Time-scale separation in a minimal model for a vector-borne disease

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CMPD5
Computational and Mathematical
Population Dynamics 5
Bahia Mar Fort Lauderdale Beach
May 19-24, 2019
partially supported by NSF

Outline

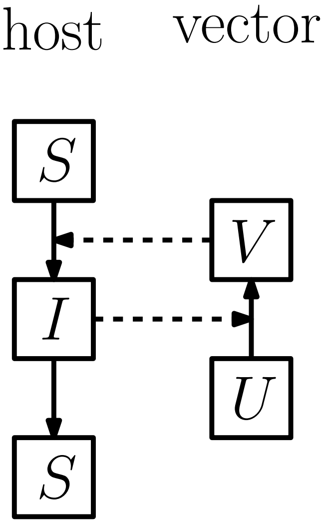
State variables in vector-borne disease modelling

Var.	Description
Host	
N	Host population density
S	Susceptible Host population density
I	Infected Host population density
R	Recovered Host population density
Vector	
M	Vector population density
U	Susceptible Vector population density
V	Infected Vector population density

Basic reproduction number

In the epidemiological literature, the basic reproduction number R_0 represents the number of secondary cases one infected case generates on average over the course of its infectious period in an otherwise uninfected population.

SISUV model



Four-dimensional system

$$\frac{dS}{dt} = \varepsilon\left(-\frac{\beta}{M}SV + \mu I\right)$$

$$\frac{dI}{dt} = \varepsilon\left(\frac{\beta}{M}SV - \mu I\right)$$

$$\frac{dU}{dt} = -\frac{\vartheta}{N}UI + \nu V$$

$$\frac{dV}{dt} = \frac{\vartheta}{N}UI - \nu V$$

SISUV model

Assumed constant host and vector population densities

$$N = S(t) + I(t), \quad M = U(t) + V(t), \quad \forall t \geq 0$$

Two-dimensional equivalent system[1]

$$\frac{dV}{dt} = \underbrace{\frac{\vartheta}{N}(M - V)I - \nu V}_{=f(V,I,\varepsilon)}$$

$$\frac{dI}{dt} = \varepsilon \underbrace{\left(\frac{\beta}{M}(N - I)V - \mu I \right)}_{=g(V,I,\varepsilon)}$$

[1] Rocha, Aguiar, Souza and Stollenwerk, *Int J Computer Math* (2013).

Equilibria SISUV model

- trivial, disease-free equilibrium

$$I^0 = 0, V^0 = 0, S^0 = N, U^0 = M$$

- interior, endemic equilibrium

$$I^* = N\frac{\beta\vartheta - \mu\nu}{(\mu + \beta)\vartheta}, V^* = M\frac{\beta\vartheta - \mu\nu}{\beta(\nu + \vartheta)}, S^* = N - I^*, U^* = M - V^*$$

In the SISUV model $R_0 = \frac{\beta\vartheta}{\mu\nu}$

- $R_0 = 1$ at the transcritical bifurcation point, where the endemic equilibrium coincides with the disease-free equilibrium
- endemic equilibrium is biologically relevant and globally asymptotically stable if $R_0 > 1$

SISUV model – Singular perturbation

Singular perturbation theory deals with systems whose solutions evolve on different time scales whose ratio is characterised by a small parameter $0 < \varepsilon \ll 1$.

It uses invariant manifolds in phase space in order to understand the global structure of the phase space or to construct orbits with desired properties.

