Evolución por Selección de resistencia a insecticida en poblaciones de mosquitos.

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Colaboradores

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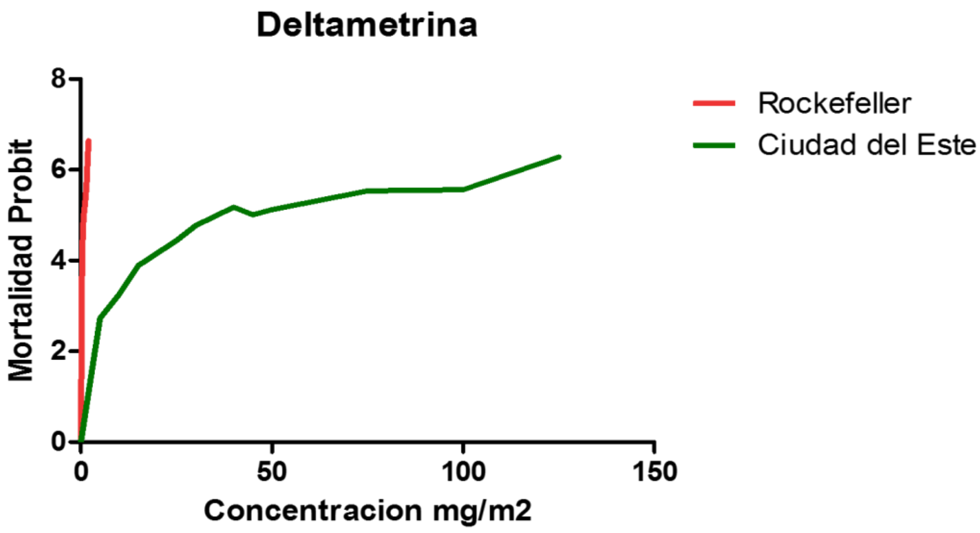
- Esta visita esta siendo financiada por el Proyecto: CONACyT
- Pastor E. Pérez - Estigarribia es alumno de doctorado en Ciencias de la Computación de la Facultad Politécnica de la Universidad Nacional de Asunción.

Antecedentes

- Experiencia reciente (Ferreira *et al.* 2015)

Protocolo est. LAFICAVE. IOC. Adaptada de WHO 1981 y 1998

CL	Ciudad del Este	Rockefeller	RR ug/m^2	Interpretación*
LC 50	41.84	0.75	55.44	Resistencia Alta
LC 90	147. 14	2.04	72 .4	Resistencia Alta

