Stability analysis of models of within-host viral dynamics

Rory Burnham

University of Melbourne

May 25, 2018

Outline

Different viruses give vastly differing outcomes for the host, thus models must be adapted to model different viruses.

Different viruses give vastly differing outcomes for the host, thus models must be adapted to model different viruses.

- What governs these differences?
- How do the parameters affect the long term behaviour?

Different viruses give vastly differing outcomes for the host, thus models must be adapted to model different viruses.

- What governs these differences?
- How do the parameters affect the long term behaviour?

In this presentation I will be discussing

- The basic model of virus dynamics and its properties
- How it can be altered to model different viruses
- How the fixed points of the model are affected by these alterations

Viruses are parasitic particles (virions) which infect the cells of a host. We can simplify the biology of viral infections into three basic functions:

Viruses are parasitic particles (virions) which infect the cells of a host. We can simplify the biology of viral infections into three basic functions:

- Virions infect vulnerable cells

Viruses are parasitic particles (virions) which infect the cells of a host. We can simplify the biology of viral infections into three basic functions:

- Virions infect vulnerable cells
- Virions replicate inside infected cells

Viruses are parasitic particles (virions) which infect the cells of a host. We can simplify the biology of viral infections into three basic functions:

- Virions infect vulnerable cells
- Virions replicate inside infected cells
- Infected cells expel virions into the system

Viruses are parasitic particles (virions) which infect the cells of a host. We can simplify the biology of viral infections into three basic functions:

- Virions infect vulnerable cells
- Virions replicate inside infected cells
- Infected cells expel virions into the system

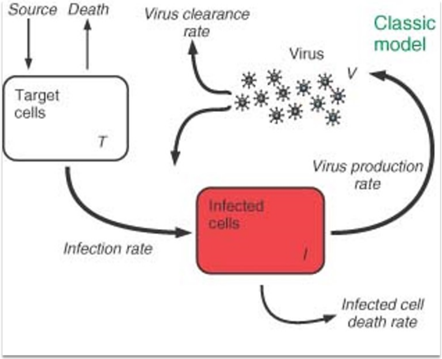


Figure: Taken from Smith et al [1]

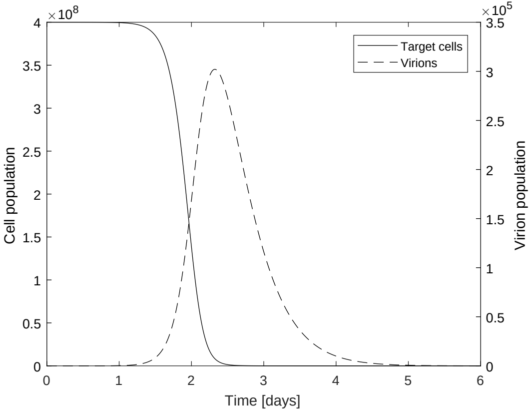
The TIV model

$$T' = -\beta TV$$

$$I' = \beta TV - \delta_I I$$

$$V' = pI - cV$$

Parameter	Description	Unit
β	The number of target cells infected by a virion per unit time	$M^{-1}t^{-1}$
δ_I	Decay rate of infected cells	t^{-1}
p	Number of virions produced by an infected cell per unit time	t^{-1}
c	Decay rate of virions	t^{-1}



T_0	V_0	β	δ_I	p	c
4e8	3.5e-1	3.4e-5	3.4	7.9e-3	3

Table: Values taken from Baccam et al [2]

R_0

Under what conditions does an infection occur?

R_0

Under what conditions does an infection occur?

- We require that each virion results in the creation of greater than 1 virion in its lifetime for the virion population to grow

R_0

Under what conditions does an infection occur?

- We require that each virion results in the creation of greater than 1 virion in its lifetime for the virion population to grow
- This number is known as the reproductive ratio

R_0

Under what conditions does an infection occur?

- We require that each virion results in the creation of greater than 1 virion in its lifetime for the virion population to grow
- This number is known as the reproductive ratio

$$R_0 =$$

R_0

Under what conditions does an infection occur?

