Robustness of a two-strain dengue fever model with respect to asymmetry

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- Talk Nico Stollenwerk:
  Modelling and model evaluation on empirical data in epidemiology: dynamic noise, chaos and predictability
  Parameter estimation framework

- Talk Maíra Aguiar:
  Descriptive and Predictive models of dengue epidemiology: an overview

- Here: Model analysis with Bifurcation analysis techniques with the focus on a two-strain dengue fever model

Outline

- Modeling two-strain dengue fever model
- Extension of classical compartment (SIR) model
- Analysis of the long-term dynamics using bifurcation theory
- Robustness w.r.t. asymmetry

Bifurcation analysis: Nonlinear Dynamical System Theory

Short-term dynamics

- Solving initial values problem
- Numerical simulations

Long-term dynamics

- Limit sets: equilibria, limit cycles and chaotic attractors
- Stability of limit sets: linearisation around limit set (eigenvalues, multiplier) or follow trajectory (Lyapunov exponents)

Dependency on parameters

- Critical parameter values (bifurcations) where dynamics changes qualitatively: eigenvalue is zero or multipliers is one

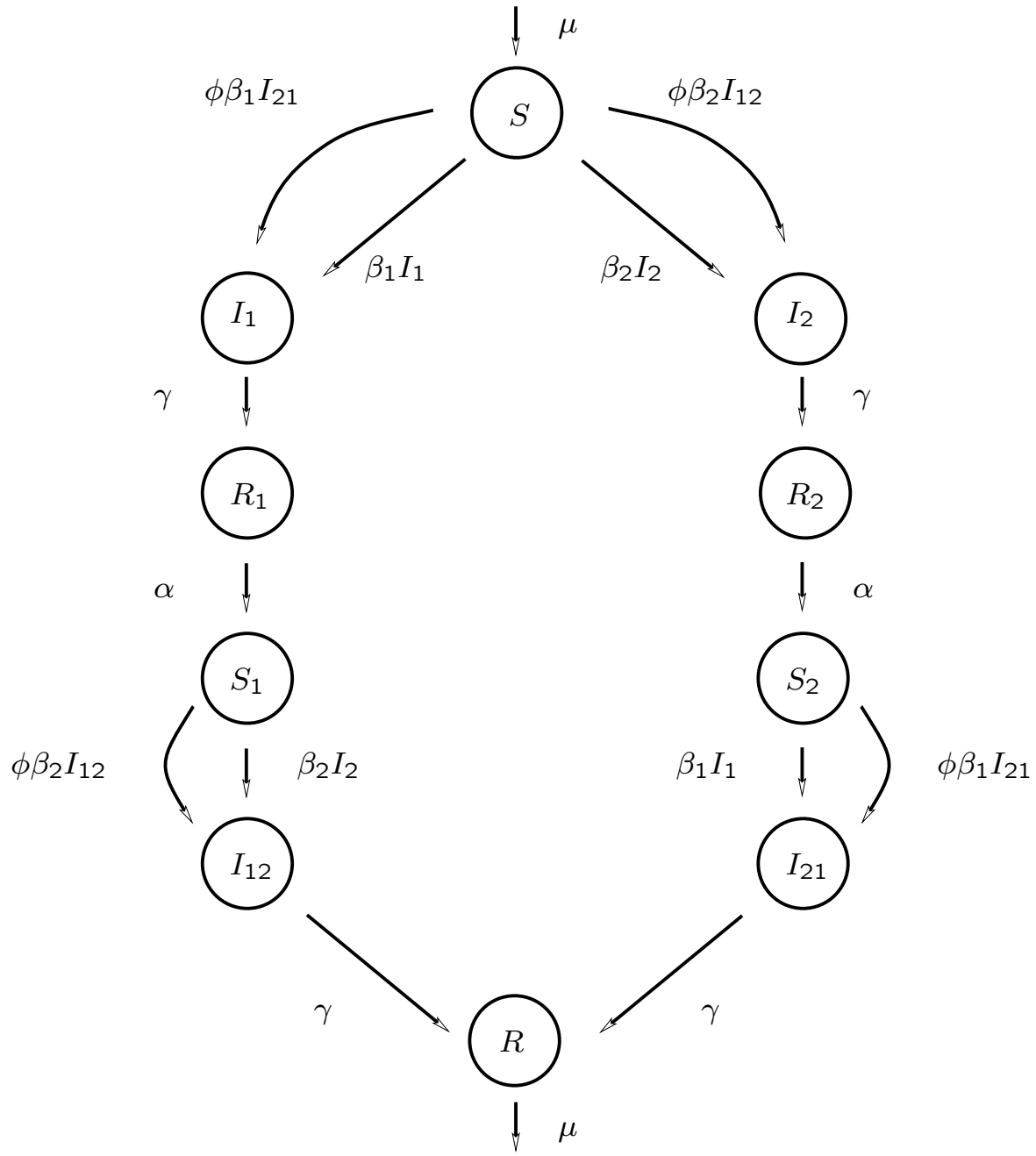
- Continuation of bifurcation points gives regions in parameter space with the same type of long-term dynamics

Three variants for 2-strain SIR model

Model 1 N. Ferguson, R. Anderson, and S. Gupta.
The effect of antibody-dependent enhancement on the transmission dynamics and persistence of multiple-strain pathogens.
Proc. Natl. Acad. Sci. USA, 96(9):790–794, 1999.

Model 2 L. Billings, I. B. Schwartz, L. B. Shaw, M. McCrary, D. S. Burke, and D. A. T. Cummings.
Instabilities in multi-serotype disease models with antibody-dependent enhancement.
Journal of Theoretical Biology, 246:18–27, 2007.

Model 3 M. Aguiar, S. Ballesteros, B. W. Kooi, and N. Stollenwerk.
The role of seasonality and import in a minimalistic multi-strain dengue model capturing differences between primary and secondary infections: complex dynamics and its implications for data analysis.
Journal of Theoretical Biology, 289:181–196, 2011.


μ
$\phi\beta_1 I_{21}$
S
$\phi\beta_2 I_{12}$
$\beta_1 I_1$
$\beta_2 I_2$
I_1
I_2
γ
γ
R_1
R_2
α
α
S_1
S_2
$\phi\beta_2 I_{12}$
$\beta_2 I_2$
$\beta_1 I_1$
$\phi\beta_1 I_{21}$
I_{12}
I_{21}
γ
γ
R
μ

Model [3]

Dengue fever: Model [3] with $\alpha < \infty$

with antibody-dependent enhancement (ADE)
and temporary cross immunity

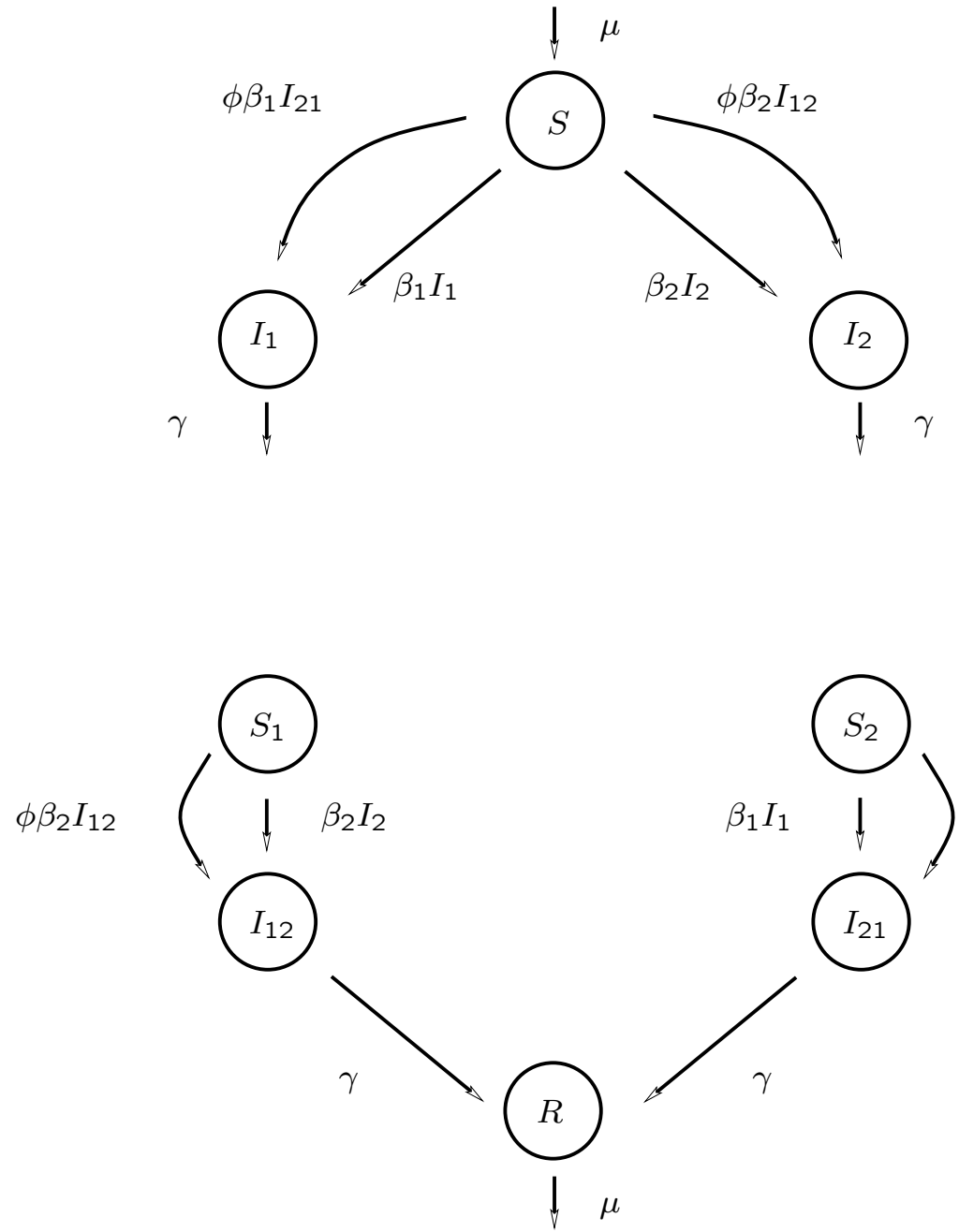
$$
\begin{aligned}
\dot{S} &= -\frac{\beta}{N} S(I_1 + \phi I_{21}) - \frac{\beta}{N} S(I_2 + \phi I_{12}) + \mu(N - S) \\
\dot{I}_1 &= \frac{\beta}{N} S(I_1 + \phi I_{21}) - (\gamma + \mu) I_1 \\
\dot{I}_2 &= \frac{\beta}{N} S(I_2 + \phi I_{12}) - (\gamma + \mu) I_2 \\
\dot{R}_1 &= \gamma I_1 - (\alpha + \mu) R_1 \\
\dot{R}_2 &= \gamma I_2 - (\alpha + \mu) R_2 \\
\dot{S}_1 &= -\frac{\beta}{N} S_1(I_2 + \phi I_{12}) + \alpha R_1 - \mu S_1 \\
\dot{S}_2 &= -\frac{\beta}{N} S_2(I_1 + \phi I_{21}) + \alpha R_2 - \mu S_2 \\
\dot{I}_{12} &= \frac{\beta}{N} S_1(I_2 + \phi I_{12}) - (\gamma + \mu) I_{12} \\
\dot{I}_{21} &= \frac{\beta}{N} S_2(I_1 + \phi I_{21}) - (\gamma + \mu) I_{21} \\
\dot{R} &= \gamma(I_{12} + I_{21}) - \mu R
\end{aligned}
$$

Var.	Description
S	from N by birth: Susceptibles to both strains
I_i	from S: Infected with strain i
	either by meeting I_i or by meeting I_{ji}
R_i	from I_i: Recovered from infection with strain i
S_i	from R_i: Immune against first infection strain i
	but susceptible to j
I_{ij}	from S_i: Reinfected with strain j
	either by meeting I_2 or by meeting I_{12}
R	from I_{ij}'s: Immune to both strains

