Vector-borne diseases: mathematical modelling, dynamics and optimal control

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Outline

1. IMAAC
2. Dengue fever modelling
3. SISUV model
   - Geometric singular perturbation technique
4. SIRUV model
   - Geometric singular perturbation technique
5. Work in progress
   - Control measures: repellents
   - 2-strain dengue SIRUV model
6. Perspectives

Work in progress, COST Action CA16227

Joint work with E. Venturino, B.W. Kooi, M. Aguiar, N. Stollenwerk within the context of CA16227 *Investigation & Mathematical Analysis of Avant-garde Disease Control via Mosquito Nano-Tech-Repellents* (2017–2021) `www.imaac.eu`

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

PR: funding from Bulgarian FNI, contract DKOST 01/29 `www.fni.bg`

IMAAC Overview

IMAAC aims at investigation and mathematical analysis of the effect of avant-garde control measures in vector-borne diseases (VBD) involving day-time active mosquitos transmitting diseases like *dengue*, *Zika*, *chikungunya* and *yellow fever*.

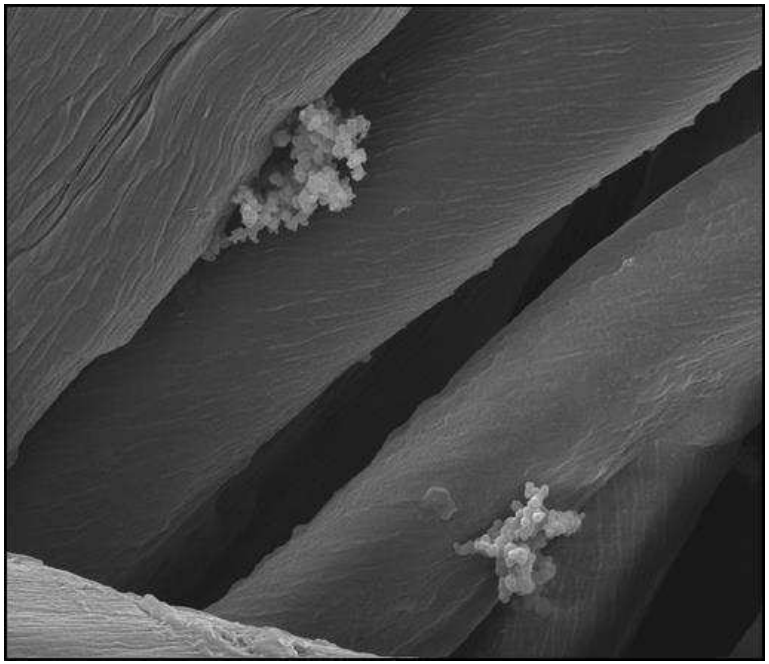


Figure: Nano particle particles on a textile substrate.

Textile, furniture and paint products can be treated with nano- and micro-particles releasing repellents or pesticides in well portioned dosage, which serve to reduce the disease burden. Such technology is already used in textile production for various purposes, and can be adapted for release of mosquito repellents and insecticides, which can be more efficient than spraying on skin or other classical ways of application.

IMAAC Overview

Figure: Commercially avalable dengue vaccine.

The key question is to study in how far such *repellency-based control measures* can help reduce the disease burden, eventually in synergy with existing *vaccines* which turned out to have a limited efficacy on their own[1]

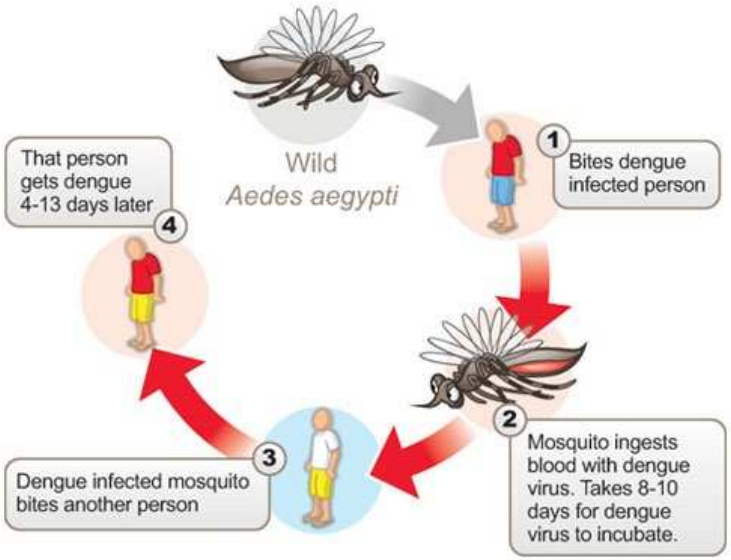
[1] M. Aguiar, N. Stollenwerk and S. B. Halstead, The Impact of the Newly Licensed Dengue Vaccine in Endemic Countries, *PLoS Negl Trop Dis*, 10 (2016): e5179

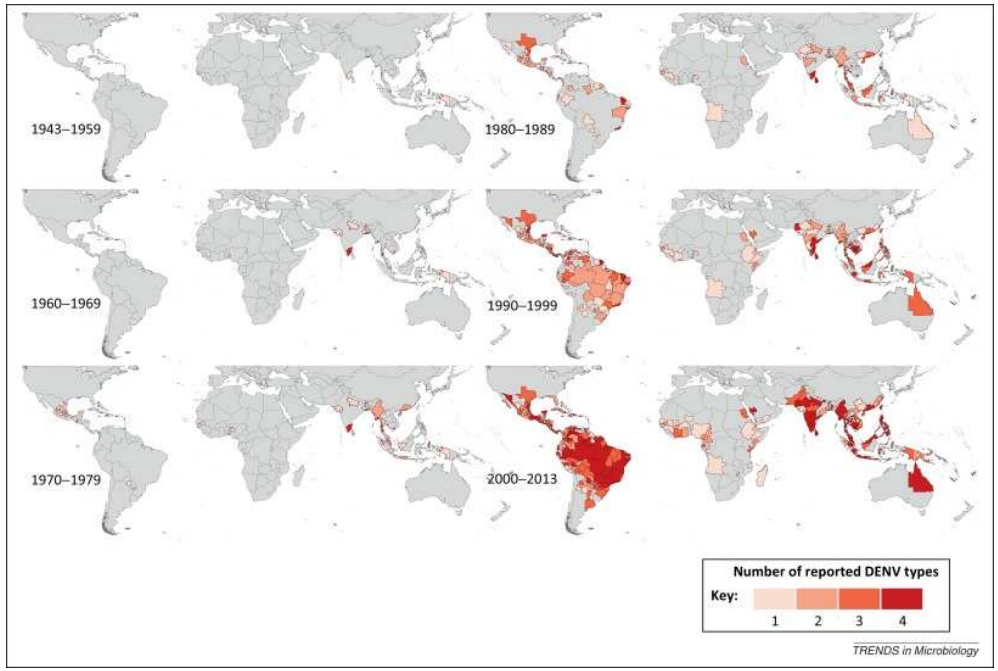
Aedes

In tropical areas, *Aedes* mosquitos cause more than 100 million symptomatic cases/year of diseases, such as dengue, yellow fever, chikungunya and Zika, and thousands of deaths. With increasing trade and travel, several *Aedes* species have been introduced into Europe and are now spreading rapidly – becoming a significant *public health risk*, which needs to be effectively addressed, as testified by recent cases of autochthonous chikungunya and dengue transmission in Croatia, France, Italy, Portugal and Spain.