- We require that each virion results in the creation of greater than 1 virion in its lifetime for the virion population to grow
- This number is known as the reproductive ratio

$$R_0 = \beta T$$

R_0

Under what conditions does an infection occur?

- We require that each virion results in the creation of greater than 1 virion in its lifetime for the virion population to grow
- This number is known as the reproductive ratio

$$R_0 = \beta T * \frac{1}{c}$$

R_0

Under what conditions does an infection occur?

- We require that each virion results in the creation of greater than 1 virion in its lifetime for the virion population to grow
- This number is known as the reproductive ratio

$$R_0 = \beta T * \frac{1}{c} * p$$

R_0

Under what conditions does an infection occur?

- We require that each virion results in the creation of greater than 1 virion in its lifetime for the virion population to grow
- This number is known as the reproductive ratio

$$R_0 = \beta T * \frac{1}{c} * p * \frac{1}{\delta_I}$$

R_0

Under what conditions does an infection occur?

- We require that each virion results in the creation of greater than 1 virion in its lifetime for the virion population to grow
- This number is known as the reproductive ratio

$$R_0 = \beta T * \frac{1}{c} * p * \frac{1}{\delta_I}$$

- We are interested in what this value is at the time of infection, so we set $T = T_0$

R_0

Under what conditions does an infection occur?

- We require that each virion results in the creation of greater than 1 virion in its lifetime for the virion population to grow
- This number is known as the reproductive ratio

$$R_0 = \beta T * \frac{1}{c} * p * \frac{1}{\delta_I}$$

- We are interested in what this value is at the time of infection, so we set $T = T_0$
- $R_0 < 1$ — virions die out before an infection occurs
- $R_0 > 1$ — the number of virions grows initially and an infection occurs

Linear stability analysis

- Find fixed points by solving $(T', I', V') = (0, 0, 0)$

Linear stability analysis

- Find fixed points by solving $(T', I', V') = (0, 0, 0)$
- $(\bar{I}, \bar{V}) = (0, 0)$ in all cases, and $\bar{T} \in [0, T_0]$

Linear stability analysis

- Find fixed points by solving $(T', I', V') = (0, 0, 0)$
- $(\bar{I}, \bar{V}) = (0, 0)$ in all cases, and $\bar{T} \in [0, T_0]$
- No single fixed point to analyse, so we set $T = T_0$ and analyse the behaviour at the time of infection

Linear stability analysis

- Find fixed points by solving $(T', I', V') = (0, 0, 0)$
- $(\bar{I}, \bar{V}) = (0, 0)$ in all cases, and $\bar{T} \in [0, T_0]$
- No single fixed point to analyse, so we set $T = T_0$ and analyse the behaviour at the time of infection

The model reduces to a $2D$ system

$$
\begin{aligned}
I' &= \beta T_0 V - \delta_I I \\
V' &= pI - cV
\end{aligned}
$$

Linear stability analysis

- Find fixed points by solving $(T', I', V') = (0, 0, 0)$
- $(\bar{I}, \bar{V}) = (0, 0)$ in all cases, and $\bar{T} \in [0, T_0]$
- No single fixed point to analyse, so we set $T = T_0$ and analyse the behaviour at the time of infection

The model reduces to a $2D$ system

$$\begin{aligned} I' &= \beta T_0 V - \delta_I I \\ V' &= pI - cV \end{aligned}$$

Under what conditions does this system tend to $(I, V) = (0, 0)$? The Jacobian given by

$$J = \begin{bmatrix} -\delta_I & \beta T_0 \\ p & -c \end{bmatrix}.$$

Linear stability analysis

- Find fixed points by solving $(T', I', V') = (0, 0, 0)$
- $(\bar{I}, \bar{V}) = (0, 0)$ in all cases, and $\bar{T} \in [0, T_0]$
- No single fixed point to analyse, so we set $T = T_0$ and analyse the behaviour at the time of infection

The model reduces to a $2D$ system

$$I' = \beta T_0 V - \delta_I I$$
$$V' = pI - cV$$

Under what conditions does this system tend to $(I, V) = (0, 0)$? The Jacobian given by

$$J = \begin{bmatrix} -\delta_I & \beta T_0 \\ p & -c \end{bmatrix}.$$

For all eigenvalues of the Jacobian, λ, we require $\mathrm{Re}(\lambda) < 0$ for stability.

