

# Competitive Exclusion in a Vector-Host Model for the Dengue Fever

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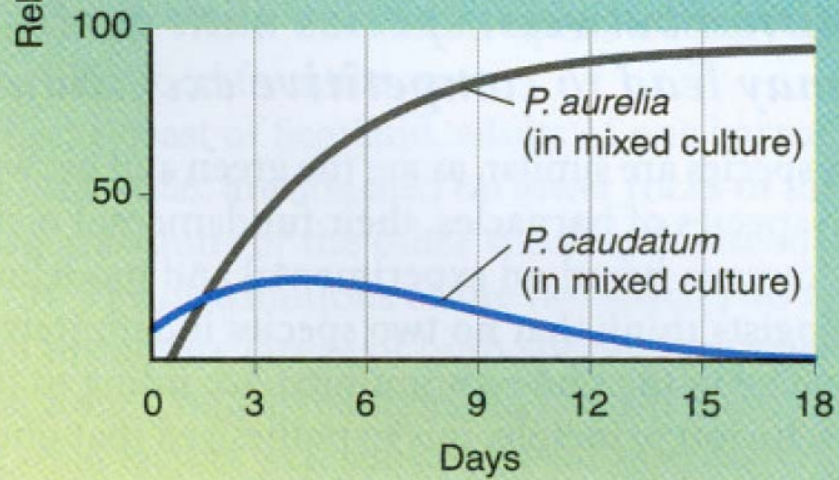
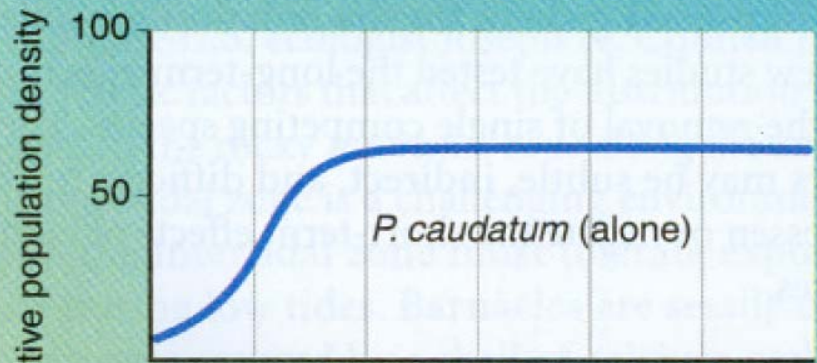
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# Outline

- Competitive Exclusion
- Dengue Fever
- SIR models
- Equilibrium Points and Stability
- Discussion

# Principle of Competitive Exclusion

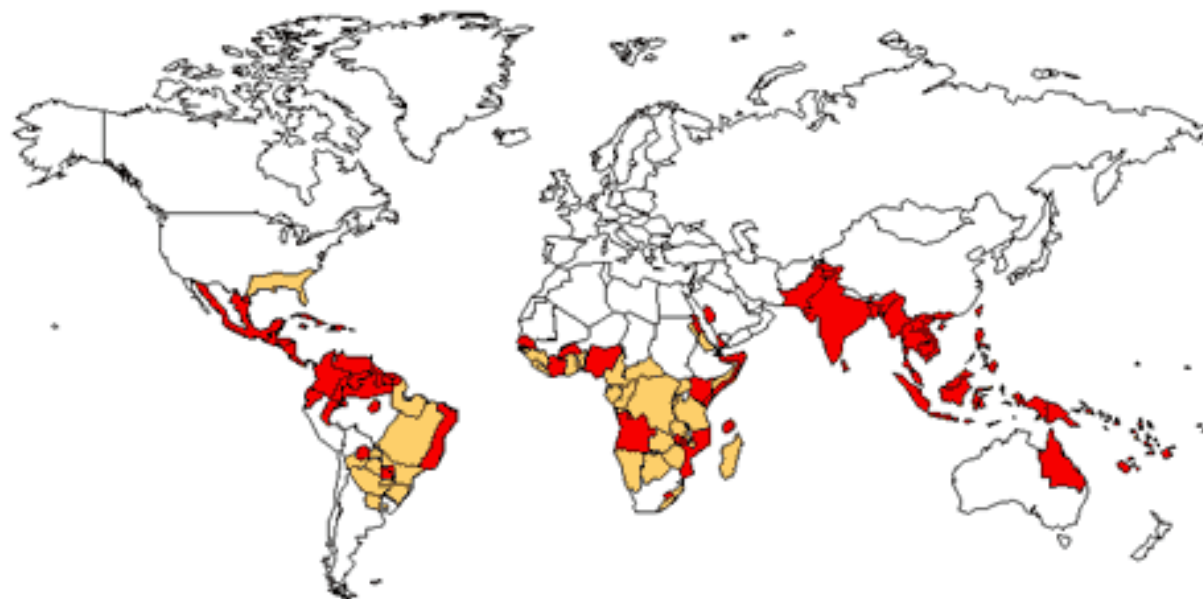
- When two or more species compete for the same basic resources, the “strongest” survives; the weaker species is driven to extinction.
- Biologist G. F. Gause in the 1930’s studied the competition for resources between *Paramecium aurelia* and *Paramecium caudatum* under various sets of culture conditions.