Dengue fever

Mathematical modelling within IMAAC focuses on *dengue fever*, a VBD transmitted via *Aedes aegypti* and *Aedes albopictus* mosquitoes.





Dengue fever modelling

- vector-host two-strain Dengue model (10 dim)
  Feng & Velasco-Hernández (1997), *J Math Biol*
- large multi-strain Dengue model (10–20+ dim)
  Aguiar, Ballesteros, Kooi & Stollenwerk (2011), *J Theor Biol*
  Aguiar, Stollenwerk & Halstead (2016), *PLoS Negl Trop Dis*
- small single-strain VBD model (2-3 dim)
  Rocha, Aguiar, Souza & Stollenwerk (2013), *Int J Computer Math*
  Rashkov, Venturino, Aguiar, Stollenwerk & Kooi (to appear), *Math Biosci Eng*

State variables in VBD modelling

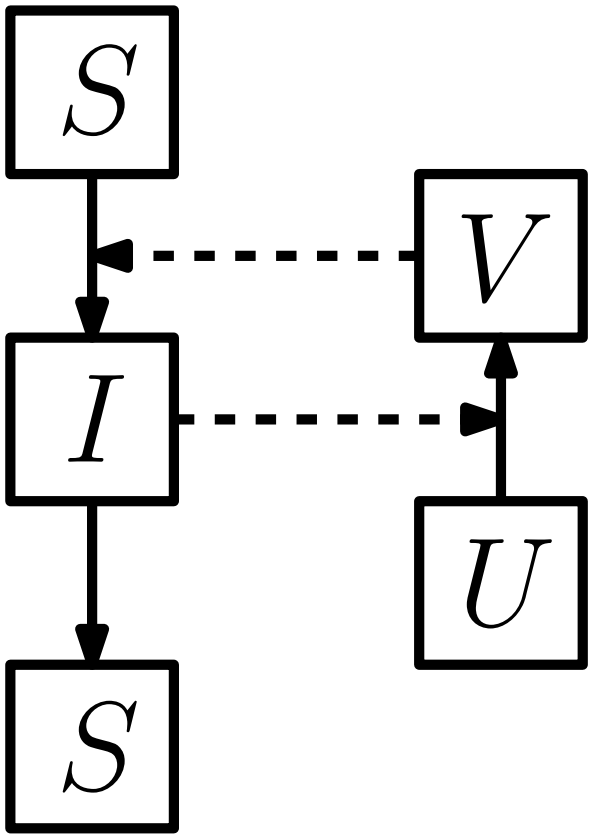
Var.	Description
Host	
N	Host population density
S	Susceptible Host population density
I	Infected Host population density
R	Recovered Host population density
Vector	
M	Vector population density
U	Susceptible Vector population density
V	Infected Vector population density

$\beta =$ the product of the biting rate r and the per-bite infection probability p_{vh} from mosquito to human

$\vartheta =$ the product of the biting rate r and the per-bite infection probability p_{hv} from human to mosquito

SISUV model Host–Vector model

host vector



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 Host–Vector model

Constant host and vector population densities
$N = S(t) + I(t)$ and $M = U(t) + V(t)$
Two dimensional equivalent system

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

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

Analysis of the SISUV model

- trivial, disease-free equilibrium $I^0 = 0, V^0 = 0$ and $S^0 = N,\ U^0 = M$
- interior, endemic equilibrium given by:

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

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

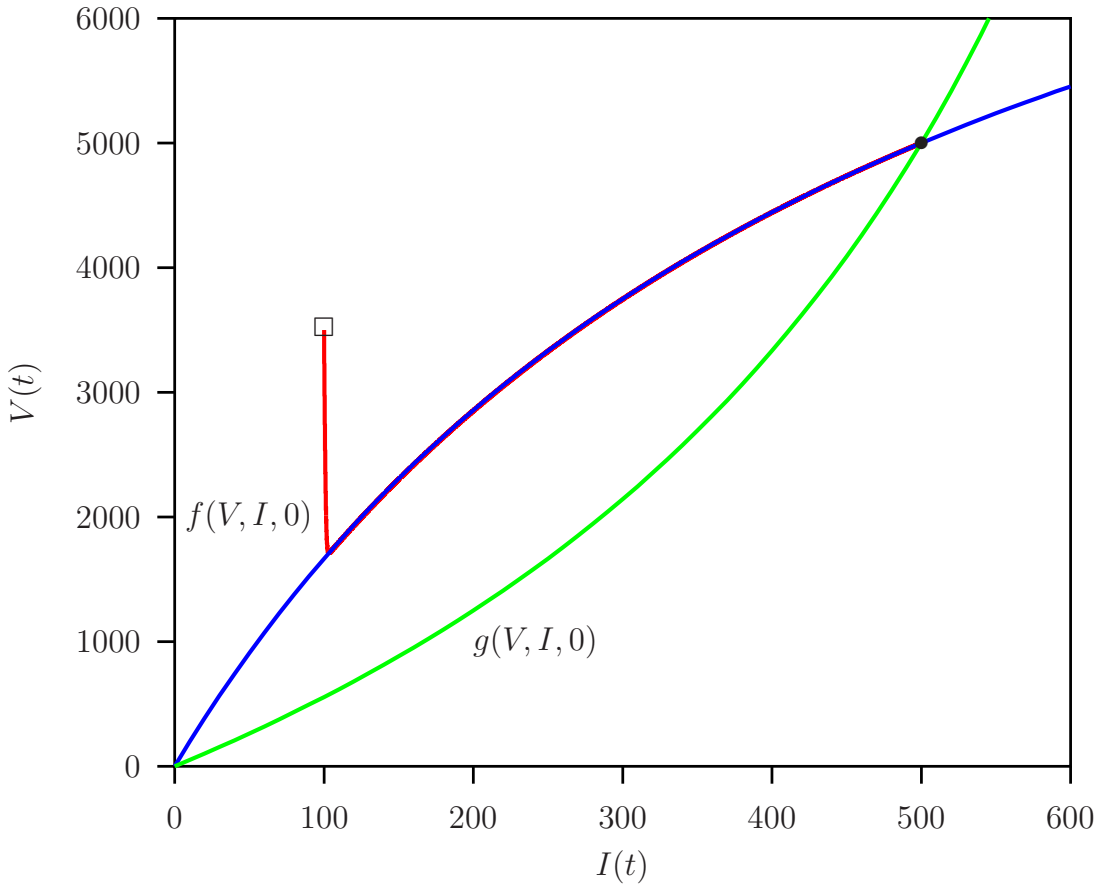
also $S^* = N - I^*$ and $U^* = M - V^*$.

Basic reproduction number

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

- $R_0 = 1$ equals one at the transcritical bifurcation point, where the endemic equilibrium coincides with the disease-free equilibrium.
- The endemic equilibrium is biologically relevant and globally asymptotically stable if $R_0 = \frac{\beta\vartheta}{\mu\nu} > 1$.

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 Singular perturbation problem

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.

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

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

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 population $I(t)$ remains constant, so that the trajectory is the vertical line in the phase-space (I, V) plot

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*:

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

After substitution of $\varepsilon = 0$ we get:

$$0 = f(V, I, 0) \quad \Leftrightarrow \quad V = \frac{\vartheta I M}{\vartheta I + N\nu}$$
$$\frac{dI}{d\tau} = g(V, I, 0) = \frac{\beta}{M}(N - I)V - \mu I$$

This is a differential algebraic system that describes the evolution of the slow variable $I(\tau)$ constrained to the set $f(V, I, 0) = 0$.