Linear stability analysis

- Find fixed points by solving $(T', I', V') = (0, 0, 0)$
- $(\bar{I}, \bar{V}) = (0, 0)$ in all cases, and $\bar{T} \in [0, T_0]$
- No single fixed point to analyse, so we set $T = T_0$ and analyse the behaviour at the time of infection

The model reduces to a $2D$ system

$$I' = \beta T_0 V - \delta_I I$$
$$V' = pI - cV$$

Under what conditions does this system tend to $(I, V) = (0, 0)$? The Jacobian given by

$$J = \begin{bmatrix} -\delta_I & \beta T_0 \\ p & -c \end{bmatrix}.$$

For all eigenvalues of the Jacobian, λ, we require $\mathrm{Re}(\lambda) < 0$ for stability.

From this we obtain the condition for stability

$$\frac{p\beta T_0}{\delta_I c} < 1.$$

How do we model chronic infections?

How do we model chronic infections?
Regrowth of target cells needs to be introduced.
Here we look at constant target cell regrowth.

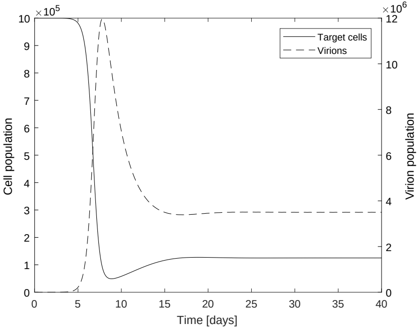
How do we model chronic infections?
Regrowth of target cells needs to be introduced.
Here we look at constant target cell regrowth.

$$T' = \sigma - \beta TV - \delta_T T$$

$$I' = \beta TV - \delta_I I$$

$$V' = pI - cV$$

How do we model chronic infections?
Regrowth of target cells needs to be introduced.
Here we look at constant target cell regrowth.



$$T' = \sigma - \beta TV - \delta_T T$$

$$I' = \beta TV - \delta_I I$$

$$V' = pI - cV$$

T_0	V_0	σ	β	δ_I	δ_T	p	c
1e6	10	1e5	2e-7	0.5	0.1	100	5

Table: Values taken from Virus Dynamics [3]

Linear stability analysis

The model has 2 fixed points

- $(\bar{T}_1, \bar{I}_1, \bar{V}_1) = (\sigma/\delta_T, 0, 0)$ (virus is cleared)
- $(\bar{T}_2, \bar{I}_2, \bar{V}_2) = \left(\frac{c\delta_I}{\beta p}, \frac{\sigma\beta p - \delta_I\delta_T c}{\beta p\delta_I}, \frac{\sigma\beta p - \delta_I\delta_T c}{\beta\delta_I c}\right)$ (chronic viral infection)

Linear stability analysis

The model has 2 fixed points

- $(\bar{T}_1, \bar{I}_1, \bar{V}_1) = (\sigma/\delta_T, 0, 0)$ (virus is cleared)
- $(\bar{T}_2, \bar{I}_2, \bar{V}_2) = \left(\frac{c\delta_I}{\beta p}, \frac{\sigma\beta p - \delta_I\delta_T c}{\beta p\delta_I}, \frac{\sigma\beta p - \delta_I\delta_T c}{\beta\delta_I c}\right)$ (chronic viral infection)

The characteristic equation is given by

$$C(\lambda) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3$$

where

$$\begin{aligned} a_1 &= \beta V + c + \delta_I + \delta_T, \\ a_2 &= \delta_I\delta_T + c\delta_T + c\delta_I + \beta\delta_I V + c\beta V - p\beta T, \\ a_3 &= c\delta_I\delta_T + c\beta\delta_I V - p\beta\delta_T T. \end{aligned}$$