Two different strains:
$i = 1, j = 2$ and $i = 2, j = 1$

$R = N - (S + I_1 + I_2 + R_1 + R_2 + S_1 + S_2 + I_{12} + I_{21})$ where N is population size

Par.	Description	Values
N	population size	100
μ	new born susceptible rate	1/65
γ	recovery rate	52
β_0	infection rate	2γ
α	temporary cross-immunity rate	∞, 2, free
ρ	external infected portion	0, free
ϕ	ratio of contribution to force of infection	0.9, free
η	seasonal force	$0, 0.2$, free
T_0	period of system	


μ
$\phi\beta_1 I_{21}$
S
$\phi\beta_2 I_{12}$
$\beta_1 I_1$
$\beta_2 I_2$
I_1
I_2
γ
γ
S_1
S_2
$\phi\beta_2 I_{12}$
$\beta_2 I_2$
$\beta_1 I_1$
$\phi\beta_1 I_{21}$
I_{12}
I_{21}
γ
γ
R
μ

Model [2]

Dengue fever: Model [2] with $\alpha = \infty$

with antibody-dependent enhancement (ADE)
without temporary cross immunity and without co-infection

$$\dot{S} = -\frac{\beta}{N} S(I_1 + \phi I_{21}) - \frac{\beta}{N} S(I_2 + \phi I_{12}) + \mu(N - S)$$

$$\dot{I}_1 = \frac{\beta}{N} S(I_1 + \phi I_{21}) - (\gamma + \mu) I_1$$

$$\dot{I}_2 = \frac{\beta}{N} S(I_2 + \phi I_{12}) - (\gamma + \mu) I_2$$

$$\dot{R}_1 = \gamma I_1 - (\alpha + \mu) R_1$$

$$\dot{R}_2 = \gamma I_2 - (\alpha + \mu) R_2$$

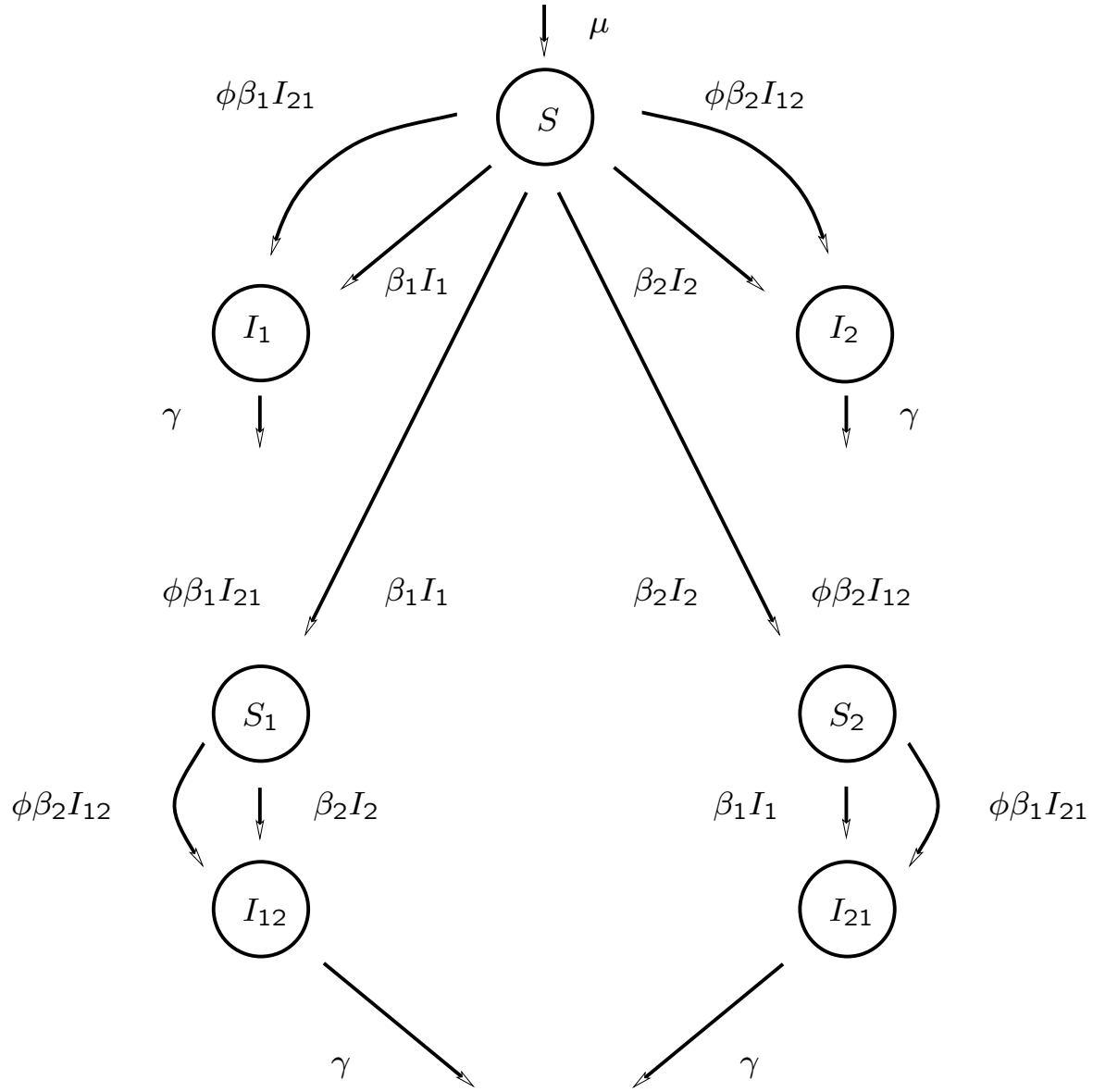
$$\dot{S}_1 = -\frac{\beta}{N} S_1(I_2 + \phi I_{12}) + \alpha R_1 \gamma I_1 - \mu S_1$$

$$\dot{S}_2 = -\frac{\beta}{N} S_2(I_1 + \phi I_{21}) + \alpha R_2 \gamma I_2 - \mu S_2$$

$$\dot{I}_{12} = \frac{\beta}{N} S_1(I_2 + \phi I_{12}) - (\gamma + \mu) I_{12}$$

$$\dot{I}_{21} = \frac{\beta}{N} S_2(I_1 + \phi I_{21}) - (\gamma + \mu) I_{21}$$

$$\dot{R} = \gamma(I_{12} + I_{21}) - \mu R$$


μ
S
$\phi\beta_1 I_{21}$
$\phi\beta_2 I_{12}$
$\beta_1 I_1$
$\beta_2 I_2$
I_1
I_2
γ
γ
$\phi\beta_1 I_{21}$
$\beta_1 I_1$
$\beta_2 I_2$
$\phi\beta_2 I_{12}$
S_1
S_2
$\phi\beta_2 I_{12}$
$\beta_2 I_2$
$\beta_1 I_1$
$\phi\beta_1 I_{21}$
I_{12}
I_{21}
γ
γ

Model [1]

Dengue fever: Model [1] with $\alpha = \infty$

with antibody-dependent enhancement (ADE)
without temporary cross immunity and with co-infection

$$\dot{S} = -\frac{\beta}{N} S(I_1 + \phi I_{21}) - \frac{\beta}{N} S(I_2 + \phi I_{12}) + \mu(N - S)$$

$$\dot{I}_1 = \frac{\beta}{N} S(I_1 + \phi I_{21}) - (\gamma + \mu) I_1$$

$$\dot{I}_2 = \frac{\beta}{N} S(I_2 + \phi I_{12}) - (\gamma + \mu) I_2$$

$$\dot{R}_1 = \gamma I_1 - (\alpha + \mu) R_1$$

$$\dot{R}_2 = \gamma I_2 - (\alpha + \mu) R_2$$

$$\dot{S}_1 = -\frac{\beta}{N} S_1(I_2 + \phi I_{12}) + \alpha R_1 \frac{\beta}{N} S(I_1 + \phi I_{21}) - \mu S_1$$

$$\dot{S}_2 = -\frac{\beta}{N} S_2(I_1 + \phi I_{21}) + \alpha R_2 \frac{\beta}{N} S(I_2 + \phi I_{12}) - \mu S_2$$

$$\dot{I}_{12} = \frac{\beta}{N} S_1(I_2 + \phi I_{12}) - (\gamma + \mu) I_{12}$$

$$\dot{I}_{21} = \frac{\beta}{N} S_2(I_1 + \phi I_{21}) - (\gamma + \mu) I_{21}$$

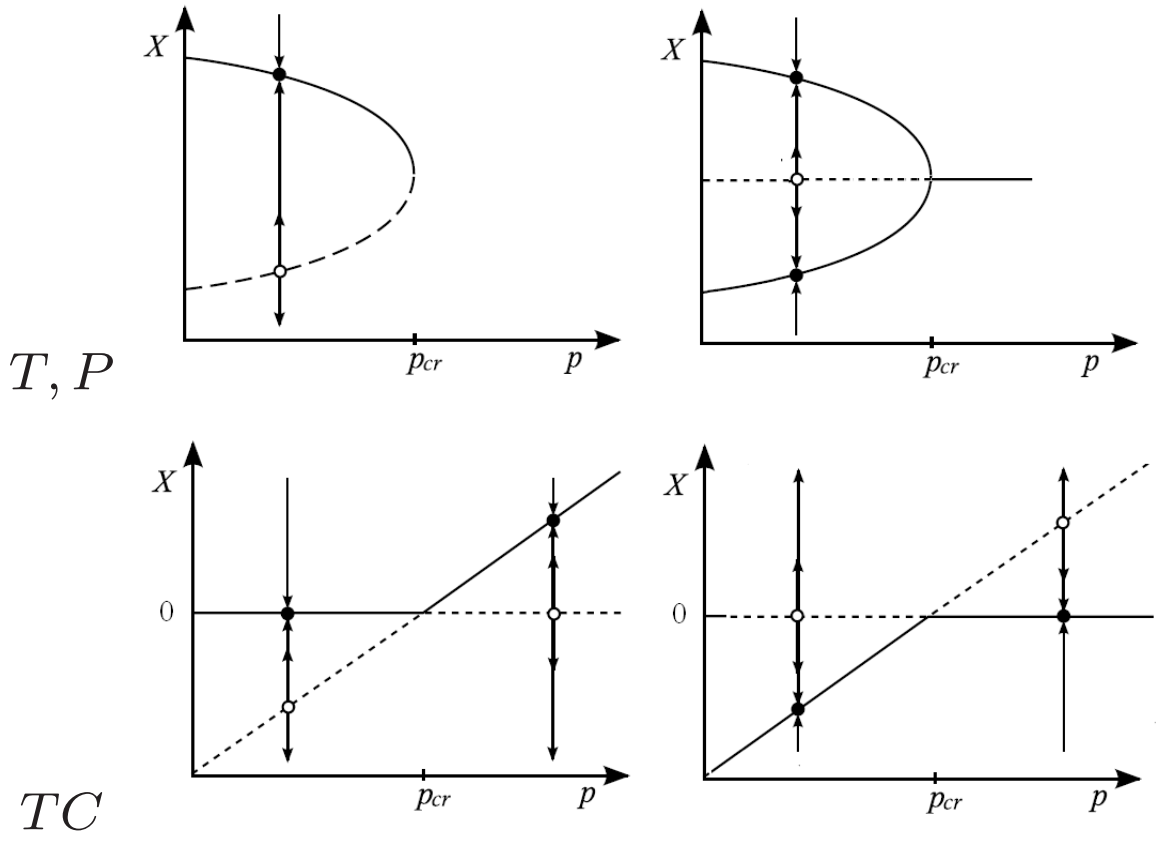
$$\dot{R} = \gamma(I_{12} + I_{21}) - \mu R$$

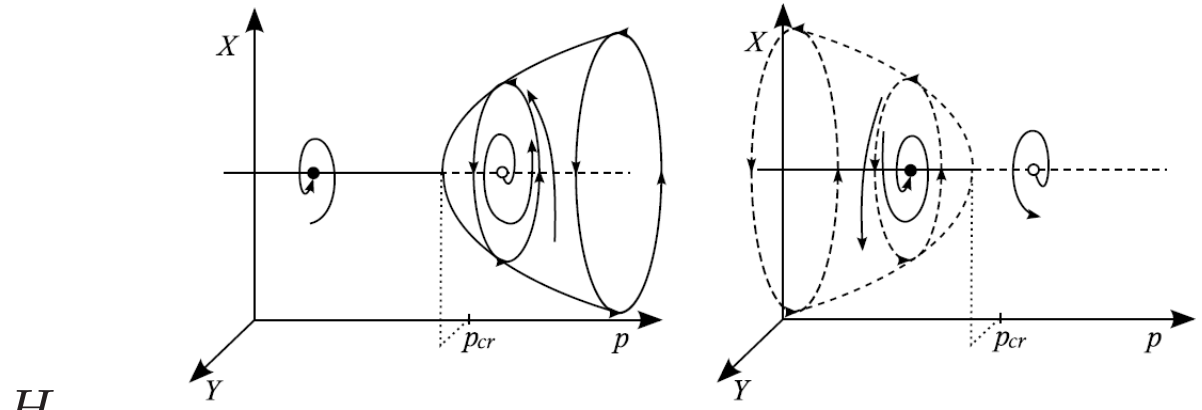
Co-infection is allowed and individuals become susceptible (S_1 and S_2) to the other strain, immediately after the first infection.