Time-scale separation

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

1. set $\varepsilon = 0$, which gives the set of fast equilibria of the fast system yielding the algebraic equation.

   This is the *critical manifold*, namely the set of equilibria on the hyperbola $f(V, I, 0) = 0$.

2. With a good hypothesis the set $f(V, I, 0) = 0$ is equivalent to $I = q(V)$ and we can substitute $V = q^{-1}(I)$.

Time-scale separation

Result is the 1-dimensional reduced system with $\varepsilon = 0$:

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

We started with a 4-dimensional system and reduced it to a 1-dimensional system in two steps:

- Assumption of constant total number of individuals in the host and vector populations (reduction by two)
- Time-scale argument (reduction by one)

Invariance equation

In order to get a better approximation for $0 < \varepsilon \ll 1$ we need an invariance equation
Using the chain rule for $I = q(V)$

$$\frac{dI}{d\tau} = g(V, q(V)) = \frac{dq}{dV}\frac{dV}{d\tau}$$

we get formally the Invariance equation :

$$\frac{dV}{d\tau} = \frac{\frac{\beta}{M}(N - q(V))V - \mu q(V)}{dq/dV} \quad , \quad \frac{dq}{dV} = \frac{\nu NM}{\vartheta(M - V)^2}$$

Geometric singular perturbation technique

For the case $0 < \varepsilon \ll 1$, we follow the geometric singular perturbation techniques.
For $\varepsilon = 0$ the f-nullcline

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

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

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 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 sufficiently small $\varepsilon > 0$.
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.

We should verify critical manifold $\mathcal{M}$ is normally hyperbolic
Otherwise canards can occur.

Application of Fenichel's theorem

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 asymptotic expansion in ε. It can (at least locally) be described as a graph

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

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

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

which yields with $I = q(V, \varepsilon)$ the invariance equation for the SISUV model:

$$\frac{\partial q(V, \varepsilon)}{\partial V}\left(\frac{\vartheta}{N}(M - V)q(V, \varepsilon) - \nu V\right) = \varepsilon\left(\frac{\beta}{M}(N - q(V, \varepsilon))V - \mu q(V, \varepsilon)\right)$$

Asymptotic expansion for the SISUV model

The following asymptotic expansion in $0 < \varepsilon \ll 1$ is introduced:

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

hence formally

$$\frac{\partial q}{\partial V}(V, \varepsilon) = \frac{dq_0}{dV} + \varepsilon \frac{dq_1}{dV} + \varepsilon^2 \frac{dq_2}{dV} + \dots$$

Substitution into the invariance equation,

$$\left(\frac{dq_0}{dV}+\varepsilon\frac{dq_1}{dV}+\varepsilon^2\frac{dq_2}{dV}+\ldots\right)\left(\frac{\vartheta}{N}(M-V)(q_0+\varepsilon q_1+\varepsilon^2 q_2+\ldots)-\nu V\right)$$
$$=\varepsilon\left(\frac{\beta}{M}(N-(q_0+\varepsilon q_1+\varepsilon^2 q_2+\ldots))V-\mu(q_0+\varepsilon q_1+\varepsilon^2 q_2+\ldots)\right)$$

gathering equal order terms of ε and assuming $V>0$ results in the following formula, accurate of order $\mathcal{O}(\varepsilon)$:

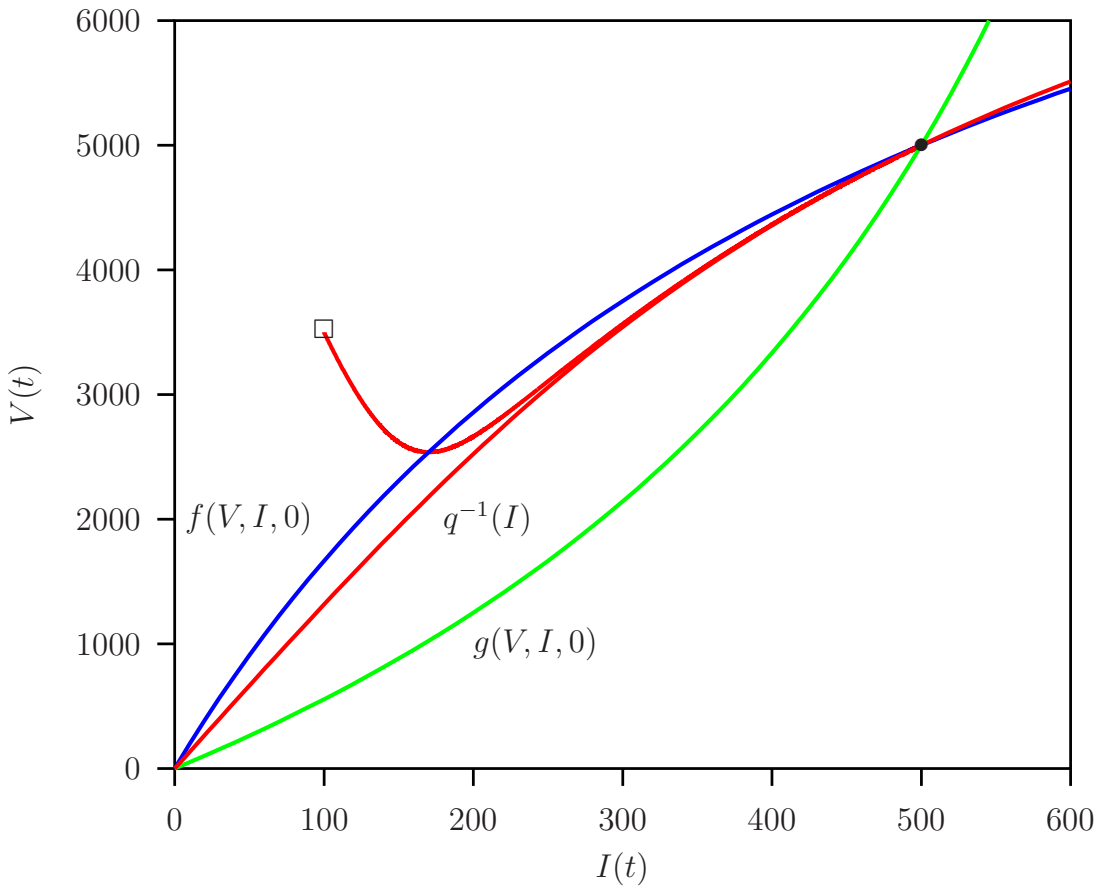
$$q_0(V)=\frac{\nu NV}{\vartheta(M-V)}$$
$$q_1(V)=\left(\frac{\beta}{\nu M}(M-V-\frac{\nu}{\vartheta}V)-\frac{\mu}{\vartheta}\right)\frac{NV}{M}\,.$$

Substitution of expression for $q_0(V)$ and $q_1(V)$ in

$$I(V,\varepsilon)=q(V,\varepsilon)=q_0(V)+\varepsilon q_1(V)$$

gives $\mathcal{O}(\varepsilon^2)$ approximation.