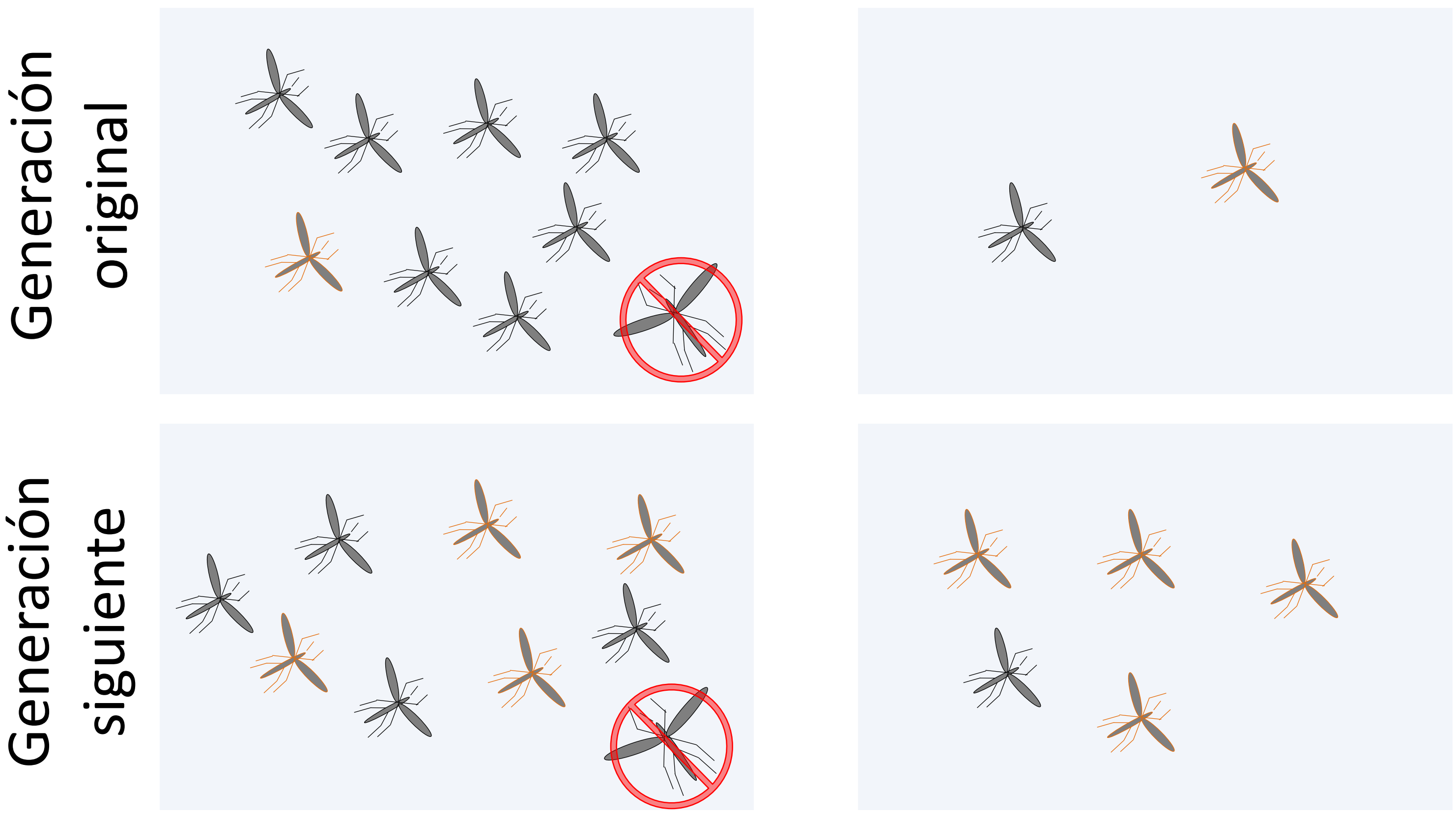


- WHO advierte que: La vida útil operativa de insecticidas es de ~5 años (Koella et al. 2009)

Problema de la evolución de la resistencia

Antes de la aplicación del insecticida

Después de la aplicación del insecticida



Modelo de la evolución de la resistencia

$$\left.\begin{aligned} V'(t) &= -(\mu_a + \delta)V(t) + e^{-\mu_i \tau_i}\frac{V(t-\tau_i)}{M(t-\tau_i)}b(M(t-\tau_i)) \\ R'(t) &= -\mu_a R(t) + e^{-\mu_i \tau_i}\frac{R(t-\tau_i)}{M(t-\tau_i)}b(M(t-\tau_i)). \end{aligned}\right\}$$

μ_a: tasa de mortalidad en adultos
δ: tasa de mortalidad inducida por el insecticida
μ_i: tasa de mortalidad en larvas
τ_i: tiempo de larvas
V y R: mosquitos vulnerables y resistentes M=V+R
b(M): tasa de natalidad para moscas de Nicholson.

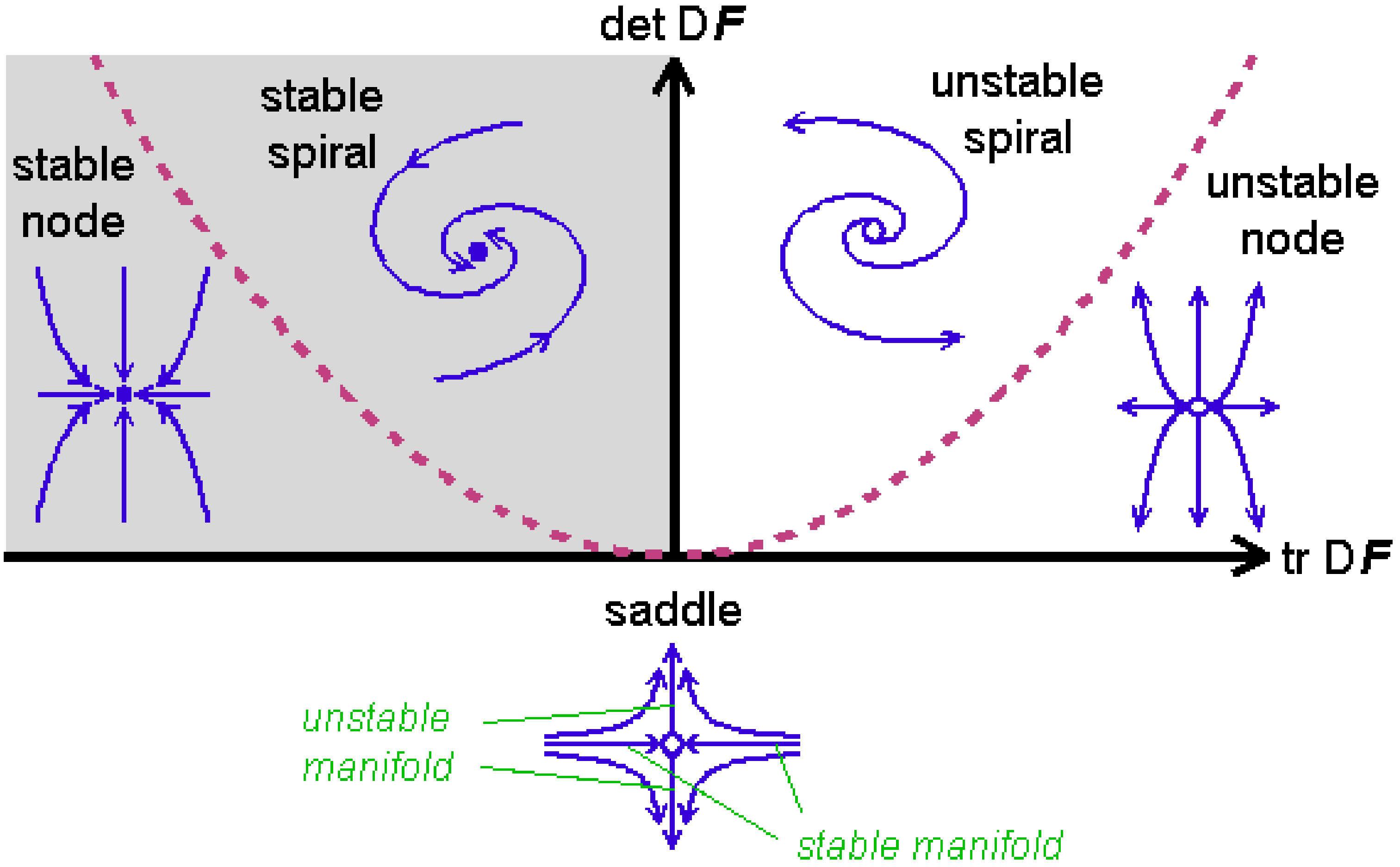
GOURLEY, Stephen A.; LIU, Rongsong; WU, Jianhong. **Slowing the evolution of insecticide resistance in mosquitoes: a mathematical model.** En *Proceedings of the Royal Society of London A: Mathematical, Physical and Engineering Sciences*. The Royal Society, 2011. p. rspa20100413.