Here the individuals that leave the susceptible class S become primary and secondary infected simultaneously and consequently one individual can be in two classes at the same time. Therefore this system cannot be closed by a class of recovered from the two infections R

Bifurcations

Symbol	Description bifurcation
Equilibrium	
H	Hopf
Equilibrium, limit cycle	
T	Tangent (saddle node)
TC	Transcritical
P	Pitchfork
Limit cycle	
TR	Torus (Neimark-Sacker)

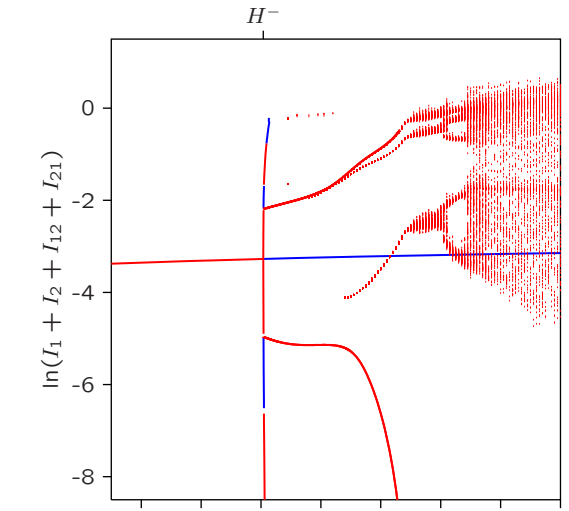

T, P
X
p_cr
p
X
p_cr
p
TC
X
0
p_cr
p
X
0
p_cr
p



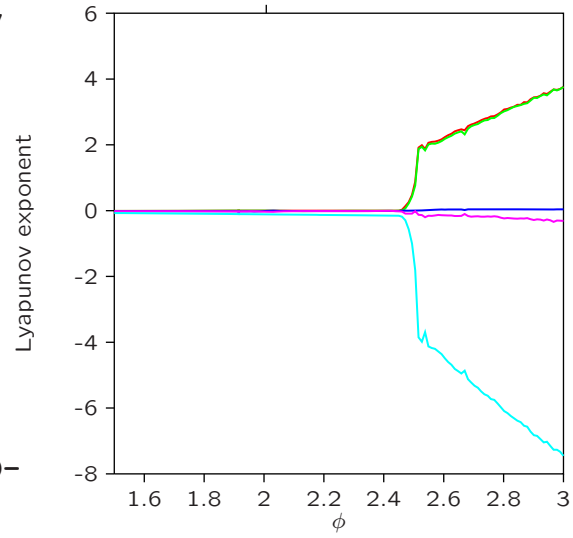
H

Model [1] with $\alpha = \infty$

without temporary cross-immunity

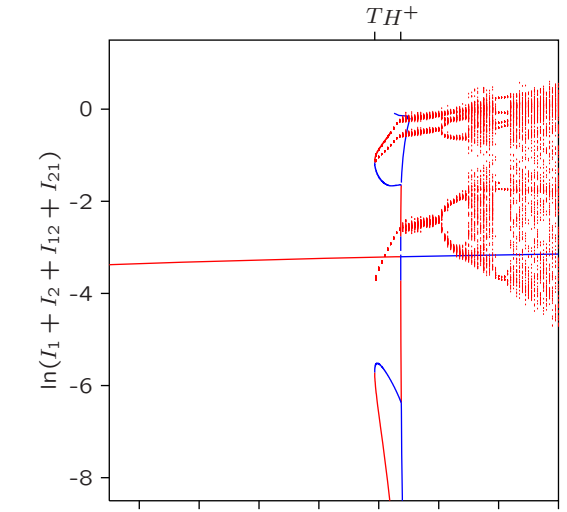


with co-infection

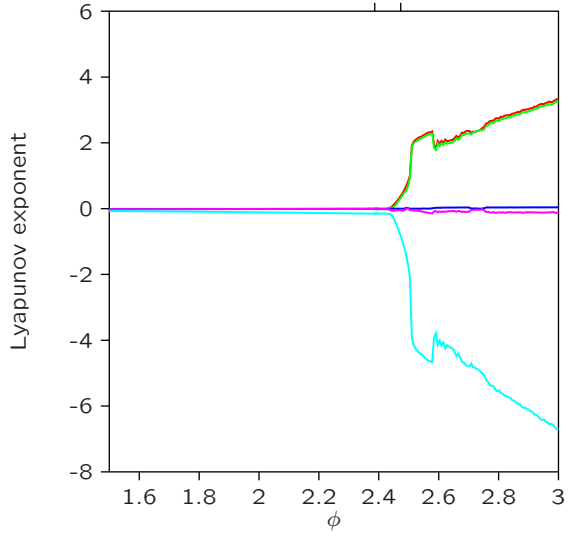


Model [2] with $\alpha = \infty$

without temporary cross-immunity



without co-infection

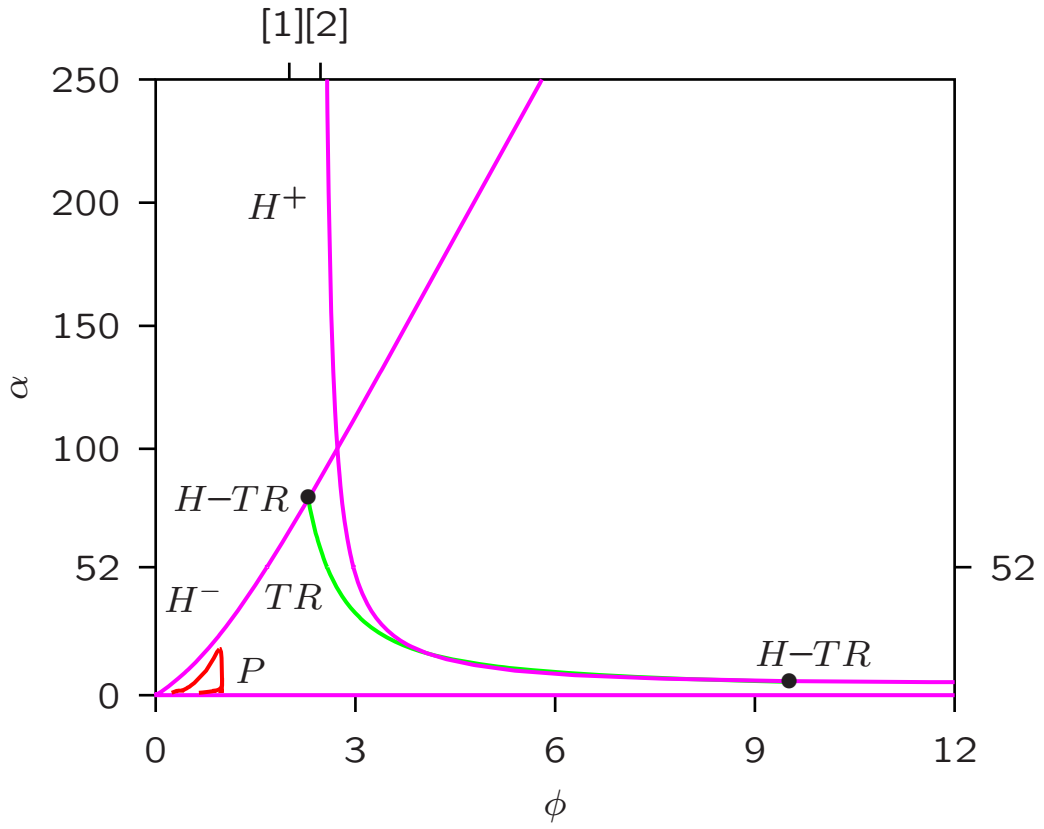


Conclusions (1)

- The results for the two models without temporary cross-immunity [1] and [2] show a similar bifurcation pattern.

- A Hopf bifurcation, subcritical, in system [2] and, supercritical, in system [1] is the organizing center for complex dynamics. At a double flip point originating from these Hopf bifurcations period-two limit cycles emanate which finally lead to chaotic dynamics.

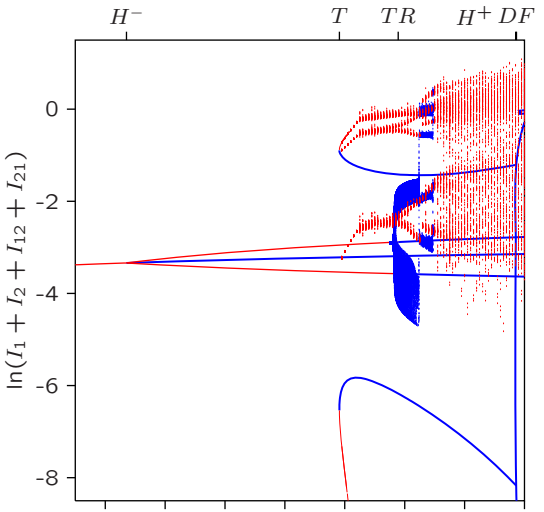
Two-parameter bifurcation diagram: α vs ϕ



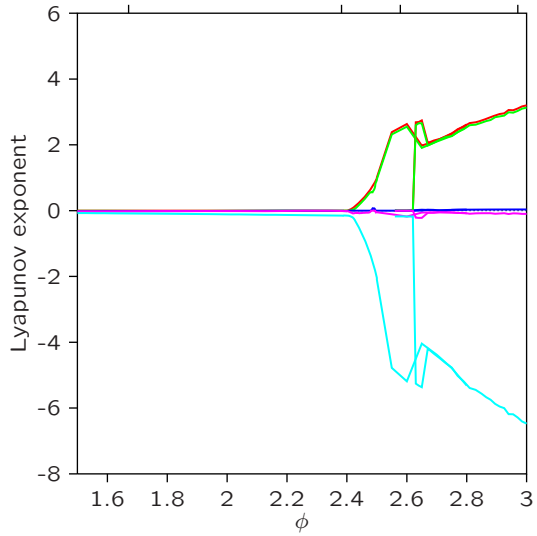
Pitchfork Torus Hopf Tangent

Model [3] with $\alpha = 52$

with temporary cross-immunity



without co-infection



Conclusions (2)

- For the model with temporary cross-immunity [3] these similar bifurcation patterns occur as in models [1] and [2].

