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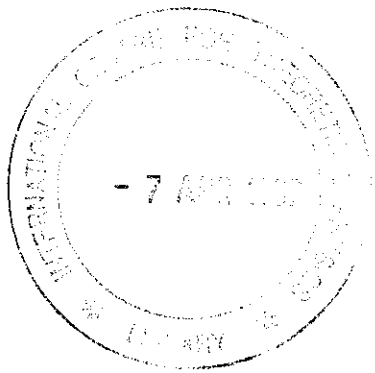
"Competitive exclusion in a vector-host model for the dengue fever"



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Competitive exclusion in a vector-host model for the dengue fever.

Proposed running head: Competitive exclusion in dengue.

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Abstract

We study a system of differential equations that models the population dynamics of an SIR vector transmitted disease with two pathogen strains. This model arose from our study of the population dynamics of dengue fever. The dengue virus presents four serotypes each induces host immunity but only certain degree of cross-immunity to heterologous serotypes. Our model has been constructed to study both the epidemiological trends of the disease and conditions that permit coexistence in competing strains. Dengue is in the Americas an epidemic disease and our model reproduces this kind of dynamics. We consider two viral strains and temporary cross-immunity. Our analysis shows the existence of an unstable endemic state ('saddle' point) that produces a long transient behavior where both dengue serotypes cocirculate. Conditions for asymptotic stability of equilibria are discussed supported by numerical simulations. We argue that the existence of competitive exclusion in this system is product of the interplay between the host superinfection process and frequency-dependent (vector to host) contact rates.

1 Introduction

Dengue fever is a viral disease endemic in many areas of the world that is invading and recolonizing regions where either it was absent or it had been eradicated. The dengue virus has 4 different serotypes. We construct and analyze a mathematical model for its transmission dynamics. The model is a system of differential equations that incorporates variable population size in both host and mosquito populations, two co-circulating strains and frequency dependent biting rates. The model constitutes a framework to discuss conditions for coexistence or competitive exclusion of closely related pathogen strains.

In the next section we give a basic background on the disease summarizing its epidemiological importance as well as the main features incorporated into our model. Then we proceed with the model formulation and discuss previous work on the principle of competitive exclusion. This section is followed by model analysis in absence of disease induced mortality (negligible virulence). Then we discuss the computational results for the case of non-negligible virulence and, finally, in the last section, we compare our findings with other models on superinfection, variable population size and frequency dependent infection rates.

1.1 Dengue fever

We start with a brief summary of the epidemiology of dengue. We follow references [23], [22] as well as others that are indicated where appropriate.

In developing countries population growth is an important factor that contributes to the increase in the incidence of communicable diseases which affect mainly the urban poor, with infants and children among the groups particularly at risk [23], [22]. Urbanization and population growth increase the demand on basic essential services such as housing, water supply, etc., and at the same time induce conditions that increase the transmission potential of some vector-borne diseases [23]. Inadequacies in water supplies require large-scale water storage which are ideal breeding habitats for *Aedes* spp mosquitoes, the vectors of dengue fever, dengue hemorrhagic fever and dengue shock syndrome as well as yellow fever. Changes in food habits lead to increase use of tinned food and more use of disposable containers that provide breeding sites to vectors of this type. In summary population growth, urbanization and poverty enhance presence and transmission of infectious diseases.

Unfortunately not only dengue has increased its incidence in urban centers of the developing world but also yellow fever, malaria and Chagas disease have been benefited. The destruction of city water supplies, temporary housing for refugees, high fertility and rural to urban migration and the steady deterioration of urban environments have led to sustained growth in density and area occupied by *Aedes aegypti* and *Aedes albopictus*, two of the main vectors of dengue virus.

Other important problems of the dengue virus in the Americas and elsewhere are the public health consequences of global warming [25]. Of concern is the potential spread of dengue through the vector *Aedes albopictus*, recently introduced to the American continent [24].

Dengue causes a spectrum of illnesses in humans ranging from clinically inapparent to severe and fatal hemorrhagic disease [8]. Classical dengue fever is generally observed in older children and adults and is characterized by sudden onset of fever, frontal headache, nausea, vomiting and other symptoms. The acute illness last for 3 to 7 days is usually benign. The hemorrhagic form of dengue and its associated dengue shock syndrome (DHF-DSS) is most commonly observed in children under the age of 15 years but it can also occur in adults [8]. It is characterized by acute onset of fever and a variety of symptoms that last 2 to 7 days. This form of dengue can terminate in death of the patient.

Dengue is produced by viruses of the genus *Togaviridae*, subgenus *Flavivirus*. Four distinct dengue viruses have been distinguished, denoted by types 1, 2, 3 and 4. Dengue viruses can infect only a restricted number of vertebrates but it is an essentially human disease [10]. Infection by any dengue virus strain produces long lasting immunity but only temporary cross-immunity to other serotypes. Three of the vectors are *Aedes aegypti* Linnaeus, *Aedes albopictus* Skuse, and *Aedes scutellaris* Walk. *Aedes aegypti* mosquitoes acquire infection from infected individuals 6 to 18 h before onset of fever and then for the duration of the fever. A minimum extrinsic incubation period of 8 to 14 days is required after an infective blood meal before the mosquito becomes infectious. The infection in the vector is for life. Dengue virus is transmitted in two cycles: urban and sylvan although, as mentioned before, it is predominantly a human virus [10].

There are no effective programs for vector control and, as a consequence, the absolute numbers of dengue infection and dengue infection rates have increased during the last 40 years [11]. Unfortunately, countries where positive results exist for vector eradication have been suffering from epidemic outbreaks: the disease is coming back. Dengue viruses were introduced in

the Americas around 1960 and since, dengue has been reported in countries where it was absent before as Cuba, México [19], the United States, most Central America, Ecuador, Perú, Paraguay, Bolivia, Argentina and Brazil [11].

Dengue transmission occurs throughout the year in endemic tropical areas but there exists, however, a distinct cyclical pattern associated with the rainy season [8]. In particular, in Thailand where the vector life cycle is highly domiciliary, temperature and humidity conditions during the rainy season favor survival of infected mosquitoes. In the Americas the situation is different since in these areas larvae develop in the outdoors. Here, peak transmission takes place in the days of highest rainfall and warmer temperatures season [8].

In regions where mosquito and humans exists, an introduction of dengue virus may produce an epidemic depending upon a) the strain of the virus (influencing magnitude and duration of viremia), b) the susceptibility of the human population, c) the density, behavior, and competence of the mosquito vector population, and d) the introduction of the virus into an area where it has contact with the local mosquito population [8]. Severity of dengue fever has been associated with secondary dengue infections although its causes are far from being explained. Epidemiological studies in Thailand suggest that an important risk factor for DHF-DSS is the presence of preexisting dengue antibody at subneutralizing levels. Also, endemic DHF-DSS is found in areas where *Aedes aegypti* densities are high and dengue virus of multiple types are endemic. Moreover, DHF-DSS is associated with individuals older than 1 year with a secondary type antibody response and with primary infections in newborn babies whose mother where immune to dengue [8], [10]. These facts led to the formulation of the secondary infection or immune enhancement hypothesis to explain it [8]. This hypothesis states that only those persons experiencing a second infection with heterologous dengue serotype present DHF-DSS. In particular it has been found that only secondary dengue-2 disease is immunologically enhanced and that infection with this virus serotype cause the majority of DSS cases [11]. Other factors are also associated with DHF-DSS. These are sex (more frequent infections in females), nutritional status (higher incidence in well-nourished babies of middle and upper socioeconomic class), and the interval between first and second infections.

To conclude this brief review of the epidemiology of dengue, we show in Table 1 a summary of dengue epidemic in several countries of the world.

1.2 Superinfection and coexistence

In dengue certain sequences of infection appear to be more damaging to the host than others. We model this process using a susceptibility coefficient (cf. [12] and [4]). This coefficient allows us to explore varying degrees of susceptibility to secondary infections and their effect on the asymptotic dynamics of the disease. Through model analysis we explore the consequences of coupling two populations that differ in the infection pattern (SIR with superinfection in the host, SI in the vector), and the effect of frequency-dependent infection rates on the coexistence of closely related strains.

