Mathematical Models of HIV and Immune Response

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Outlines

- Basic Virus Model

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- Virus Evolution and Disease Progression Model

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- 2-D HIV disease progression model-2

What is a Virus?

Virus:

- A virus is basically a microorganism wrapped up in a protein coat.
- It reproduces inside a living cell by using cell's metabolic machinery.
- It enters a cell using cell's receptor and the viral genome(DNA or RNA) is exposed in the cell.
- Newly generated virus particles leave the cell.

Reference: Killer Cell Dynamics(by Dominik Wodarz)

What is Immune Response?

Immune Responses:

- Immune responses can be divided into two branches: (i) Innate or nonspecific responses and (ii) specific, adaptive responses.
- Innate immune responses are unable to specifically recognize the physical structure of the pathogen.
- Specific immune cells can recognize pathogen protein and start to divide.
- They increase in number and fight effectively the pathogen.

Reference: Killer Cell Dynamics(by Dominik Wodarz)

Antigen and Epitope

Antigen: Antigen is a substance that is able to induce the generation of a specific immune response.

Epitope: The site of an antigen that is actually recognized by the immune cell receptor is called an epitope. The same pathogen can have various epitopes, each of which is recognized by a separate specific immune cell.

Reference: Killer Cell Dynamics(by Dominik Wodarz)

Virus-Cell Reaction

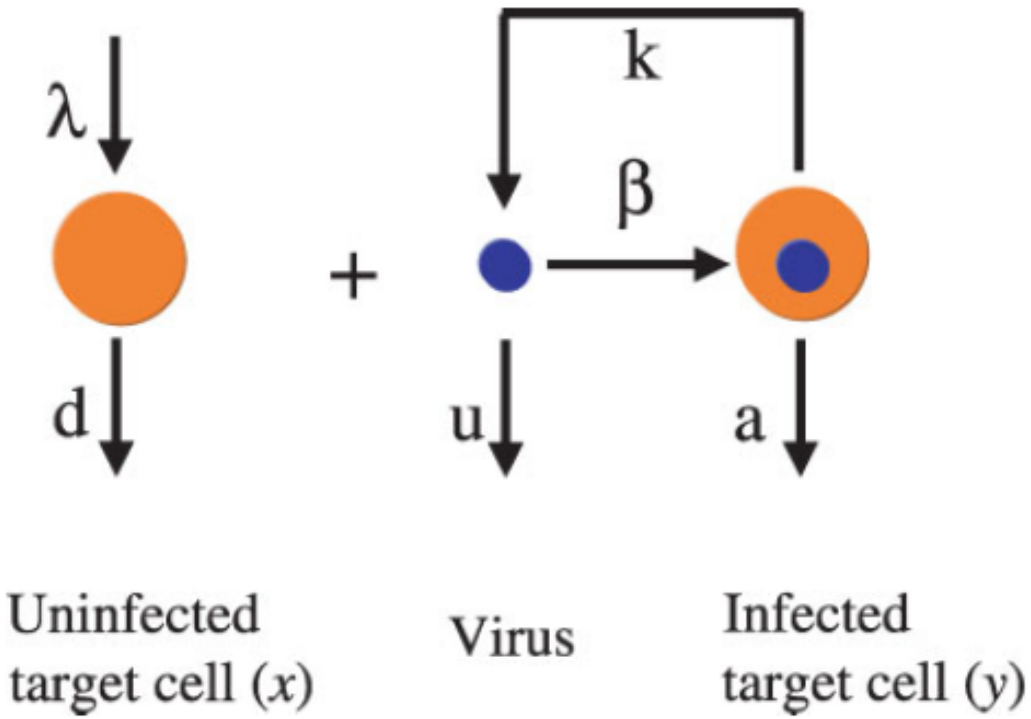


Figure: virus-cell reaction

Reference: Mathematical models of HIV pathogenesis and treatment.

Basic Virus Model

$$\begin{cases} \dfrac{dx}{dt} = \lambda - dx - \beta xv \\ \dfrac{dy}{dt} = \beta xv - ay \\ \dfrac{dv}{dt} = ky - uv \end{cases} \tag{1}$$

Here,

$x =$ uninfected cell
$y =$ infected target cell
$v =$ virus

Basic Virus Model Continued

Initial Condition:
Before infection, $y = 0, v = 0$ and consequently, $x = \frac{\lambda}{d}$.
So $E_0 = (x_0, y_0, v_0) = (\lambda/d, 0, 0)$ is an equilibrium point.