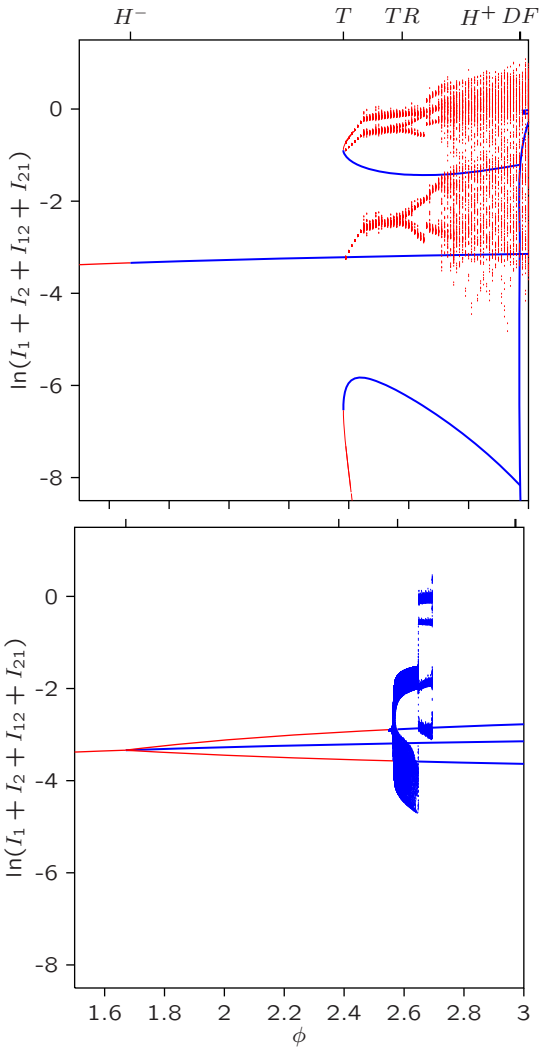
- Superposed on this dynamics there is complex behaviour which originates from a second Hopf bifurcation. The origination limit cycle becomes unstable at a Torus bifurcation. The dynamics remains on the torus and is quasi-periodic. For higher ϕ values this dynamics becomes chaotic.

- For even higher values the two chaotic attractors merge.

Model [3]

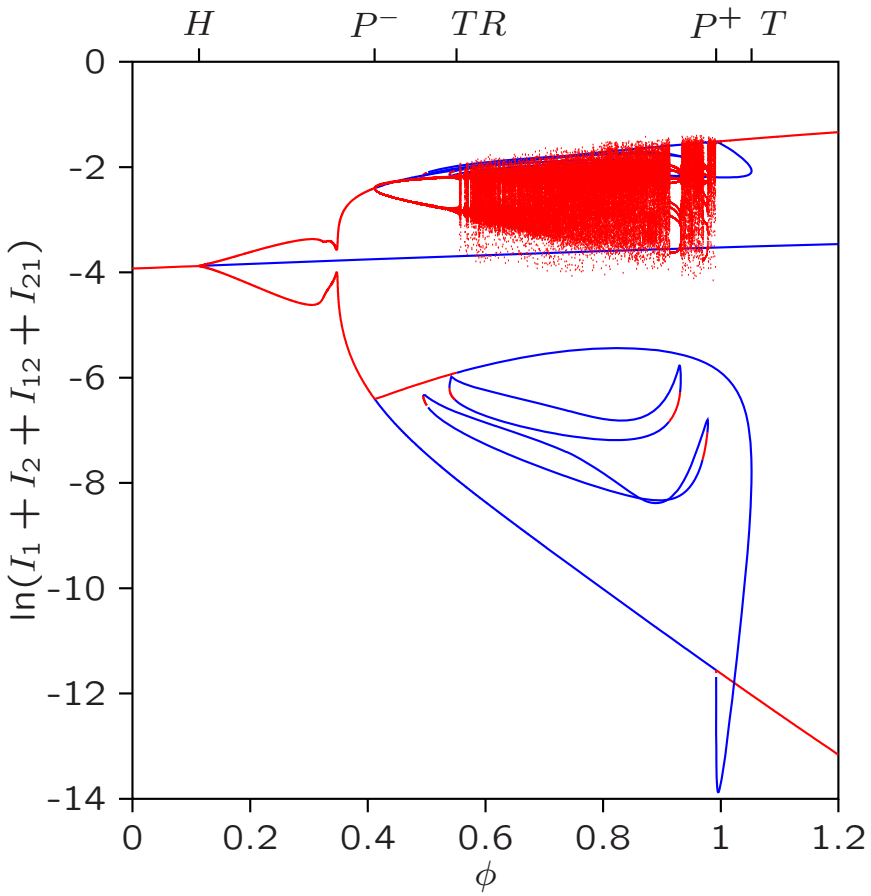
one route to chaos

other route to chaos



One-parameter bifurcation diagram: $\alpha = 2$

total infected $I_1 + I_2 + I_{12} + I_{21}$



Stable Unstable

All three models possess Symmetries

Symmetries

Symmetries due to the multi-strain structure of the model

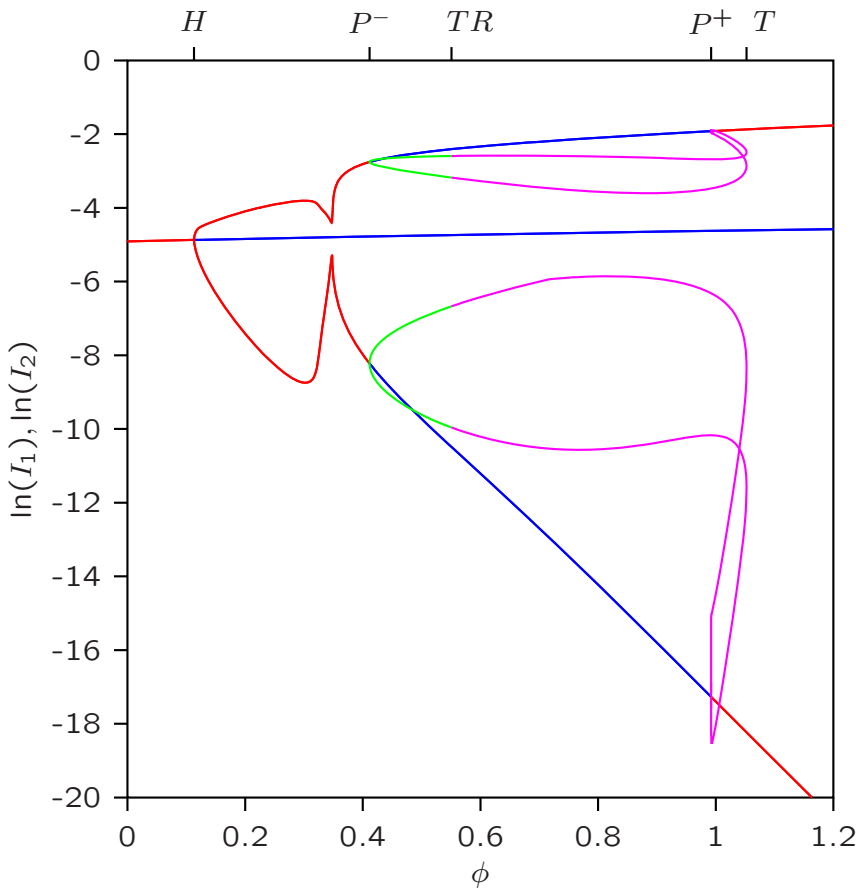
Symmetry transformation matrix $\mathbf{S}$

$$\mathbf{S} := \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix} \begin{matrix} S \\ I_1 \\ I_2 \\ R_1 \\ R_2 \\ S_1 \\ S_2 \\ I_{12} \\ I_{21} \\ R \end{matrix}$$

We have the following symmetry:

$$\underline{x}^* = \begin{pmatrix} S^* \\ I_1^* \\ I_2^* \\ R_1^* \\ R_2^* \\ S_1^* \\ S_2^* \\ I_{12}^* \\ I_{21}^* \\ R^* \end{pmatrix} \quad \Rightarrow \quad \mathbf{S}\underline{x}^* = \begin{pmatrix} S^* \\ I_2^* \\ I_1^* \\ R_2^* \\ R_1^* \\ S_2^* \\ S_1^* \\ I_{21}^* \\ I_{12}^* \\ R^* \end{pmatrix}$$

One-parameter bifurcation diagram: $\alpha = 2$,
ϕ free variable
I_1 and I_2

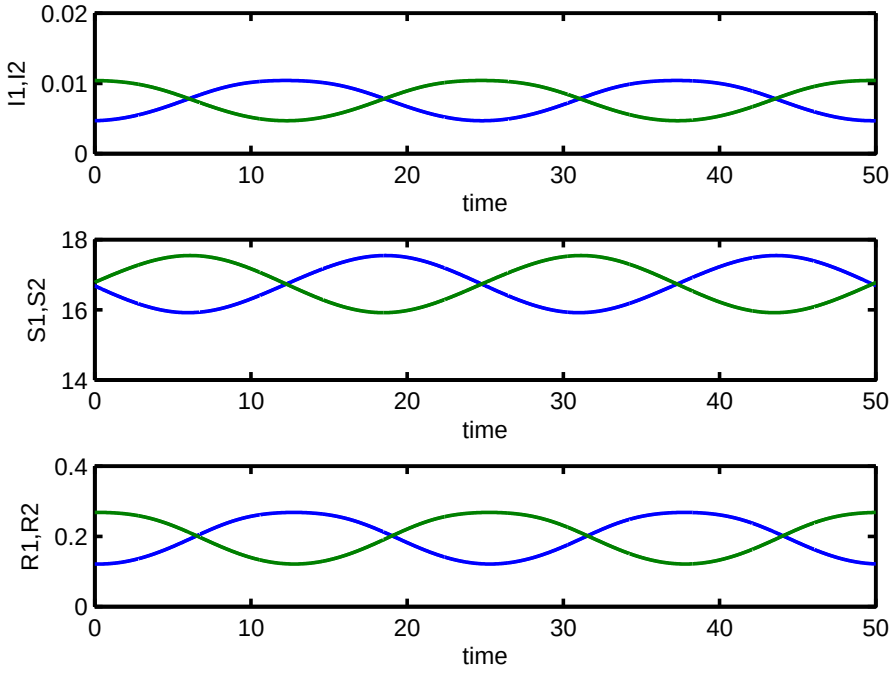


Stable Unstable Stable Unstable

For $\alpha = 2$

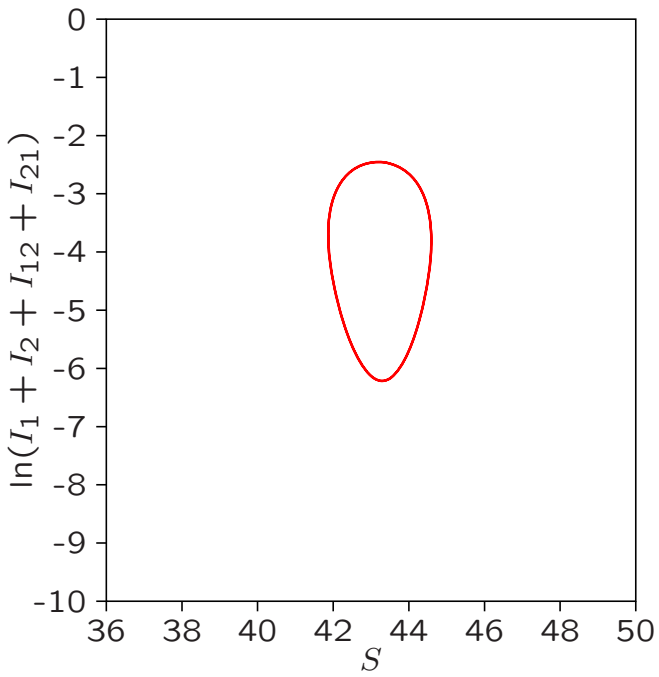
- below Hopf $\Rightarrow$ Fixed equilibrium
- Hopf H and Pitchfork P^- $\Rightarrow$
  Symmetric stable limit cycle
- Pitchfork $P^-$and Torus TR $\Rightarrow$
  Two noninvariant $\mathbf{S}$-conjugate cycles
- Pitchfork P^- and Pitchfork P^+ $\Rightarrow$ Chaos