After some algebra we again arrive at the condition for virus clearance being

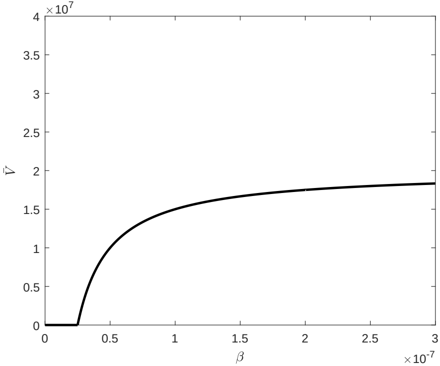
$$R_0 = \frac{p\beta\sigma}{\delta_I c \delta_T} < 1.$$

If $R_0 > 1$, the chronic viral fixed point gains stability

After some algebra we again arrive at the condition for virus clearance being

$$R_0 = \frac{p\beta\sigma}{\delta_I c \delta_T} < 1.$$

If $R_0 > 1$, the chronic viral fixed point gains stability



Logistic target cell regrowth

Can we model short terms infections with models that include target cell regrowth?

Logistic target cell regrowth

Can we model short terms infections with models that include target cell regrowth?

$$
\begin{aligned}
T' &= \sigma T\left(1 - \frac{T+I}{T_0}\right) - \beta TV \\
I' &= \beta TV - \delta_I I \\
V' &= pI - cV
\end{aligned}
$$

Logistic target cell regrowth

Can we model short terms infections with models that include target cell regrowth?

$$
\begin{aligned}
T' &= \sigma T\left(1 - \frac{T+I}{T_0}\right) - \beta TV \\
I' &= \beta TV - \delta_I I \\
V' &= pI - cV
\end{aligned}
$$

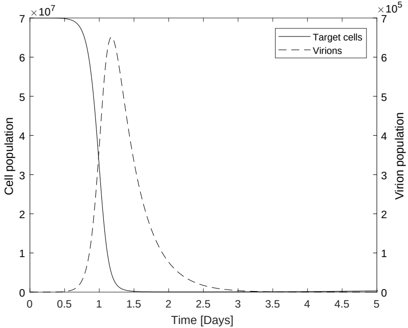
- For $T + I \ll T_0$, resembles exponential growth
- As $T + I \to T_0$ growth tends towards 0

Logistic target cell regrowth

Can we model short terms infections with models that include target cell regrowth?

$$T' = \sigma T\left(1 - \frac{T+I}{T_0}\right) - \beta T V$$
$$I' = \beta T V - \delta_I I$$
$$V' = pI - cV$$

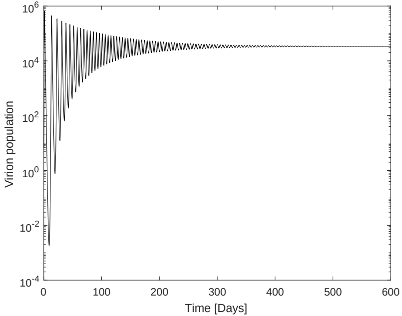
- For $T + I \ll T_0$, resembles exponential growth
- As $T + I \to T_0$ growth tends towards 0



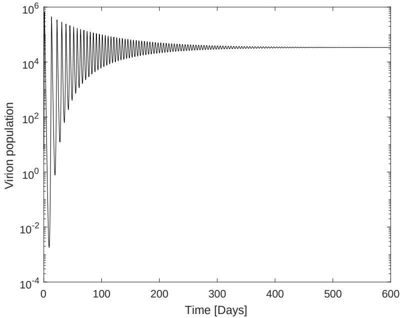
T_0	V_0	σ	β	δ_I	p	c
7e7	10	0.8	2e-5	3	0.35	20

Table: Values taken from Cao et al [4]