ODE sin retardo

$$\begin{cases} \dot{V} = -\mu_s V + e^{-\mu_i \tau_i} \frac{V}{M} b(M) \\ \dot{R} = -\mu_n R + e^{-\mu_i \tau_i} \frac{R}{M} b(M) \end{cases}$$

μ_n: tasa de mortalidad en adultos
μ_s: ($\mu_n+\omega$) tasa de mortalidad inducida por el insecticida mas tasa de mortalidad en adultos
μ_i: tasa de mortalidad en larvas
τ_i: tiempo de larvas
V y R: mosquitos vulnerables y resistentes M=V+R
b(M): tasa de natalidad para moscas de Nicholson.

Linear stability analysis.



https://elmer.unibas.ch/pendulum/bif.htm

Análisis del modelo: puntos de equilibrio

- Hay tres puntos de equilibrio
- 1. $x^*=(V,R)=(0,0)$
- 2. $x^*=(V,R)=(0,R^*)$
- 3. $x^*=(V,R)=(V^*,0)$

Caracterización de los puntos de equilibrio

$$F(x) = \begin{cases} \dot{V} = f_1(V, R) \\ \dot{R} = f_2(V, R) \end{cases} \quad \text{No lineal}$$

$$F(x^* + \varepsilon\tilde{x}) \approx F(x*) + \left.\frac{\partial F}{\partial x}\right|_{x^*} (\varepsilon\hat{x}) + \left.\frac{\partial^2 F}{\partial x^2}\right|_{x^*} \frac{(\varepsilon\hat{x})^2}{2!} + \ldots$$

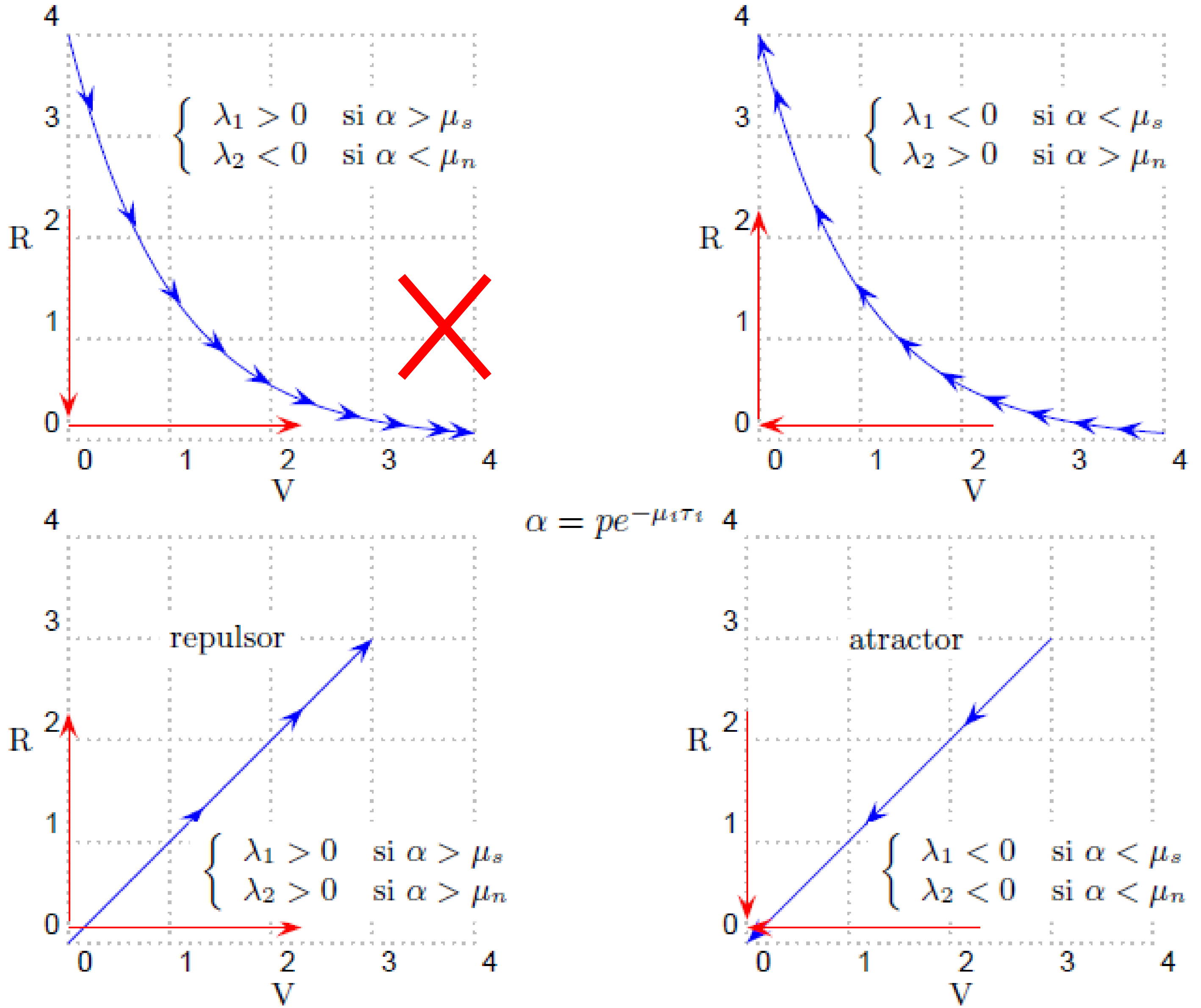
$$A = \frac{\partial F}{\partial x} = \begin{pmatrix} \frac{\partial f_1}{\partial V} & \frac{\partial f_1}{\partial R} \\ \frac{\partial f_2}{\partial V} & \frac{\partial f_2}{\partial R} \end{pmatrix} \quad \Rightarrow \quad \dot{\hat{x}} = A\hat{x}$$

