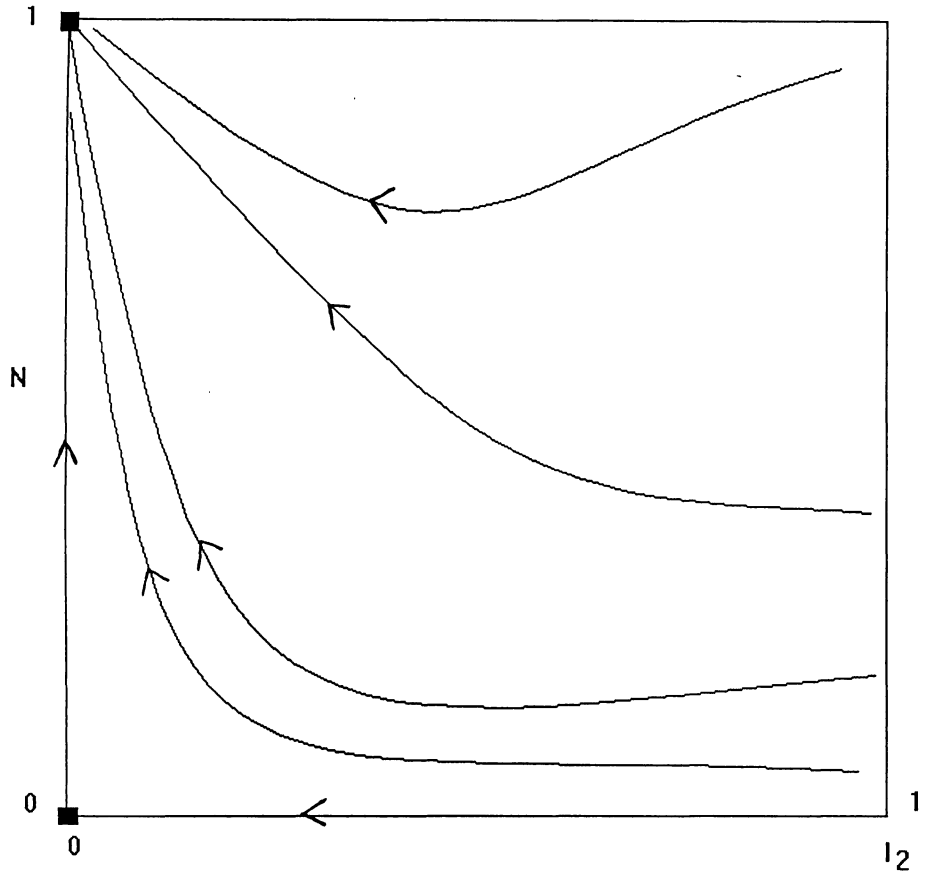
v2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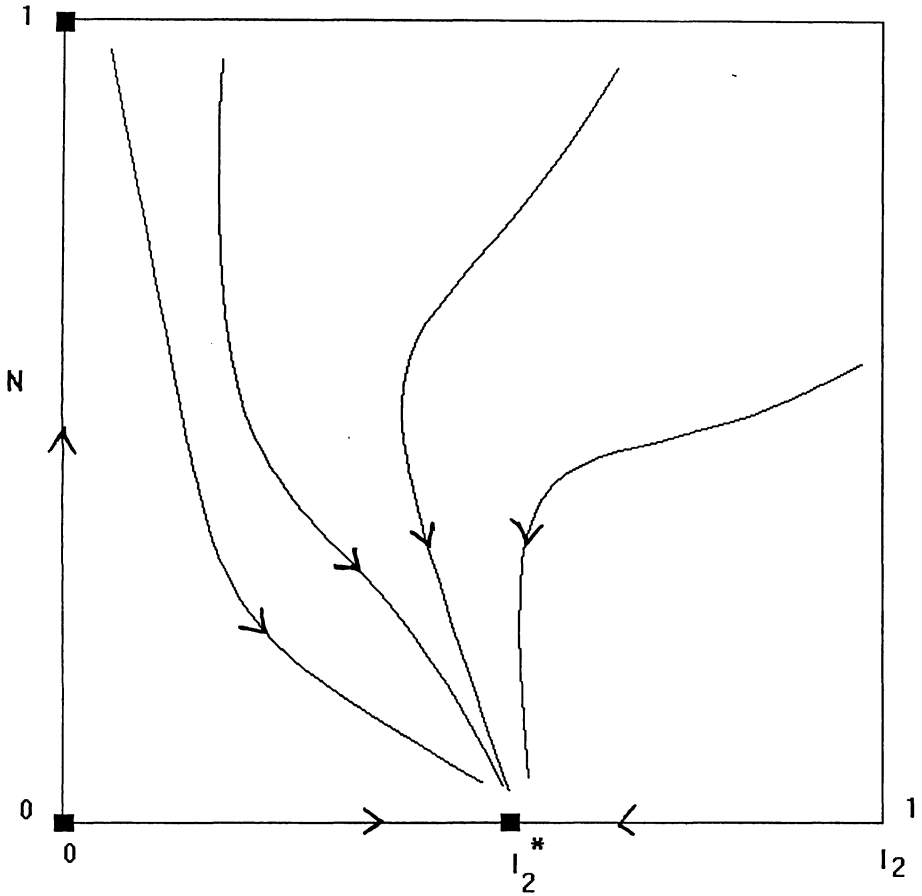
0
1
I_2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