# Dengue Fever

- There are 4 strains of the Dengue virus.
- Infection by any dengue virus strain produces long lasting immunity but only temporary cross-immunity to other serotypes.
- Spread by mosquitoes, mainly *Aedes aegypti*.
- Some symptoms include: sudden onset of fever, severe headache, muscle and joint pain, rashes, nausea, and vomiting.
- Secondary infections can lead to Dengue Hemorrhagic Fever and Dengue Shock Syndrome. Additional symptoms include: hemorrhagic tendency, thrombocytopenia, weak rapid pulse, hypotension, etc.

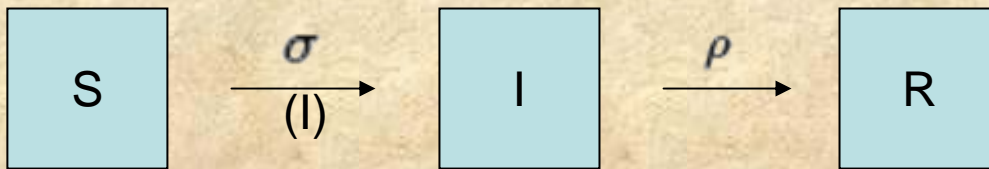
# World Distribution of Dengue - 2000



- Areas infested with *Aedes aegypti*
- Areas with *Aedes aegypti* and dengue epidemic activity

# SIR Model

- The virus is not lethal.
- Length of epidemic is short enough that the population remains constant; i.e. no births/deaths.



$\sigma$  : infection rate

$\rho$  : recovery rate

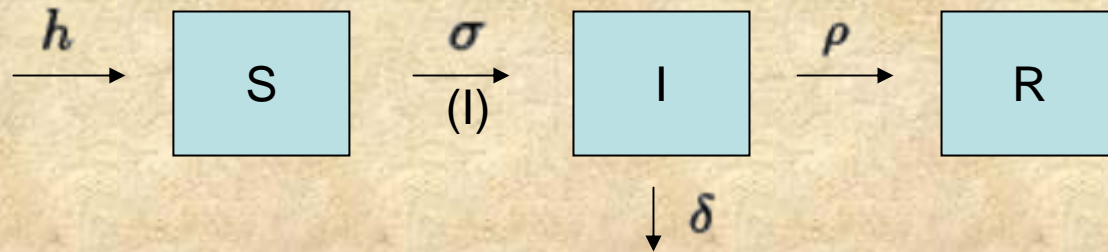
$$S' = -\sigma SI$$

$$I' = \sigma SI - \rho I$$

$$R' = \rho I$$

# SIR Model

- The virus can be lethal.
- The population size is variable.



$h$  : host recruitment rate

$u^{-1}$  : host life expectancy

$\delta$  : disease-induced death rate

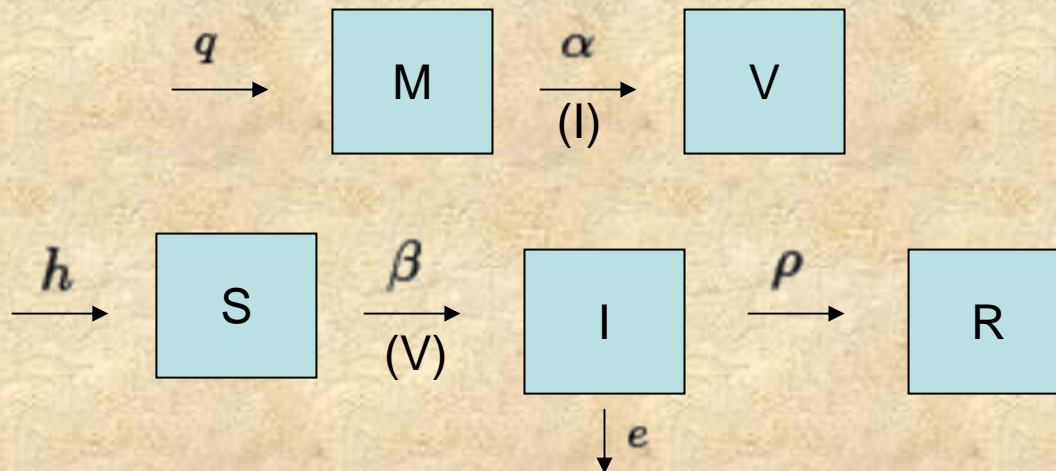
$$S' = h - \sigma SI - uS$$

$$I' = \sigma SI - (\rho + \delta + u)I$$

$$R' = \rho I - uR$$

# SIR Model with Carrier

- Susceptibles are not infected by contact with infected hosts, but by a carrier of the virus (vector).
- Vectors are infected by infected hosts.
- Vectors follow an SI model. Vectors do not recover or die from disease.