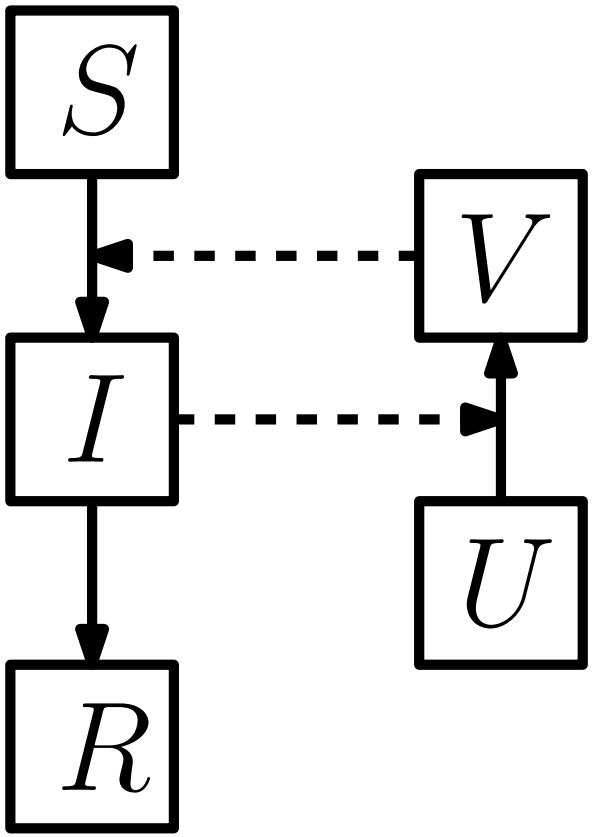
Phase-space plot SISUV model



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

SIRUV model Host–Vector model

host vector



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

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

$$\frac{dR}{dt} = \gamma I - \mu R$$

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

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

Constant host and vector population densities

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

reduce it to a 3-dimensional system

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

Equilibria

There is a trivial equilibrium $S^0 = N, I^0 = 0, V^0 = 0$ and an endemic equilibrium whenever $R_0 = \frac{\vartheta\beta}{\nu(\mu+\gamma)} > 1$:

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

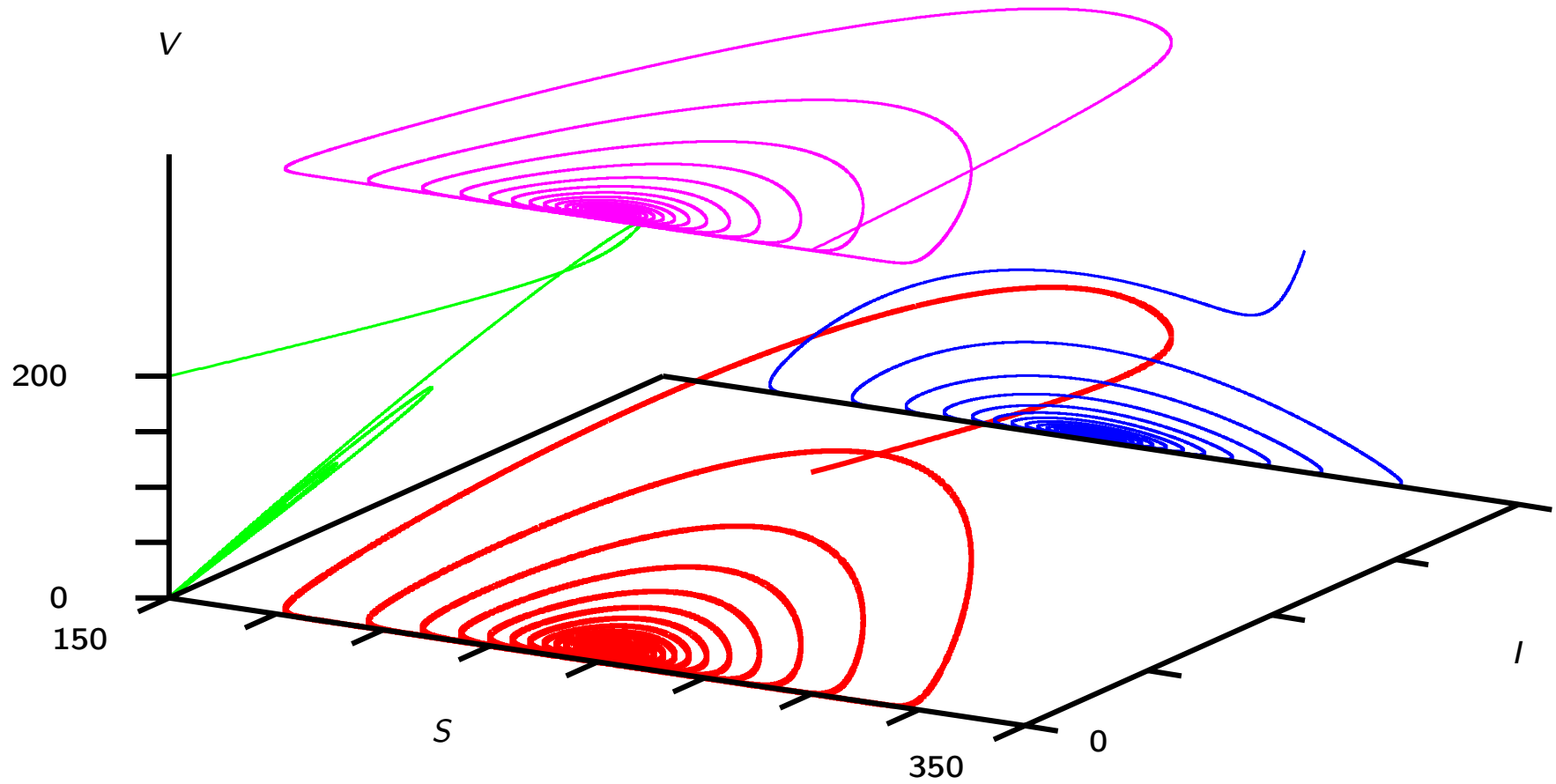
and furthermore $R^* = N - (S^* + I^*)$ and $U^* = M - V^*$

Theorem

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

[a] 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* (to appear)

Figure: Phase-space result for the SIRUV model.



Singular perturbation of SIRUV model

The slow manifold is 2-dimensional. Using the time-scale argument we get for $\varepsilon = 0$ the two-dimensional nullspace

$$\left\{ V(S,I) \middle|\ g_1(S,V,I) = 0,\ g_2(S,V,I) = 0 \right\}$$

In the SIRUV model, using the QSSA approach with $\varepsilon = 0$, gives the set of fast equilibria

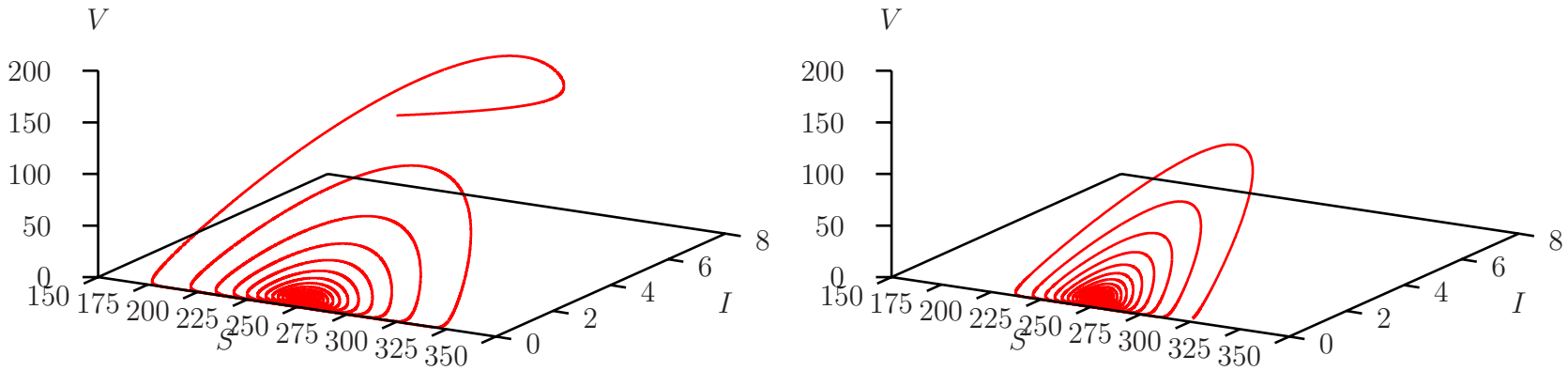
$$\mathcal{M} = \left\{ 0 \le S \le N,\ I = \frac{\nu N V}{\vartheta(M-V)}, 0 \le I \le N \middle| 0 \le V \le M \right\},$$