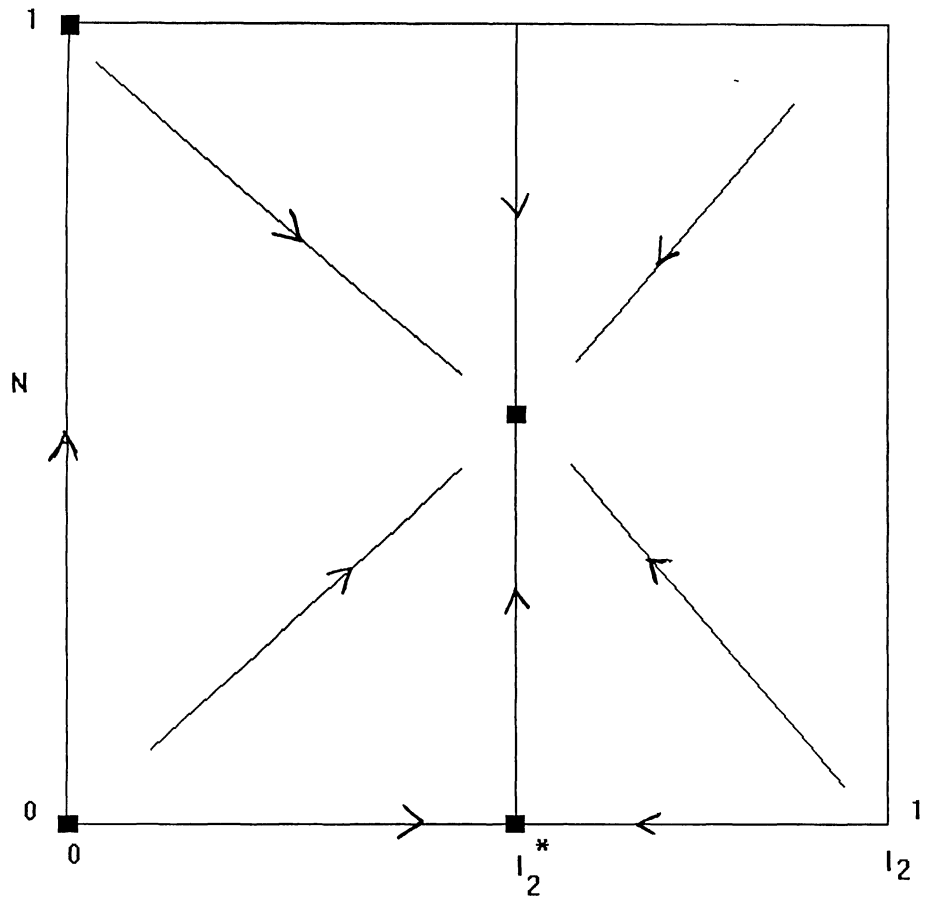
I_2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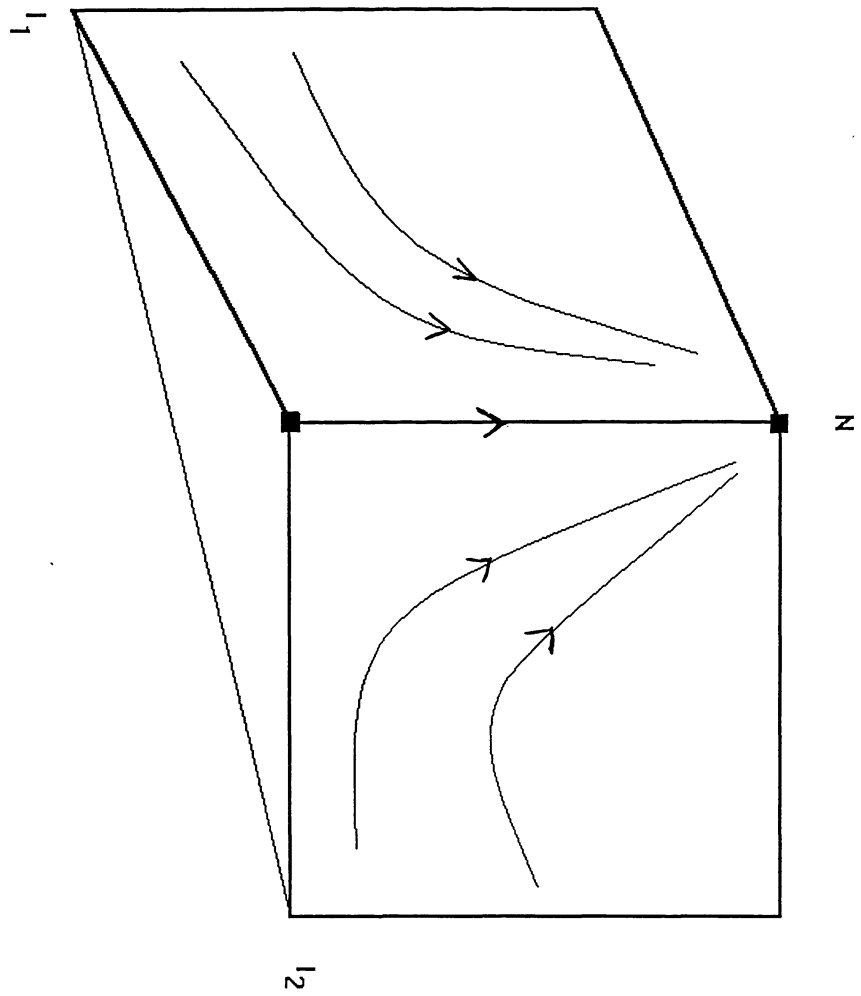