limit cycles: $\phi = 0.12$, between H and P^-



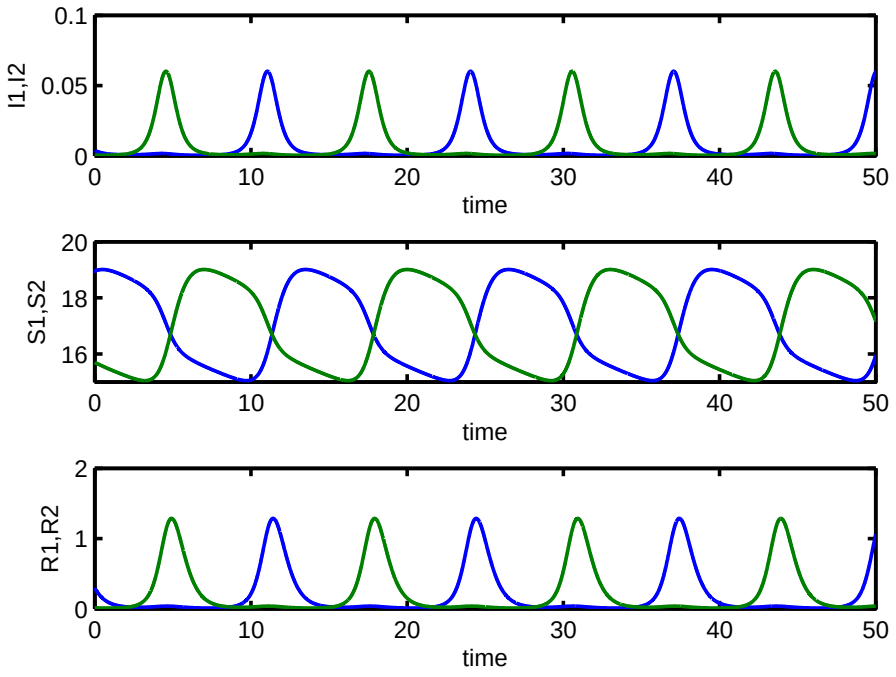
Stable symmetric $\mathbf{S}$-invariant cycle

limit cycles: $\phi = 0.4$, between H and P^-

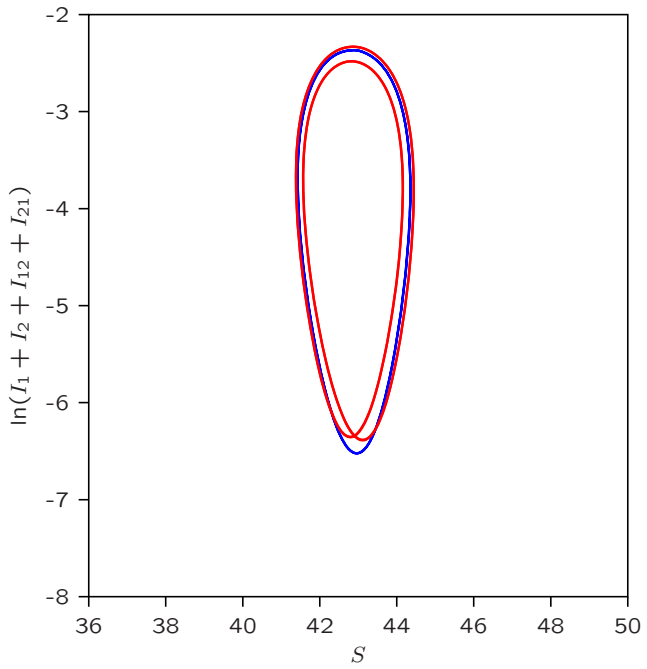


Stable symmetric $\mathbf{S}$-invariant cycle

limit cycles: $\phi = 0.4$, between H and P^-



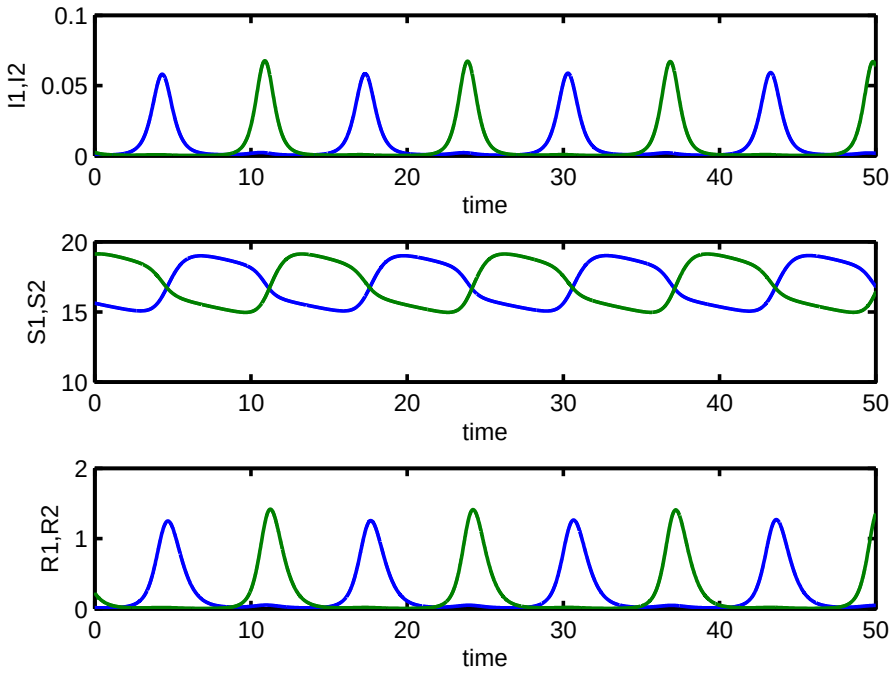
limit cycles: $\phi = 0.42$, between P^- and TR



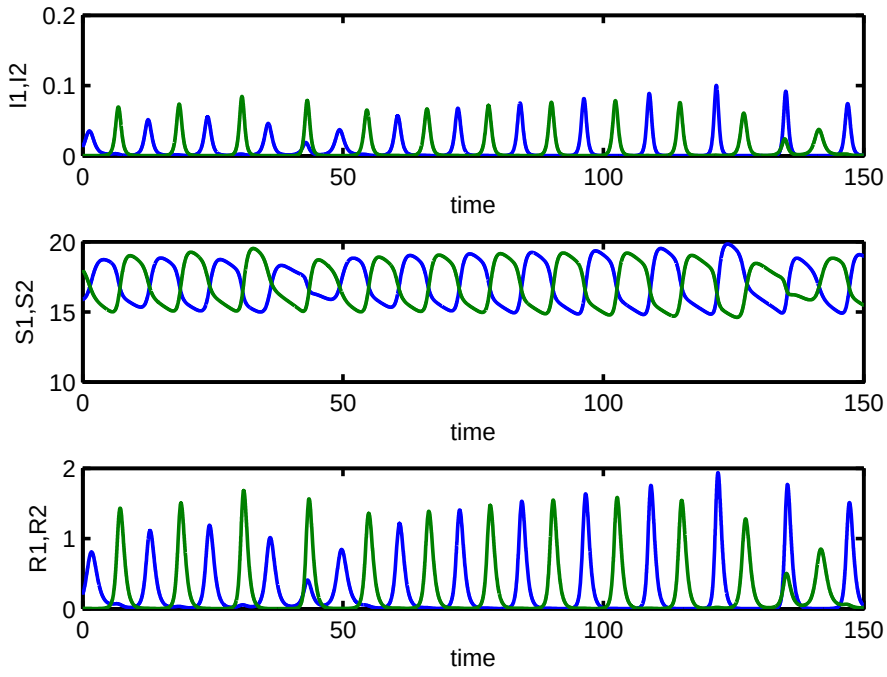
Unstable symmetric $\mathbf{S}$-invariant cycle

Stable Two noninvariant $\mathbf{S}$-conjugate cycles

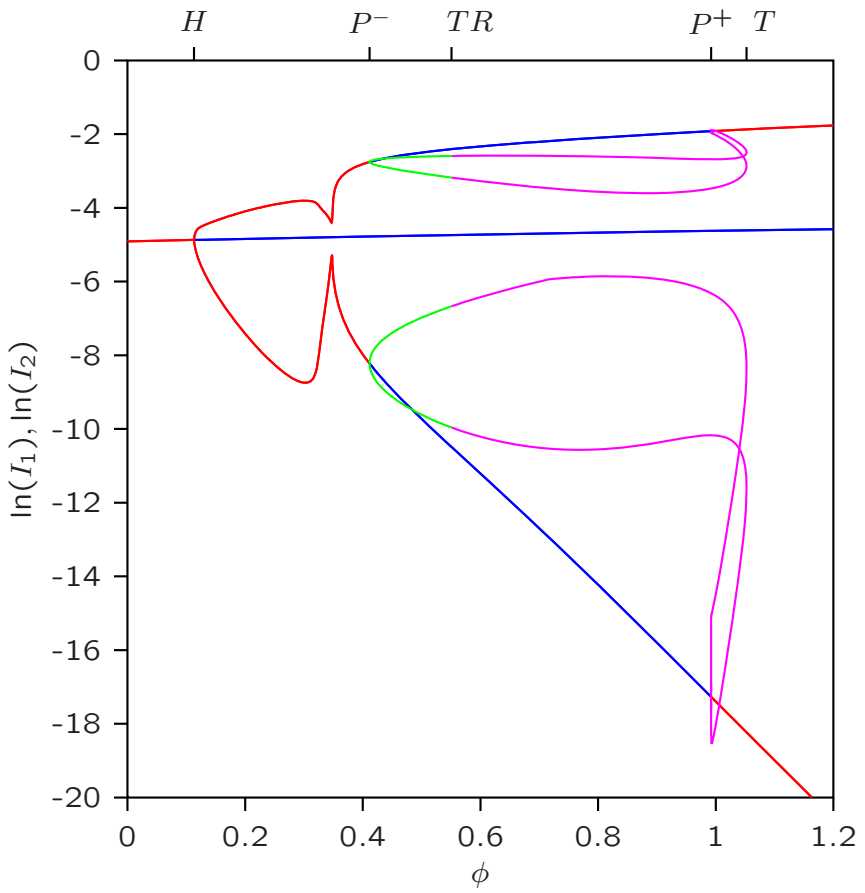
limit cycles: $\phi = 0.42$, between P^- and TR



limit cycles: $\phi = 0.6$, between TR and P^+

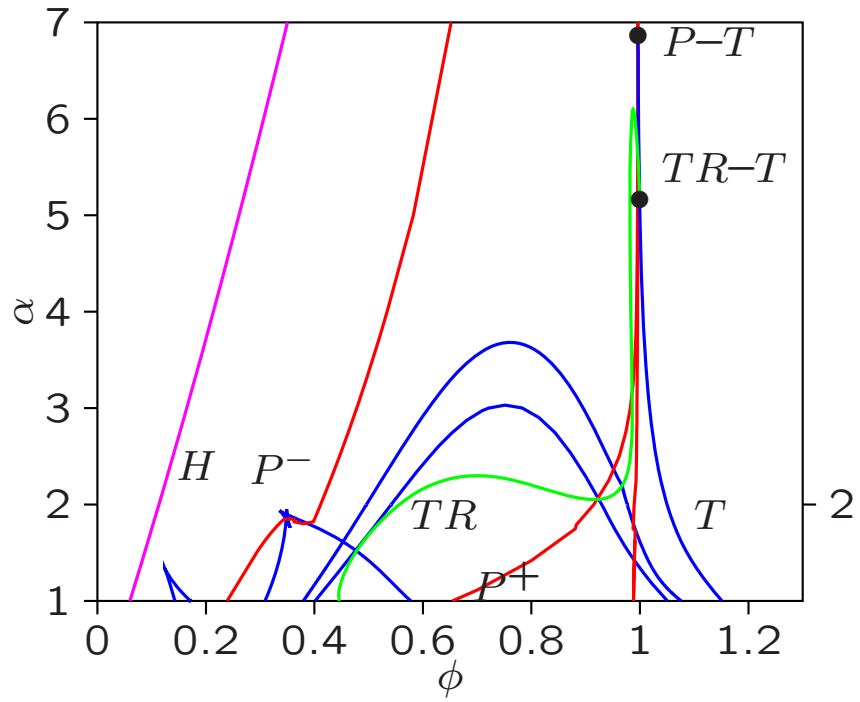


One-parameter bifurcation diagram: $\alpha = 2$,
ϕ free variable
I_1 and I_2



Stable Unstable Stable Unstable

Two-parameter bifurcation diagram:
α, ϕ free variables



Introduction of asymmetry

We assume that the infection rate for the two strains differ

$\beta_1 = \beta + \varepsilon$ and $\beta_2 = \beta - \varepsilon$ with $\beta = 2\gamma$