Most diseases are produced by an spectrum of closely related pathogens rather than by single strains and dengue is clearly an example of this assertion. In dengue an analogous phenomenon to superinfection (Nowak and May [21], May and Nowak [16]) occurs. One strain invades the host population, produces a brief period of temporary immunity to other strains but when the immunity is lost the host becomes susceptible to reinfection with another strain. In dengue, before reinfection can occur, there is a period where the host is resistant, in varying degrees, to all strains [8]. In dengue fever we are thus confronted with a vector-transmitted disease, co-circulating strains, certain degree of cross-immunity or even increased susceptibility to infection, and a variable host population size. Under these conditions one important theoretical problem that we address here is that of the coexistence of all strains or the eventual extinction of some of them. A similar problem has been theoretically explored by several authors [12], [2], [13], [5].

There are numerous published results discussing the problem of coexistence in pathogen-host interactions. Levin and Pimentel [12] constructed a mathematical SI model where the population in the absence of disease grows exponentially. Two strains with different virulences compete with each other. The most virulent strain can 'takeover' hosts already infected with the less virulent strain. With these assumptions a globally stable equilibrium is possible where both strains may coexist [3]. The stability of the positive equilibrium is only guaranteed for certain range of values of superinfection. Outside this range one of the boundary equilibria is asymptotically stable.

Bremermann and Thieme [2] postulate a competitive exclusion principle in an SIR epidemic in a population with variable size. Several strains compete for a single host population. The pathogens differ on their virulence. In this model virulence is a strictly convex function of the transmission rate implying that the evolution of virulence leads to a transmission rate that

maximizes the basic reproductive number of the pathogen [2].

Castillo-Chavez et al. [13] 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. Mena-Lorca, Velasco-Hernandez and Castillo-Chavez [17] studied the effect of variable population, virulence and density-dependent population regulation. In this model too, coexistence is feasible only in certain window of parameter space.

2 A mathematical model for dengue with two strains

Previous models for dengue fever are reported in [26] and [20]. The former is a cost-effectiveness model for the management of dengue. It addresses sociological-epidemiological issues that we do not consider here. The second model follows the same basic methodology that we adopt. This model [20] incorporates an incubation or latent period for both mosquitoes and humans. Both total populations of hosts and vectors are considered constant. The model predicts an asymptotically stable endemic state if the basic reproductive number is greater than one.

In the model that we analyze here, we consider variable population sizes of both hosts and vector populations, we do not incorporate the exposed compartment, but include instead the existence of a second co-circulating strain that can produce secondary infections in those individuals either susceptible or already recovered from a primary infection with a different strain.

2.1 Model equations

Consider a human population settled in a region where a mosquito population of the genus *Aedes* is present and carrier of the dengue virus.

Model equations then stand as follows ($' = d/dt$):

$$\begin{aligned} S'(t) &= h - (B_1 + B_2)S - uS, \\ I_1'(t) &= B_1 S - \sigma_2 B_2 I_1 - uI_1, \\ I_2'(t) &= B_2 S - \sigma_1 B_1 I_2 - uI_2, \\ Y_1'(t) &= \sigma_1 B_1 I_2 - (e_1 + u + r)Y_1, \\ Y_2'(t) &= \sigma_2 B_2 I_1 - (e_2 + u + r)Y_2 \\ R'(t) &= r(Y_1 + Y_2) - uR \end{aligned} \tag{1}$$

and

$$\begin{aligned} M'(t) &= q - (A_1 + A_2)M - \delta M, \\ V_1'(t) &= A_1 M - \delta V_1, \\ V_2'(t) &= A_2 M - \delta V_2. \end{aligned} \tag{2}$$

$N = S + I_1 + I_2 + Y_1 + Y_2 + R$ and $T = M + V_1 + V_2$ are the host and vector total population sizes respectively (see Table 2 for other parameter definitions and values). Primary infections in human hosts are produced by either of the two strains at rates

$$B_i = \beta_i V_i/(c + \omega_h N)$$

for $i = 1, 2$ (in vector to host transmission). Primary infections in vectors are produced at rates

$$A_i = \alpha_i(I_i + Y_i)/(c + \omega_v N).$$

These function forms describe frequency-dependent disease transmission. Both are special cases of the Holling type II functional response [6] and are also generalizations the contact rates of the Ross-Macdonald model for Malaria [1] and for Chagas disease [27].

We assume that once a mosquito is infected it never recovers and it cannot be reinfected with a different strain of virus. Secondary infections, therefore, may take place only in the host. Two cases can occur: either previously I_1 individuals are infected by strain 2, through contact with infected mosquitoes V_2, becoming Y_2 hosts, or previously I_2 individuals are infected with strain 1, through contact with V_1 mosquitoes, to become Y_1 infected hosts, at rates $\sigma_1 B_1 I_2$ and $\sigma_2 B_2 I_1$, respectively. Here, σ_i is a positive real number that may mimic either cross-immunity ($\sigma_i < 1$) or increased susceptibility ($\sigma_i > 1$) by immune enhancement. This type of dynamics is analogous to superinfection (cf. [21]). In dengue, the immunity developed after infection is a factor that does not appear in superinfection models. In dengue, either of the primary infected populations can be reinfected with the other strain. General results on the effects of cross-immunity in SIS and SI models respectively [21], [17], indicate that for certain values of σ coexistence of competing strains is possible. As we will show, the existence of cross-immunity together with the induction of specific permanent immunity, and frequency dependent contact rates, prevent coexistence. The generic outcome of our model is competitive exclusion although, in some cases, in a very long time scale.

To summarize, if $\sigma_i < 1$, primary infections confer partial immunity to strain i; if $\sigma_i = 1$ secondary infections with strain i take place as if they were primary infections, and if $\sigma_i > 1$ primary infections increase susceptibility to strain i. Once an individual has suffered from both infections it gets immunity to both strains at a rate r independent of the sequence of infections.

Since the equation for the total vector population is

$$T' = q - \delta T,$$

we have that as $t \to \infty$, $T(t) \to q/\delta$. This allows us to substitute $M = q/\delta - V_1 - V_2$ making the equation for M in (2) redundant.

2.2 Basic reproductive number

Let

$$\Omega = \{(S, I_1, I_2, Y_1, Y_2, R, V_1, V_2) \ : \ S + I_1 + I_2 + Y_1 + Y_2 + R \leq h/u,$$

$$V_1 + V_2 \leq q/\delta\}$$

be the set bounded by the total host and vector population in the absence of disease. We can immediately identify three equilibrium solutions to (1—2), the disease-free equilibrium $E_0^* = (S^*, 0, 0, 0, 0, 0, 0, 0)$ and the two (boundary) equilibria

$$E_1^* = (S_1^*, I_1^*, 0, 0, 0, 0, V_1^*, 0),$$

where only strain 1 survives, and

$$E_2^* = (S_2^*, 0, I_2^*, 0, 0, 0, 0, V_2^*)$$

where only strain 2 survives.

The basic reproduction number is defined as the number of secondary infections that a single infectious individual produces in a population where all hosts are susceptible. It provides an invasion criterion for the initial spread of the virus in a susceptible population

To find the basic reproductive number for our model we equate (1–2) to zero and rewrite it as

$$\begin{aligned} S &= h/(u + B_1 + B_2), \\ I_i &= B_i S/(u + \sigma_j B_j), \ i \neq j, \ i, j = 1, 2, \\ Y_i &= \sigma_i B_i I_j/(u + e_j + r), \ i \neq j, \ i, j = 1, 2, \end{aligned}$$

$$\begin{aligned} R &= r(Y_1+Y_2)/u, \\ V_1 &= qA_1/(\delta+A_1+A_2), \\ V_2 &= qA_2/(\delta+A_1+A_2). \end{aligned}$$

Let $K = (B_1, B_2, A_1, A_2)'$ ($'$ denotes transpose). Substituting the above expressions into the definition of B_i and A_i we obtain a system of four nonlinear algebraic equations in terms of B_i and A_i. We denote this system by $\Phi(K)$. The solutions of $K = \Phi(K)$ give, by construction, all the equilibrium points of (1–2). This equation also allows an easy computation of the next generation operator [7] and the associated basic reproduction number. By construction, the next-generation operator is simply the Jacobian of Φ evaluated at the disease-free equilibrium (given by $B_1 = B_2 = A_1 = A_2 = 0$):

$$D\Phi(0) = \begin{pmatrix} 0 & 0 & \frac{\beta_1 h}{u^2(c+h\omega_h/u)} & 0 \\ 0 & 0 & 0 & \frac{\beta_2 h}{u^2(c+h\omega_h/u)} \\ \frac{\alpha_1 q}{\delta^2(c+h\omega_v/u)} & 0 & 0 & 0 \\ 0 & \frac{\alpha_2 q}{\delta^2(c+h\omega_v/u)} & 0 & 0 \end{pmatrix}.$$

The basic reproduction number is therefore

$$\mathcal{R}_0 = \max\{\sqrt{R_1},\ \sqrt{R_2}\}$$

with

$$R_i = \frac{\alpha_i \beta_i h q/\delta u}{u\delta(c+h\omega_h/u)(c+h\omega_v/u)}.$$

This formula is a generalization of the Ross-Macdonald basic reproductive number to the case of multiple strains, frequency-dependent contact rates and variable population size in both host and vector.