$$\frac{dI}{dt} = \varepsilon g(V, I, \varepsilon) \quad \text{slow variable}$$

$$\frac{dV}{dt} = f(V, I, \varepsilon) \quad \text{fast variable}$$

SISUV model – fast system

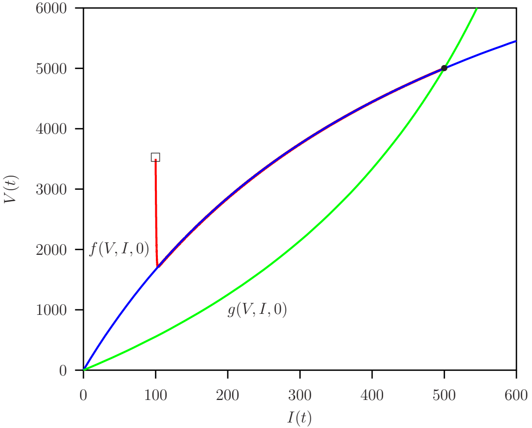
With $\varepsilon = 0$ we have the fast system

$$\frac{dI}{dt} = 0$$

$$\frac{dV}{dt} = f(V, I(0), 0) = \frac{\vartheta}{N}(M - V)I(0) - \nu V$$

The infected host population I remains constant over t, so that the trajectory is a vertical line in the (I, V) phase space plot

Phase-space plot SISUV model



The solid line is the trajectory starting at the point □. Two curves represent the two nullclines $f(V, I, 0) = 0$ and $g(V, I, 0) = 0$

SISUV model – slow system

With a change of time-scale $\tau = \varepsilon t$ the resulting system with $\varepsilon \ll 1$ is called the *slow or reduced system*:

$$\varepsilon \frac{dI}{d\tau} = \varepsilon g(V, I, \varepsilon) = \varepsilon \left(\frac{\beta}{M}(N - I)V - \mu I \right)$$

$$\varepsilon \frac{dV}{d\tau} = f(V, I, \varepsilon) = \frac{\vartheta}{N}(M - V)I - \nu V$$

Substitution of $\varepsilon = 0$ gives a differential-algebraic system describing the evolution of the slow variable $I(\tau)$ constrained to the set $f = 0$.

$$0 = f(V, I, 0) \quad \Leftrightarrow \quad V = \frac{\vartheta I M}{\vartheta I + N\nu}$$

$$\frac{dI}{d\tau} = g(V, I, 0) = \frac{\beta}{M}(N - I)V - \mu I$$

Time-scale separation

These heuristic results suggest the following approach for dealing with the two different time scales:

1. set $\varepsilon = 0$ in the slow system, which gives the set of fast equilibria $f = 0$.

   The *critical manifold* is the f-nullcline.

2. with a good Ansatz the relation $f(V, I, 0) = 0$ can be rewritten as $I = q(V)$ and we can substitute $V = q^{-1}(I)$.
3. the result is the 1-dimensional reduced system with $\varepsilon = 0$:

$$\frac{dI}{d\tau} = g(q^{-1}(I), I, 0) = \frac{\beta}{M}(N - I)q^{-1}(I) - \mu I$$

Geometric singular perturbation technique

In order to get a better approximation for $0 < \varepsilon \ll 1$, we follow the geometric singular perturbation technique.

For $\varepsilon = 0$ the f-nullcline

$$\left\{(V, I) | f(V, I, 0) = 0, V \geq 0, I \geq 0\right\}$$

consists of the critical manifold

$$\mathcal{M} = \left\{(V, I) | I = \frac{\nu V N}{\vartheta(M - V)},\ 0 \leq V \leq M\ , 0 \leq I \leq N\right\}$$

$\mathcal{M}$ forms a set of equilibria of the fast system

Application of Fenichel's theorem

Fenichel's theorem states that there exists ε_0 such that for $0 < \varepsilon < \varepsilon_0$, there exist locally invariant manifolds $\mathcal{M}_\varepsilon$, $\mathcal{O}(\varepsilon)$-close and diffeomorphic to $\mathcal{M}$. Using their invariance, the perturbed manifold $\mathcal{M}_\varepsilon$ can be approximated by an asymptotic expansion in ε.
It can (at least locally) be described as a graph

$$\left\{(V, I) | I = q(V, \varepsilon), V \geq 0, I \geq 0\right\}$$

due to normal hyperbolicity and inverse function theorem.
This manifold is invariant when the invariance equation holds

$$\frac{dI}{d\tau} = \frac{dI}{dV}\frac{dV}{d\tau} = \frac{\partial q(V, \varepsilon)}{\partial V}\frac{dV}{d\tau}$$