# SIR Model with Carrier

$h$  : host recruitment rate

$q$  : vector recruitment rate

$u^{-1}$  : life expectancy of host

$\delta^{-1}$  : life expectancy of vector

$e$  : disease induced death rate

$\beta$  : host infection rate

$\alpha$  : vector infection rate

$$S' = h - \beta SV - uS$$

$$I' = \beta SV - (\rho + e + u)I$$

$$R' = \rho I - uR$$

$$N = S + I + R$$

$$M' = q - \alpha MI - \delta M$$

$$V' = \alpha MI - \delta V$$

$$T = M + V$$

S: susceptibles

I: infects

R: recovered

N: total host population

M: uninfected vectors

V: infected vectors

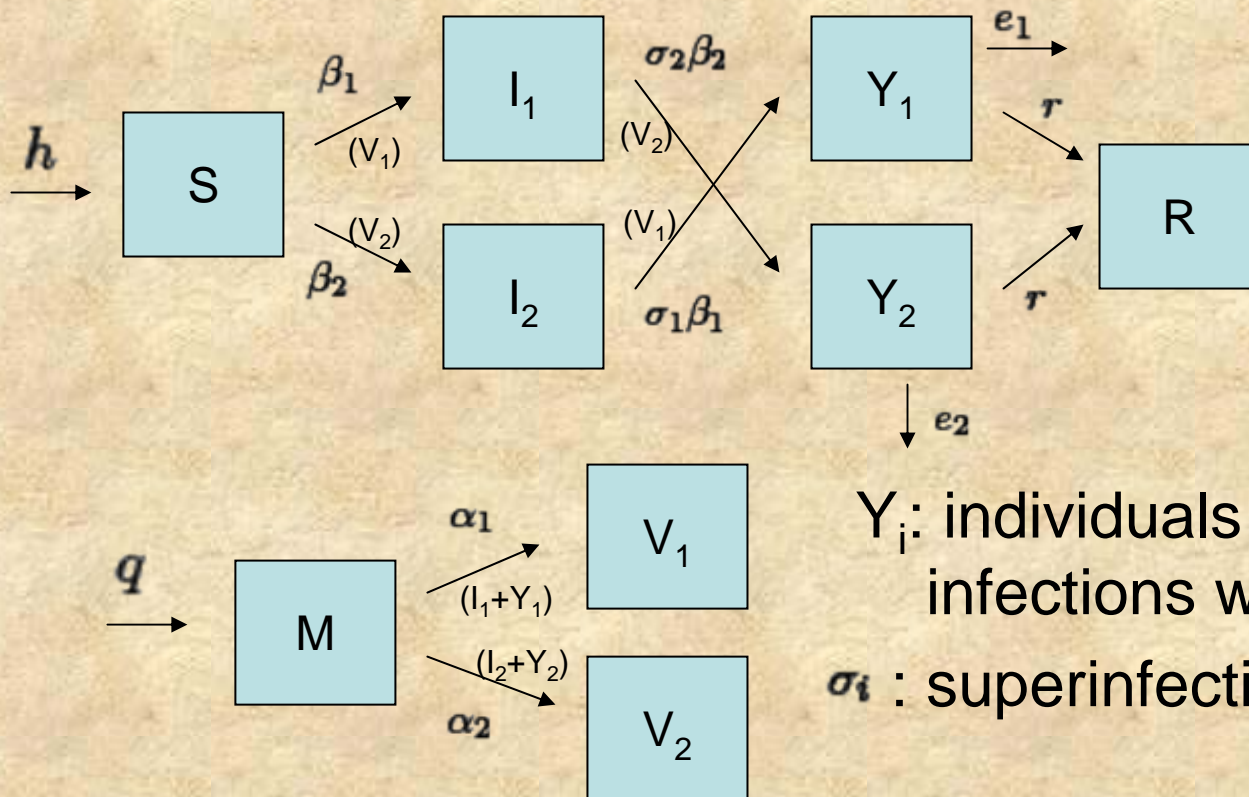
T: total vector population

# Assumptions for forming an SIR Model for Dengue

- There are two strains of the virus.
- Once a mosquito is infected it never recovers and it cannot be reinfected with a different strain of virus.
- The second co-circulating strain can produce secondary infections in individuals either susceptible or already recovered from a primary infection with the other strain.
- Infected individuals develop immunity to the strain they are infected with.
- Secondary dengue infections are more severe. Only those persons experiencing a second infection with heterologous dengue serotype present DHF-DSS.