It follows then that if $\mathcal{R}_0 > 1$, then the disease is able to invade the host population. Otherwise, if $\mathcal{R}_0 \leq 1$ the virus eventually disappears from the host population (local result).

3 Equilibrium points

We are interested in the conditions that guarantee the permanence of dengue as an endemic disease. There are, in our model, boundary equilibria (where only one strain is present), and the coexistence equilibrium. In the following section we analyze the former. Its existence is determined by the relative

magnitude of the basic reproductive number of each strain. After that, we present the numerical results that characterize the stability properties of the coexistence equilibrium.

3.1 Boundary equilibria

Whenever $R_j < 1$ then B_j, A_j both vanish. Therefore, $R_i > 1$, $R_j < 1$, $i \neq j$, $i, j = 1, 2$, implies the existence of E_i^* which is also a unique endemic equilibrium (where only one strain is present). Under these conditions the asymptotic dynamics of system (1–2) is completely contained in an invariant manifold $\Omega_i \subset \Omega$ defined as

$$\Omega_i = \{(S_i, I_i, V_i) : \ 0 < S_i + I_i \leq h/u, \ 0 < V_i \leq q/\delta\}.$$

For $V_j = I_j = Y_j = R = 0$ (within Ω_i) our model is described by the equations

$$\begin{aligned} S'(t) &= h - B_i S - uS, \\ I_i'(t) &= B_i S - uI_i, \\ V_i'(t) &= \frac{\alpha_i I_i}{c + \omega_v N}(q/\delta - V_i) - \delta V_i, \end{aligned} \tag{3}$$

with the total host population size (in Ω_i) satisfying the equation

$$N'(t) = h - uN.$$

In (3) the unique (non-trivial) equilibrium point is the projection of E_i^* onto the subspace Ω_i. Moreover, virulence (extra mortality induced by the virus) plays no role in this asymptotic system.

Since $N(t) \longrightarrow h/u$ as $t \longrightarrow \infty$, (3) can be reduced further to the equations

$$\begin{aligned} I_i'(t) &= \frac{\beta_i V_i}{c + \omega_h h/u}(h/u - I_i) - uI_i, \\ V_i'(t) &= \frac{\alpha_i I_i}{c + \omega_v h/u}(q/\delta - V_i) - \delta V_i, \end{aligned}$$

that are equivalent to the Ross Macdonald malaria model (Aron and May [1]). Therefore, whenever $R_i > 1$, this limiting system is globally asymptotically stable in Ω_i [18].

3.1.1 Boundary equilibria when virulence is negligible

To obtain precise results on the existence and stability properties of equilibrium points we assume that dengue does not produce significant mortality ($e_j = 0$). The assumption is not justifiable in all regions where dengue is endemic but it is a useful first approximation.

In the absence of virulence, the host population is asymptotically constant and therefore we can reduce the dimension of our model equations by one. We drop the equation for S. Let $\omega_h = \omega_v = \omega$, $\hat{N} = h/u$ and $\hat{T} = q/\delta$ and take $e_i = 0$.

To facilitate the analysis and interpretation of our results we compute the Jacobian matrix of (1-2) by reordering it as indicated in (4) below.

Consider the boundary equilibrium

$$E_1^* = (V_1^*, I_1^*, V_2^*, I_2^*, Y_1^*, Y_2^*, R^*) \tag{4}$$

where

$$V_2^* = I_2^* = Y_1^* = Y_2^* = R^* = 0$$

and

$$V_1^* = \frac{u\delta(R_1 - 1)}{b_1(\delta + a_1\hat{N})},\ I_1^* = \frac{u\delta(R_1 - 1)}{a_1(b_1\hat{T} + u)},$$

with

$$a_i = \frac{\alpha_i}{c + \omega\hat{N}},\ b_i = \frac{\beta_i}{c + \omega\hat{N}}.$$

With this new order the Jacobian has the form

$$J(E_1^*) = \begin{pmatrix} G_1 & G_2 \\ 0 & G_4 \end{pmatrix},$$

where

$$G_1 = \begin{pmatrix} -\delta - a_1 I_1^* & a_1(\hat{T} - V_1^*) \\ b_1(\hat{N} - I_1^*) & -u - b_1 V_1^* \end{pmatrix},$$

$$G_4 = \begin{pmatrix} -\delta & a_2(\hat{T} - V_1^*) & 0 & a_2(\hat{T} - V_1^*) & 0 \\ b_2(\hat{N} - I_1^*) & -u - \sigma_1 b_1 V_1^* & 0 & 0 & 0 \\ 0 & \sigma_1 b_1 V_1^* & -(u + r) & 0 & 0 \\ \sigma_2 b_2 I_1^* & 0 & 0 & -(u + r) & 0 \\ 0 & 0 & r & r & -u \end{pmatrix}.$$

The eigenvalues of $J(E_1^*)$ are given by the eigenvalues of G_1 and G_4. When $R_1 > 1$, G_1 has two eigenvalues with negative real parts. Eigenvalues of G_4 are given by $-u$, $-(u+r)$ and by the roots of the polynomial

$$\lambda^3 + A\lambda^2 + B\lambda + C = 0$$

where

$$\begin{aligned} A &= 2u + \sigma_1 b_1 V_1^* + r + \delta, \\ B &= (u+r)\Big(u + \sigma_1 b_1 V_1^*\Big) + \delta(u + \sigma_1 b_1 V_1^*) - u\delta\frac{R_2}{R_1} - \sigma_2 a_2 b_2 \frac{\delta V_1^*}{a_1}, \\ C &= \delta(u + \sigma_1 b_1 V_1^*)(u+r) - (u+r)u\delta\frac{R_2}{R_1} - (u + \sigma_1 b_1 V_1^*)\sigma_2 a_2 b_2 \frac{\delta V_1^*}{a_1}. \end{aligned}$$

In the above we have used the equivalencies

$$(\hat{N} - I_1^*)(\hat{T} - V_1^*) = \frac{\hat{N}\hat{T}}{R_1},\ \frac{u}{b_1 V_1^*} = \frac{\delta + a_1\hat{N}}{\delta(R_1 - 1)},\ I_1^*(\hat{T} - V_1^*) = \frac{\delta V_1^*}{a_1}.$$

Our threshold parameters are given in terms of bounds for the superinfection coefficients σ_1 and σ_2. Thus, they set bounds for the level of induced resistance or increased susceptibility that each strain produces in the host.

Let

$$\begin{aligned} \sigma_1^* &= \max\Big\{0,\ (\frac{R_2}{R_1} - 1)\frac{\delta + a_1\hat{N}}{\delta(R_1 - 1)}\Big\}, \\ \sigma_2^* &= f(\sigma_1) = \frac{\delta(u+r)}{a_2 b_2 I_1^*(\hat{T} - V_1^*)}\Big(1 - \frac{u}{u + \sigma_1 b_1 V_1^*}\frac{R_2}{R_1}\Big). \end{aligned} \tag{5}$$

Then the following hold

Lemma 1:

1. $\sigma_1 > \sigma_1^*$ *implies* $\sigma_2^* > 0$;
2. $\sigma_1 > \sigma_1^*$ *and* $\sigma_2 < \sigma_2^*$ *implies* $A > 0$, $B > 0$, $C > 0$ *and* $AB > C$;
3. $\sigma_1 < \sigma_1^*$ *or* $\sigma_2 > \sigma_2^*$ *imply* $C < 0$.