Long term behaviour

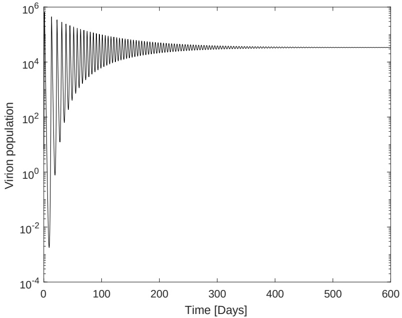


Long term behaviour



- System tends towards a non-zero virus fixed point via damped oscillation

Long term behaviour



- System tends towards a non-zero virus fixed point via damped oscillation
- Initial transient reaches 10^{-3} virions, stochastic extinction likely

Stability analysis

Fixed points are given by

- $(\bar{T}_1, \bar{I}_1, \bar{V}_1) = (T_0, 0, 0)$
- $(\bar{T}_2, \bar{I}_2, \bar{V}_2) = \left(\frac{c\delta_I}{p\beta}, \frac{\sigma c(p\beta T_0 - c\delta_I)}{p\beta(p\beta T_0 + \sigma c)}, \frac{p}{c}\bar{I}\right)$

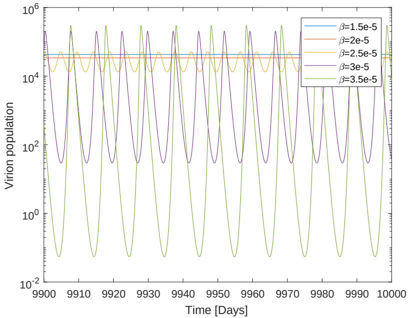
Stability of these fixed points is again dependent on $R_0 = p\beta T_0/(\delta_I c)$. What happens when these parameters are varied further?

Stability analysis

Fixed points are given by

- $(\bar{T}_1, \bar{I}_1, \bar{V}_1) = (T_0, 0, 0)$
- $(\bar{T}_2, \bar{I}_2, \bar{V}_2) = \left(\frac{c\delta_I}{p\beta}, \frac{\sigma c(p\beta T_0 - c\delta_I)}{p\beta(p\beta T_0 + \sigma c)}, \frac{p}{c}\bar{I} \right)$

Stability of these fixed points is again dependent on $R_0 = p\beta T_0/(\delta_I c)$. What happens when these parameters are varied further?

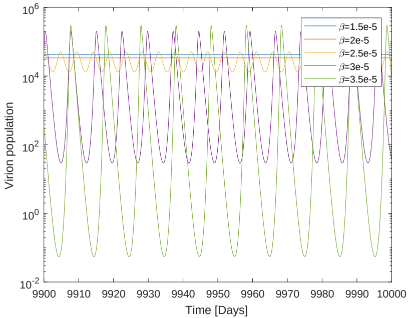


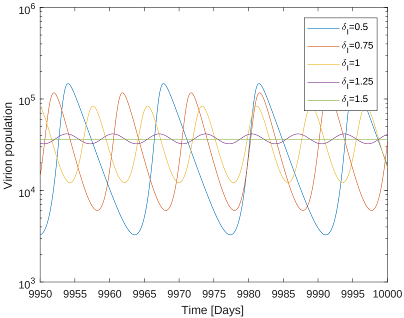
Stability analysis

Fixed points are given by

- $(\bar{T}_1, \bar{I}_1, \bar{V}_1) = (T_0, 0, 0)$
- $(\bar{T}_2, \bar{I}_2, \bar{V}_2) = \left(\frac{c\delta_I}{p\beta}, \frac{\sigma c(p\beta T_0 - c\delta_I)}{p\beta(p\beta T_0 + \sigma c)}, \frac{p}{c}\bar{I} \right)$

Stability of these fixed points is again dependent on $R_0 = p\beta T_0/(\delta_I c)$. What happens when these parameters are varied further?