Asymptotic expansion of $\mathcal{M}_\varepsilon$ for the SISUV model

Introduce an asymptotic expansion in $0 < \varepsilon \ll 1$

$$I(V) = q(V, \varepsilon) = q_0(V) + \varepsilon q_1(V) + \varepsilon^2 q_2(V) + \dots$$

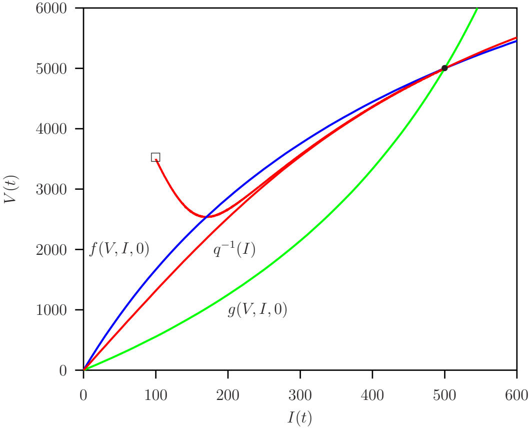
Formally differentiating by V and substituting into the invariance equation, gathering equal order terms of ε and assuming $V > 0$ results in

$$I(V, \varepsilon) = q(V, \varepsilon) = q_0(V) + \varepsilon q_1(V) + \mathcal{O}(\varepsilon^2)$$

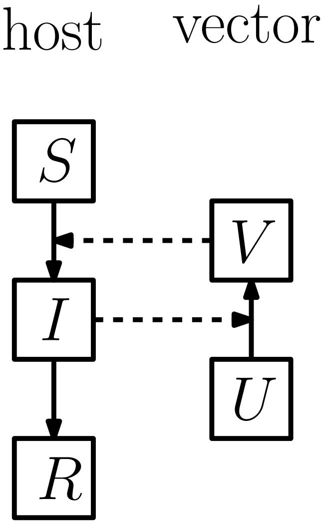
with

$$q_0(V) = \frac{\nu N V}{\vartheta(M - V)}$$
$$q_1(V) = \left(\frac{\beta}{\nu M}(M - V - \frac{\nu}{\vartheta}V) - \frac{\mu}{\vartheta} \right) \frac{NV}{M} .$$

Invariant manifold SISUV model



One line is the trajectory starting at the point □. The other is the curve $V(I) = q^{-1}(I, \varepsilon)$. Two nullclines $f(V, I, 0) = 0$ and $g(V, I, 0) = 0$.



$$\frac{dS}{dt} = \varepsilon\left(-\frac{\beta}{M}SV + \mu(N-S)\right)$$

$$\frac{dI}{dt} = \varepsilon\left(\frac{\beta}{M}SV - (\gamma+\mu)I\right)$$

$$\frac{dR}{dt} = \varepsilon\left(\gamma I - \mu R\right)$$

$$\frac{dU}{dt} = -\frac{\vartheta}{N}UI + \nu(M-U)$$

$$\frac{dV}{dt} = \frac{\vartheta}{N}UI - \nu V$$

SIRUV model

Assuming constant host and vector population densities

$$N = S(t) + I(t) + R(t), \quad M = U(t) + V(t), \quad \forall t \geq 0$$

yields an equivalent 3-dimensional system[2]

$$\begin{aligned}
\frac{dS}{dt} &= \varepsilon g_1(S, I, V) = \varepsilon \left(-\frac{\beta}{M} SV + \mu(N - S) \right) , \\
\frac{dI}{dt} &= \varepsilon g_2(S, I, V) = \varepsilon \left(\frac{\beta}{M} SV - (\gamma + \mu) I \right) , \\
\frac{dV}{dt} &= f(S, I, V) = \frac{\vartheta}{N}(M - V)I - \nu V .
\end{aligned}$$

[2] Rashkov, Venturino, Aguiar, Stollenwerk, and Kooi, *Math Biosci Eng 16* (2019), 4314-4338.