The proofs of 1 and 3 are straightforward. To show 2, let $\sigma_1 > \sigma_1^*$ and $\sigma_2 < \sigma_2^*$. It is easy to see that $\sigma_2 < \sigma_2^*$ implies $C > 0$. Note that

$$\delta(u + \sigma_1 b_1 V_1^*) > u\delta\frac{R_2}{R_1}.$$

Hence

$$B(u+\sigma_1 b_1 V_1^*) \geq (u+\delta)(u+\sigma_1 b_1 V_1^*)\delta - (u+\sigma_1 b_1 V_1^*)\sigma - 2a_2 b_2 I_1^*(\hat{T}-V_1^*) \geq C,$$

but $C > 0$, therefore $B > 0$. To show that $AB > C$ we note that $\sigma_2 < f(\sigma_1)$, thus obtaining

$$\sigma_2 a_2 b_2 I_1^*(\hat{T} - V_1^*) \leq \delta(u+r) - u\delta \frac{u+r}{u+\sigma_1 b_1 V_1^*} \frac{R_2}{R_1}.$$

It follows then that

$$\begin{aligned} AB &\geq (2u + \sigma_1 b_1 V_1^* + r + \delta) \cdot \Big((u+r)(u+\sigma_1 b_1 V_1^* + \delta) + \delta(u+\sigma_1 b_1 V_1^*) \\ &\quad - u\delta \frac{R_2}{R_1} - \delta(u+r) + u\delta \frac{u+r}{u+\sigma_1 b_1 V_1^*} \frac{R_2}{R_1} \Big) \\ &> (u+r)\Big(\delta(u+\sigma_1 b_1 V_1^*) - u\delta \frac{R_2}{R_1}\Big). \end{aligned}$$

Since

$$C < \delta(u+\sigma_1 b_1 V_1^*)(u+r) - (u+r)u\delta \frac{R_2}{R_1},$$

it follows that

$$AB > C.$$

Using the Routh-Hurwitz criteria we have the following result:

Corollary

The boundary equilibrium E_1^* is locally asymptotically stable if $\sigma_1 > \sigma_1^*$, and $\sigma_2 < \sigma_2^*$. Otherwise it is unstable.

Lemma 1 and the corollary say that whenever the superinfection coefficient of the first strain is above threshold there are values of the second superinfection coefficient that give asymptotic stability of the boundary equilibrium E_1^*. Since it is only required that $\sigma_1^* > 0$ and $\sigma_2^* > 0$, the asymptotic stability of E_1^* is guaranteed in principle either when the first strain induces resistance or when it increases susceptibility to the second strain.

Using the definition of f given in (5) we have

Lemma 2:

1. *If* $R_2 < R_1$, *then* $\sigma_1^* = 0$, $f(\sigma_1^*) = f(0) > 0$, $f'(\sigma_1) > 0$.

2. *If* $R_2 > R_1$, *then* $\sigma_1^* > 0$, $f(\sigma_1^*) = 0$, $f(0) < 0$ *and* $f'(\sigma_1) > 0$.

Define $D_1 = \lim_{\sigma_1 \to \infty} f(\sigma_1)$. Then the region of stability of E_1^* given by Lemma 2 is shown in Figures 1 and 2 for both cases ($f(0) > 0$ and $f(0) < 0$).

Using the symmetry between the two dengue strains, we can perform a similar analysis for the other boundary equilibrium E_2^* (where the second strain wins). In this case we have $V_2^* > 0$ and $I_2^* > 0$, and we can define

$$\begin{aligned} \sigma_2^* &= \max\Big\{0,\ (\frac{R_1}{R_2} - 1)\frac{\delta + a_2\hat{N}}{\delta(R_2 - 1)}\Big\}, \\ \sigma_1^* &= g(\sigma_2) = \frac{\delta(u+r)}{a_1 b_1 I_2^*(\hat{T} - V_2^*)}\Big(1 - \frac{u}{u + \sigma_2 b_2 V_2^*}\frac{R_1}{R_2}\Big). \end{aligned} \tag{6}$$

Without loss of generality assume $R_1 > R_2 > 1$. Then we can draw a bifurcation diagram in parameter space (σ_1, σ_2). See Figure 3.

Putting together the three lemmas and the corollary above, we summarize our results in the following lemma about the local stability properties of both boundary equilibria (where we use the definition of g given in (6)):

Lemma 3:

1. E_1^* *is locally asymptotically stable if* $\sigma_2 < f(\sigma_1)$ *for every* $\sigma_1 > 0$, *and unstable if* $\sigma_2 > f(\sigma_1)$.

2. E_2^* *is locally asymptotically stable if* $\sigma_2 > g^{-1}(\sigma_1)$ *for every* $\sigma_1 > 0$, *and unstable if* $\sigma_2 < g^{-1}(\sigma_1)$.

3. E_1^* *and* E_2^* *are locally asymptotically stable if* $g^{-1}(\sigma_1) < \sigma_2 < f(\sigma_1)$.

Note that it is possible to have threshold values of σ_1^* and σ_2^* such that both E_1^* and E_2^* are locally asymptotically stable. This conclusion indicates, at the very least, that there are situations where the asymptotic dynamics of our model depends on the initial conditions.

3.1.2 Boundary equilibria and virulence

When $e_j > 0$, we can no longer claim that the total host population is asymptotically constant and one has to work with the full system (1–2).

In this section we provide a rough sketch of the stability properties of the boundary equilibria for this case.

The local stability analysis of E_i^* (equilibrium with only strain i present) can be determined by computing $D\Phi(E_i^*)$. The eigenvalues of this matrix around this equilibrium are

$$\lambda_i = R_i^{-1}, \text{ and } \mu_i = R_j\psi(\sigma_i, \sigma_j, R_i),\ i \neq j,$$

where ψ is a multiplicative perturbation of R_j that depends on the basic reproductive number of strain i as well as on the superinfection indices σ_1 and σ_2. This perturbation has the general form

$$\psi = \psi_i(\sigma_i, R_i) + \psi_j(\sigma_j, R_i),\ i \neq j,$$

where

$$\psi_i = \frac{c_1}{u + c_2\sigma_i(R_i - 1)},\ \psi_j = \frac{c_3\sigma_j(R_i - 1)}{c_4(e_j + r + u)},$$

with c_1, c_2, c_3 and c_4 positive constants. In particular ψ satisfies $\partial\psi_i/\partial\sigma_i < 0$, and $\partial\psi_j/\partial\sigma_j > 0$ and $\partial\psi_j/\partial e_j < 0$.

Note that the stability of the equilibrium point E_i^* is favored (μ_i tends to reduce its magnitude) when the virulence (extra host mortality induced by the virus) of strain j is large.

Moreover, in the limiting case were $\sigma_i = \sigma_j = 0$ (no superinfection occurring), $\psi = R_1^{-1}$. Therefore, the condition $R_j < 1 < R_i$ makes Φ a local contraction around E_i^*. Thus, the local asymptotic stability of E_1^* in Ω follows.

However, if $0 < \sigma_i < \sigma_j$, E_i^* may cease to be an attractor under Φ (with the condition $R_j < 1 < R_i$ holding). In this case E_i^* is still a global attractor in Ω_i and (locally) a saddle point in Ω.

It is important to mention that whenever $R_i > 1$ and $R_j > 1$ simultaneously, both equilibria E_i^* and E_j^* exists. Their stability properties depend on the magnitude of μ_i and μ_j respectively (λ_i and λ_j are always less than one whenever $R_i > 1$ and $R_j > 1$). For $e_i > 0$ numerical simulations give essentially the same result as for the case $e_i = 0$.

3.2 Characterization of the interior endemic equilibrium

In this section we present results from numerical simulations that provide strong evidence for the existence of an interior endemic equilibrium, that is, an equilibrium point with positive densities of both infected host types.

In these simulations we explored the interdependence of three key parameters: the basic reproductive number, the superinfection coefficients and the disease-induced death rate for each strain.

Variable population size can have a very dramatic effect on the result of a competitive interaction [17]. In particular it can 'reduce' the area of parameter space on which coexistence is possible (compared with the equivalent model with constant total population size). The following results were found through the numerical simulation of model (1–2) when $e_i > 0$:

1. Whenever $R_i > 1$ for $i = 1, 2$ there exists an equilibrium point in the interior of Ω. This point has a local unstable and a local stable manifold of positive dimension (see Figure 5).

2. If $R_i > 1 > R_j$ then the boundary equilibrium E_j^* and the interior endemic equilibrium do not exist and the boundary equilibrium E_i^* is globally asymptotically stable (Figure 4).

3. When $R_i > R_j > 1$, the superinfection coefficients σ_1 and σ_2 may change the asymptotic behavior of the system, rendering strain j as the winner over strain i (which would be the winner if $\sigma_1 = \sigma_2 = 1$, see Figure 6).