# SIR Model with Two Pathogen Strains

- The primary infection may either give cross-immunity or increased susceptibility to the second strain. This is determined by the coefficient  $\sigma$ .



$Y_i$ : individuals with secondary infections with strain  $i$

$\sigma_i$ : superinfection coefficient

# SIR Model with Two Pathogen Strains

$$S' = h - \beta_1 S V_1 - \beta_2 S V_2 - u S$$

$$I_1' = \beta_1 S V_1 - \sigma_2 \beta_2 I_1 V_2 - u I_1$$

$$I_2' = \beta_2 S V_2 - \sigma_1 \beta_1 I_2 V_1 - u I_2$$

$$Y_1' = \sigma_1 \beta_1 I_2 V_1 - (e_1 + u + r) Y_1$$

$$Y_2' = \sigma_2 \beta_2 I_1 V_2 - (e_2 + u + r) Y_2$$

$$R' = r(Y_1 + Y_2) - u R$$

$$N = S + I_1 + I_2 + Y_1 + Y_2 + R$$

$$M' = q - \alpha_1 (I_1 + Y_1) M - \alpha_2 (I_2 + Y_2) M - \delta M$$

$$V_1' = \alpha_1 (I_1 + Y_1) M - \delta V_1$$

$$V_2' = \alpha_2 (I_2 + Y_2) M - \delta V_2$$

$$T = M + V_1 + V_2$$

# SIR Model for Dengue with Two Pathogen Strains

- The infection rates should not be constant, but instead depend on the host population size, since the biting rates for the mosquitoes will be population dependent.

$c$ : rescaling parameter

$\omega_i$ : saturation parameter

$$B_i = \frac{\beta_i V_i}{(c + \omega_h N)}$$

$$A_i = \frac{\alpha_i (I_i + Y_i)}{(c + \omega_v N)}$$

$$S' = h - (B_1 + B_2)S - uS$$

$$I_1' = B_1 S - \sigma_2 B_2 I_1 - uI_1$$

$$I_2' = B_2 S - \sigma_1 B_1 I_2 - uI_2$$

$$Y_1' = \sigma_1 B_1 I_2 - (e_1 + u + r)Y_1$$

$$Y_2' = \sigma_2 B_2 I_1 - (e_2 + u + r)Y_2$$

$$R' = r(Y_1 + Y_2) - uR$$

$$N = S + I_1 + I_2 + Y_1 + Y_2 + R$$

$$M' = q - (A_1 + A_2)M - \delta M$$

$$V_1' = A_1 M - \delta V_1$$

$$V_2' = A_2 M - \delta V_2$$

$$T = M + V_1 + V_2$$

# Equilibrium Points

$$\Omega = \{(S, I_1, I_2, Y_1, Y_2, R, V_1, V_2) : S + I_1 + I_2 + Y_1 + Y_2 + R \leq \frac{h}{\mu}, V_1 + V_2 \leq \frac{g}{\delta}\}$$

- Disease-Free Equilibrium

$$E_0^* = (S^*, 0, 0, 0, 0, 0, 0, 0)$$

- Boundary Equilibrium

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

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

- Coexistence Equilibrium

$$E_3^* = (S^*, I_1^*, I_2^*, Y_1^*, Y_2^*, R, V_1^*, V_2^*)$$

# Equilibrium Points ( $e_i = 0, i = 1, 2$ )

Letting  $\hat{N} = h/u$ ,  $\hat{T} = q/\delta$ , and  $\omega_h = \omega_v = \omega$ :

$$E_0^* = (\hat{N}, 0, 0, 0, 0, 0, 0, 0)$$

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

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

$$V_i^* = \frac{u\delta(R_i - 1)}{b_i(\delta + a_i\hat{N})} \quad I_i^* = \frac{u\delta(R_i - 1)}{a_i(b_i\hat{T} + u)}$$

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

# Basic Reproductive Number

- The number of secondary infections that a single infectious individual produces in a population where all hosts are susceptible.

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

where  $R_i$  is the basic reproductive number for the  $i$ -th strain of the virus.

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

# Numerical Results for the Importance of the Reproductive Numbers

- If  $R_1, R_2 < 1$ , then the virus eventually disappears from the host population.
- If  $R_i > 1 > R_k$ , then  $E_k^*$  and  $E_3^*$  do not exist, and  $E_i^*$  is globally asymptotically stable. Strain  $i$  remains in the population.
- If  $R_i > R_k > 1$ , then  $E_1^*, E_2^*$  are both locally asymptotically stable.  $E_3^*$  exists but is a saddle. Only one strain will remain over time, but it is not necessarily strain  $i$ .