Análisis de estabilidad lineal

¿ Cual es el comportamiento cualitativo del sistema?
¿Cuales son las soluciones?

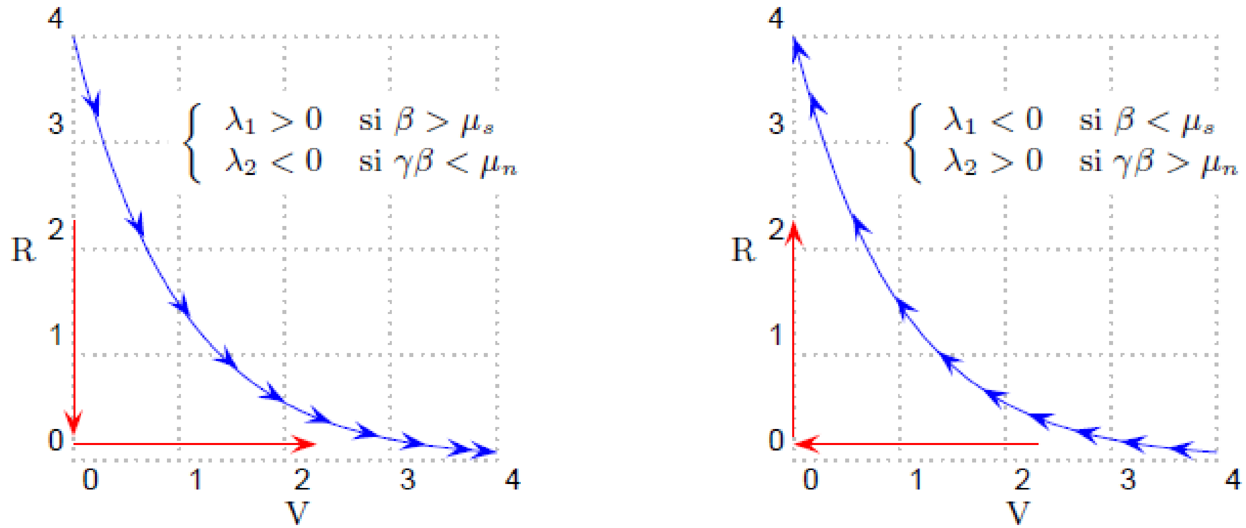
Punto trivial

$$\lambda\ A|_{x^*} = \begin{cases} \lambda_1 = \frac{p}{e^{\mu_i\tau_i}} - \mu_s \\ \lambda_2 = \frac{p}{e^{\mu_i\tau_i}} - \mu_n. \end{cases}$$