For $\varepsilon = 0$ the system is symmetric again

This is the natural starting point for increasing the degree of asymmetry

All other parameters are still symmetric. In reality also other asymmetries will attributes to the effects studied

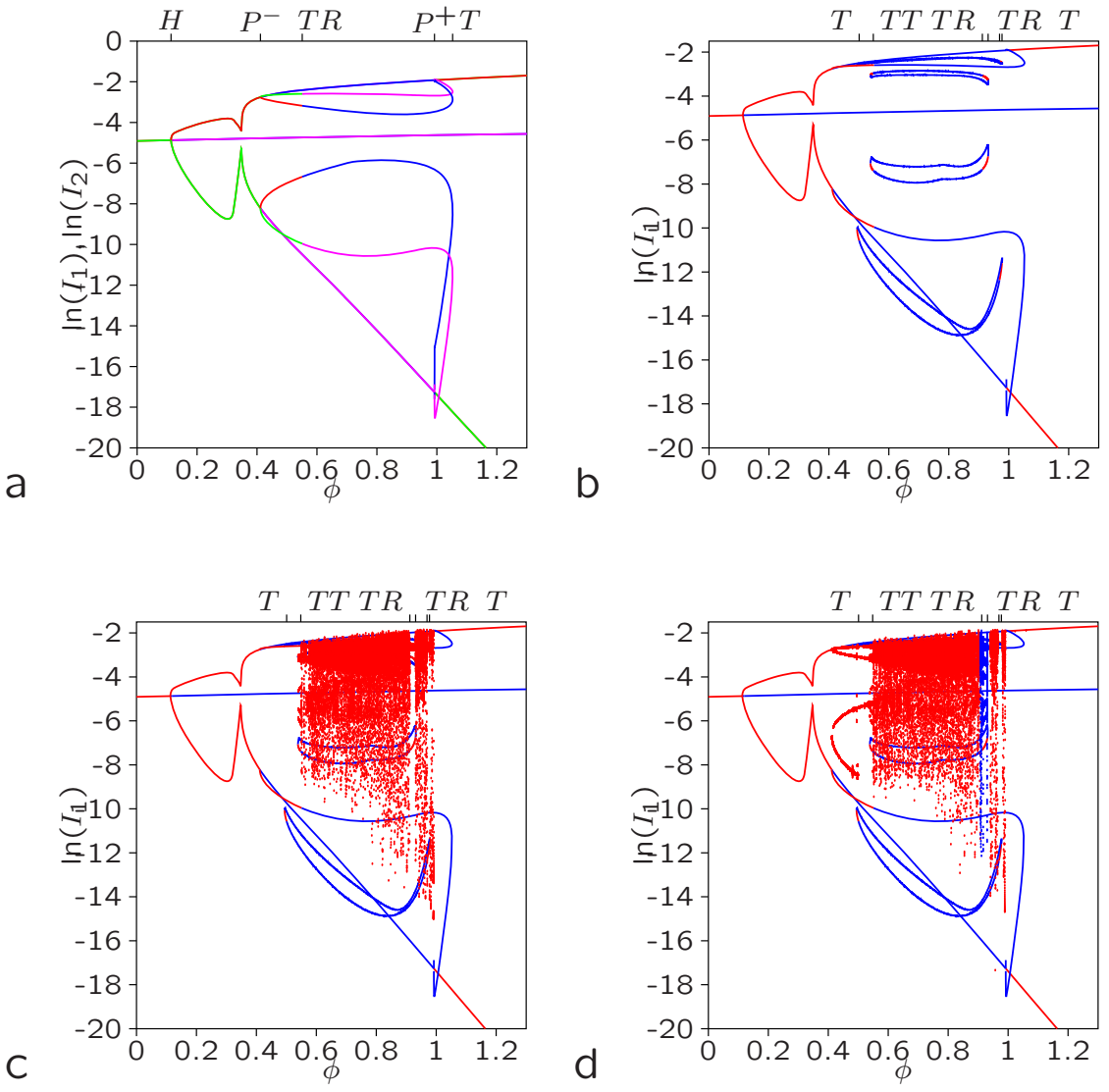
Asymmetric dengue fever model

$$\dot{S} = -\frac{\beta_1}{N} S(I_1 + \phi I_{21}) - \frac{\beta_2}{N} S(I_2 + \phi I_{12}) + \mu(N - S)$$
$$\dot{I}_1 = \frac{\beta_1}{N} S(I_1 + \phi I_{21}) - (\gamma + \mu) I_1$$
$$\dot{I}_2 = \frac{\beta_2}{N} S(I_2 + \phi I_{12}) - (\gamma + \mu) I_2$$
$$\dot{R}_1 = \gamma I_1 - (\alpha + \mu) R_1$$
$$\dot{R}_2 = \gamma I_2 - (\alpha + \mu) R_2$$
$$\dot{S}_1 = -\frac{\beta_2}{N} S_1(I_2 + \phi I_{12}) + \alpha R_1 - \mu S_1$$
$$\dot{S}_2 = -\frac{\beta_1}{N} S_2(I_1 + \phi I_{21}) + \alpha R_2 - \mu S_2$$
$$\dot{I}_{12} = \frac{\beta_2}{N} S_1(I_2 + \phi I_{12}) - (\gamma + \mu) I_{12}$$
$$\dot{I}_{21} = \frac{\beta_1}{N} S_2(I_1 + \phi I_{21}) - (\gamma + \mu) I_{21}$$
$$\dot{R} = \gamma(I_{12} + I_{21}) - \mu R$$

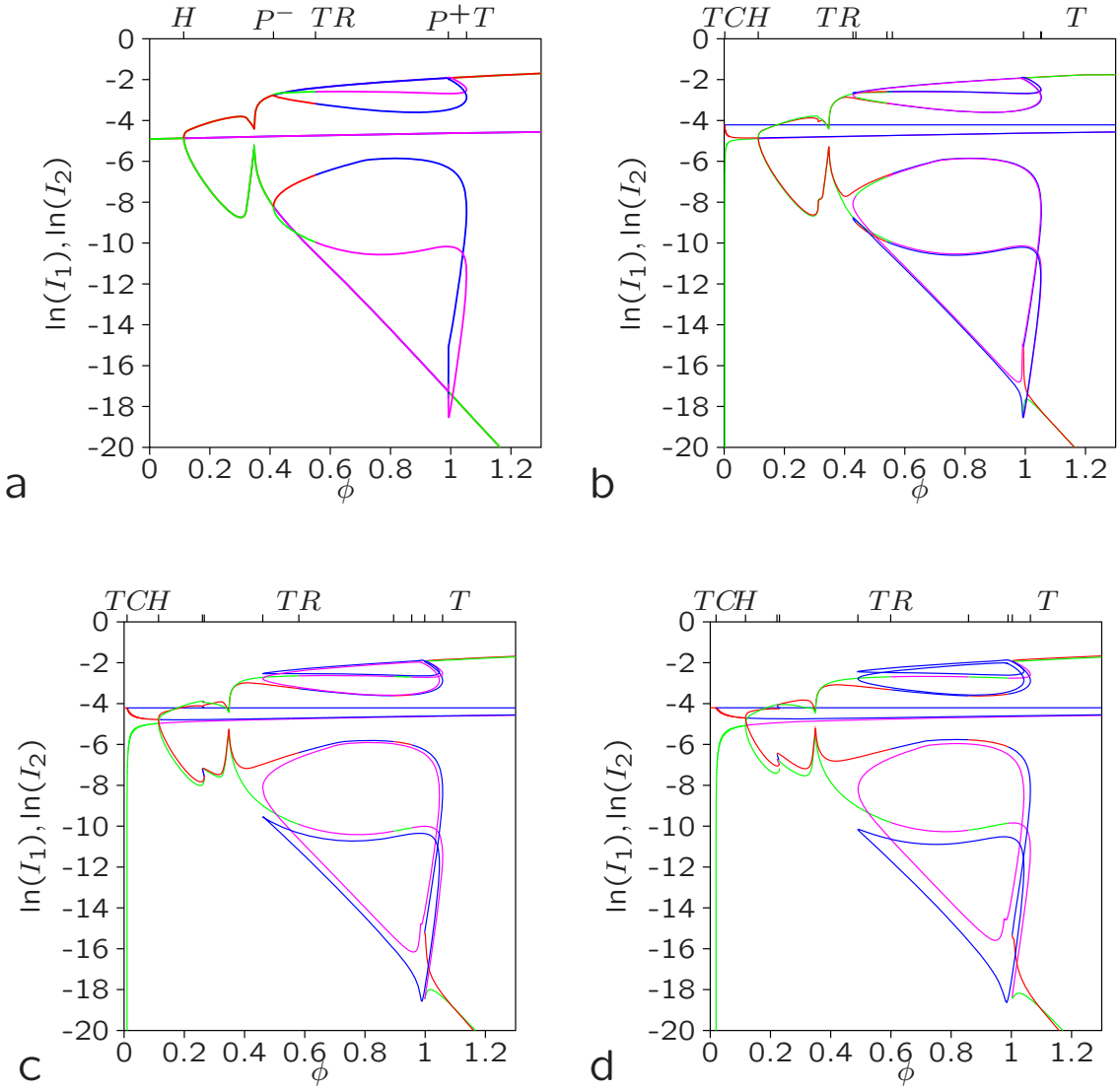
Where:

$\beta_1 = \beta + \varepsilon$ and $\beta_2 = \beta - \varepsilon$ with $\beta = 2\gamma$

