Exploring differential equation models of the HIV infection

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Introduction

Understanding HIV

According to estimates by WHO and UNAIDS, 35 million people were living with HIV globally at the end of 2013. That same year, some 2.1 million people became newly infected, and 1.5 million died of AIDS-related causes.

Understanding HIV

Why HIV?

- Math and Biology

Understanding HIV

Why HIV?

- Math and Biology

- AIDS epidemic

Understanding HIV

Why HIV?

- Math and Biology
- AIDS epidemic
- Mathematical Modeling

Understanding HIV

Why HIV?

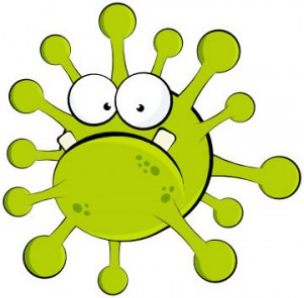
- Math and Biology
- AIDS epidemic
- Mathematical Modeling
- Differential Equations

Understanding HIV

What is HIV?

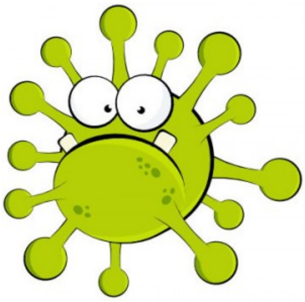
Definition

A *virus* is a small infectious agent that replicates only inside the living cells of other organisms.



Understanding HIV

What is HIV?



Definition

A *virus* is a small infectious agent that replicates only inside the living cells of other organisms.

- Host

Understanding HIV

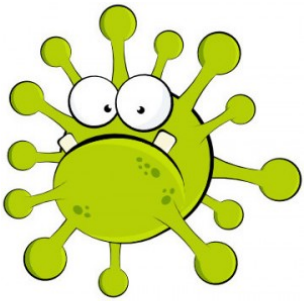
What is HIV?

Definition

A *virus* is a small infectious agent that replicates only inside the living cells of other organisms.

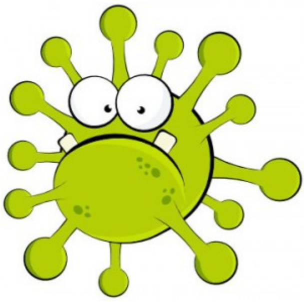
- Host

- Immune System



Understanding HIV

What is HIV?



Definition

A *virus* is a small infectious agent that replicates only inside the living cells of other organisms.

- Host
- Immune System
- AIDs

Simple HIV Dynamic Model

$$\frac{dV}{dt} = P - cV \tag{1}$$

- V is the virus concentration
- t represents time in days
- P is some function representing the rate of the virus production, here we assume is some constant
- c is the clearance rate constant
- Let $V(0) = V_0$, where V_0 is the initial virus concentration

Simple HIV Dynamic Model

$$\frac{dV}{dt} = P - cV$$

Simple HIV Dynamic Model

Definition

A continuous model has a *steady state* or *equilibrium* at V_s if $\frac{dV}{dt} = f(V_s) = 0$.