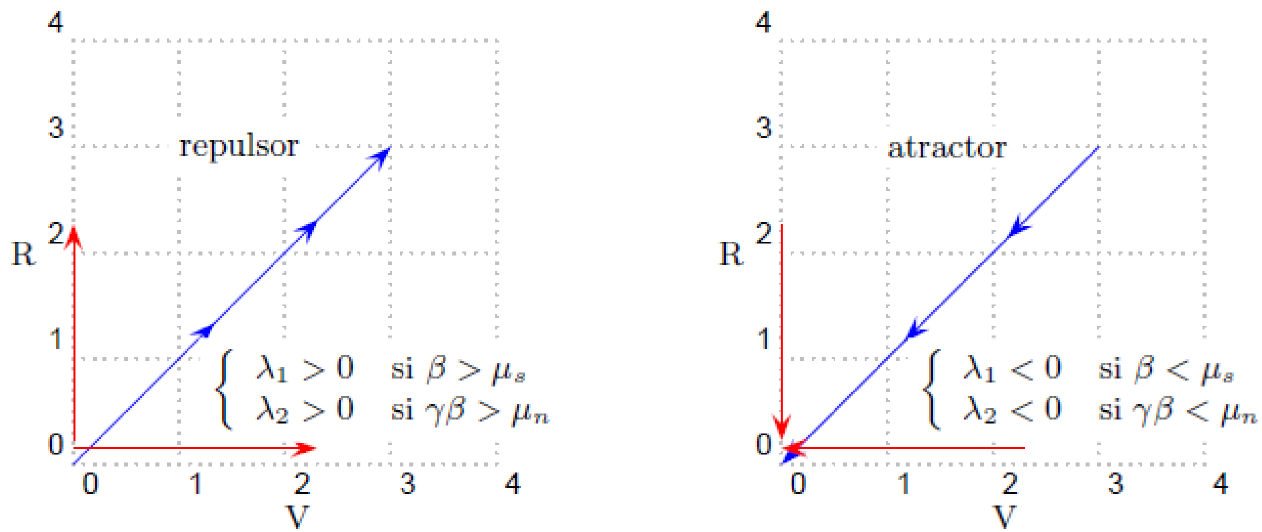


Punto no trivial

$$x^* = (V, R) = (0, R^*)$$



$$\beta = \mu_n e^{-2\mu_i\tau_i};\ \gamma = (1 - \mu_i\tau_i + \ln(\mu_n/p))$$

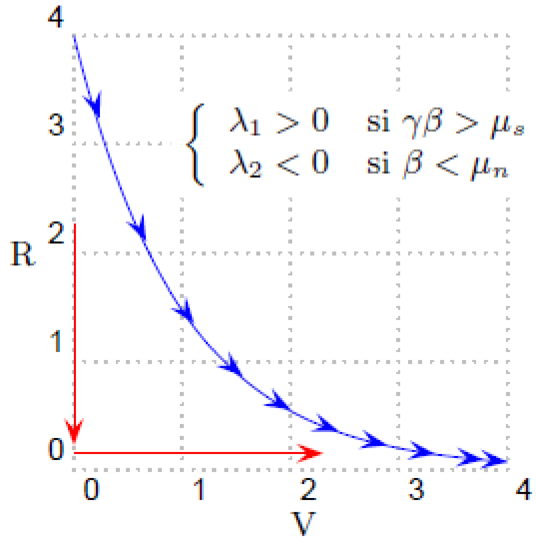


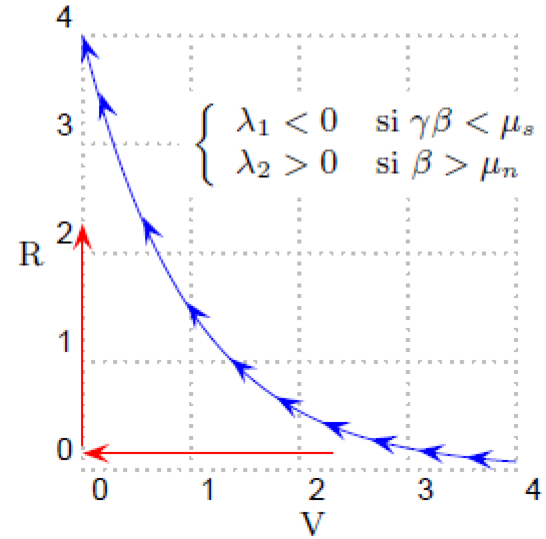
$$\lambda\ A|_{x^*} = \begin{cases} \lambda_1 = \mu_n e^{-2\mu_i\tau_i} - \mu_s \\ \lambda_2 = (1 - \mu_i\tau_i + \ln(\mu_n/p))\mu_n e^{-2\mu_i\tau_i} - \mu_n. \end{cases}$$