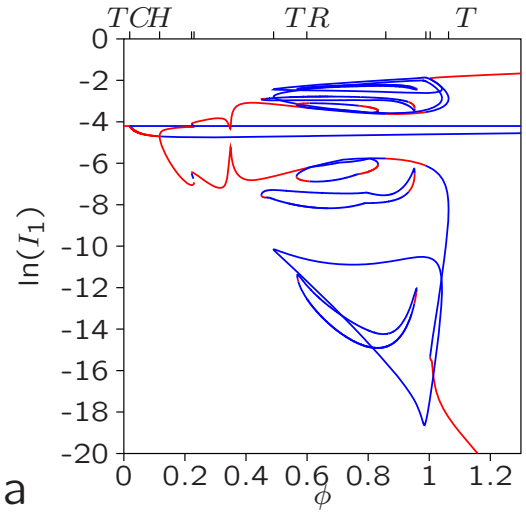
$\varepsilon = 0$



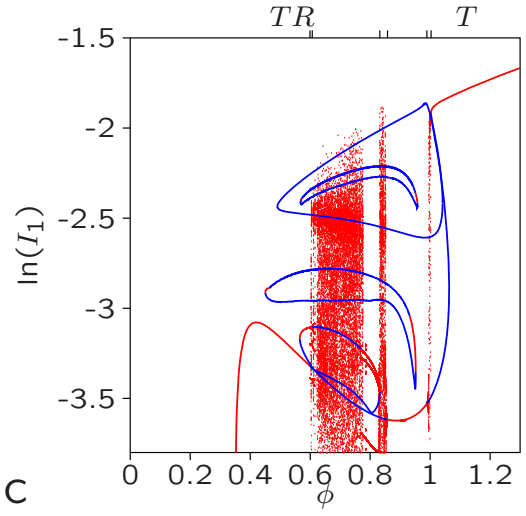
$\varepsilon = 0,\ 0.1\ , 0.5\ , 1$



$\varepsilon = 1$

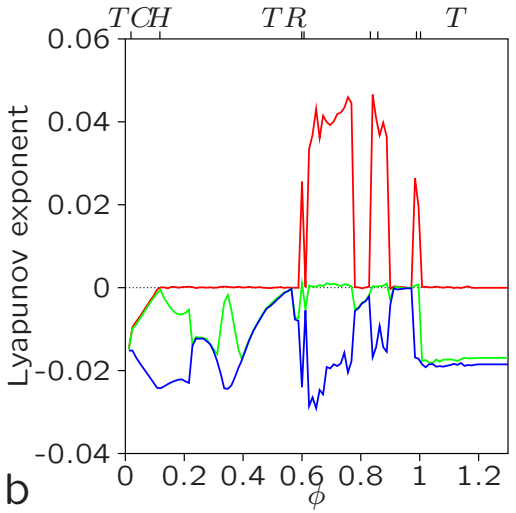


a

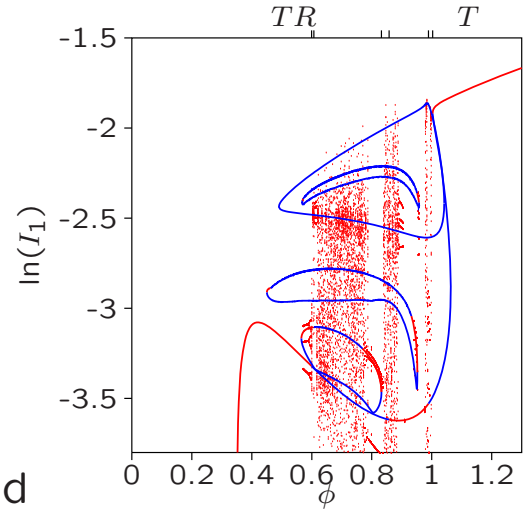


c

$\varepsilon = 1$

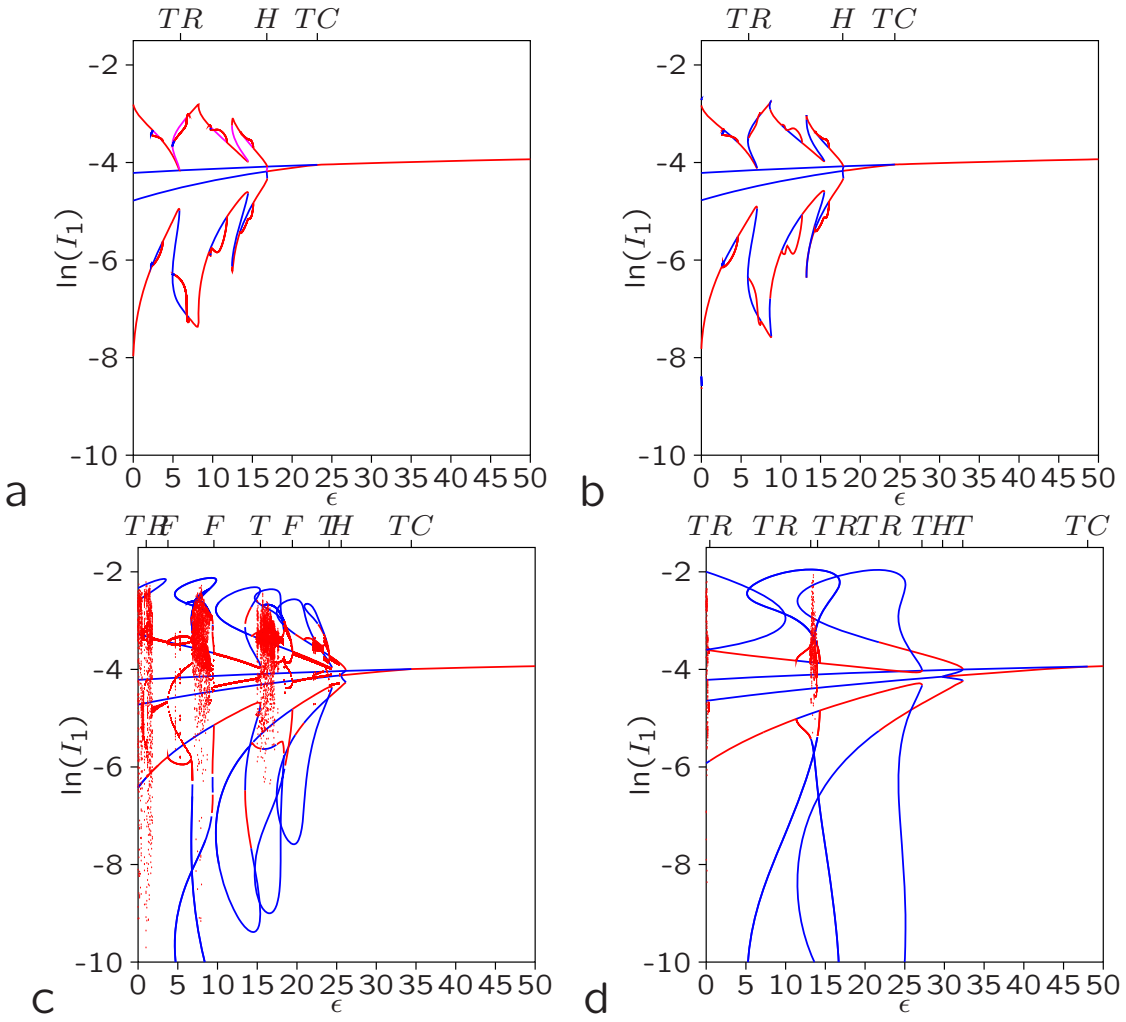


b



d

$\phi = 0.4$ $\phi = 0.42$ $\phi = 0.6$ $\phi = 0.9$



basic reproduction number (or ratio)

For $\varepsilon = 0$ we have $R_0 = \beta/(\gamma + \mu) > 1$

$R_0 < 1$: disease-free equilibrium $\underline{x}^0$ is stable

$R_0 > 1$: disease-free equilibrium $\underline{x}^0$ is unstable: generally leading to time-convergence to a stable endemic equilibrium $\underline{\widehat{x}}$.

Disease-free equilibrium :

$$\underline{x}^0 = \left(S^0\ I_1^0\ I_2^0\ I_{12}^0\ I_{21}^0\ S_1^0\ S_2^0\ R_1^0\ R_2^0\ R^0\right)^T$$

$$= \left(N\ 0\ \ 0\ \ 0\ 0\ 0\ \ 0\ 0\ \ 0\ 0\right)^T$$

Disease-free equilibrium

All individuals are susceptible $S^0 = N$ and all other classes are zero

The Jacobian matrix of the 9 dimensional system evaluated at the disease-free equilibrium

$$\begin{pmatrix}
-\mu & -\beta_1 & -\beta_2 & -\beta_2\phi & -\beta_1 & 0 & 0 & 0 & 0 \\
0 & \beta_1 - \gamma - \mu & 0 & 0 & \beta_1\phi & 0 & 0 & 0 & 0 \\
0 & 0 & \beta_2 - \gamma - \mu & \beta_2\phi & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & -\gamma - \mu & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & -\gamma - \mu & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & -\mu & 0 & \alpha & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & -\mu & 0 & \alpha \\
0 & \gamma & 0 & 0 & 0 & 0 & 0 & -\alpha - \mu & 0 \\
0 & 0 & \gamma & 0 & 0 & 0 & 0 & 0 & -\alpha - \mu
\end{pmatrix}$$

The eigenvalues are:

$$\lambda_1 = -(\gamma + \mu)\,, \lambda_2 = -(\gamma + \mu)\,,$$
$$\lambda_3 = -(\alpha + \mu)\,, \lambda_4 = -(\alpha + \mu)\,,$$
$$\lambda_5 = -\mu\,,$$
$$\lambda_6 = -\mu\,,$$
$$\lambda_7 = -\mu\,,$$
$$\lambda_8 = \beta + \varepsilon - \gamma - \mu\,,$$
$$\lambda_9 = \beta - \varepsilon - \gamma - \mu\,.$$

Since all parameters except ε are positive the stability depends on the sign of the two eigenvalues: $\beta + \varepsilon - \gamma - \mu$ and $\beta - \varepsilon - \gamma - \mu$. So, a one-strain dengue virus is endemic when either $\beta + \varepsilon > \gamma + \mu$ or $\beta - \varepsilon > \gamma + \mu$

There are two one-strain models namely:

$$\underline{\widehat{x}}_1 = \left(\widehat{S}\ \hat{I}_1\ 0\ 0\ 0\ \hat{S}_1\ 0\ \hat{R}_1\ 0\ \right)^T$$
$$\underline{\widehat{x}}_2 = \left(\widehat{S}\ 0\ \hat{I}_2\ 0\ 0\ 0\ \ \hat{S}_2\ 0\ \hat{R}_2\ \right)^T$$

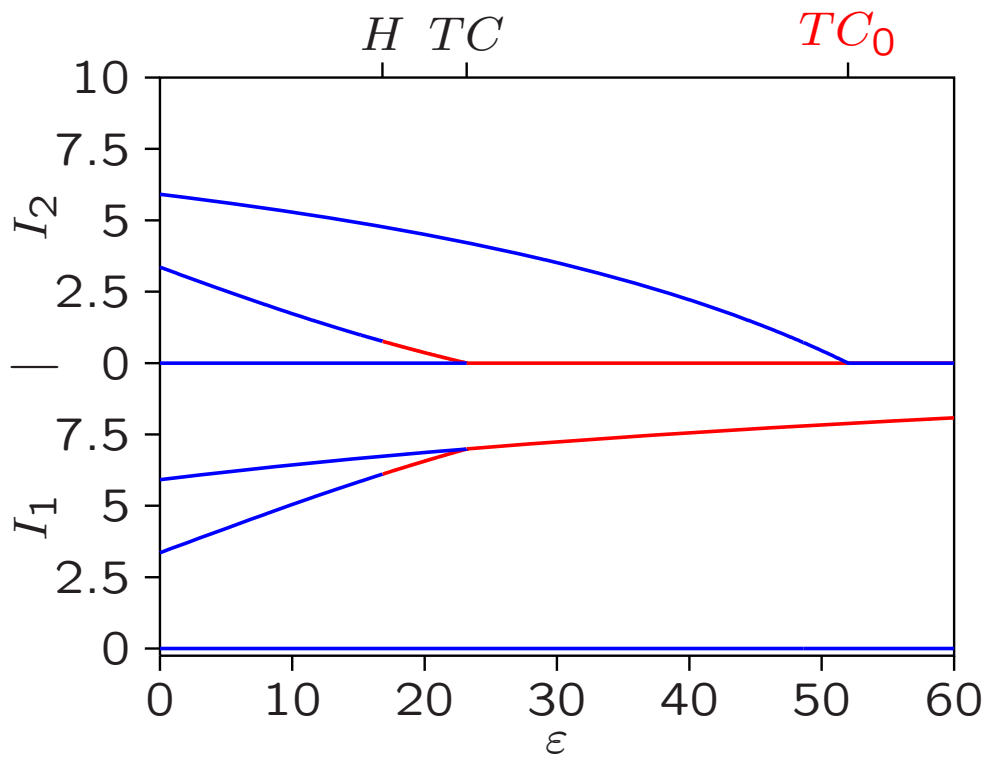
The one-strain $\underline{\widehat{x}}_1$ can invade the disease-free system and becomes endemic when $\varepsilon > \gamma + \mu - \beta$ and with $\beta = 2\gamma$ we get $\varepsilon > \mu - \gamma$.

Hence, within the interval $\varepsilon \in [-(\gamma - \mu), \gamma - \mu]$, including $\varepsilon = 0$, both one-strains separately are endemic or invasive.

The transcritical bifurcations denoted by TC_0 are given by

$$\varepsilon = \mp(\gamma - \mu)$$

One-parameter diagram $\phi = 0.4$
perturbation parameter: ε



Stable Unstable

Now we consider the conditions for both strains to be present simultaneously.