Simple HIV Dynamic Model

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Simple HIV Dynamic Model

$$\frac{dV}{dt} = P - cV$$

Find the steady state by setting equal to 0 and solving for V_s

Simple HIV Dynamic Model

$$\frac{dV}{dt} = P - cV$$

Find the steady state by setting equal to 0 and solving for V_s
Then

$$P - cV_s = 0$$

$$V_s = \frac{P}{c}$$

Simple HIV Dynamic Model

$$\frac{dV}{dt} = P - cV$$

Find the steady state by setting equal to 0 and solving for V_s
Then

$$P - cV_s = 0$$

$$V_s = \frac{P}{c}$$

$$V(t) = V_s = \frac{P}{c}$$

Simple HIV Dynamic Model

Theorem

A general solution to system (1) is

$$V = \frac{P - (P - cV_0)e^{-ct}}{c}$$

Simple HIV Dynamic Model

Example

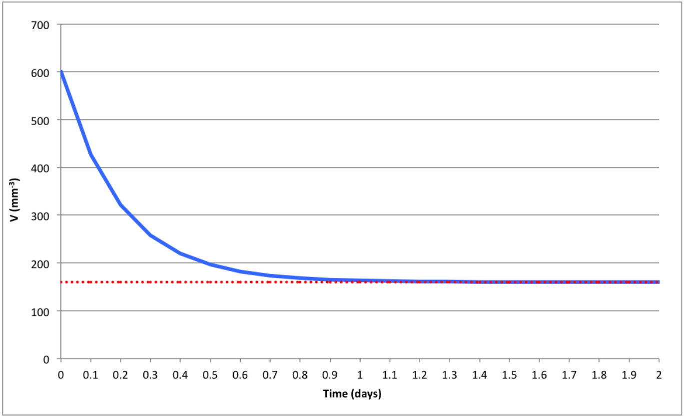
Let $c = 5 \text{ day}^{-1}$, $P = 800 \text{ mm}^3\text{day}^{-1}$, $V(0) = 600 \text{ mm}^{-3}$

$$V = \frac{P - (P - cV_0)e^{-ct}}{c}$$

Simple HIV Dynamic Model

Example

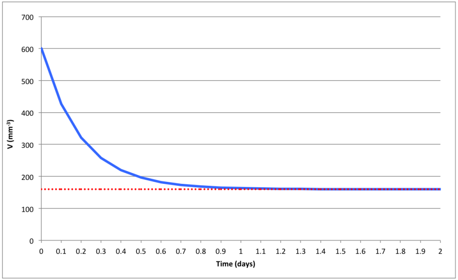
Let $c = 5\ \text{day}^{-1}$, $P = 800\ \text{mm}^3\text{day}^{-1}$, $V(0) = 600\ \text{mm}^{-3}$



Simple HIV Dynamic Model

Solution and Stability Discussion

$$V = \frac{P - (P - cV_0)e^{-ct}}{c}$$

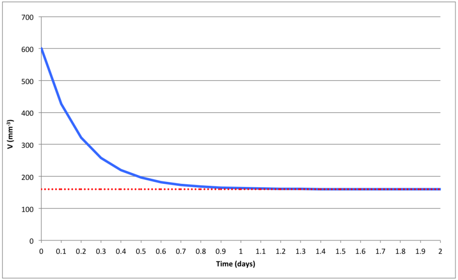


$$t \to \infty ?$$

Simple HIV Dynamic Model

Solution and Stability Discussion

$$V = \frac{P - (P - cV_0)e^{-ct}}{c}$$



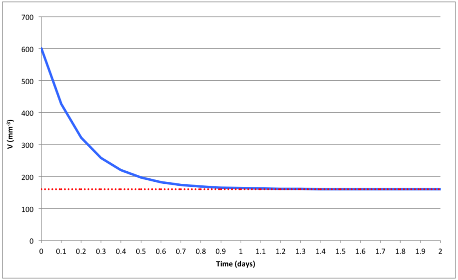
$$t \to \infty?$$

$$\frac{P}{c} = \frac{800}{5} = 160 \ \mathbf{mm}^{-3}$$

Simple HIV Dynamic Model

Solution and Stability Discussion

$$V = \frac{P - (P - cV_0)e^{-ct}}{c}$$



$$t \to \infty?$$

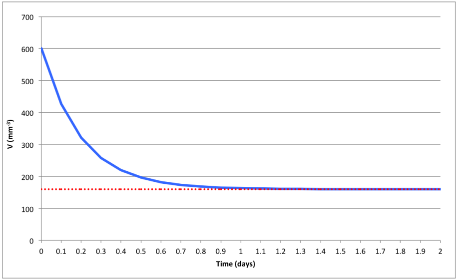
$$\frac{P}{c} = \frac{800}{5} = 160 \ \mathbf{mm}^{-3}$$

Increase P? Increase c?