Punto no trivial

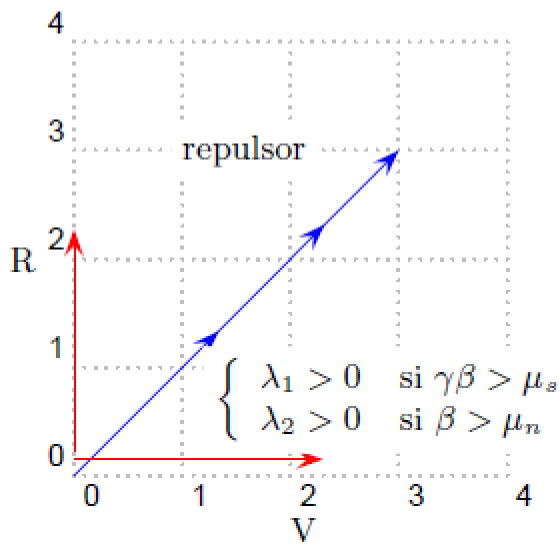
$$x^* = (V, R) = (V^*, 0)$$

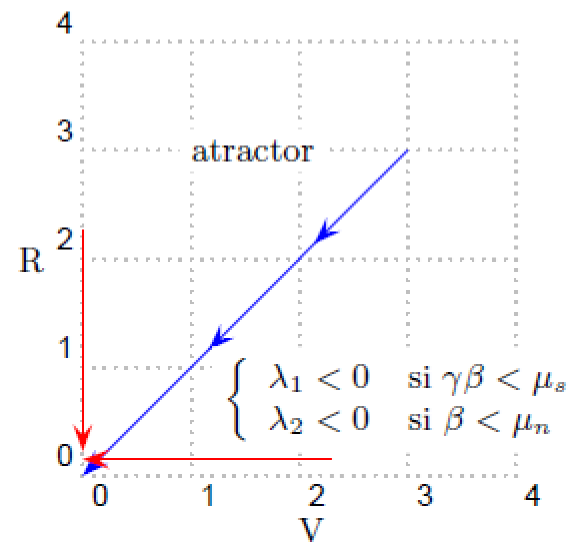
$$\lambda\ A|_{x^*} = \begin{cases} \lambda_1 = (1 - \mu_i \tau_i + \ln(\mu_s/p))\mu_s e^{-2\mu_i \tau_i} - \mu_s \\ \lambda_2 = \mu_s e^{-2\mu_i \tau_i} - \mu_n \end{cases}$$



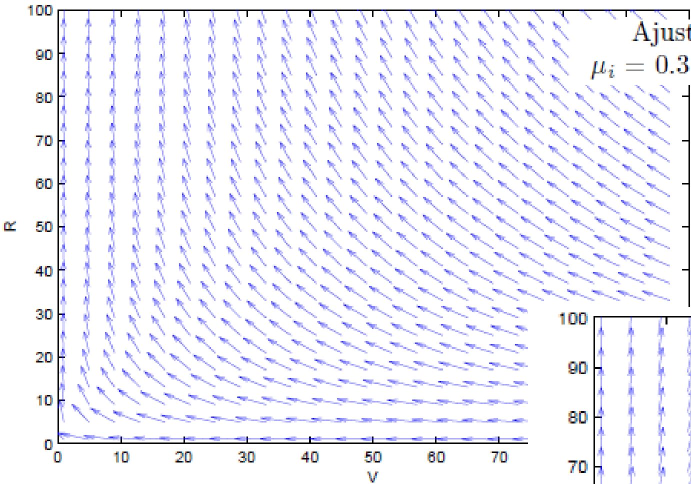


$$\beta = \mu_n e^{-2\mu_i \tau_i};\ \gamma = (1 - \mu_i \tau_i + \ln(\mu_n/p))$$





Diagramas de fase y estabilidad

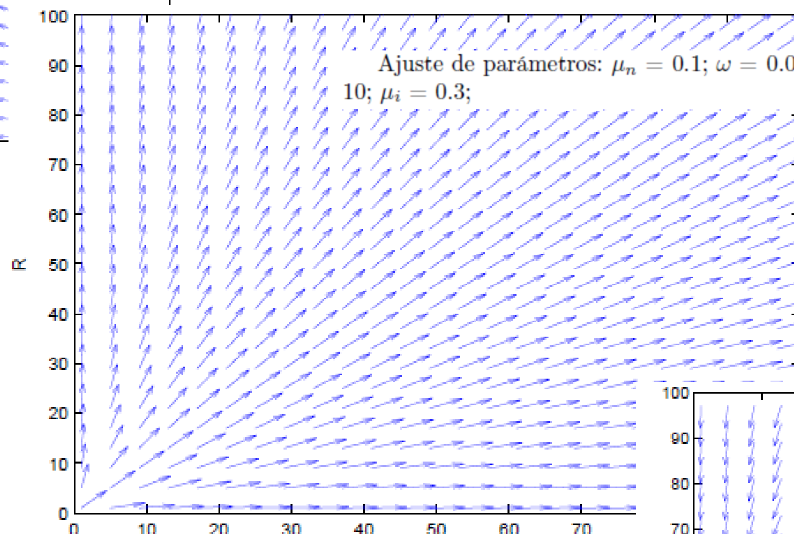


Ajuste de parámetros: $\mu_n = 0.1$; $\omega = 0.5$; $\mu_s = (\mu_n + \omega)$; $p = 8$; $q = 1/100000$; $\tau_i = 10$; $\mu_i = 0.3$;

$x^* = (0, 0)$
Lambda 1 = -0.2017
Lambda 2 = 0.2983

$x^* = (0, R^*)$
Lambda 1 = -0.5998
Lambda 2 = -0.6016

$x^* = (V^*, 0)$
Lambda1 = -0.6068
Lambda2 = -0.0985



Ajuste de parámetros: $\mu_n = 0.1$; $\omega = 0.001$; $\mu_s = (\mu_n + \omega)$; $p = 8$; $q = 1/100000$; $\tau_i = 10$; $\mu_i = 0.3$;