Hence, the system with hyperbolic expression

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

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

SIRUV model



Left panel: Phase-space result for the SIRUV model

Right panel: Phase-space result for the reduced system where $V(S, I)$ is described by the zero order asymptotic expansion or QSSA approach

We assume: critical manifold $\mathcal{M}$ is normally hyperbolic
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 asymptotic expansion in ε. It can be described as a graph

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

This manifold is invariant when the following equality holds

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

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

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

Asymptotic expansion for the SIRUV model

The following asymptotic expansion in $0 < \varepsilon \ll 1$ is now introduced:

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

hence

$$\frac{dp(S,I,\varepsilon)}{d\tau} = \frac{\partial p_0}{\partial S}\frac{dS}{d\tau} + \frac{\partial p_0}{\partial I}\frac{dI}{d\tau} + \varepsilon\left(\frac{\partial p_1}{\partial S}\frac{dS}{d\tau} + \frac{\partial p_1}{\partial I}\frac{dI}{d\tau}\right) + \dots$$

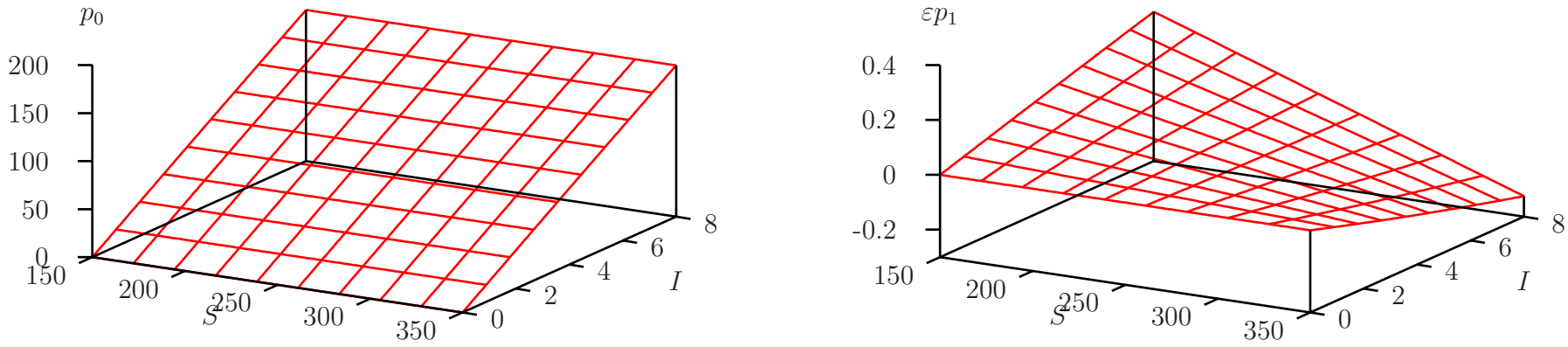
Substituting into the invariance equation, gathering the zero order terms of ε and assuming $V > 0$ gives the following result with $\mathcal{O}(\varepsilon^2)$ accuracy:

$$p_0(S, I) = \frac{\vartheta M I}{\vartheta I + \nu N} ,$$
$$p_1(S, I) = -\frac{M\nu\vartheta N^2}{(\vartheta I + \nu N)^3} \left(\frac{\beta\vartheta S I}{\vartheta I + \nu N} - (\gamma + \mu) I \right) .$$

The reduced model is described by a two-dimensional SI-system with $V(S, I)$ given with $\mathcal{O}(\varepsilon^2)$ accuracy:

$$V(S, I) = p(S, I, \varepsilon) = p_0(S, I) + \varepsilon p_1(S, I) ,$$

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

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

Numerical experiments show that

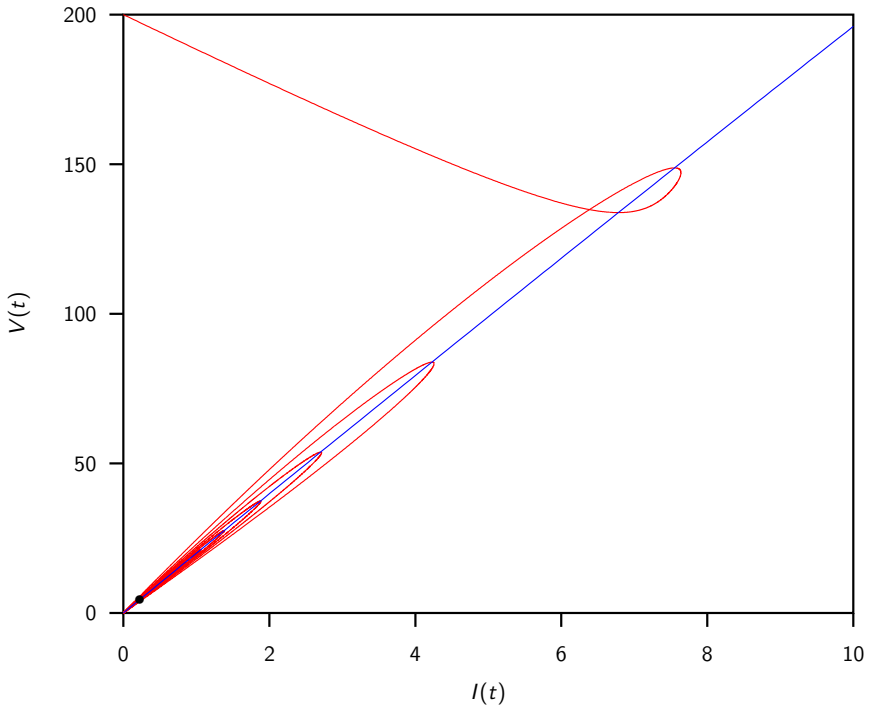
- either spurious equilibria can occur when the trajectory starts not sufficiently close to the equilibrium
- or the trajectory escapes to infinity

Results are not shown here
Refer also to the examples in Hek (2010)[2]