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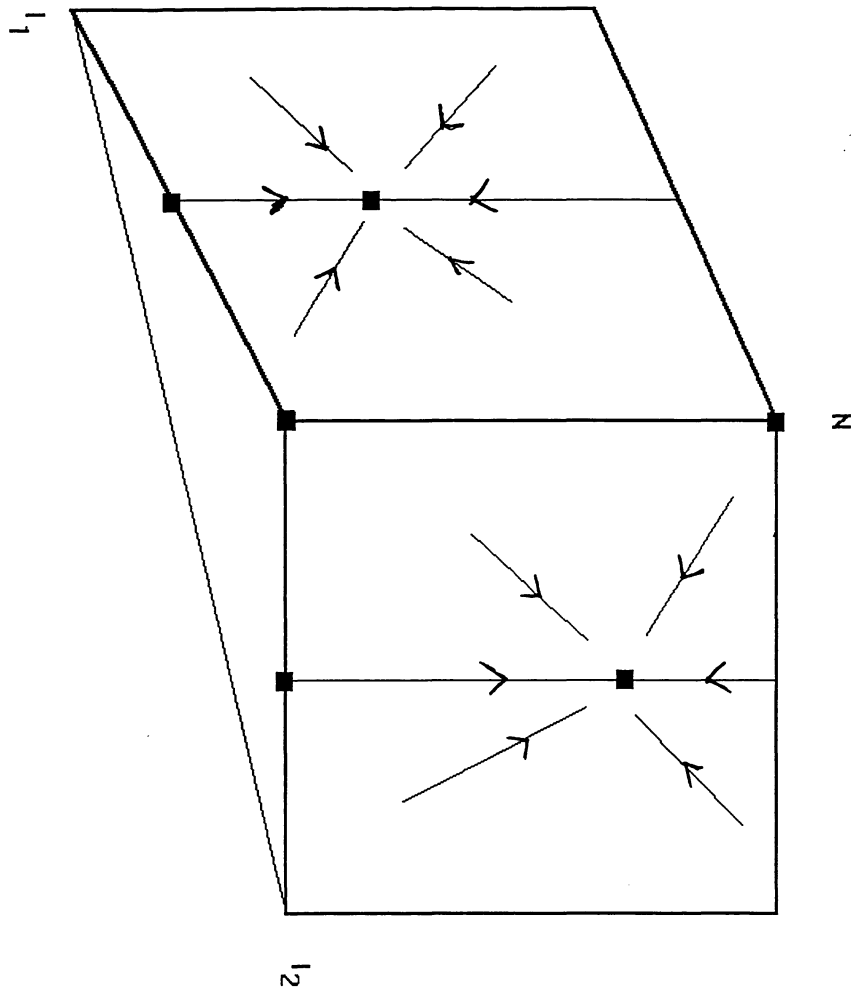
l_2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l2

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l_2