# Importance of the Superinfection Coefficients

- These results were found algebraically for  $e_i = 0$ ,  $i = 1, 2$ . For  $e_i > 0$ , numerical simulations gave essentially the same result.
- $E_1^*$  is locally asymptotically stable if  $\sigma_2 < f(\sigma_1)$  for every  $\sigma_1 > 0$ , and unstable if  $\sigma_2 > f(\sigma_1)$ .
- $E_2^*$  is locally asymptotically stable if  $\sigma_2 > g^{-1}(\sigma_1)$  for every  $\sigma_1 > 0$ , and unstable if  $\sigma_2 < g^{-1}(\sigma_1)$ .
- $E_1^*$  and  $E_2^*$  are locally asymptotically stable if  $g^{-1}(\sigma_1) < \sigma_2 < f(\sigma_1)$ .
- Where do the functions  $f$  and  $g$  come from?

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

$$A = 2u + \sigma_1 b_1 V_1^* + r + \delta,$$

$$B = (u+r)(u + \sigma_1 b_1 V_1^*) + \delta(u + \sigma_1 b_1 V_1^*) - u\delta \frac{R_2}{R_1} - \sigma_2 a_2 b_2 \frac{\delta V_1^*}{a_1},$$

$$C = \delta(u + \sigma_1 b_1 V_1^*) (u + r) - (u + r) u \delta \frac{R_2}{R_1} - (u + \sigma_1 b_1 V_1^*) \sigma_2 a_2 b_2 \frac{\delta V_1^*}{a_1}.$$

In the above we have used the equivalencies

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

Our threshold parameters are given in terms of bounds for the superinfection coefficients  $\sigma_1$  and  $\sigma_2$ . Thus, they set bounds for the level of induced resistance or increased susceptibility that each strain produces in the host.

Let

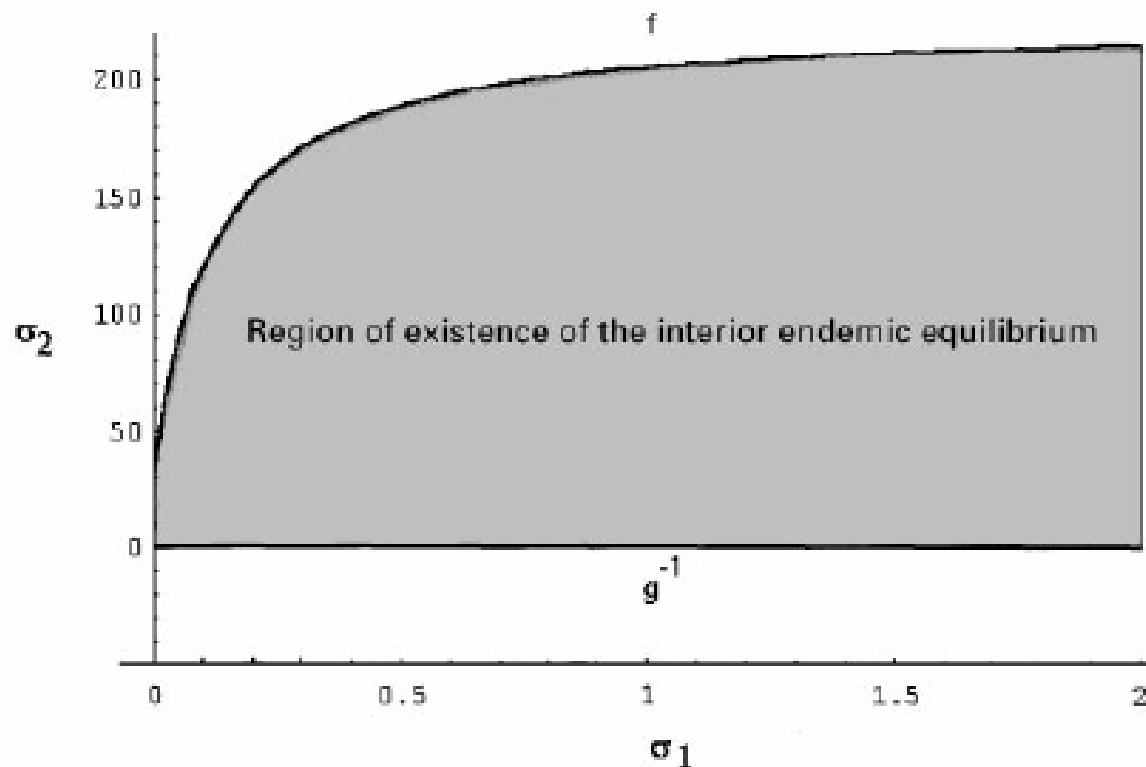
$$\sigma_1^* = \max \left\{ 0, \left( \frac{R_2}{R_1} - 1 \right) \frac{\delta + a_1 \hat{N}}{\delta(R_1 - 1)} \right\},$$

$$\sigma_2^* = f(\sigma_1) = \frac{\delta(u + r)}{a_2 b_2 I_1^* (\hat{T} - V_1^*)} \left( 1 - \frac{u}{u + \sigma_1 b_1 V_1^*} \frac{R_2}{R_1} \right). \quad (5)$$