Equilibria SIRUV model

- trivial, disease-free equilibrium $S^0 = N, I^0 = 0, V^0 = 0$
- endemic equilibrium whenever $R_0 = \frac{\vartheta\beta}{\nu(\mu+\gamma)} > 1$:

$$S^* = N\frac{\nu(\gamma+\mu)+\mu\vartheta}{\vartheta(\beta+\mu)}, \quad I^* = \mu N\frac{\beta\vartheta-\nu(\gamma+\mu)}{\vartheta(\beta+\mu)(\gamma+\mu)}$$

$$V^* = \mu M\frac{\beta\vartheta-\nu(\gamma+\mu)}{\beta(\nu(\gamma+\mu)+\mu\vartheta)},$$

Theorem

When $R_0 > 1$, the endemic equilibrium is locally asymptotically stable. It is a spiral as long as μ is sufficiently small.

Heuristic analysis SIRUV model

It is convenient to analyse the behaviour of the fast variable V in the (V, I)-system with the slow variable $\bar{S}$ as a parameter

$$\frac{dI}{dt} = \frac{\beta}{M}\bar{S}V - (\mu+\gamma)I, \quad \frac{dV}{dt} = \frac{\vartheta}{N}(M-V)I - \nu V$$

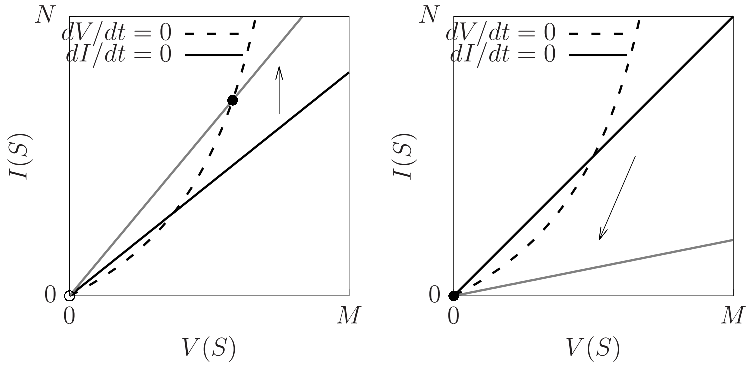
Theorem

Let $S_c = \frac{\nu(\mu+\gamma)}{\vartheta\beta}N$. For $\bar{S} \leq S_c$, trivial equilibrium $(0,0)$ is the single global asymptotically stable equilibrium. For $\bar{S} \geq S_c$, the interior equilibrium

$$I^*(\bar{S}) = \frac{\beta\bar{S}}{(\mu+\gamma)}\left(1 - \frac{\nu(\mu+\gamma)N}{\vartheta\beta\bar{S}}\right), \; V^*(\bar{S}) = M\left(1 - \frac{\nu(\mu+\gamma)N}{\vartheta\beta\bar{S}}\right)$$

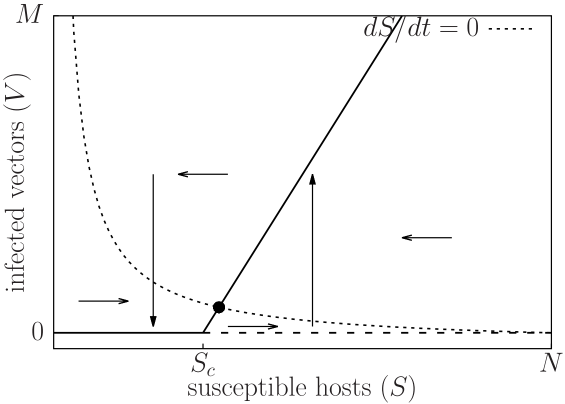
is globally asymptotically stable.