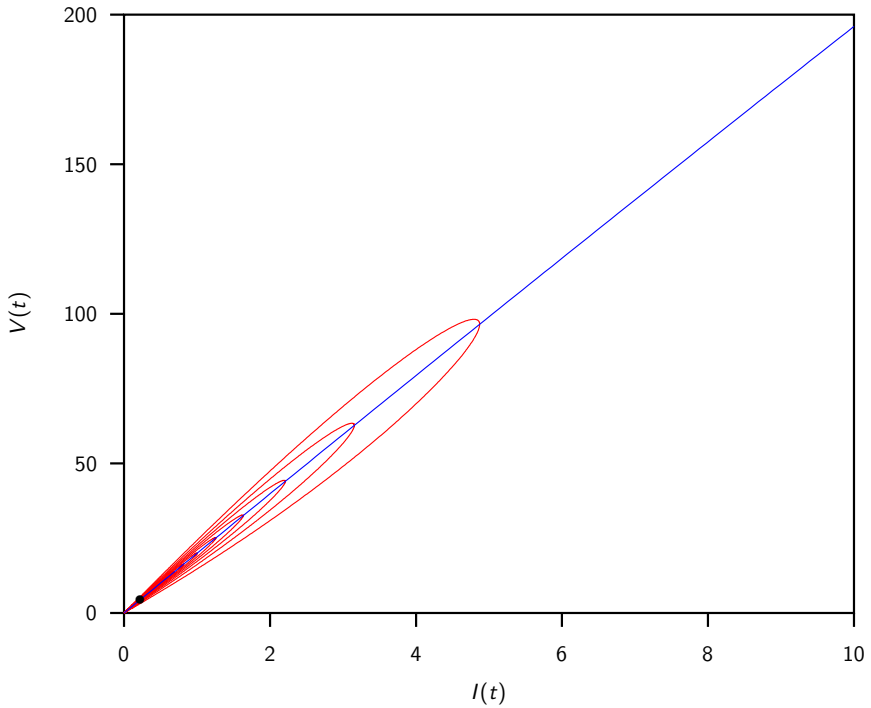
[2] G. Hek, Geometric singular perturbation theory in biological practice, *J Math Biol*, **60** (2010), 347–386.

Trajectory in (I, V) space

SIRUV model



Reduced SIRUV model



The point • is endemic stable spiral equilibrium

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Use of repellents

- The use of repellents reduces the biting rate of the mosquitoes, and should alter the overall dynamics of virus transmission between hosts and vectors.
- We must alter the infection parameters β, ϑ to account for the changes in behaviour of mosquitoes due to use of repellent-treated textiles, etc.
- If the host population uses products with repellents (u) with maximum efficacy k_r, there is a decrease in the biting rate due to the repellence action, and the probability of not receiving a mosquito bite will be $k_r u$
- New biting rate is $r_{new} = (1 - k_r u)r$, and the infection parameters under repellent use u become
  - $\beta = (1 - k_r u)\beta$ for mosquito vector to human host
  - $\vartheta = (1 - k_r u)\vartheta$ from human host to mosquito vector

Optimal control problem

Objective:

- minimise the number of individuals infected with VBD (with treatment costs per person a)
- keep the cost of control as low as possible: ordering, production and shipping costs for the treated products p_2, distribution cost p_1

Define objective function

$$J(u) = \int_0^T \left(aI(t) + p_1 N u(t) + \frac{p_2}{2} u^2(t) \right) \, dt$$

Note that textiles treated with repellent have a finite lifetime (maximum number of wash cycles)

Optimal control problem

Find $u : [0, T] \to \mathbb{R}^+$, with $0 \leq u(t) \leq u_{\max} < 1$ such that

$$J(u) \to \min \tag{1}$$

subject to

$$\begin{aligned}
\frac{dS}{dt} &= -\frac{\beta(1 - k_r u)}{M} SV + \mu(N - S), \\
\frac{dI}{dt} &= \frac{\beta(1 - k_r u)}{M} SV - (\gamma + \mu) I, \\
\frac{dV}{dt} &= \frac{\vartheta(1 - k_r u)}{N} (M - V) I - \nu V \ .
\end{aligned}$$

with given initial conditions $S(0), I(0), V(0) > 0$, and final time T.

Control measure and R_0

modified R_0 with repellent-treated textiles as control

$$R_0 = \frac{\beta\vartheta(1-k_r u)^2}{\nu(\gamma+\mu)}$$

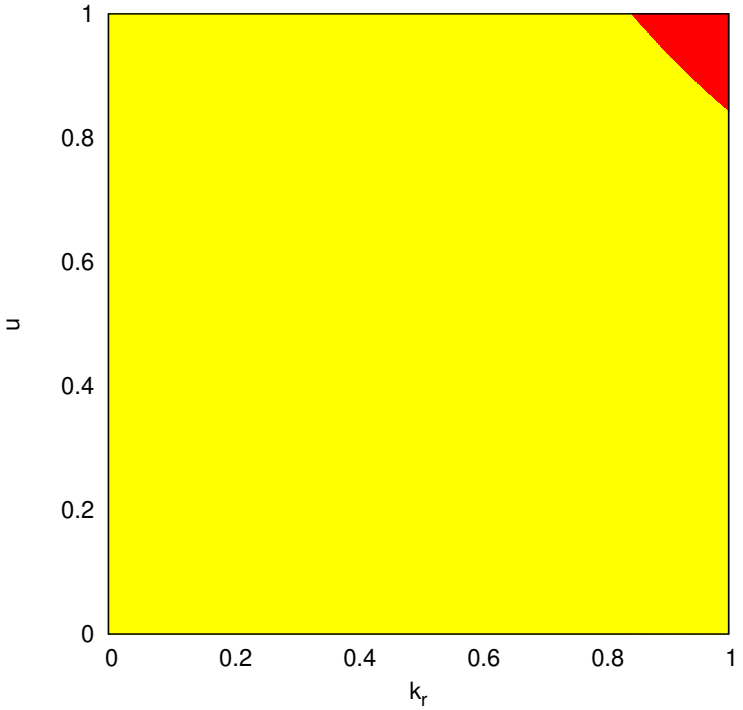


Figure: Combinations (k_r, u) such that $R_0 > 1$ (yellow) and $R_0 < 1$ (red).

Usage of such measures *alone* cannot eradicate a VBD

Co-state system

The associated co-state system for (1) is defined by differentiating the Hamiltonian:

$$\frac{d\psi_1}{dt} = (\frac{\beta}{M}(1-k_r u)V + \mu)\psi_1 - \frac{\beta}{M}(1-k_r u)V\psi_2$$
$$\frac{d\psi_2}{dt} = -a + (\gamma+\mu)\psi_2 - \frac{\vartheta(1-k_r u)}{N}(M-V)\psi_3$$
$$\frac{d\psi_3}{dt} = \frac{\beta}{M}(1-k_r u)S\psi_1 - \frac{\beta}{M}(1-k_r u)V\psi_2 + (\frac{\vartheta(1-k_r u)}{N}I + \nu)\psi_3$$

with transversality condition $\psi_i(T) = 0, i = 1, 2, 3.$

Using Pontryagin's maximum principle, we solve for the control

$$u = \min\{u_{\max}, \max\{0, u^*\}\}$$

with

$$u^* = -\frac{Np_1}{p_2} - \frac{k_r}{p_2}\left(\frac{\beta}{M}SV\psi_1 - \frac{\beta}{M}SV\psi_2 - \frac{\vartheta}{N}(M-V)I\psi_3\right).$$

Parameters must be estimated from field experiments (entomologists from IMAAC).