$x^* = (0, 0)$
Lambda 1 = 0.29737
Lambda 2 = 0.2983

$x^* = (0, R^*)$
Lambda 1 = -0.1008
Lambda 2 = -0.1026

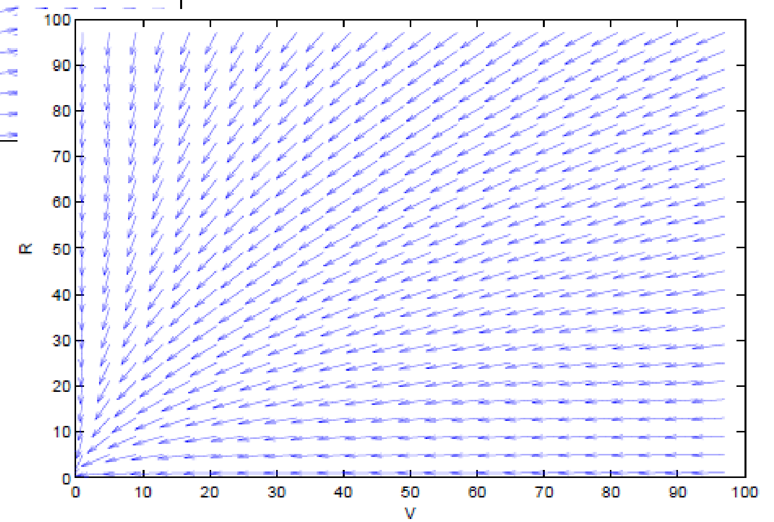
$x^* = (V^*, 0)$
Lambda1 = -0.1026
Lambda2 = -0.09975

$x^* = (0, 0)$
Lambda 1 = -2.6017
Lambda 2 = -1.6017

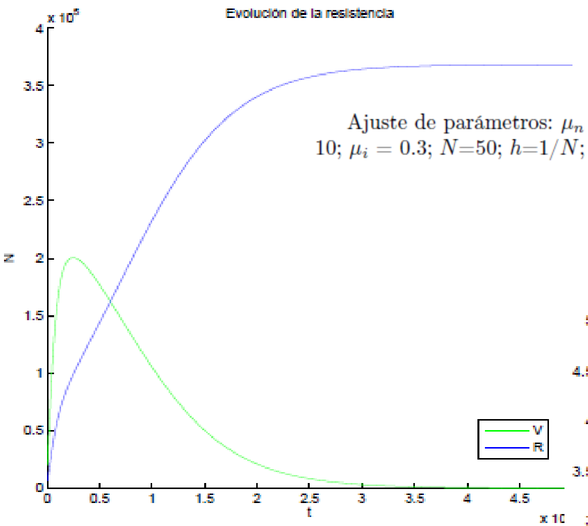
$x^* = (0, R^*)$
Lambda 1 = -2.9950
Lambda 2 = -3.0168

$x^* = (V^*, 0)$
Lambda1 = -3.0222
Lambda2 = -1.9926

Ajuste de parámetros: $\mu_n = 2$; $\omega = 1$; $\mu_s = (\mu_n + \omega)$; $p = 8$; $q = 1/100000$; $\tau_i = 10$; $\mu_i = 0.3$;



Simulación numérica

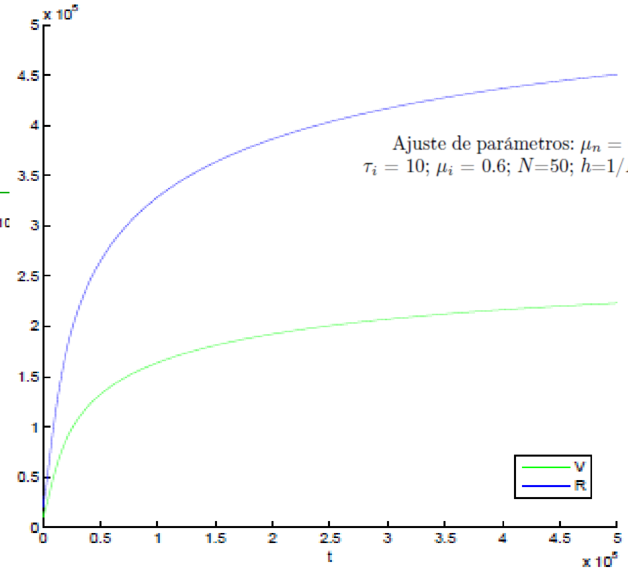


Ajuste de parámetros: $\mu_n = 0.01$; $\omega = 0.01$; $\mu_s = (\mu_n + \omega)$; $p = 8$; $q = 1/100000$; $\tau_i = 10$; $\mu_i = 0.3$; N=50; h=1/N; $Nmax$=1000*N; V= 0.2e5; R=0.6e4;

$x^* = (0, 0)$
Lambda 1 = 0.3783
Lambda 2 = 0.3883

$x^* = (0, R^*)$
Lambda 1 = -0.0200
Lambda 2 = -0.0202

$x^* = (V^*, 0)$
Lambda1 = -0.0204
Lambda2 = -0.0100

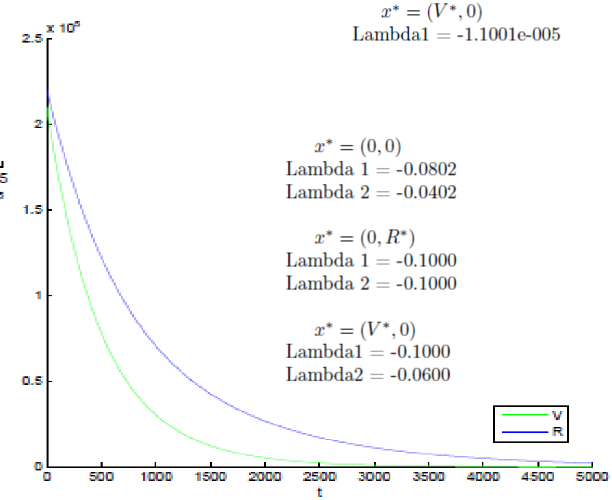


Ajuste de parámetros: $\mu_n = 0.00001$; $\omega = 0.000001$; $\mu_s = (\mu_n + \omega)$; $p = 8$; $q = 1/100000$; $\tau_i = 10$; $\mu_i = 0.6$; N=50; h=1/N; $Nmax$=1000*N; V= 0.2e5; R=0.6e4;