Simple HIV Dynamic Model

Solution and Stability Discussion

$$\frac{dV}{dt} = c(\frac{P}{c} - V)$$

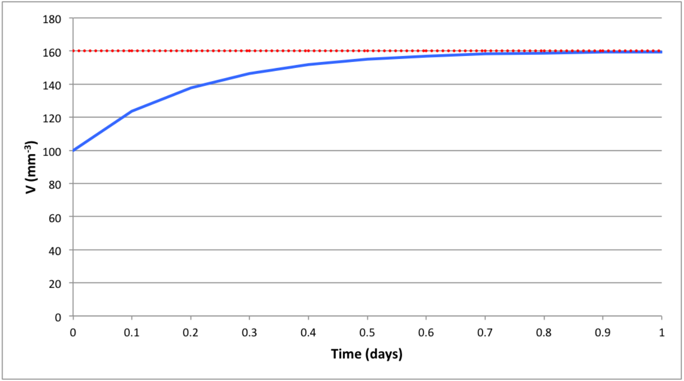


$$\frac{dV}{dt} < 0$$

Simple HIV Dynamic Model

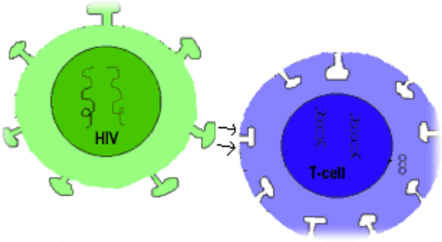
Solution and Stability Discussion

$$V(0) = 100mm^{-3} < \frac{P}{c} = 160mm^{-3}$$



Population Dynamics

What are CD4+ T cells?



Population Dynamics

$$\dot{T} = s - dT + aT(1 - \frac{T}{T_{max}}) \quad (2)$$

- s is the rate at which new T cells are made
- d is the death rate
- a is the maximum proliferation rate
- T_{max} is the T cell population density at which proliferation shuts off
- Let $T(0) = T_0$, where T_0 is the initial uninfected CD4+ T-cell population size

Population Dynamics

Find the steady state by setting equal to 0 and solving for T

$$\begin{aligned}\dot{T} &= s - dT + aT(1 - \frac{T}{T_{max}}) \\ &= s + (a - d)T - \frac{a}{T_{max}}T^2\end{aligned}$$

Population Dynamics

Find the steady state by setting equal to 0 and solving for T

$$\begin{aligned}\dot{T} &= s - dT + aT(1 - \frac{T}{T_{max}}) \\ &= s + (a-d)T - \frac{a}{T_{max}}T^2\end{aligned}$$

Using the quadratic formula

$$\begin{aligned}T &= \frac{(-a+d) \pm \sqrt{(a-d)^2 + \frac{4as}{T_{max}}}}{\frac{-2a}{T_{max}}} \\ &= \frac{-T_{max}}{2a}\left[(-a+d) \pm \sqrt{(a-d)^2 + \frac{4as}{T_{max}}}\right]\end{aligned}$$

Population Dynamics

$$T^{+} = \frac{T_{max}}{2a}\left[(a-d) + \sqrt{(a-d)^2 + \frac{4as}{T_{max}}}\right]$$

$$T^{-} = \frac{T_{max}}{2a}\left[(a-d) - \sqrt{(a-d)^2 + \frac{4as}{T_{max}}}\right]$$

Population Dynamics

Theorem

A general solution to system (2) is

$$T = \frac{T^{-} - T^{+}Ae^{Kt}}{1 - Ae^{Kt}}$$

where $A = \frac{T_0 - T^{+}}{T_0 - T^{-}}$ *and* $K = -\frac{a}{T_{max}}(T^{-} - T^{+})$

Population Dynamics

Proof:

$$\frac{dT}{dt} = -\frac{a}{T_{max}}(T - T^{-})(T - T^{+})$$

Population Dynamics

Proof:

$$\frac{dT}{dt} = -\frac{a}{T_{max}}(T - T^-)(T - T^+)$$

$$\int \frac{dT}{(T - T^-)(T - T^+)} = \int -\frac{a}{T_{max}}\mathrm{d}t$$

Population Dynamics

Proof:

$$\frac{dT}{dt} = -\frac{a}{T_{max}}(T - T^-)(T - T^+)$$

$$\int \frac{dT}{(T - T^-)(T - T^+)} = \int -\frac{a}{T_{max}}\mathrm{d}t$$

$$\frac{1}{(T^- - T^+)}\left[\int \frac{dT}{(T - T^-)} - \int \frac{dT}{(T - T^+)}\right] = -\frac{a}{T_{max}}t + c$$

where c is some constant

Population Dynamics

Proof cont'd:

$$\ln\left|\frac{T - T^-}{T - T^+}\right| = (T^- - T^+)(-\frac{a}{T_{max}}t + c)$$

Population Dynamics

Proof cont'd:

$$\ln\left|\frac{T - T^-}{T - T^+}\right| = (T^- - T^+)(-\frac{a}{T_{max}}t + c)$$

Let $K = -\frac{a}{T_{max}}(T^- - T^+)$.