Dependence of nullclines on $\bar{S}$



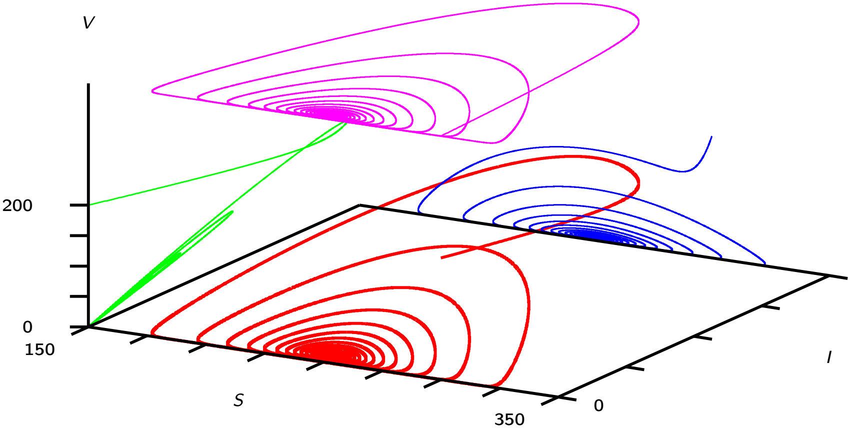
Left panel: with $\bar{S} > S_c$, the trajectory converges to the interior equilibrium
Right panel: when $\bar{S} < S_c$, the trajectory approaches the origin

Fast and slow flow in the SV-plane



The locus of *fast* equilibria V^* is shown as solid line.
long arrows: direction of fast V-flow
short arrows: direction of slow S-flow
The interior equilibrium (S^*, V^*) is shown as •

Figure: Phase-space result for the SIRUV model.



SIRUV model – slow system

With a change of time-scale $\tau = \varepsilon t$ the resulting system with $\varepsilon \ll 1$ is called the *slow or reduced system*:

$$\varepsilon \frac{dS}{d\tau} = \varepsilon g_1(S, I, V, \varepsilon) = \varepsilon \left(-\frac{\beta}{M} SV + \mu(N - S) \right)$$

$$\varepsilon \frac{dI}{d\tau} = \varepsilon g_2(S, I, V, \varepsilon) = \varepsilon \left(\frac{\beta}{M} SV - (\gamma + \mu) I \right)$$

$$\varepsilon \frac{dV}{d\tau} = f(V, I, \varepsilon) = \frac{\vartheta}{N}(M - V)I - \nu V$$

Substitution of $\varepsilon = 0$ gives an differential-algebraic system describing the evolution of the slow variables $S(\tau), I(\tau)$ constrained to the set $f = 0$

$$0 = f(S, I, V, 0) \quad \Leftrightarrow \quad V = \frac{\vartheta IM}{\vartheta I + N\nu}$$

$$\frac{dS}{d\tau} = g_1(S, I, V, 0), \quad \frac{dI}{d\tau} = g_2(S, I, V, 0)$$

Singular perturbation of SIRUV model

Using the time-scale argument with $\varepsilon = 0$, we obtain the two-dimensional f-nullspace, consisting of the critical manifold

$$\mathcal{M} = \left\{ 0 \le S \le N,\ I = \frac{\nu N V}{\vartheta(M - V)}, 0 \le I \le N \middle| 0 \le V \le M \right\},$$

The system with hyperbolic expression

$$V(S, I) = \frac{\vartheta M I}{\nu N + \vartheta I}$$

is the reduced system.
Note $V(S, I)$ is the same as $V(I)$ in the SISUV model

Fenichel's theorem states that there exists ε_0 such that for $0 < \varepsilon < \varepsilon_0$, there are locally invariant manifolds $\mathcal{M}_\varepsilon$. Using its invariance, the perturbed manifold $\mathcal{M}_\varepsilon$ can be approximated by an asymptotic expansion in ε.