$x^* = (0, 0)$
Lambda 1 = 0.0198
Lambda 2 = 0.0198

$x^* = (0, R^*)$
Lambda 1 = -1.1000e-005
Lambda 2 = -1.1001e-005

$x^* = (V^*, 0)$
Lambda1 = -1.1001e-005



$x^* = (0, 0)$
Lambda 1 = -0.0802
Lambda 2 = -0.0402

$x^* = (0, R^*)$
Lambda 1 = -0.1000
Lambda 2 = -0.1000

$x^* = (V^*, 0)$
Lambda1 = -0.1000
Lambda2 = -0.0600

Ajuste de parámetros: $\mu_n = 0.06$; $\omega = 0.04$; $\mu_s = (\mu_n + \omega)$; $p = 8$; $q = 1/100000$; $\tau_i = 10$; $\mu_i = 0.6$; N=50; h=1/N; $Nmax$=1000*N; V=2.1e5; R=2.2e5;

Modelado de resistencia a los insecticidas durante la infestación de poblaciones de *Aedes* por *Wolbachia*.

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FACULTAD POLITECNICA
28 AÑOS CONSTRUYENDO EL FUTURO

LCCA

Control genético: *Wolbachia*

El remplazo de la población puede evitar que el nicho ecológico vuelva a ser ocupado, mientras que la eliminación conduciría al repoblamiento.

Consideraciones del modelo propuesto

- Competencia por recursos limitados
- Evolución de la resistencia a insecticidas por selección y mutación
- Control genético con *Walbachia*

DDE con seis estados variables

- **From birth rates $r_U(t), v_U(t), r_W(t), v_W(t)$ to adult numbers $R_U(t), V_U(t), R_W(t), V_W(t)$**

The model is a delay-differential equation with 6 state variables: the variables p and q model the total population in the larva stage, and the variables $R_U(t), V_U(t), R_W(t), V_W(t)$ model the four different adult stages.

$$s(t) = r_U(t) + v_U(t) + r_W(t) + v_W(t) \tag{1a}$$

$$\dot{p} = -s(t-\tau)e^{-q(t)} + s(t) - \mu(p(t))p(t) \tag{1b}$$

$$\dot{q} = \mu(p(t)) - \mu(p(t-\tau)) \tag{1c}$$

The variable $s(t)$ represents the total number of births of larvas at time t. The variable $p(t)$ represents the total number of larvas at time t. The function μ is increasing.

$$\dot{R}_U = r_U(t-\tau)e^{-q(t)} - \mu_{u,R}R_U(t) \tag{1d}$$

$$\dot{V}_U = v_U(t-\tau)e^{-q(t)} - \mu_{u,V}V_U(t) \tag{1e}$$

$$\dot{R}_W = r_W(t-\tau)e^{-q(t)} - \mu_{w,R}R_W(t) \tag{1f}$$

$$\dot{V}_W = v_W(t-\tau)e^{-q(t)} - \mu_{w,V}V_W(t) + \mu_{w,V}V^*(t) \tag{1g}$$

The term in red corresponds to addition of adult vulnerable mosquitos infected by Wolbachia.

DDE con seis estados variables

- **From adult numbers $R_U(t), V_U(t), R_W(t), V_W(t)$ to birth rates $r_U(t), v_U(t), r_W(t), v_W(t)$**

The birth rates are given as functions of the adult numbers. They take into account the cytoplasmic incompatibility.

$$S(t) = R_U(t) + V_U(t) + R_W(t) + V_W(t) \tag{1h}$$

$$r_U(t) = \alpha_U(S(t))\ ((1-\rho_R)R_U(t) + \rho_V V_U(t))\frac{R_U(t)+V_U(t)}{S(t)} \tag{1i}$$

$$v_U(t) = \alpha_U(S(t))\ (\rho_R R_U(t) + (1-\rho_V)V_U(t))\frac{R_U(t)+V_U(t)}{S(t)} \tag{1j}$$

$$r_W(t) = \alpha_W(S(t))\ ((1-\rho_R)R_W(t) + \rho_V V_W(t)) \tag{1k}$$

$$v_W(t) = \alpha_W(S(t))\ (\rho_R R_W(t) + (1-\rho_V)V_W(t)) + v^*(t) \tag{1l}$$

The variable $S(t)$ represents the total number of adults at time t. The functions α_U, α_W are decreasing and converge to 0 at infinity, and $\alpha_U \geq \alpha_W$. The constants $0 \leq \rho_V \leq 1$ (respectively $0 \leq \rho_R \leq 1$) is the proportion of resistant (resp. vulnerable) offspring produced by a vulnerable (resp. resistant) female. The term in red corresponds to addition of vulnerable larvas infected by Wolbachia.

gracias
aguije
obrigado