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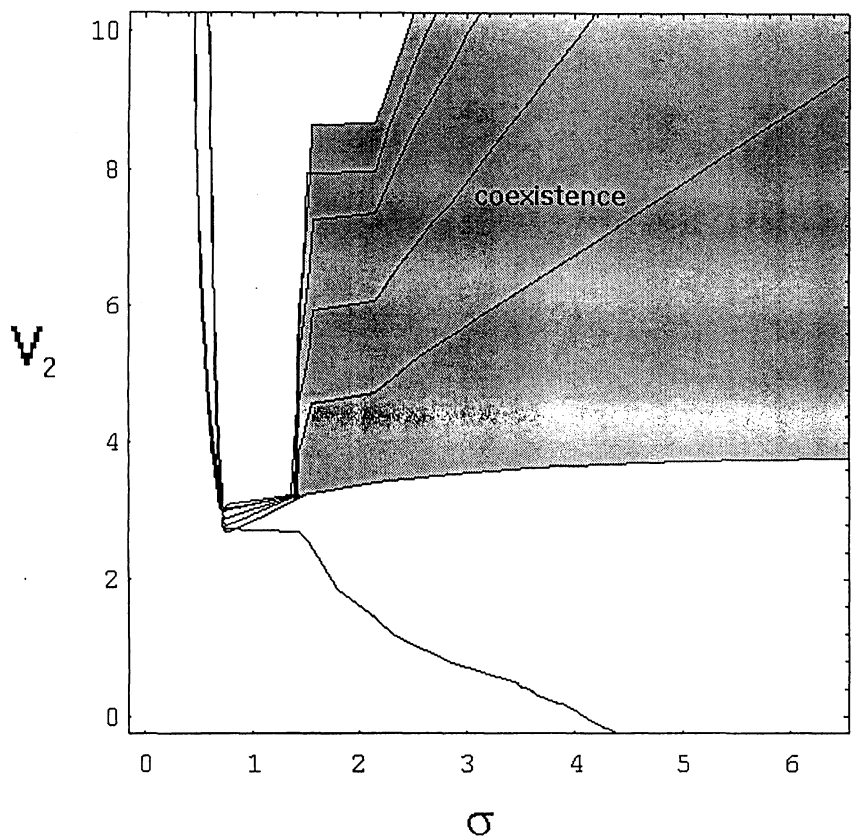
l_2



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