Population Dynamics

Proof cont'd:

$$\ln\left|\frac{T - T^-}{T - T^+}\right| = (T^- - T^+)(-\frac{a}{T_{max}}t + c)$$

Let $K = -\frac{a}{T_{max}}(T^- - T^+)$.
Then

$$\left|\frac{T - T^-}{T - T^+}\right| = e^{Kt+C}$$

where C is some constant

Population Dynamics

Proof cont'd:

$$\ln\left|\frac{T-T^-}{T-T^+}\right| = (T^- - T^+)(-\frac{a}{T_{max}}t + c)$$

Let $K = -\frac{a}{T_{max}}(T^- - T^+)$.
Then

$$\left|\frac{T-T^-}{T-T^+}\right| = e^{Kt+C}$$

where C is some constant

$$\frac{T-T^-}{T-T^+} = Ae^{Kt}$$

where A is some constant

Population Dynamics

Proof cont'd:

$$\frac{T - T^-}{T - T^+} = Ae^{Kt}$$

Let $t = 0$ such that $T(0) = T_0$ and solve for A. Then

$$\frac{T_0 - T^-}{T_0 - T^+} = Ae^{K(0)}$$

Population Dynamics

Proof cont'd:

$$\frac{T - T^-}{T - T^+} = Ae^{Kt}$$

Let $t = 0$ such that $T(0) = T_0$ and solve for A. Then

$$\frac{T_0 - T^-}{T_0 - T^+} = Ae^{K(0)}$$

$$A = \frac{T_0 - T^-}{T_0 - T^+}$$

Population Dynamics

Proof cont'd:

$$\frac{T - T^-}{T - T^+} = Ae^{Kt}$$

Let $t = 0$ such that $T(0) = T_0$ and solve for A. Then

$$\frac{T_0 - T^-}{T_0 - T^+} = Ae^{K(0)}$$

$$A = \frac{T_0 - T^-}{T_0 - T^+}$$

Then solving for T we obtain

$$T = \frac{T^- - T^+ Ae^{Kt}}{1 - Ae^{Kt}}$$

Population Dynamics

Example

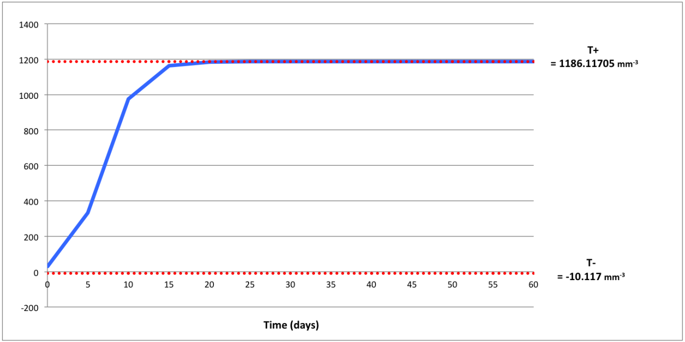
Let $T_{max} = 1200$ mm^{3}day^{-1}, $a = 0.5$ day^{-1}, $d = 0.01$ day $^{-1}$, $s = 5$ day^{-1}mm^{-1}

$$T = \frac{T^{-} - T^{+} A e^{Kt}}{1 - A e^{Kt}}$$

Population Dynamics

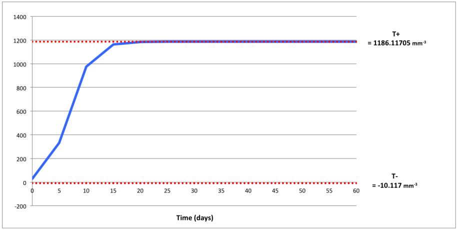
Example

Let $T_0 = 30$ mm^{-3} $T_{max} = 1200$ mm^{3}day^{-1}, $a = 0.5$ day^{-1}, $d = 0.01$ day $^{-1}$, $s = 5$ day^{-1}mm^{-1}