4. When $R_i > R_j > 1$ and both boundary equilibria are locally asymptotically stable, there exists a separatrix that cuts Ω into two disjoint basins of attraction (one for each boundary equilibrium, see Figure 5).

Model simulations show that in the host population there is no long-term persistence of both strains. However, the unusual nature of the endemic equilibrium (a 'saddle' point) produces a relatively prolonged (years of duration) quasi-steady state when both R_i are greater than one. Given the inherent time-scale of the disease (months), this quasi-steady state would look as an stable endemic equilibrium (see Figures 5 and 6). Under these conditions there are two possibilities depending on how many of the boundary equilibria are locally stable. If only one of them is locally asymptotically stable our computer simulations indicate that this equilibrium is also globally asymptotically stable. Thus the competitive exclusion of one of the strains occurs.

Our computer simulations also indicate that even though the initial outbreak of primary infection is driven by the strain with the highest reproductive number, it is precisely this strain the one that can be competitively

excluded. This occurs if the primary infection enhances (increases susceptibility to) secondary infections (see Figure 6). Therefore, the strain with the smallest reproductive number may end up persisting in the host.

The second possibility occurs when both boundary equilibria exist and both are locally asymptotically stable. In this case the outcome of the interaction—competitive exclusion of one strain—, depends on the initial conditions (Figure 5).

4 Discussion

The incorporation of full vector-host dynamics in a multiple strain epidemiological system has been partially analyzed in this work. Conditions for existence and stability properties of the interior endemic equilibrium point are somewhat unusual. Although existence of the endemic equilibrium is still a function of the basic reproduction numbers of each strain (both basic reproduction numbers must be greater than one), the endemic equilibrium is always unstable with stable and unstable manifolds of non-zero dimension. To illustrate this point numerical simulations were carried out based on the numbers reported in [15] for the basic reproductive number of the 1990-91 epidemic in Brazil. R_0 had an average value of 2.03. Previous work in Mexico reported an average reproduction number of 1.33 with a maximum of 2.41 (cited in [15]). The parameter values that we have chosen give basic reproduction numbers for both strains of about 2.

The existence of an interior endemic equilibrium point with this characterization produces a potentially unpredictable long-term behavior (see Figure 5). New infection waves after the primary epidemic burst will settle to a transient, apparently stable, low level of endemicity where strains cocirculate. However, as time passes, the prevalence of one of the strains will eventually and steadily increase while the other strain disappears. Which of the strains will be the winner depends on the initial conditions preexisting when the new strain arrived and on the level of susceptibility induced by the primary infection (Figures 4 and 5). Of course, if during the transient phase, a new wave of infection appears, it will not be possible to predict which strain will become endemic. In general, as Figure 3 shows, the region where both boundary equilibria are locally asymptotically stable is large and, according to our model, most dengue epidemics fall into this situation.

As shown in Figure 3, the existence of two locally asymptotically stable boundary equilibria, and therefore the existence of an (unstable) interior

endemic equilibrium is guaranteed for a biologically feasible range of values of the superinfection indices σ_1 and σ_2. This range covers cases when both primary infections induce resistance to secondary infections or when susceptibility is enhanced.

It appears that for feasible values of σ_i (e.g. $\sigma_i \in (0.1, 2)$) and whenever $R_i > R_j$, the interior equilibrium exists unless σ_j is either very small or very large. In Figure 3 we illustrate the case when $R_1 > R_2$ (see Figure 3 legend for parameter values used). We conclude that the presence of superinfection forces the existence of the interior equilibrium. However, it appears that superinfection cannot induce stability in this state. In the case of Figure 3, the endemic interior equilibrium would cease to exist for a value of $\sigma_2 \approx 0.001$ but then only the boundary equilibrium E_1^* would be asymptotically stable.

Gupta, Swinton and Anderson [9] show in a model for malaria that coexistence is a likely outcome when cross-immunity is taken into account. Although malaria is a parasitic, not a viral disease, the mathematical structure of the model allows some comparisons with ours since both deal with a vector transmitted disease. Gupta et al. generalize directly the Ross-Macdonald model for malaria studied by Aron and May [1] introducing cross-immunity and two infected host subtypes: those that are infected and infectious, and those that are infected but uninfectious. Thus, essentially there is a reduction in the net number of infected individuals that can transmit the disease. However all infected individuals can hold the parasite. In particular, the rate at which parasites become ineffective to transmission, i.e., the hosts becomes infected but not infectious, is exponential, guaranteeing the presence of positive densities (however small) of each type of infected hosts for all time. Thus, the Gupta et al. model effectively creates a refuge for each parasite strain. Moreover, the total host population is considered constant. The assumption of constant host population size is achieved by defining the recruitment rate in such a way as to balance the output from all system compartments. This factor alone when associated with cross-immunity is enough to enhance coexistence in models for directly transmitted diseases [21], [16]. In the case of our general model all infected individuals are infectious; thus there are no refuges. Also, by definition, we take virulence as extra mortality induced by the disease. This prevents the existence of a constant population size for the host. We do not define the recruitment rate for the total population so as to balance disease mortality losses (and therefore achieve a constant size in the host population). This would be equivalent, in our case, to require that the extra-mortality rate is compensated exactly by the cure rate of the disease and, therefore, population variability would be

independent of disease dynamics. However, even in this case (no virulence) our model predicts competitive exclusion of one of the strains.

The main reason that explains why in our model coexistence is an improbable outcome resides, we believe, in the coupling of two populations, each with a different pattern of disease progression.

The structure of the equations that describe the transmission dynamics in the host population is that of an SIR model with superinfection and variable population size. In a directly transmitted disease with this structure and no virulence one would expect analogous results to those of Nowak and May [21]: coexistence of both strains as a rule. Our model also incorporates an SI model without superinfection in the vector population. In a directly transmitted disease this structure would predict competitive exclusion of the strain with lower basic reproductive number [2].

When we couple both of these types of epidemics into one, our host-vector model (1–2), the outcome is competitive exclusion of one of the strains if at least one of the basic reproductive numbers is greater than one. In a sense, the vector dynamics dominates the dynamics of the coupled system. The reason for this is that the vector-host relationship is asymmetric. The vector chooses the host. In this case we have modeled the contact rates according to a generalization of the Ross-Macdonald model: the contact rate is frequency dependent [6] (depends on the ratios of vector numbers to host numbers for both types of strains). Thus, what our results show is that *coexistence promoted by superinfection in the host population is 'broken' by frequency dependent dynamics in the biting (contact) rates, thus resulting in the competitive exclusion of one strain even when an interior steady-state exists.*

Other models that incorporate cross-immunity and multiple strains have been studied [12], [14], [17]. We compare our results with the original one that introduced this idea of competition of multiple strains in epidemic models, namely the Levin and Pimentel paper [12]. In summary, the conclusions of [12] are that in a variable host population system coexistence is possible in a bounded region of parameter space. Outside this region, depending on the relative magnitudes of parameter values one of the two strains wins and competitively excludes the other. This model was originally designed for the theoretical study of myxomatosis as a control factor of an exponentially growing population. The fact that virulence is the growth regulatory factor in this model determines the existence of a coexistence region in parameter space. In the dengue model that we analyze here, the disease is not the unique factor that regulates growth. Permanent immunity is also explicitly

introduced into the model. Even in the case when virulence is negligible competitive exclusion is the rule. The existence of frequency-dependent contact rates closes the window of coexistence.

The model analyzed here does not incorporates the effects of age structure. Dengue in tropical Asia affects particularly children with ages between 5 and 15 years old, with a modal age of 5 years [26]. The same reference indicates that in 1987 more than 600 000 cases of dengue were reported in Southeast Asia with 24 000 deaths: 90% of both cases and deaths were children. The risk of infection is obviously an age dependent factor. Moreover, the influence of physiological structure into the dynamics of dengue may have an influence in the likelihood of coexistence of both strains. The need for a model that incorporates age structure into the dengue population dynamics is thus justified.

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Figure captions

- Table 1. Absolute numbers of dengue hemorrhagic fever cases and deaths reported to the World Health Organization regional offices. NR: not reported. (From Halstead,1992).

- Table 2. Parameter definitions and values used in the simulations illuestrated in the figures.

- Figure 1. Graph on the parameter space (σ_1, σ_2) for case 1 of Lemma 1. In this case $R_1 < R_2$, $f(0) = 0$. The shaded area corresponds to parameters values that render the boundary equilibrium for strain 1 locally asymptotically stable.