It can be described as a graph

$$\big\{(S, I, V) | V = p(S, I, \varepsilon), V \geq 0, I \geq 0\big\}$$

This manifold is invariant when

$$\frac{dV}{d\tau} = \frac{\partial V}{\partial S}\frac{dS}{d\tau} + \frac{\partial V}{\partial I}\frac{dI}{d\tau}$$

which yields with $V = p(S, I, \varepsilon)$ the invariance equation

$$\frac{dp(S,I)}{d\tau} = \frac{\partial p(S,I)}{\partial S}\frac{dS}{d\tau} + \frac{\partial p(S,I)}{\partial I}\frac{dI}{d\tau}$$

Asymptotic expansion of $\mathcal{M}_\varepsilon$ for the SIRUV model

Introduce an asymptotic expansion in $0 < \varepsilon \ll 1$

$$V(S,I) = p(S,I,\varepsilon) = p_0(S,I) + \varepsilon p_1(S,I) + \varepsilon^2 p_2(S,I) + \ldots$$

Differentiating formally by S, I, substituting into the invariance equation, gathering the zero order terms of ε and assuming $V > 0$ gives

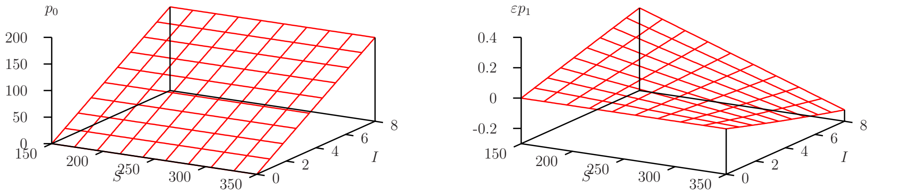
$$V(S,I) = p(S,I,\varepsilon) = p_0(S,I) + \varepsilon p_1(S,I) + \mathcal{O}(\varepsilon^2),$$

with

$$p_0(S,I) = \frac{\vartheta M I}{\vartheta I + \nu N},$$

$$p_1(S,I) = -\frac{M\nu\vartheta N^2}{(\vartheta I + \nu N)^3}\left(\frac{\beta\vartheta S I}{\vartheta I + \nu N} - (\gamma+\mu) I\right).$$

Figure: Plots of the coefficients of first two terms in the asymptotic expansion for $V = p(S, I, \varepsilon)$ with $\varepsilon = 1/365$



The size of the first-order term in the right panel shows that the contribution of the p_1 term is marginal

Observations

The usage of such a power series approximation is, however, counterproductive if we don't know its radius of convergence

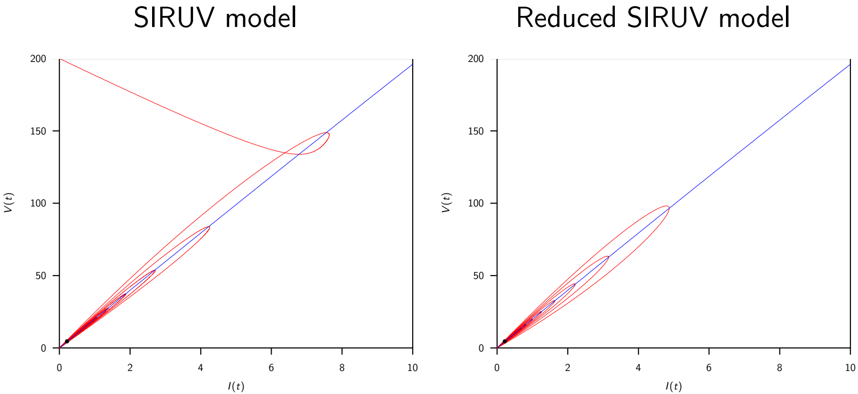
Numerical experiments show that

- either spurious equilibria can occur when the trajectory starts not sufficiently close to the equilibrium
- or the trajectory escapes to infinity

Results are not shown here
Refer also to the examples in Hek (2010)[3]

[3] G. Hek, Geometric singular perturbation theory in biological practice, *J Math Biol*, **60** (2010), 347–386.