Basic Reproduction Number: The number of newly infected cells that arise from one infected cell when almost all cells are uninfected is the basic reproduction number. It is given by,

$$\mathcal{R}_0 = \frac{\beta\lambda k}{(adu)}$$

Basic Virus Model Continued

- If $\mathcal{R}_0 < 1$ then the virus population fails to spread and goes extinct.
- If $\mathcal{R}_0 > 1$ then infection can spread and the system converges to the positive equilibrium given by,

$$E_1 = \left(x = \frac{\lambda}{d\mathcal{R}_0}, y = \frac{(\mathcal{R}_0 - 1)du}{\beta k}, v = \frac{(\mathcal{R}_0 - 1)d}{\beta} \right)$$

Characteristics of HIV

- HIV is not latent during the asymptomatic phase of the infection.
- Patients take on average 10 years to progress from infection to AIDS.
- During the early stages of infection, virus population are relatively homogeneous but during the course of progression, they greatly diversifies.
- Virus adaptation and evolution results in emergence of strains that are more damaging to the immune system.
- HIV mainly infects two types of immune cells. They are macrophages and CD4 T cells.
- HIV uses CCR5(present on macrophages and CD4 T cells) and CXCR4(moostly present on CD4 T cells) co-receptors for efficient entry into cells.
- In 50% of patients, development of AIDS is due to the emergence of X4 virus.

HIV Disease Progression Model

The following model describes antigenic escape dynamics.

$$\begin{cases} \dfrac{dv_i}{dt} = v_i(r - px_i - sz), & i = 1 \cdots n \\ \dfrac{dx_i}{dt} = kv_i - bx_i - uvx_i, & i = 1, \cdots n \\ \dfrac{dz}{dt} = k'v - bz - uvz \end{cases} \tag{2}$$

Here,

v_i =population size of virus mutant labeled i
x_i = immune response specifically directed against virus strain i
z = the group-specific immune response
$v = \sum v_i$ =the total virus population

HIV Disease Progression Model Continued

Parameters:

r = the average rate of replication of all different virus strains
p = efficacy of strain specific immune responses
k = rate at which p are evoked
s = efficacy of group specific immune responses
k' = rate at which s are evoked
b = rate at which immune response decays in the absence of further stimulation
u = ability of virus to impair immune responses

HIV Disease Progression Model Continued

The rate at which total virus population changes is obtained from equation (2).

$$\frac{dv}{dt} = v\left(r - \frac{pkv}{b+uv}D - \frac{sk'v}{b+uv}\right) \tag{3}$$

Where, $D = \sum (v_i/v)^2$ is called Simpson index(which is a inverse measure for viral diversity). D is always between 0 and 1.

HIV Disease Progression Model Continued

From equation (3), we can see that v converges to the steady state

$$v^* = \frac{rb}{sk' + pkD - ru} \tag{4}$$

We see from equation (4) that decreasing D (increasing diversity) increases the total population size and thus triggers disease progression.

HIV Disease Progression Model Continued

The model has three qualitatively different courses of infection. They are,

- If $ru > sk' + pk$, there is no asymptomatic phase and virus population immediately replicates to high levels.
- If $sk' > ru$, there is chronic infection but no disease. Here, the group-specific immune responses alone an control the virus.
- The third situation arises when $sk' + pk > ru > sk'$.

HIV Disease Progression Model Continued

Diversity Threshold:

The threshold of viral diversity is,

$$D = \frac{ru - sk'}{pk} \tag{5}$$

As soon as this threshold is exceeded, the virus population escapes from control by the immune responses and tends to arbitrarily high densities.

2-D HIV Model-1

Assumptions:

- There is only one virus strain present.
- Consider there is a combined immune response instead of group-specific and strain-specific immune responses.

2-D HIV Model-1 Continued

The Model:

$$\begin{cases} \dfrac{dv}{dt} = vr - \alpha vy \\ \dfrac{dy}{dt} = \beta v - \gamma y - \mu vy \end{cases} \tag{6}$$

Here,

$v =$ the total virus population

$y =$ the immune response

2-D HIV Model-1 Continued

Parameters:

$r =$ the rate of replication of virus population
$\alpha =$ efficacy of immune responses
$\beta =$ the rate at which α are evoked
$\gamma =$ the rate at which immune responses decay in the absence of further stimulation
$\mu =$ ability of virus to impair immune responses

2-D HIV Model-1 Continued

The followings hold for the model-1:

- Positivity of solution
- Existence and uniqueness of solution

2-D HIV Model-1 Continued

Equilibrium points:

There are two equilibrium points of this system. They are,

$EP_0 = (v_0, y_0) = (0, 0)$ and $EP_1 = (v_1, y_1) = \left(\frac{r\gamma}{\alpha\beta - r\mu}, \frac{r}{\alpha} \right)$

Jacobian:

$$J = \begin{bmatrix} r - \alpha y & -\alpha v \\ \\ \beta - \mu y & -\gamma - \mu v \end{bmatrix}$$