Phase planes

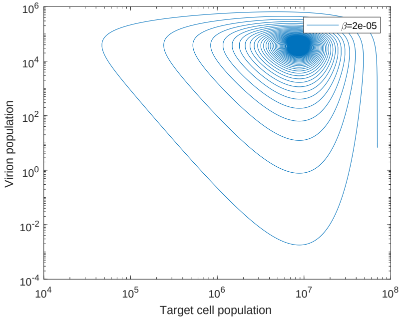


Figure: Stable fixed point

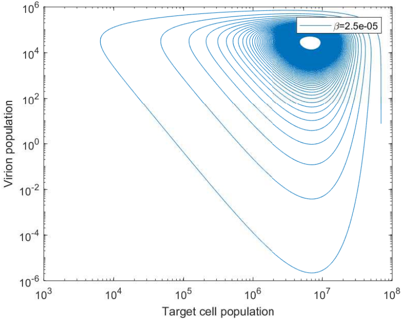


Figure: Stable limit cycle

Bifurcation diagrams

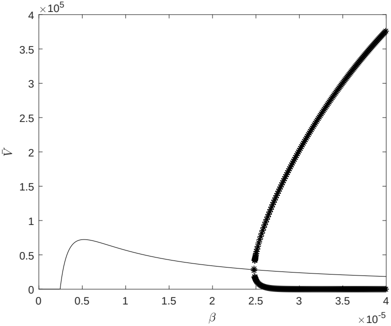


Figure: β bifurcation diagram

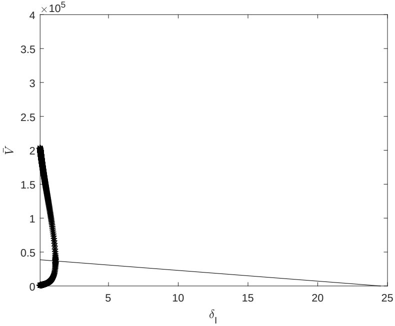


Figure: δ_I bifurcation diagram

Similar bifurcations occur for the other parameters in R_0.

Innate immune response

Further compartments of the biology of viral infections are often included. How do these compartments affect the fixed points of the model? Here we model the effects of the innate immune system.

Innate immune response

Further compartments of the biology of viral infections are often included. How do these compartments affect the fixed points of the model? Here we model the effects of the innate immune system.

The innate immune response is the first line of defence against viral infections. Innate immune response is modelled by including 3 different mechanisms

Innate immune response

Further compartments of the biology of viral infections are often included. How do these compartments affect the fixed points of the model? Here we model the effects of the innate immune system.

The innate immune response is the first line of defence against viral infections. Innate immune response is modelled by including 3 different mechanisms

1. Direct killing of infected cells by innate immune cells

Innate immune response

Further compartments of the biology of viral infections are often included. How do these compartments affect the fixed points of the model? Here we model the effects of the innate immune system.

The innate immune response is the first line of defence against viral infections. Innate immune response is modelled by including 3 different mechanisms

1. Direct killing of infected cells by innate immune cells

2. Suppression of the production of virions by infected cells

Innate immune response

Further compartments of the biology of viral infections are often included. How do these compartments affect the fixed points of the model? Here we model the effects of the innate immune system.

The innate immune response is the first line of defence against viral infections. Innate immune response is modelled by including 3 different mechanisms

1. Direct killing of infected cells by innate immune cells
2. Suppression of the production of virions by infected cells
3. Causing target cells to become resistant to infection

Including these mechanisms into the TIV model gives us the following set of equations

$$
\begin{aligned}
\frac{dT}{dt} &= \sigma(T+R)\left(1-\frac{T+R+I}{T_0}\right) - \beta TV + \rho R - \phi FT,\\
\frac{dI}{dt} &= \beta TV - \delta_I I - \kappa IF,\\
\frac{dR}{dt} &= \phi FT - \rho R,\\
\frac{dV}{dt} &= \frac{p}{1+sF} I - cV,\\
\frac{dF}{dt} &= qI - dF.
\end{aligned}
$$

Including these mechanisms into the TIV model gives us the following set of equations

$$\begin{aligned}
\frac{dT}{dt} &= \sigma(T+R)\left(1-\frac{T+R+I}{T_0}\right)-\beta TV+\rho R-\phi FT,\\
\frac{dI}{dt} &= \beta TV-\delta_I I-\kappa IF,\\
\frac{dR}{dt} &= \phi FT-\rho R,\\
\frac{dV}{dt} &= \frac{p}{1+sF}I-cV,\\
\frac{dF}{dt} &= qI-dF.
\end{aligned}$$