Trajectory in (I, V) space



The point • is endemic stable spiral equilibrium

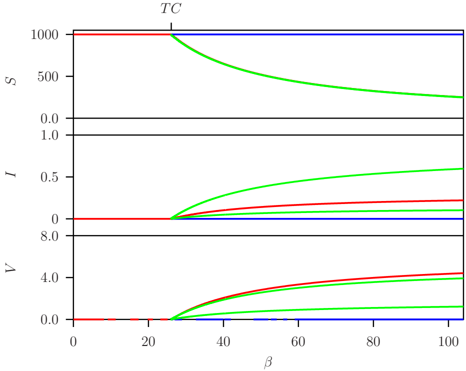
Role of seasonality

Introduce seasonality in the SIRUV system by assuming that the density of the vector population M changes in a perfect sinusoidal way, motivated by dengue fever epidemiology data

$$M(t) = M_0 \left(1 + \rho \cos(2\pi t)\right)$$

with a reference value M_0 and amplitude ρ

Numerical bifurcation analysis for reference parameter set gives the role of vector on the epidemics by calculation of the threshold value of β where the disease becomes endemic



curve: non-seasonal equilibria
curve: seasonal maximum and minimum, TC transcritical bifurcation

Limit cycles

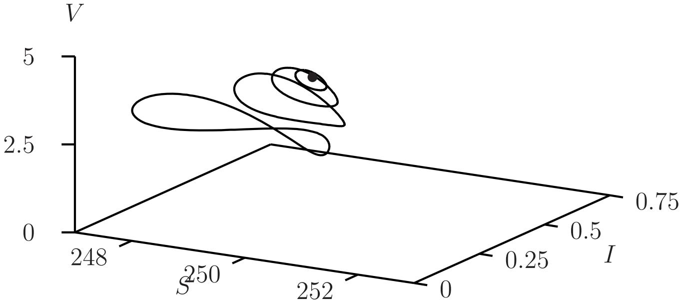


Figure: The amplitude of cycles is proportional to the value of ρ. The period of oscillation equals that of the forcing term.

Thank you for your attention!

P. Rashkov, E. Venturino, M. Aguiar, N. Stollenwerk, B.W. Kooi, On the role of vector modeling in a minimalistic epidemic model, *Math Biosci Eng* 16 (2019), 4314-4338

work in CA16227 *Investigation & Mathematical Analysis of Avant-garde Disease Control via Mosquito Nano-Tech Repellents* `www.imaac.eu`

PR, EV, BWK: partially supported by `www.cost.eu`

EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

Funded by the Horizon 2020 Framework Programme of the European Union

PR: partially suported by Bulgarian Fund for Scientific Research (FNI), contract DKOST 01/29 `www.fni.bg`

ФОНД НАУЧНИ ИЗСЛЕДВАНИЯ

МИНИСТЕРСТВО НА ОБРАЗОВАНИЕТО И НАУКАТА

Parameters

Parameter	Description	SIRUV	SISUV
Host			
N	Host population density	1000	1000
β	Infection rate	$730/7$	0.2
μ	Susceptible birth rate	$1/65$	0.1
γ	Recovery rate	$365/7$	n/a
Vector			
M	Vector population density	10000	10000
ϑ	Infection rate	73	73
ν	Susceptible birth rate	36.5	36.5
ρ	Magnitude sinusoidal fluctuation vector	0.9	n/a

Fenichel's theorem

Theorem

Suppose $\mathcal{M}$ is compact and normally hyperbolic, that is, the eigenvalues λ of the Jacobian $\frac{\partial f}{\partial V}(V, I)|_{\mathcal{M}}$ are uniformly bounded away from the imaginary axis.
Then there exists $\varepsilon_0 > 0$ such that the critical manifold persists as a locally invariant slow manifold $\mathcal{M}_\varepsilon$ of the full problem that is $\mathcal{O}(\varepsilon)$ close to $\mathcal{M}$ for $0 < \varepsilon < \varepsilon_0$. The restriction of the flow to $\mathcal{M}_\varepsilon$ is a small perturbation of the flow of the limiting problem.[a]

[a] G. Hek, Geometric singular perturbation theory in biological practice, *J Math Biol*, **60** (2010), 347–386.