Population Dynamics

Solution and Stability Discussion

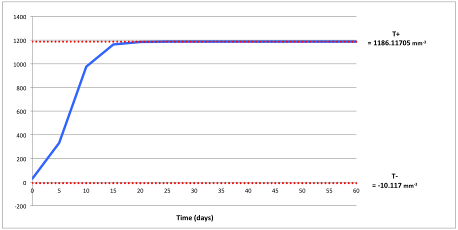


$$T = \frac{T^- - T^+ A e^{Kt}}{1 - A e^{Kt}}$$

$$t \to \infty ?$$

Population Dynamics

Solution and Stability Discussion



$$T = \frac{T^- - T^+ A e^{Kt}}{1 - A e^{Kt}}$$

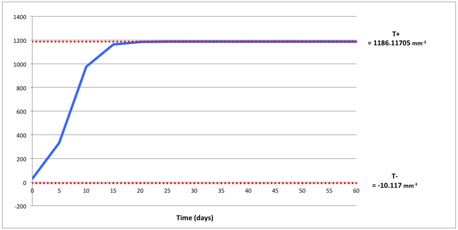
$$t \to \infty ?$$

$$\lim_{t \to \infty} \frac{-10.117 + 41.5141 e^{0.98t}}{1 + 0.035 e^{0.98t}} = 1186.11705 mm^{-3}$$

$$\lim_{t \to -\infty} \frac{-10.117 + 41.5141 e^{0.98t}}{1 + 0.035 e^{0.98t}} = -10.117 mm^{-3}$$

Population Dynamics

Solution and Stability Discussion



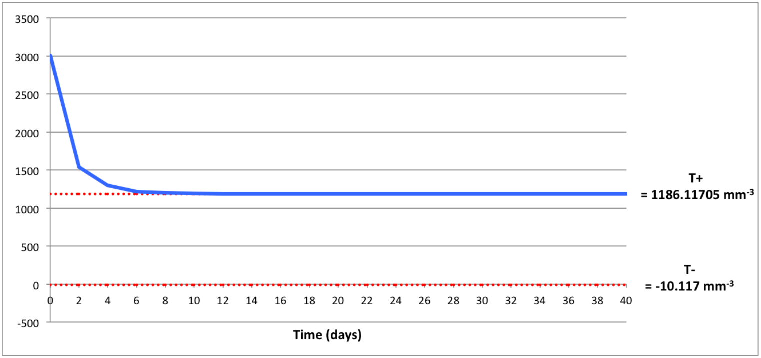
$$\frac{dT}{dt} = -\frac{a}{T_{max}}(T - T^{-})(T - T^{+})$$

$$\frac{dT}{dt} > 0$$

Population Dynamics

Solution and Stability Discussion

$$T(0) = 3000mm^{-3}$$



Model of HIV infection of CD4+ T-cells with cure rate

A cure rate?

Model of HIV infection of CD4+ T-cells with cure rate

$$\left\{\begin{array}{lcl}\dot{T} & = & s - dT + aT(1 - \frac{T}{T_{max}}) - \beta TV + \rho I,\\ \dot{I} & = & \beta TV - \delta I - \rho I,\\ \dot{V} & = & qI - cV,\end{array}\right. \tag{3}$$

- T = target cells, I = infected cells, V = viral load of virions
- ρ is the rate of "cure"
- Rate of infection is given by βTV, with β being the infection rate constant
- δ is the death rate of infective cells,
- q is the reproductively rate of infected cells

Diagram of Mathematical Model

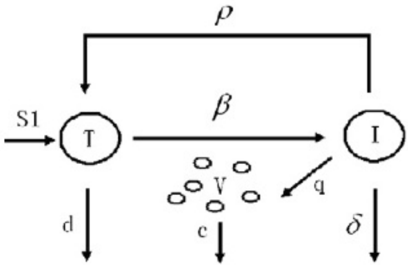


Figure: Diagram representation of the mathematical model for HIV treatment.

Model of HIV infection of CD4+ T-cells with cure rate

$$\begin{cases} \dot{T} & = & s - dT + aT(1 - \frac{T}{T_{max}}) - \beta TV + \rho I, \\ \dot{I} & = & \beta TV - \delta I - \rho I, \\ \dot{V} & = & qI - cV \end{cases}$$

Notice that system (3) must have $T(0) \geq 0$, $I(0) \geq 0$, $V(0) \geq 0$.

Find the steady state by setting equal to 0 and solving for T, I, and V.