- Figure 2. Graph on the parameter space (σ_1, σ_2) for case 2 of Lemma 1. In this case $R_1 < R_2$, $f(0) = 0$. The shaded area corresponds to parameters values that render the boundary equilibrium for strain 1 locally asymptotically stable.

- Figure 3. Region of parameter space (σ_1, σ_2) where both boundary equilibria are locally asymptotically stable. Fixed parameter values are $r = 0.71/\text{day}$, $\mu = 0.000039/\text{day}$, $\delta = 0.71/\text{day}$, $h = 0.9775$, $\alpha_1 = 0.002$, $\alpha_2 = 0.015$, $\beta_1 = 0.001$, $\beta_2 = 0.001$, $c = 10$, $\hat{T} = 50000$, $\hat{N} = 25000$. The corresponding basic reproduction numbers are $R_1 = 2.4$ and $R_2 = 2.08$.

- Figure 4. Phase plot in the space (I_1, I_2) for values of the superinfection indices outside the shaded area shown in Figure 3. The graph was computed with the same parameter values shown in Figure 3 but with $\sigma_1 = 5$, $\sigma_2 = 0.05$, and positive disease-induced death rates $e_1 = 0.0001/\text{day}$, $e_2 = 0.0005/\text{day}$. These parameter values give $\sigma_2 < g^{-1}(\sigma_1) = 0.1$. In this case strain 1 competitively excludes strain 2. The final outcome of the disease (which strains wins) is independent of initial conditions. The black square indicates the boundary equilibrium point. The unit of measurement of I_1 and I_2 is number of cases.

- Figure 5. Phase plot in the space (I_1, I_2) for values of the superinfection indices outside the shaded area shown in Figure 3. The graph was computed with the same parameter values shown in Figure 3

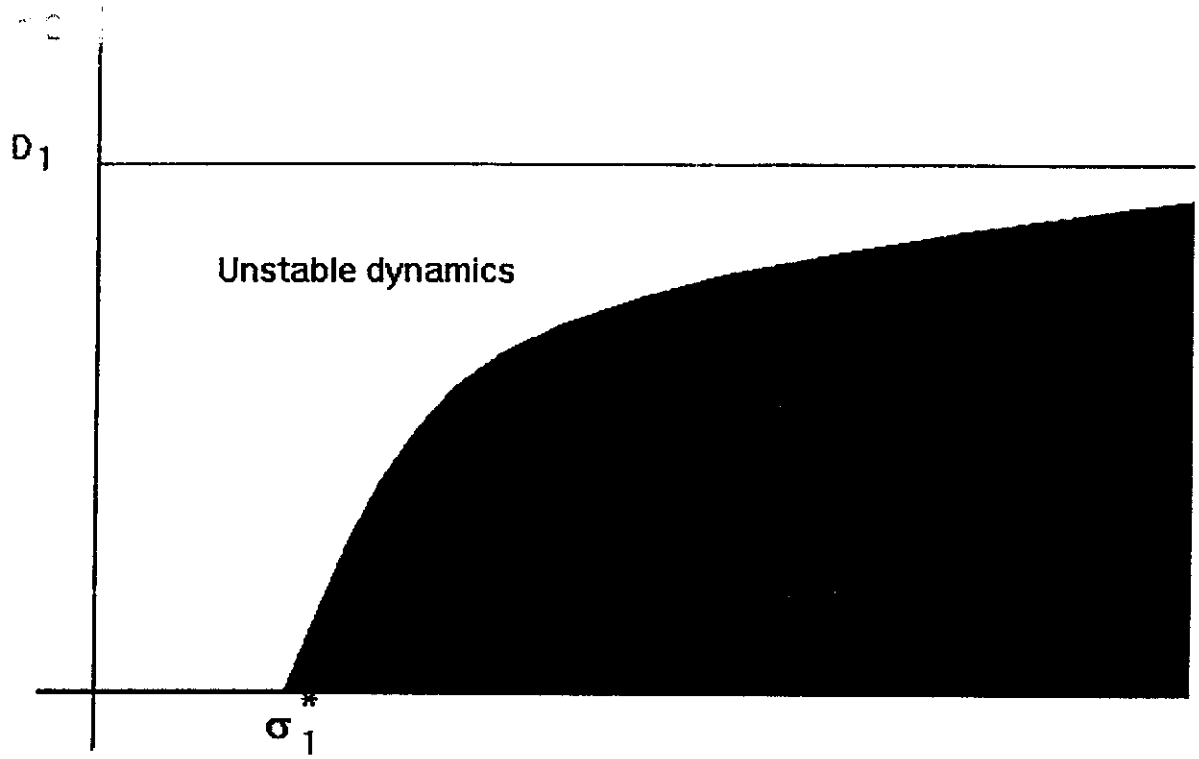
but with $\sigma_1 = 1$, $\sigma_2 = 4.2$, and positive disease-induced death rates $e_1 = 0.0001$/day, $e_2 = 0.0005$/day. The presence of a saddle point in the interior of the region and the existence of a separatrix may be conjectured. Note that the final outcome of the disease (which strains wins) depends on initial conditions. The black square indicates the endemic equilibri um point. The unit of measurement of I_1 and I_2 is number of cases.

- Figure 6. Time plot of model (1-2) for a period of 5 years. The graph shows the total numbers of infected individuals for each strain $I_1 + Y_1$ and $I_2 + Y_2$. Parameter values are the same as for Figure 3 except for the following: $\alpha_1 = 0.005$, $\alpha_2 = 0.005$, $\beta_1 = 0.005$, $\beta_2 = 0.007$, $\sigma_1 = 4$, $\sigma_2 = 1.2$. There are two curves, one for each strain. For about 3 years both strains seem to increase and coexist. Only in the fourth year strain 1 clearly wins over strain 2. Note that strain 2 increases faster at the beginning of the epidemic but it is this strain the one that goes extinct.

	Philippines		Viet Nam		China		Thailand		PDR Laos	
Year	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
1981	123	8	35,323	408	NR	NR	25,641	194	NR	NR
1982	305	31	39,806	361	NR	NR	22,250	159	NR	NR
1983	1,684	130	149,519	1,798	85,293	3,032	30,022	231	NR	NR
1984	2,545	89	30,498	368	NR	NR	69,597	451	22	14
1985	NR	NR	45,107	399	NR	NR	80,076	542	1,759	15
1986	687	30	46,266	511	NR	NR	29,060	206	365	43
1987	859	27	354,517	1,566	NR	NR	170,630	896	3,914	91
1988	2,922	68	85,160	826	51,510	1,259	26,926	189	1,212	27
1989	305	14	40,205	289	37,996	907	69,204	280	NR	NR
1990	588	27	37,569	255	38,062	2,626	113,855	422	60	3
Total	10,018	424	863,970	6,781	212,861	7,824	637,261	3,570	7,332	193

Symbol	Parameter definition	value
h	host recruitment rate	variable
u^{-1}	host life expectancy	70 years
r^{-1}	mean length of infectious period in host	14 days
α_i	vector per capita infection rate (biting rate $\times$ vector infection probability)	$(0, 0.05)$
β_i	host per capita infection rate (biting rate $\times$ host infection probability)	$(0, 0.05)$
q	vector recruitment rate	variable
δ^{-1}	vector life expectancy	14 days
c	rescaling parameter (α_i/c and β_i/c infection rates when N small)	1
ω_i	saturation parameter (α_i/ω_i and β_i/ω_i give maximum infection rates)	0.5
e_i	disease-induced per-capita death rate	variable
σ_i	susceptibility index to strain i	$(0, 5)$