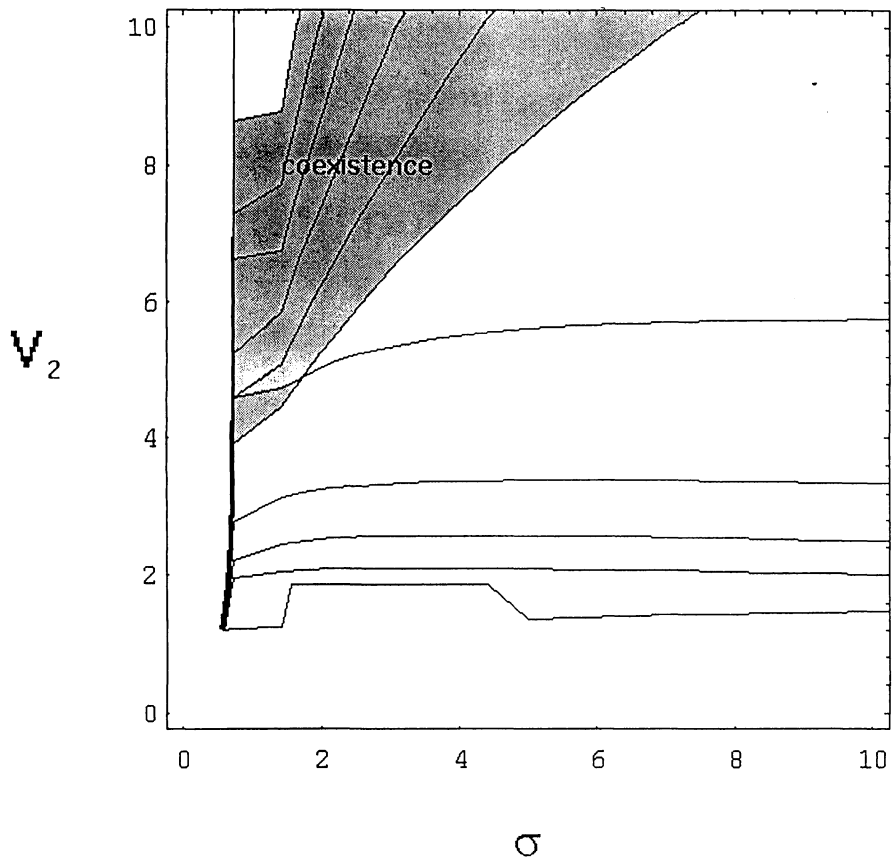

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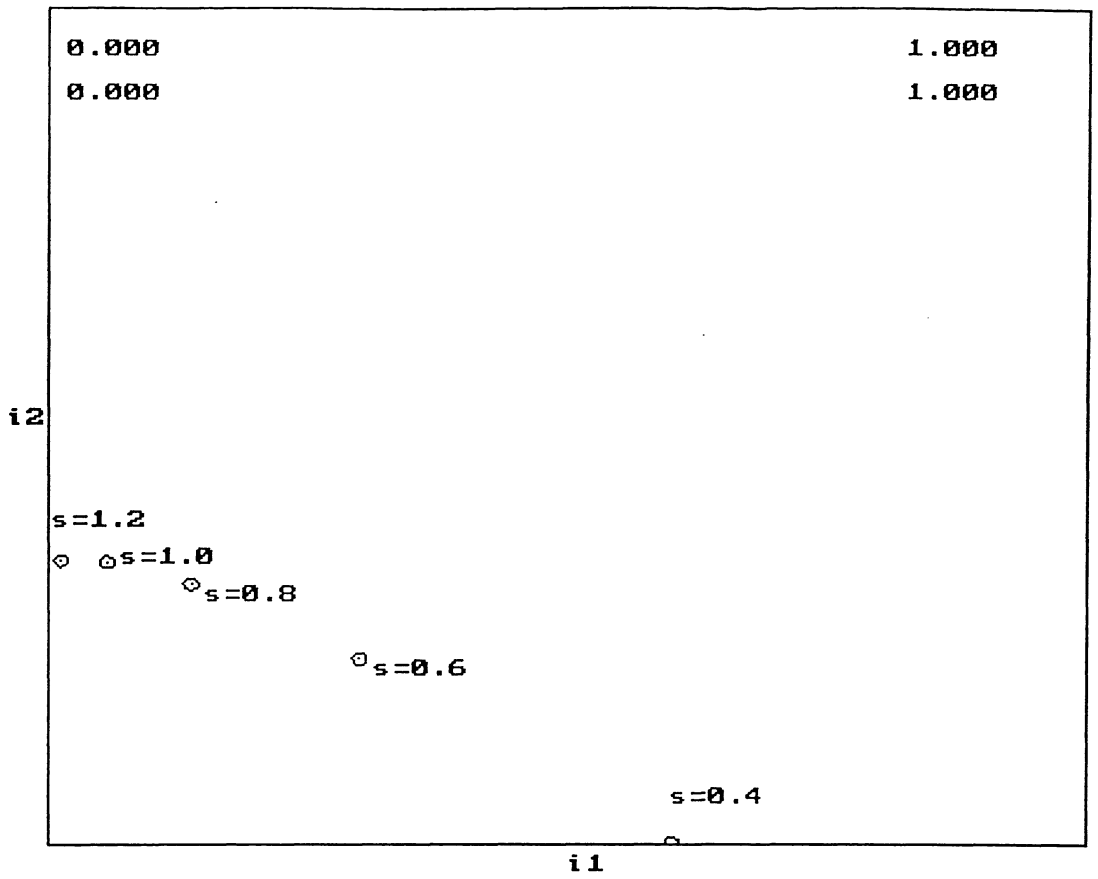
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