Model of HIV infection of CD4+ T-cells with cure rate

Theorem

The nonnegative equilibria of system (3) are $\hat{E} = (\hat{T}, 0, 0)$ *and* $\bar{E} = (\bar{T}, \bar{I}, \bar{V})$ *where* $\hat{T} = \frac{T_{max}}{2a}(a - d + \sqrt{(a-d)^2 + \frac{4as}{T_{max}}})$, $\bar{T} = \frac{(\delta-\rho)\frac{c}{q}}{\beta}$, $\bar{I} = \frac{1}{\delta}[s - dT + aT(1 - \frac{T}{T_{max}})]$, $\bar{V} = \frac{q}{c}\bar{I}$

[1]

[1] Zhou, Xueyong, Song, Xinyu, and Shi, Xiangyun. "A differential equation model of HIV infection of CD4+ T-cells with cure rate." J. Math. Anal. Appll. 342 (2008): 1342-1355.

Jacobian Matrix

$$\frac{dT}{dt} = s - dT + aT(1 - \frac{T}{T_{max}}) - \beta TV + \rho I$$

$$\frac{dI}{dt} = \beta TV - \delta I - \rho I$$

$$\frac{dV}{dt} = qI - cV$$

Jacobian Matrix

$$\frac{dT}{dt} = s - dT + aT(1 - \frac{T}{T_{max}}) - \beta TV + \rho I$$
$$\frac{dI}{dt} = \beta TV - \delta I - \rho I$$
$$\frac{dV}{dt} = qI - cV$$

$$J = \begin{pmatrix} a - d - \frac{2aT}{T_{max}} - \beta V & \rho & -\beta T \\ \beta V & -(\delta + \rho) & \beta T \\ 0 & -q & \gamma + c \end{pmatrix}$$

Example with cure rate

Example

Table 1
Variables and parameters for viral spread

Parameters and variables		Values
Dependent variables		
T	Uninfected CD4$^+$ T-cell population size	1000 mm^{-3}
I	Infected CD4$^+$ T-cell density	0
V	Initial density of HIV RNA	10^{-3} mm^{-3}
Parameters and constants		
s	Source term for uninfected CD4$^+$ T-cells	5 day^{-1} mm^{-3}
d	Natural death rate of CD4$^+$ T-cells	0.01 day^{-1}
a	Growth rate of CD4$^+$ T-cell population	0.5 day^{-1}
T_{max}	Maximal population level of CD4$^+$ T-cells	1200 mm^3 day^{-1}
β	Rate CD4$^+$ T-cells become infected with virus	0.0002 mm^{-3}
ρ	Rate of cure	0.01 day^{-1}
δ	Blanket death rate of infected CD4$^+$ T-cells	1 day^{-1}
q	Reproductively rate of the infected CD4$^+$ T-cells	800 mm^3 day^{-1}
c	Death rate of free virus	5 day^{-1}

2

[2] Zhou, Xueyong, Song, Xinyu, and Shi, Xiangyun. "A differential equation model of HIV infection of CD4+ T-cells with cure rate." J. Math. Anal. Appll. 342 (2008): 1342-1355.

Example with cure rate

Example

$$\bar{E} = (\bar{T}, \bar{I}, \bar{V})$$

where $\bar{T} = \frac{(\delta - \rho)\frac{c}{q}}{\beta}$, $\bar{I} = \frac{1}{\delta}[s - dT + aT(1 - \frac{T}{T_{max}})]$, $\bar{V} = \frac{q}{c}\bar{I}$

$$\bar{E} = (31.5625000, 20.05054525, 3208.087240)$$

with initial conditions $T(0) = 30$, $I(0) = 400$, $V(0) = 600$.

Jacobian Matrix

$\bar{E} = (31.5625000, 20.05054525, 3208.087240)$

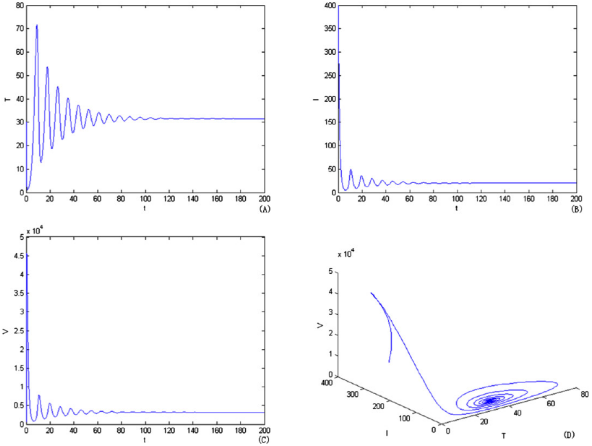
$$J = \begin{pmatrix} -0.1177920 & 0.01 & -0.0063125 \\ 0.6416174 & -1.01 & 0.0063125 \\ 0 & 800 & -5 \end{pmatrix}$$