- κ controls killing of infected cells
- s controls the strength of virion suppression
- ϕ controls the creation of resistant cells

Killing of infected cells

κ varied, $\phi = s = 0$

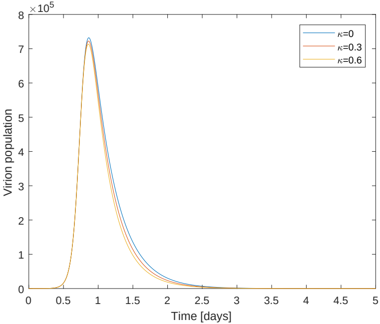


Figure: Initial transient

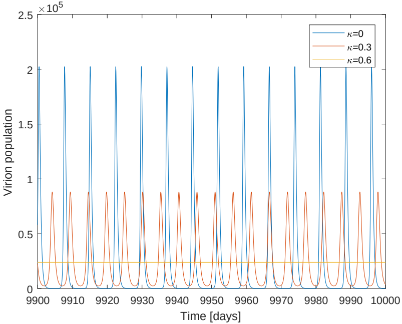


Figure: Long term behaviour

Suppression of virion production

s varied, $\phi = \kappa = 0$

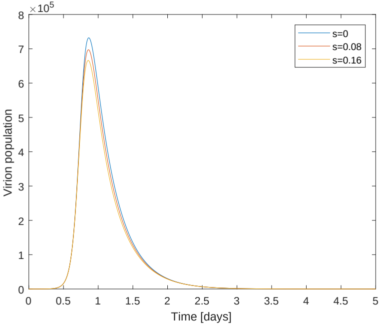


Figure: Initial transient

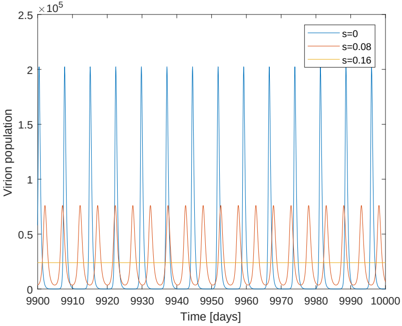


Figure: Long term behaviour

Creation of virus resistant cells

ϕ varied, $\kappa = s = 0$

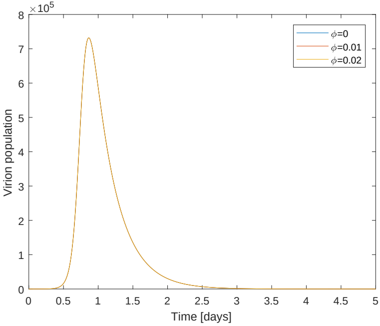


Figure: Initial transient

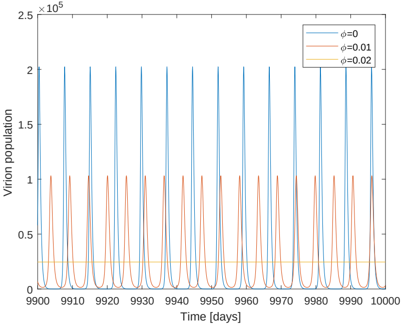


Figure: Long term behaviour

Bifurcation diagrams: κ

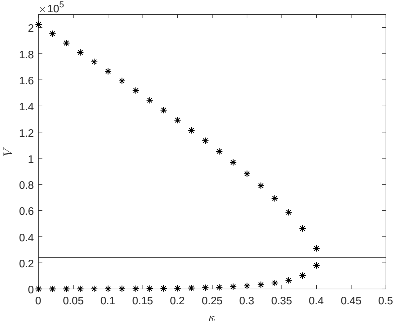


Figure: κ small

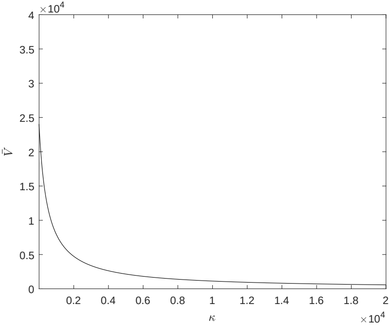


Figure: κ large

Bifurcation diagrams: s

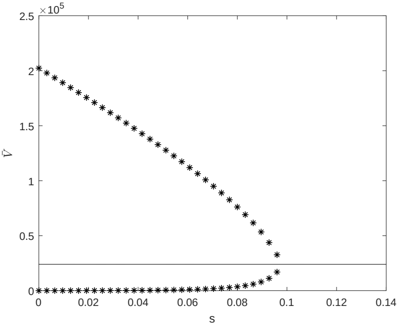


Figure: s small

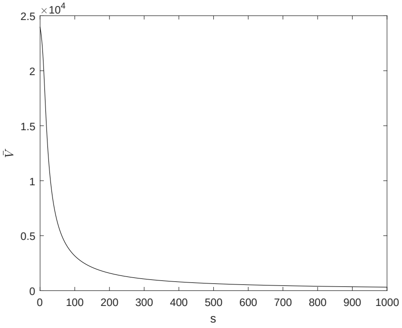


Figure: s large

Bifurcation diagrams: ϕ

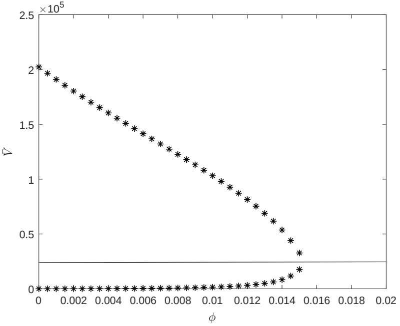


Figure: ϕ small

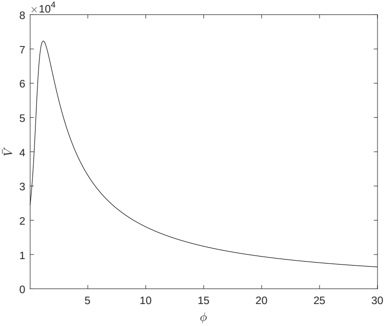


Figure: ϕ large

- Hopf bifurcations with respect to κ, s and ϕ
- Virus tends to zero as parameters get large
- Inclusion of resistant cells initially increases fixed point

Summary

Summary

- The TIV model and R_0 dependence

Summary