Table 2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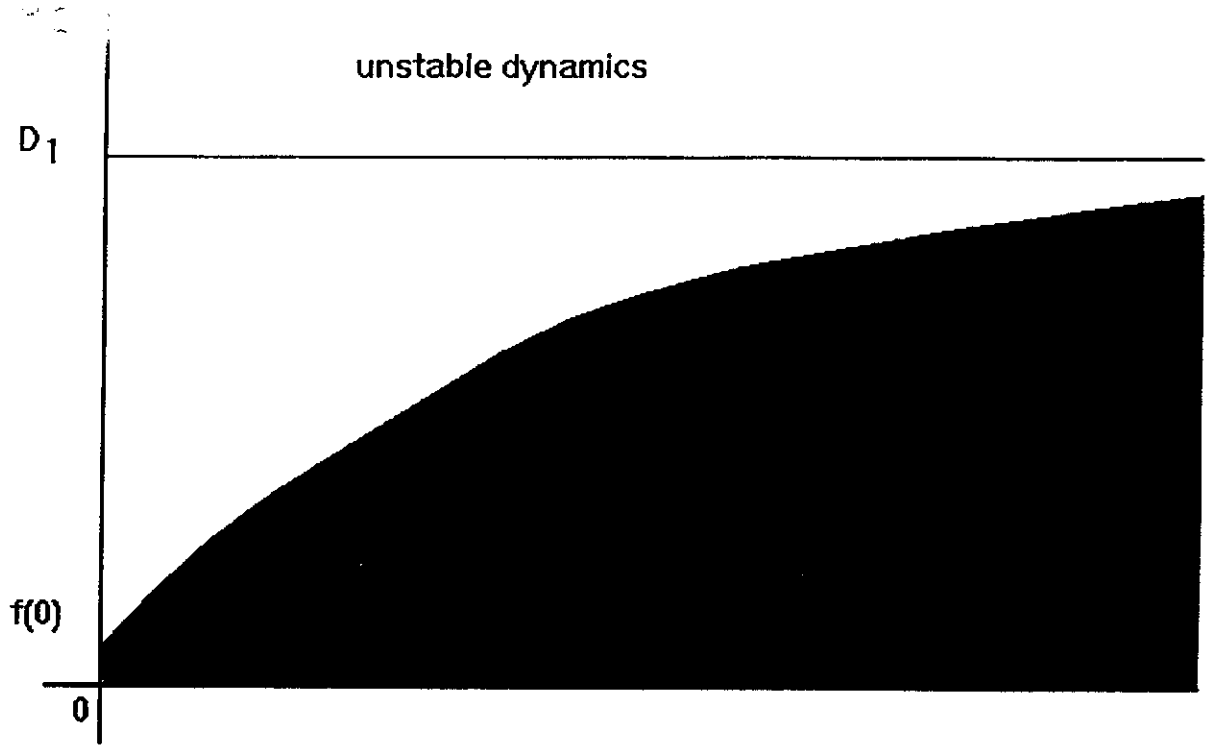
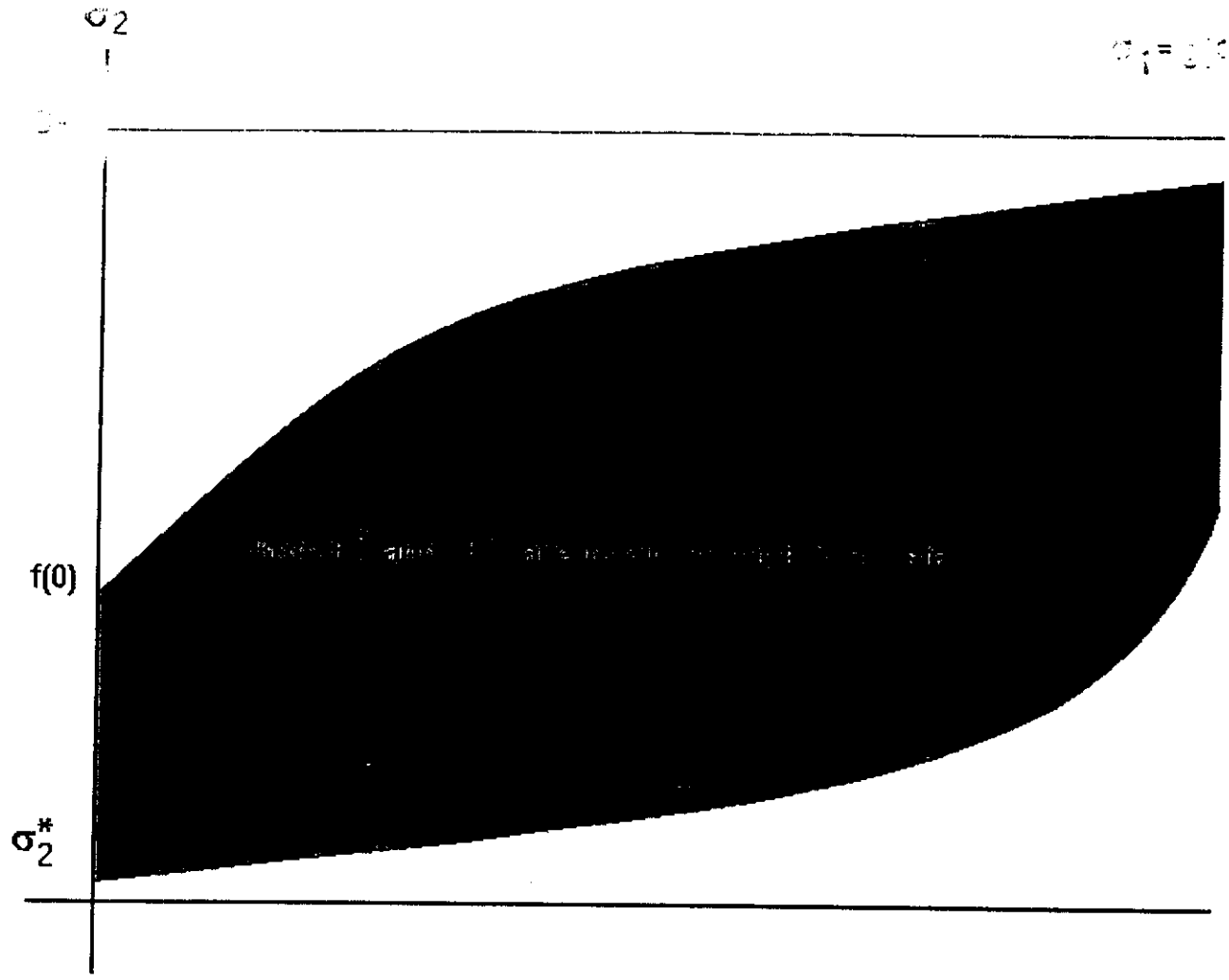
Unstable dynamics
σ_1^*