$\lambda_1 = -6.099892570,\ \lambda_2 = -0.04401348053 - 0.7238701657I,$
$\lambda_3 = -0.04401348053 + 0.7238701657I$

Example with cure rate

$\bar{E}(31.56250000, 20.05054525, 3208.087240)$ with $T(0) = 30,\ I(0) = 400,\ V(0) = 600$

Example



[3]

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[3] Zhou, Xueyong, Song, Xinyu, and Shi, Xiangyun. "A differential equation model of HIV infection of CD4+ T-cells with cure rate." J. Math. Anal. Appll. 342 (2008): 1342-1355.

Conclusions

- Differential Equations

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- Steady State

Conclusions

- Differential Equations
- Steady State
- Simple to Complicated Models

Conclusions

- Differential Equations
- Steady State
- Simple to Complicated Models
- Tools for studying behavior

Acknowledgements

- Professor Zhu
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- Supporting friends and family

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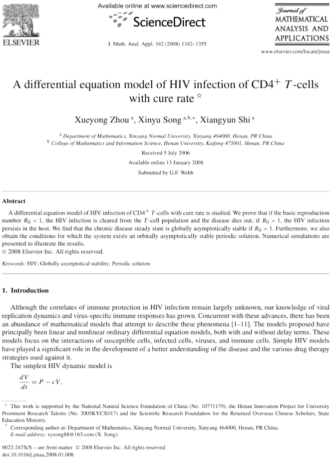

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A differential equation model of HIV infection of $CD4^+$ T-cells with cure rate ☆

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Abstract

A differential equation model of HIV infection of $CD4^+$ T-cells with cure rate is studied. We prove that if the basic reproduction number $R_0 < 1$, the HIV infection is cleared from the T-cell population and the disease dies out; if $R_0 > 1$, the HIV infection persists in the host. We find that the chronic disease steady state is globally asymptotically stable if $R_0 > 1$. Furthermore, we also obtain the conditions for which the system exists an orbitally asymptotically stable periodic solution. Numerical simulations are presented to illustrate the results.

Keywords: HIV; Globally asymptotical stability; Periodic solution

1. Introduction

Although the correlates of immune protection in HIV infection remain largely unknown, our knowledge of viral replication dynamics and virus-specific immune responses has grown. Concurrent with these advances, there has been an abundance of mathematical models that attempt to describe these phenomena [1–11]. The models proposed have principally been linear and nonlinear ordinary differential equation models, both with and without delay terms. These models focus on the interactions of susceptible cells, infected cells, viruses, and immune cells. Simple HIV models have played a significant role in the development of a better understanding of the disease and the various drug therapy strategies used against it.

The simplest HIV dynamic model is

$$\frac{dV}{dt} = P - cV,$$

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0022-247X/$ – see front matter
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Bibliography

·David Brown - Washington Post Staff Writer. "Model Predicts Halt to Africa's AIDS Epidemic." The Washington Post. N.p., 26 Nov. 2008. Web. 16 Mar. 2015.

·Eaton, Jeffrey W., Leigh F. Johnson, Joshua A. Salomon, Till Brnighausen. "HIV Treatment as Prevention: Systematic Comparison of Mathematical Models of the Potential Impact of Antiretroviral Therapy on HIV Incidence in South Africa." Ed. John Bartlett. PLoS Medicine 9.7 (2012): E1001245. Web.

·Keeling, Matthew James., and Pejman Rohani. "Introduction to Simple Epidemic Models." Modeling Infectious Diseases in Humans and Animals. Princeton: Princeton UP, 2008. 16-21. Print.

·Zhou, Xueyong, Song, Xinyu, and Shi, Xiangyun. "A differential equation model of HIV infection of CD4+ T-cells with cure rate." J. Math. Anal. Appll. 342 (2008): 1342-1355.

Questions/Comments

Thank you!