Numerical solution

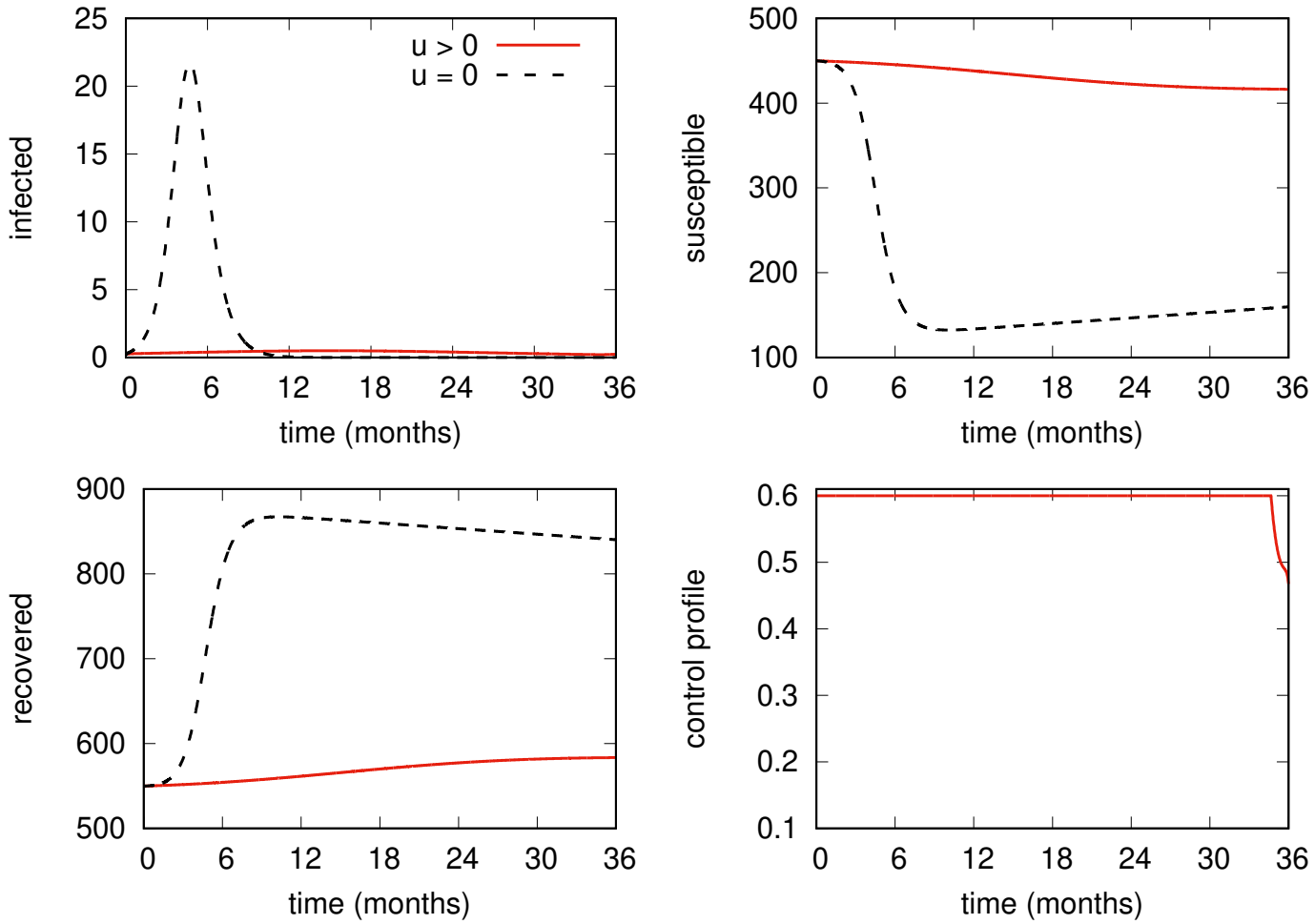
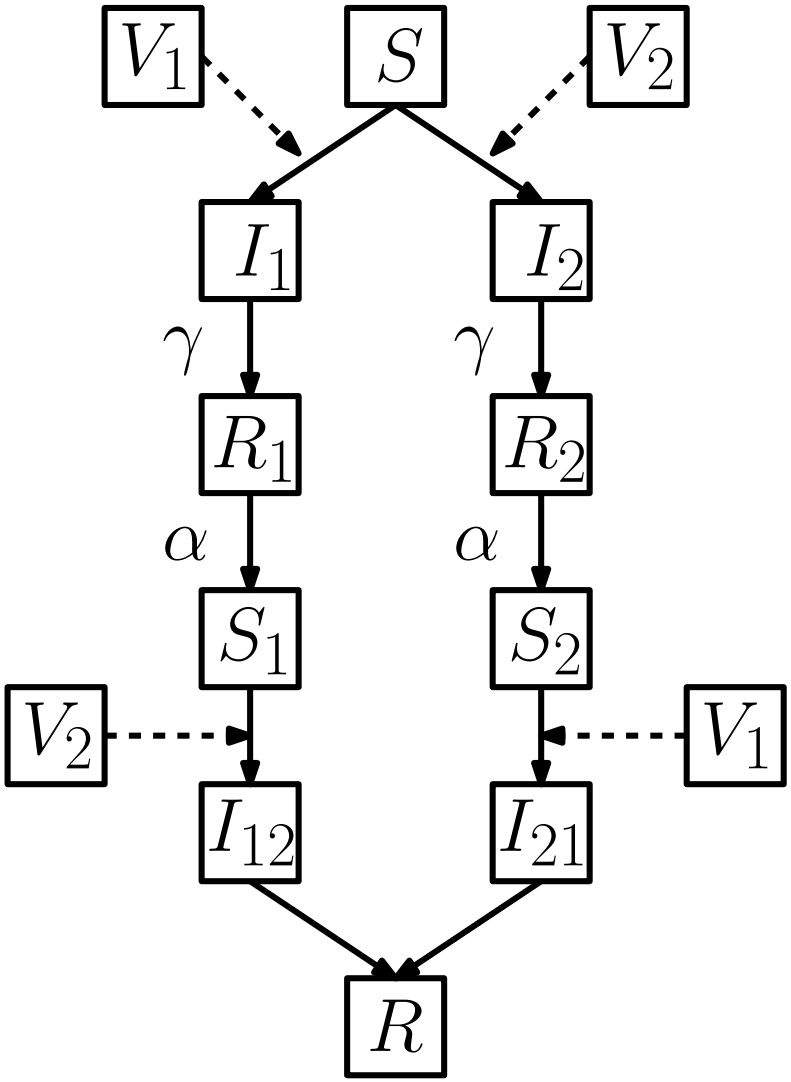


Figure: Sample solution for the optimal control problem.