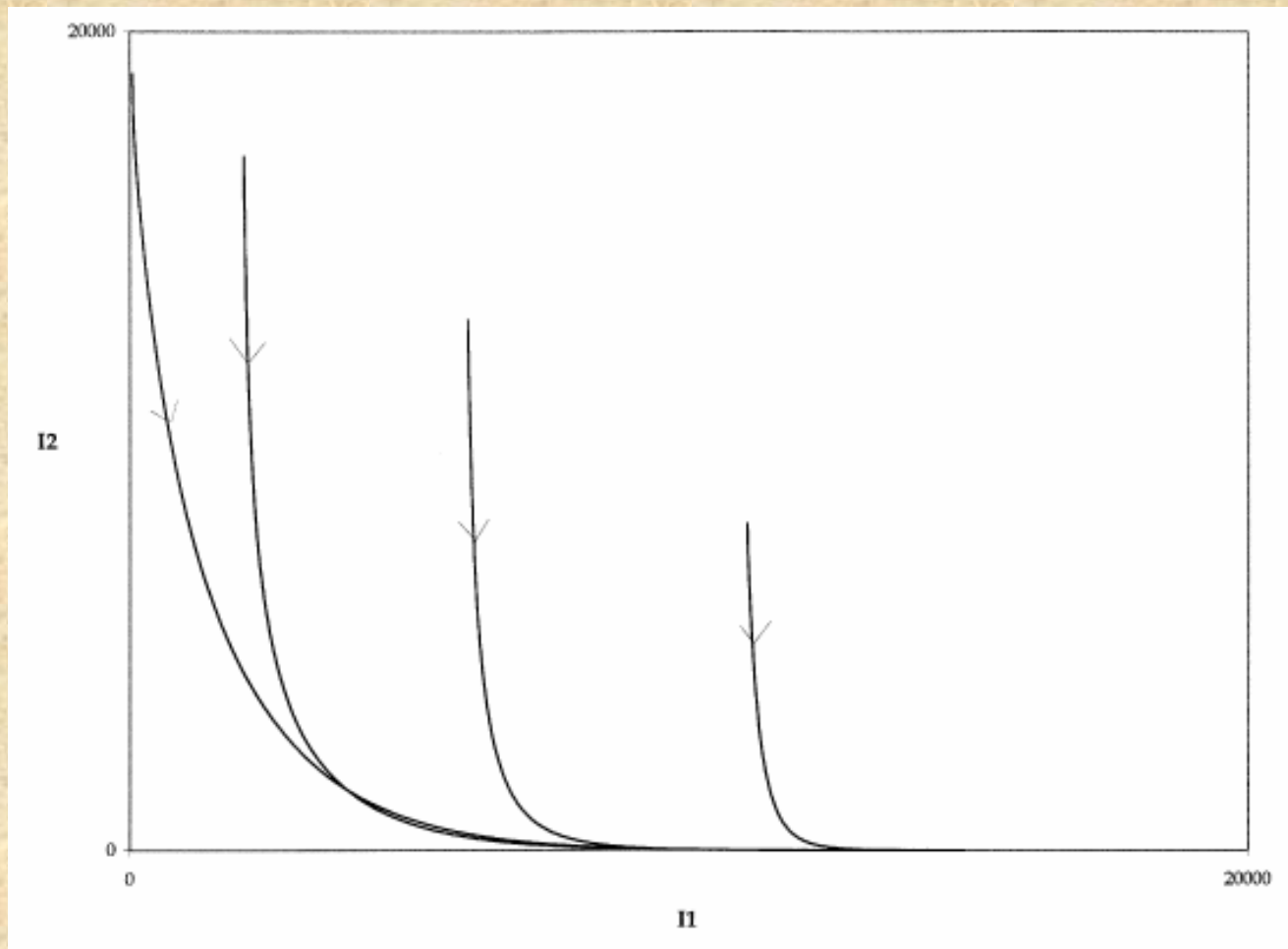
Then the following hold

**Lemma 1.**

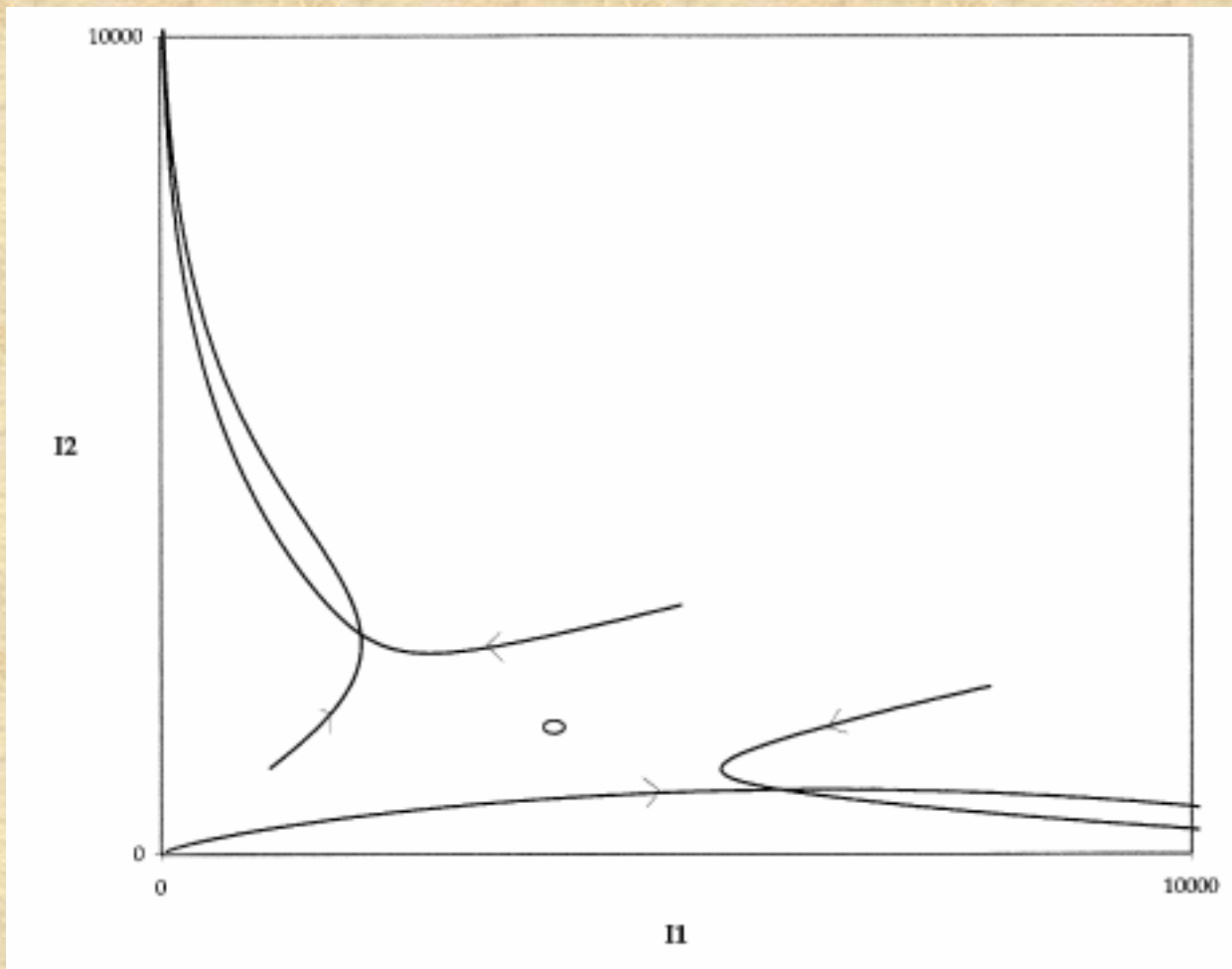
1.  $\sigma_1 > \sigma_1^*$  implies  $\sigma_2^* > 0$ ;
2.  $\sigma_1 > \sigma_1^*$  and  $\sigma_2 < \sigma_2^*$  implies  $A > 0$ ,  $B > 0$ ,  $C > 0$  and  $AB > C$ ;
3.  $\sigma_1 < \sigma_1^*$  or  $\sigma_2 > \sigma_2^*$  imply  $C < 0$ .