Expression that fixes the curve TC where the equilibrium equals $\underline{\widehat{x}}_i$, $i = 1, 2$ changes stability

Five eigenvalues λ_i, $i = 1, \cdots, 5$ are the same as earlier. Last four of the 9 eigenvalues are:

$$\lambda_6 = -\frac{\beta_1\,\mu}{\gamma+\mu}$$

$$\lambda_7 = \frac{-\beta_1\,\mu + \sqrt{\mu^2{\beta_1}^2 - 4\,\mu\beta_1\,(\mu+\gamma)^2 + 4\mu\,(\mu+\gamma)^3}}{2(\gamma+\mu)}$$

$$\lambda_8 = \frac{-\beta_1\,\mu - \sqrt{\mu^2{\beta_1}^2 - 4\,\mu\beta_1\,(\mu+\gamma)^2 + 4\mu\,(\mu+\gamma)^3}}{2(\gamma+\mu)}$$

$$\lambda_9 = \frac{\beta_2\,\phi\,\alpha\gamma\,(\beta_1-\gamma-\mu) - (\beta_1-\beta_2)(\alpha+\mu)(\gamma+\mu)^2}{(\mu+\alpha)(\gamma+\mu)\beta_1}$$

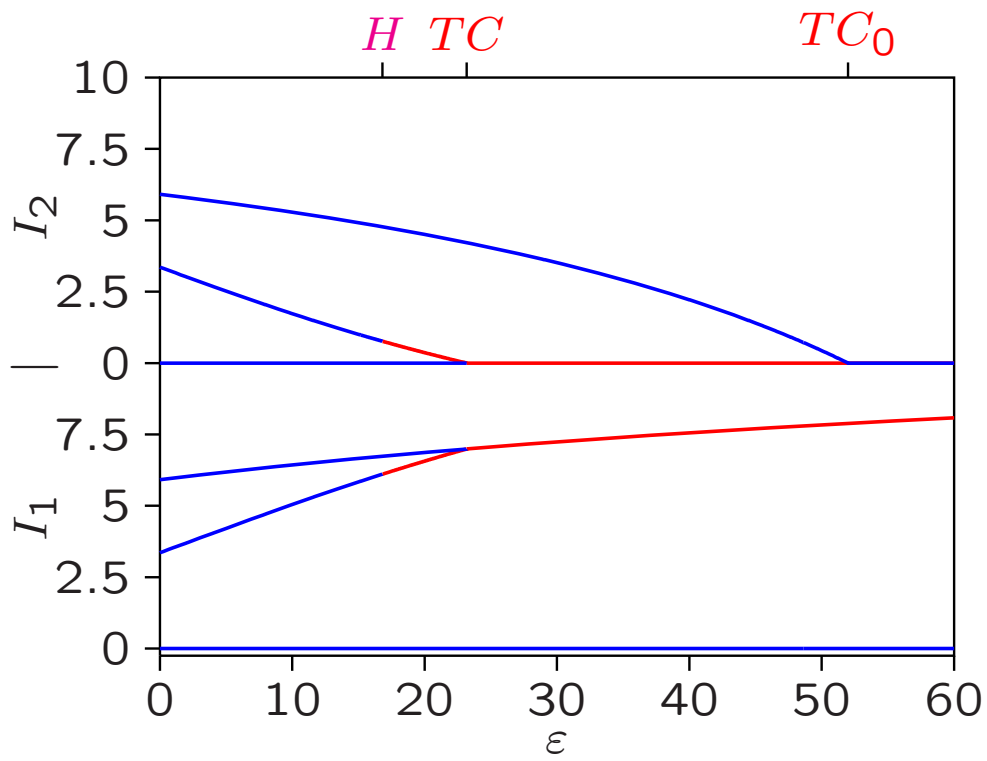
The single eigenvalue that can change sign under (positive) parameter variation is λ_9 while the real parts of all other eigenvalues are always negative.

Thus the condition that determines the transcritical bifurcation TC reads

$$0 = (\beta - \varepsilon)\phi\,\alpha\gamma(\beta + \varepsilon - \gamma - \mu) - 2\varepsilon(\mu + \alpha)(\gamma + \mu)^2$$

Note that when λ_9 becomes positive the five dimensional one-strain system S, S_1, I_1, R_1, R gets invaded by a five dimensional system, namely the three components S_2, I_2, R_2 together with the two double infected classes I_{12} and I_{21}

One-parameter diagram $\phi = 0.4$
perturbation parameter: ε

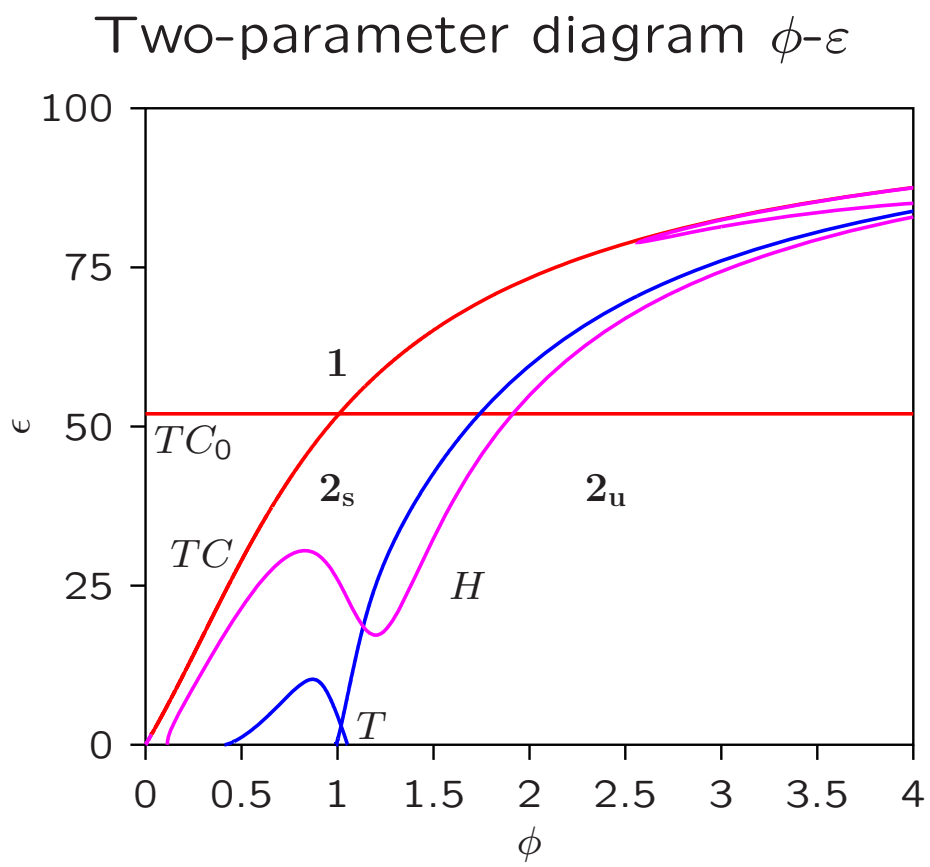


Stable Unstable

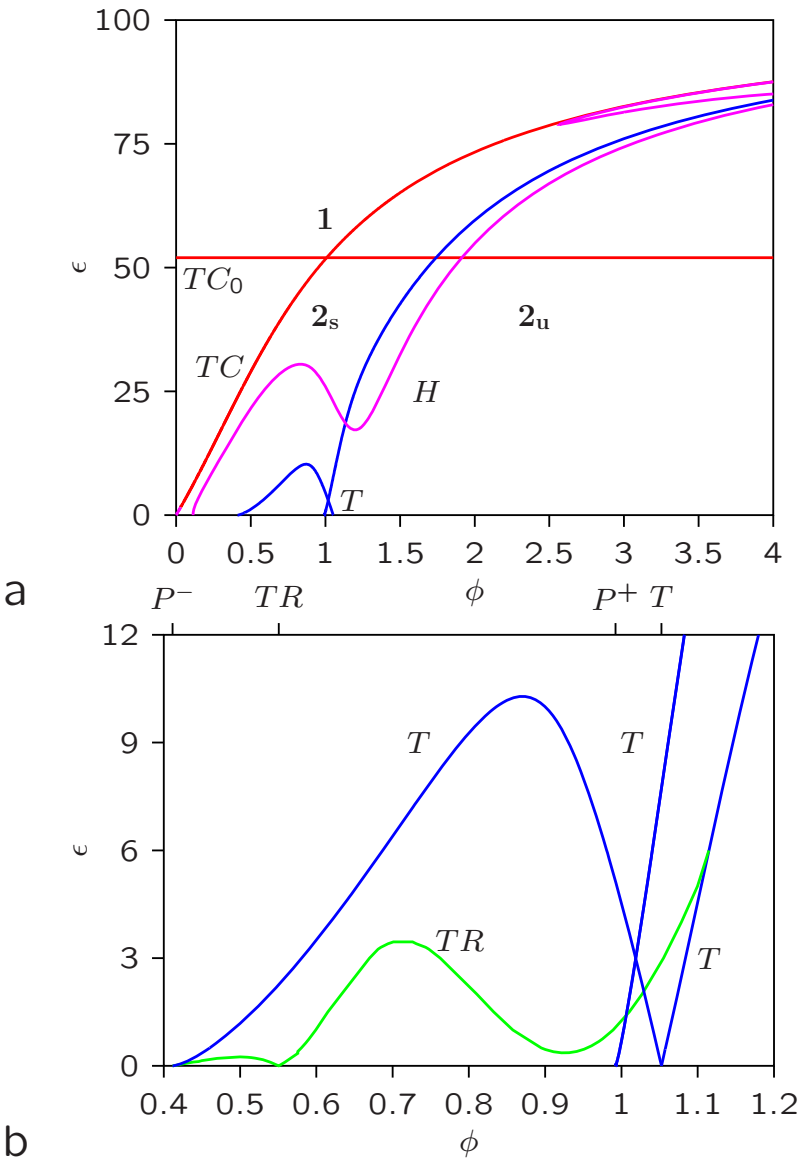
Hopf bifurcation

Equation for Hopf bifurcation can be derived in principle is a similar way

Here we show numerically calculated Hopf bifurcation curve in a two-parameter diagram ϕ-ε



Transcritical Hopf Tangent


100
75
50
25
0
ϵ
$\mathbf{1}$
TC_0
$\mathbf{2_s}$
$\mathbf{2_u}$
TC
H
T
0 0.5 1 1.5 2 2.5 3 3.5 4
ϕ
a
P^- TR P^+ T
12
9
6
3
0
T
T
TR
T
0.4 0.5 0.6 0.7 0.8 0.9 1 1.1 1.2
ϕ
b

Conclusions (1)

- With modelling multi-strain epidemics it is tempting to assume identical epidemiological parameters for all strains to minimise the number of parameters and equations

- Motive is that all strains are dengue virus correlated with *Aedes aegypti* vectors

- Taking exact equal parameter values implies mathematical model possesses symmetry

- Robustness of structurally unstable pitchfork bifurcation is important: organizing center for branches on which complex dynamics occur

Conclusions (2)

- To study existence of endemic equilibrium the *basic reproduction number* R_0 is introduced in the epidemiological literature.

- R_0, is the size of the second generation of infected going back to one infected individual in an otherwise totally susceptible population.

Conclusions (3)

- $R_0 = 1$ is directly related to an equilibrium. Related to an invasion criterion only when evaluated at a disease-free equilibrium (TC).

- In certain situations $R_0 = 1$ directly relates to the invasion criterion.
  When the growth rate of the infected class is proportional to the size of the infected class itself and the boundary equilibrium results from the zero size of the class then the invasion rate is equal to the growth rate of the infected class

Conclusions (4)

- Classification of exchange of stability between a boundary equilibrium and an interior equilibrium as a transcritical bifurcation puts the evaluation of the invasion threshold into the context of bifurcation theory.

- Possible effects of environment are taken into account

- Different types of transcritical bifurcation, namely catastrophic and non-catastrophic, and various degenerated forms, for instance coalition with a tangent (or saddle-node) bifurcation.

Conclusions (5)

- Bifurcation analysis approach is uniform for all types of long-term dynamics (equilibrium, limit cycle or chaotic attractor)

- Bifurcation analysis and Lyapunov exponent analysis are complementary

- Algorithms and computer packages (AUTO, MatCont) are available to calculate the thresholds.

- Asymmetry matters is important for parameter estimation

Literature

- Kooi, B.W., Aguiar, M., & Stollenwerk, N. 2013. Bifurcation analysis of a family of multi-strain epidemiology models. *Journal of Computational and Applied Mathematics*, DOI: 10.1016/j.cam.2012.08.008.

- Kooi, B.W., Aguiar, M., & Stollenwerk, N. 2013. Analysis of an asymmetric two-strain dengue model, Submitted.