unstable dynamics
D 1
f(0)
0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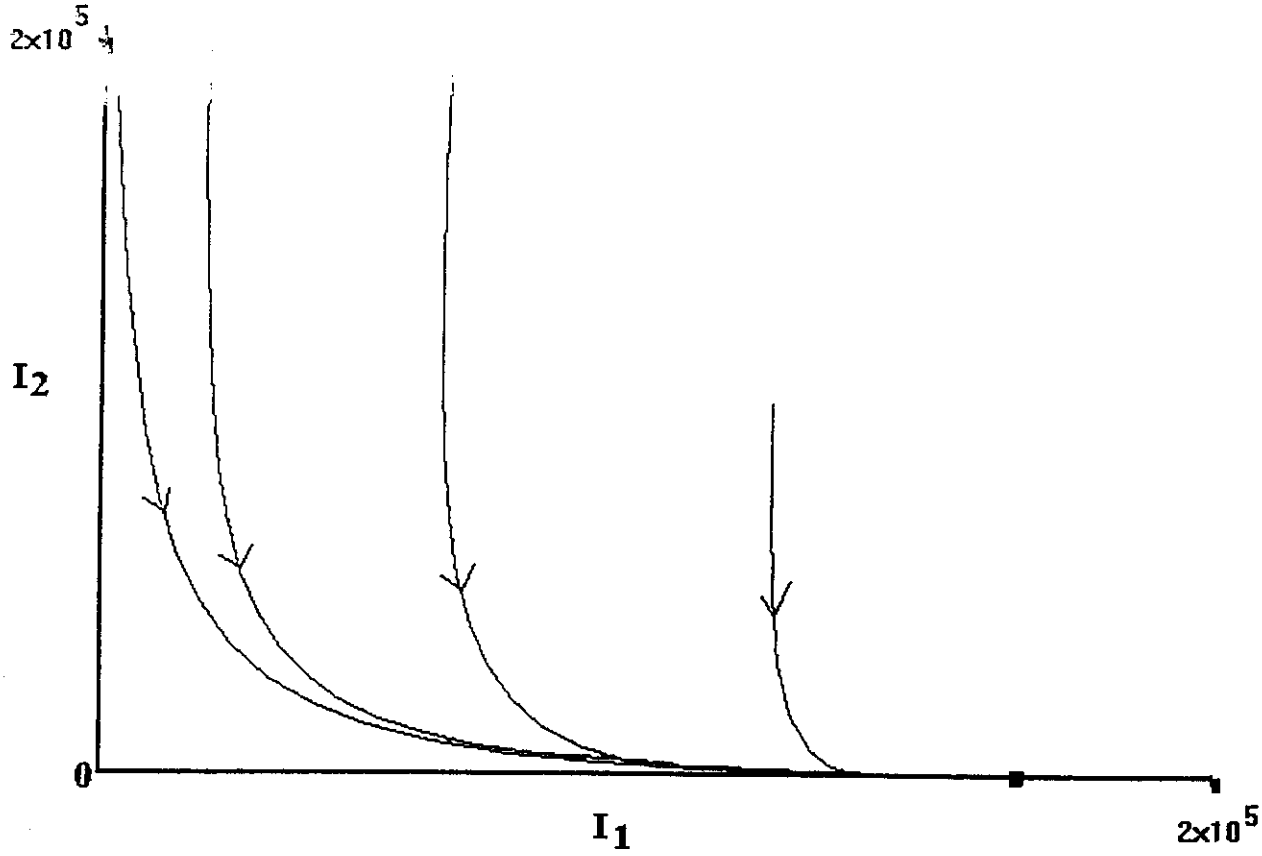
f(0)
σ_2^*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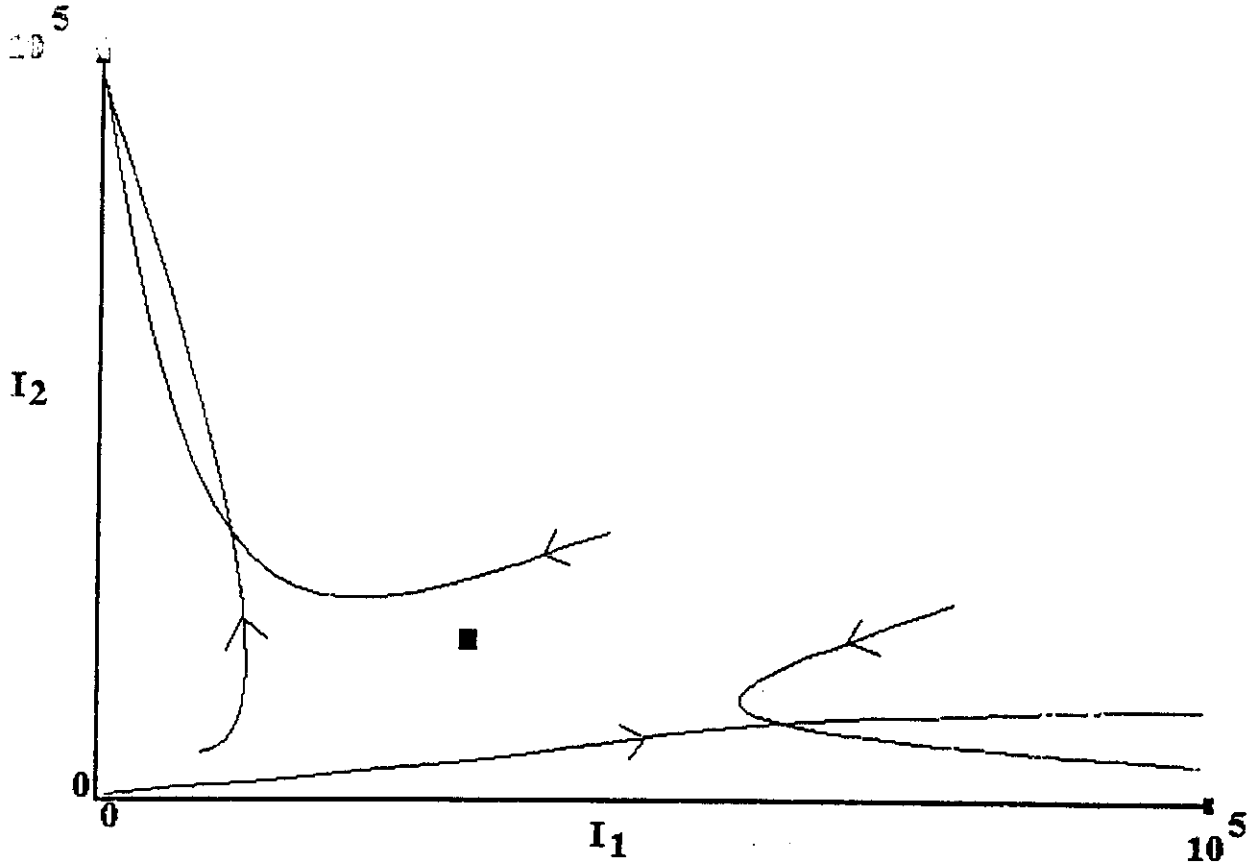
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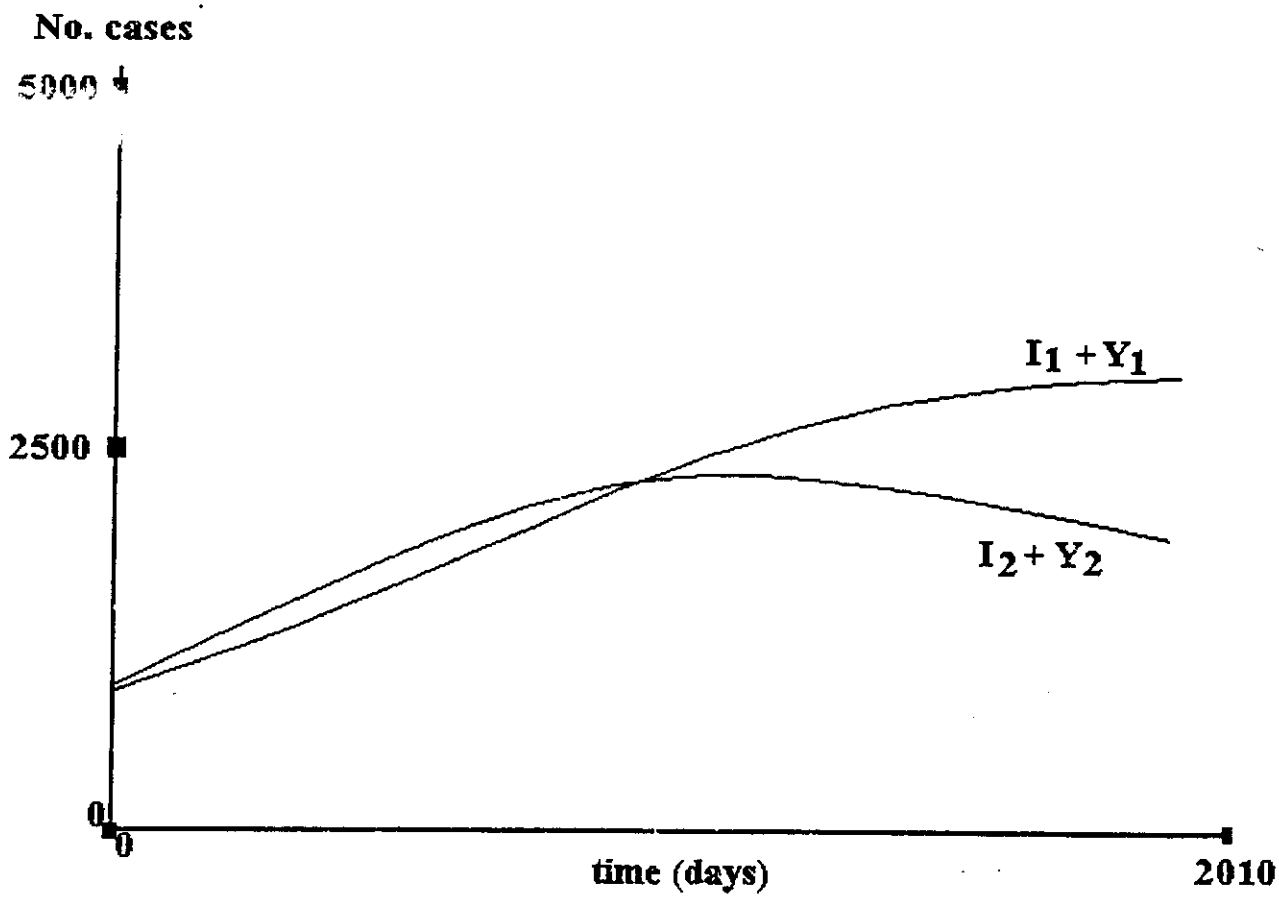
No. cases
5000
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0
0
$I_1 + Y_1$
$I_2 + Y_2$
time (days)
2010