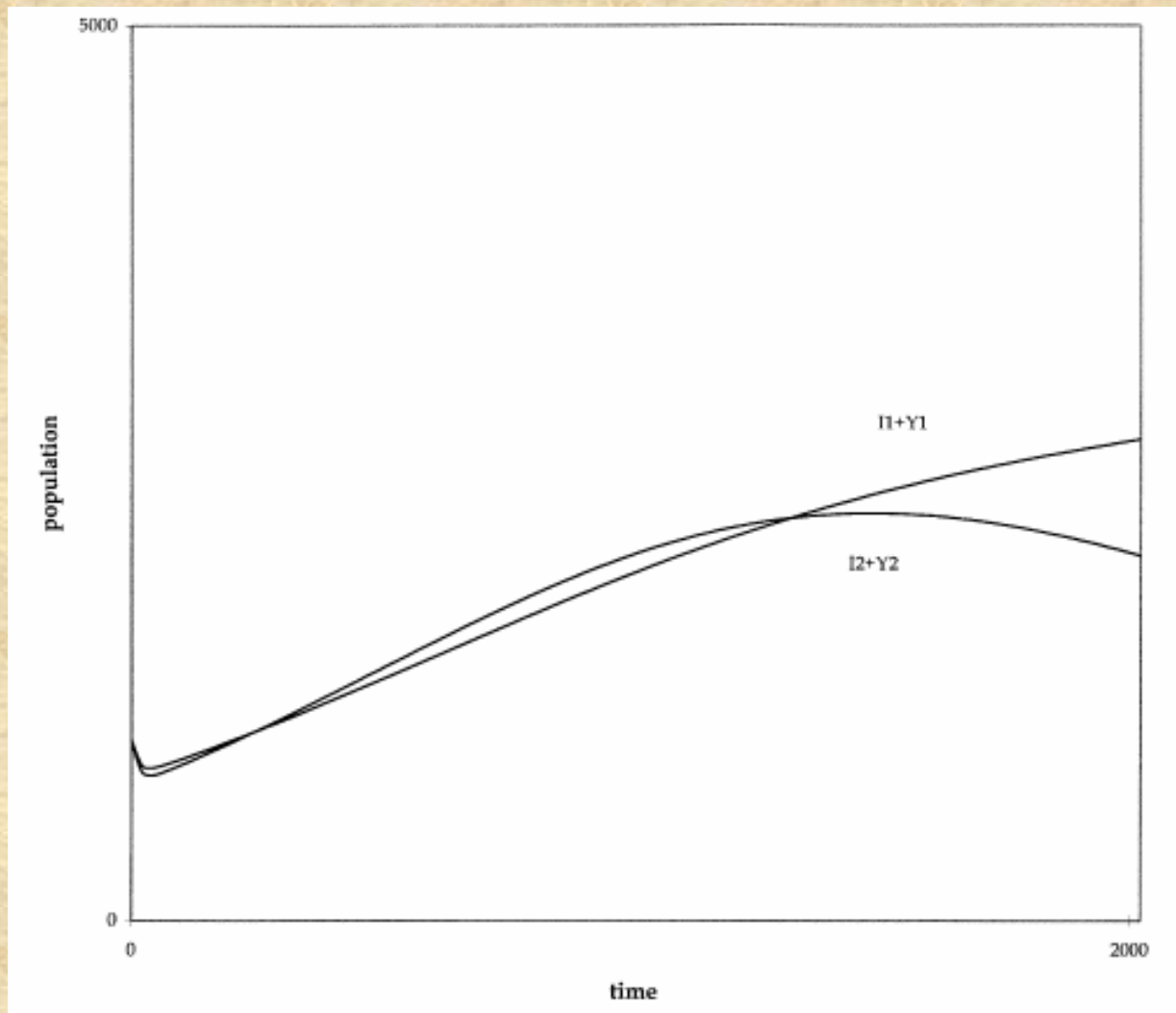
**Fig. 3.** Region of parameter space  $(\sigma_1, \sigma_2)$  where both boundary equilibria are locally asymptotically stable. Fixed parameter values are  $r = 0.71/\text{day}$ ,  $\mu = 0.000039/\text{day}$ ,  $\delta = 0.71/\text{day}$ ,  $h = 0.9775$ ,  $\alpha_1 = 0.002$ ,  $\alpha_2 = 0.015$ ,  $\beta_1 = 0.001$ ,  $\beta_2 = 0.001$ ,  $c = 10$ ,  $\hat{T} = 50\,000$ ,  $\hat{N} = 25\,000$ . The corresponding basic reproduction numbers are  $R_1 = 2.4$  and  $R_2 = 2.08$



- Units: Number of cases of infection with strain  $i$ .
- Parameter values give  $\sigma_2 < g^{-1}(\sigma_1) = 0.1$ .
- $e_1 = 0.0001/\text{day}$  and  $e_2 = 0.0005/\text{day}$
- Strain 1 competitively excludes strain 2.



- Parameter values give  $g^{-1}(\sigma_1) < \sigma_2 < f(\sigma_1)$ .
- $e_1 = 0.0001/\text{day}$  and  $e_2 = 0.0005/\text{day}$
- The outcome of the disease depends on initial conditions.



- Strain 2 increases faster at the beginning. It has the higher reproductive number.
- Both strains appear to coexist for about 3 years.
- Strain 1 starts to take over around year 4.

# Discussion

- Nowak and May (1994) showed that if the strains are directly transmitted (instead of through a vector), there will be coexistence of both strains.
- Bremermann and Thieme (1989) showed that an SI model with direct transmission of two strains and without superinfection predicts competitive exclusion of the strain with the lower basic reproductive number.
- When these equations are coupled in this host-vector model, competitive exclusion occurs if at least one of  $R_1$ ,  $R_2$  are greater than 1. The vector dynamics dominate.

# Discussion

- 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.

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