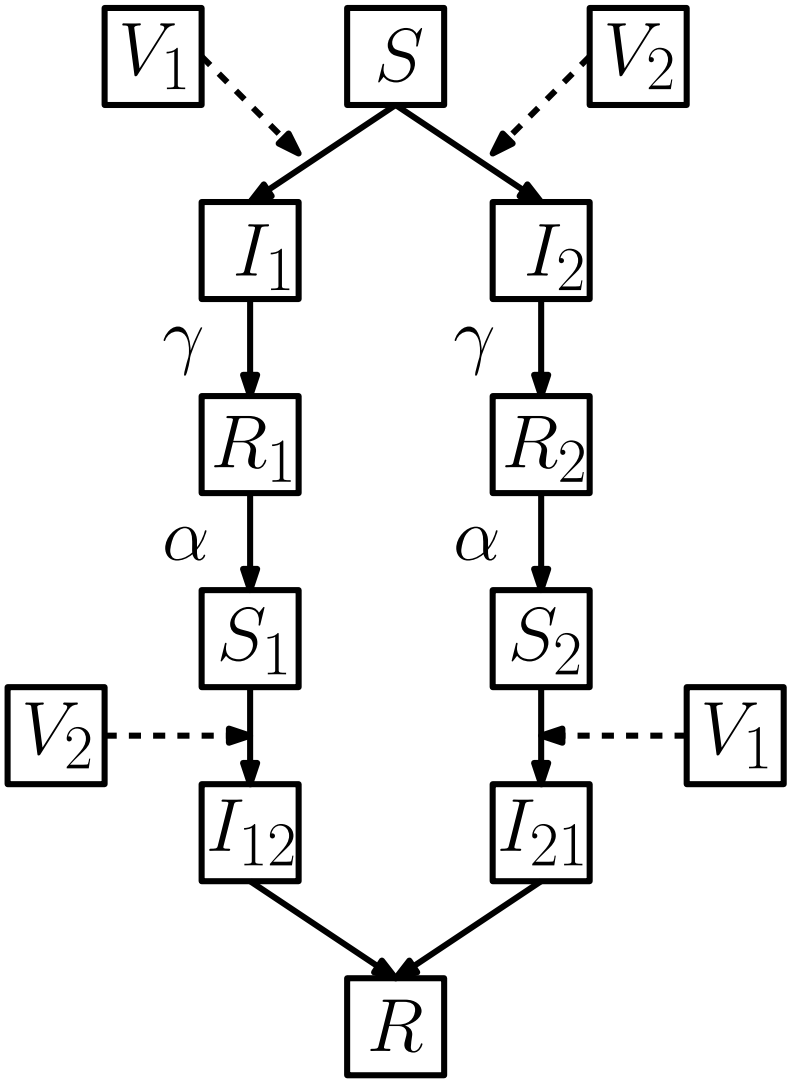
2-strain dengue SIRUV model



This model is more realistic because reinfections with a different virus serotype/strain do occur and usually cause a severe form of dengue leading to hospitalisation.

After a period of temporary cross-immunity $(1/\alpha)$, seropositive susceptibles with a previous dengue infection (S_1, S_2), can be re-infected with a different strain and become classes I_{12} and I_{21}.

2-strain dengue SIRUV model



Individuals experiencing a severe form of dengue (classes I_{12}, I_{21}) have a higher rate of hospitalisation, and a lower contact rate with mosquitoes, decreasing ϑ by a fraction $\phi < 1$.

Recovered from both infections and life-long immune against both serotypes individuals belong to class R.

We assume host and vector populations are constant.

Equations

$$
\begin{aligned}
S' &= -\frac{\beta}{N} S(V_1 + V_2) + \mu(N - S) \\
I_1' &= \frac{\beta}{N} S V_1 - (\gamma + \mu) I_1 \\
I_2' &= \frac{\beta}{N} S V_2 - (\gamma + \mu) I_2 \\
I_{12}' &= \frac{\beta}{N} S_1 V_2 - (\gamma + \mu) I_{12} \\
I_{21}' &= \frac{\beta}{N} S_2 V_1 - (\gamma + \mu) I_{21} \\
S_1' &= \alpha R_1 - \mu S_1 - \frac{\beta}{N} S_1 V_2 \\
S_2' &= \alpha R_2 - \mu S_2 - \frac{\beta}{N} S_2 V_1 \\
R_1' &= \gamma I_1 - (\alpha + \mu) R_1 \\
R_2' &= \gamma I_2 - (\alpha + \mu) R_2 \\
V_1' &= \frac{\vartheta}{N} (M - V_1 - V_2)(I_1 + \phi I_{21}) - \nu V_1 \\
V_2' &= \frac{\vartheta}{N} (M - V_1 - V_2)(I_2 + \phi I_{12}) - \nu V_2
\end{aligned}
$$

Control measures: repellents

- Similarly to the small model, we introduce as control measure u_1 textile product with mosquito repellents
- If the host population uses products with repellents (u_1) with maximum efficacy k_r, there is a decrease in the biting rate due to the repellence action, and the probability of not receiving a mosquito bite will be $k_r u_1$
- New biting rate is $r_{new} = (1 - k_r u_1)r$, and the infection parameters β, ϑ under repellent use become
  - $\beta = (1 - k_r u_1)\beta$ for mosquito to human
  - $\vartheta = (1 - k_r u_1)\vartheta$ from human to mosquito

Numerical results

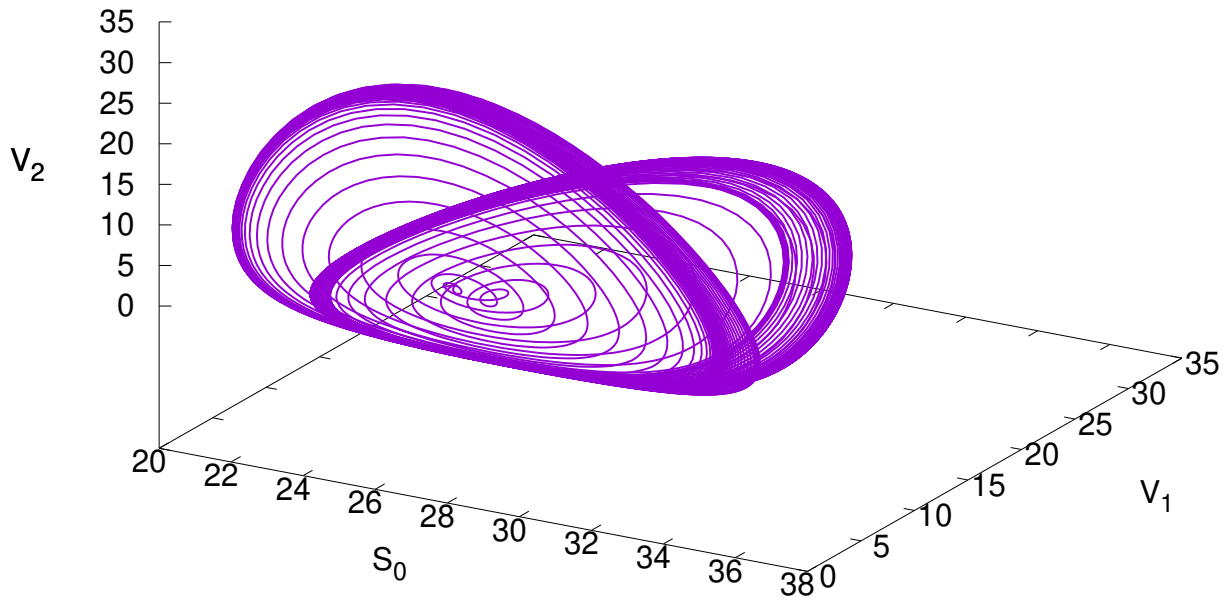


Figure: Simulation without control measures ($u_1 = 0$). Presence of chaotic attractor.

Preliminary results

- Due to the presence of temporary cross-immunity ($\alpha \neq 0$), coexistence of both virus strains in the host and vector populations is possible[3]
- This is one major difference from the dengue model by Feng and Velasco-Hernandez (1997), where the coexistence equilibrium is a saddle point and one strain always goes extinct
- However, the model exhibits very complex dynamics dependent on ϕ: limit cycles, torus bifurcations, and chaotic behaviour

[3] B.W. Kooi, M. Aguiar and N. Stollenwerk, Bifurcation analysis of a family of multi-strain epidemiology models, *J Comput Appl Math*, **252** (2013), 148–158.

Perspectives

- Reduction of complexity in the large 2-strain dengue model by singular perturbation analysis
- Sensitivity analysis giving role of vector dynamics
- Sensitivity analysis giving role of vector dynamics combined with seasonal forcing of the vector population
- Analysis of introduction of control measures in the model (repellents, vaccine): question of stabilisability of a high-dimensional ODE system

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THANK YOU FOR YOUR ATTENTION!

MERCI BEAUCOUP DE VOTRE ATTENTION!

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
Control			
$u_{\max}$	Maximum coverage	0.6	
k_r	Maximum efficacy	0.45	
a	Individual treatment cost	10/3	
p_1	Distribution cost	1/300	
p_2	Background costs	10/3	