- The TIV model and R_0 dependence
- Introduction of target cell regrowth

Summary

- The TIV model and R_0 dependence
- Introduction of target cell regrowth
- Hopf bifurcations and the emergence of stable limit cycles

Summary

- The TIV model and R_0 dependence
- Introduction of target cell regrowth
- Hopf bifurcations and the emergence of stable limit cycles
- Inclusion of innate immunity compartment

Summary

- The TIV model and R_0 dependence
- Introduction of target cell regrowth
- Hopf bifurcations and the emergence of stable limit cycles
- Inclusion of innate immunity compartment
- Dampening effect the innate immune compartment has on oscillations

Amber M. Smith and Alan S. Perelson. "Influenza A virus infection kinetics: quantitative data and models". In: *WIREs Systems Biology and Mediciney* 8 (2011). DOI: 10.1002/wsbm.129.

Prasith Baccam et al. "Kinetics of Influenza A Virus Infection in Humans". In: *Journal of Virology* 80.15 (2006), pp. 7590–7599. DOI: 10.1128%2FJVI.01623-05.

Martin A. Nowak and Robert M. May. *Virus Dynamics*. Great Clarendon St, Oxford: Oxford University Press, 2000.

Pengxing Cao et al. "Innate Immunity and the Inter-exposure Interval Determine the Dynamics of Secondary Influenza Virus Infection and Explain Observed Viral Hierarchies". In: *PLoS Computational Biology* 28 (2015). DOI: 10.1371/journal.pcbi.1004334.

Thank you for listening!