2-D HIV model-1 continued

Stability:

- $J(0,0)$ gives eigenvalues $\lambda_1 = r > 0$ and $\lambda_2 = -\gamma < 0$. So $(0,0)$ is a saddle point and hence unstable.
- $J(v_1, y_1) = \begin{bmatrix} 0 & \frac{-\alpha r\gamma}{\alpha\beta - r\mu} \\ \beta - \frac{\mu r}{\alpha} & \frac{-\alpha\beta\gamma}{\alpha\beta - r\mu} \end{bmatrix}$

So, $Tr(J) = \frac{-\alpha\beta\gamma}{\alpha\beta - r\mu} \begin{cases} < 0, & \text{if } \frac{\beta}{\mu} > \frac{r}{\alpha} \\ > 0, & \text{if } \frac{\beta}{\mu} < \frac{r}{\alpha} \end{cases}$

and $Det(J) = r\gamma > 0$.

2-D HIV model-1 continued

Case-I:

If $\frac{\beta}{\mu} > \frac{r}{\alpha}$, then the equilibrium point (v_1, y_1) is Locally asymptotically stable (L.A.S).

2-D HIV model-1 continued

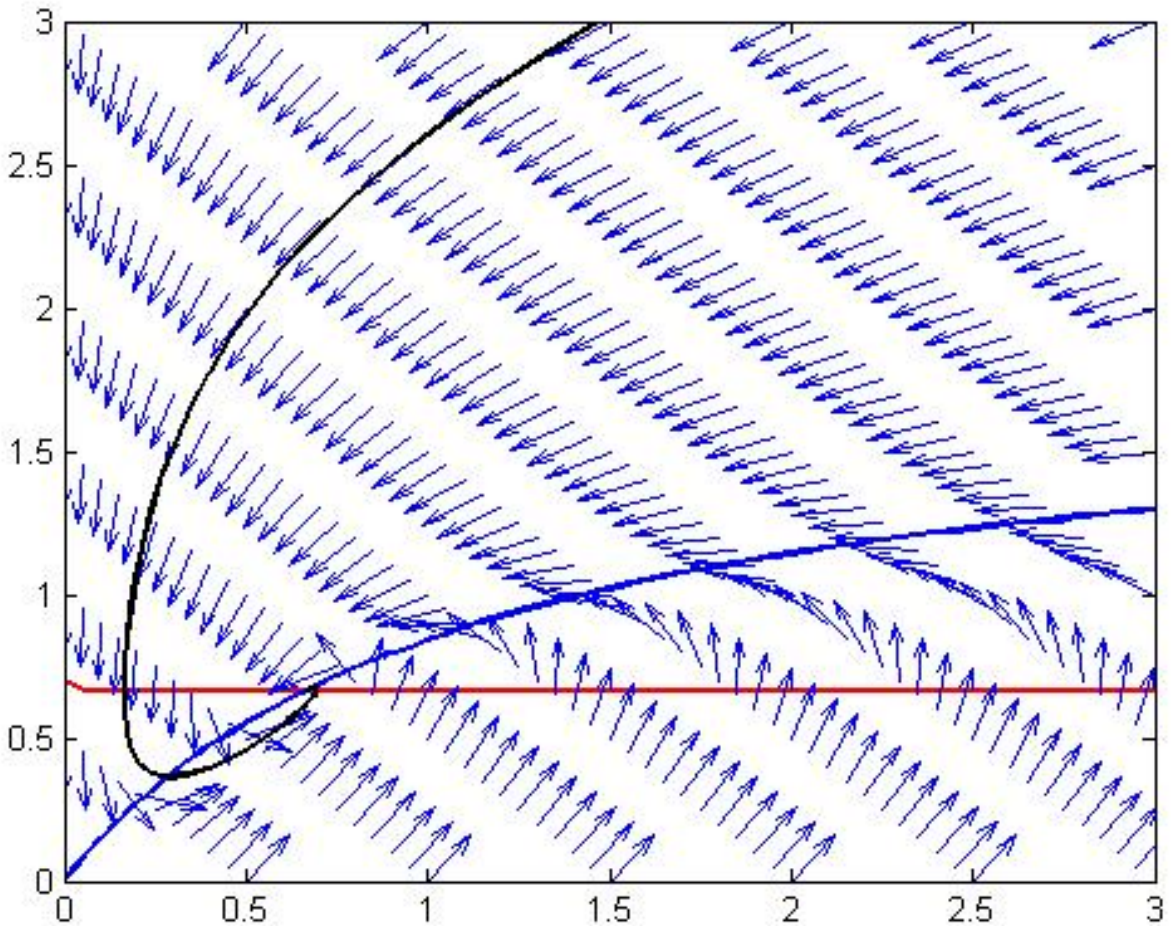
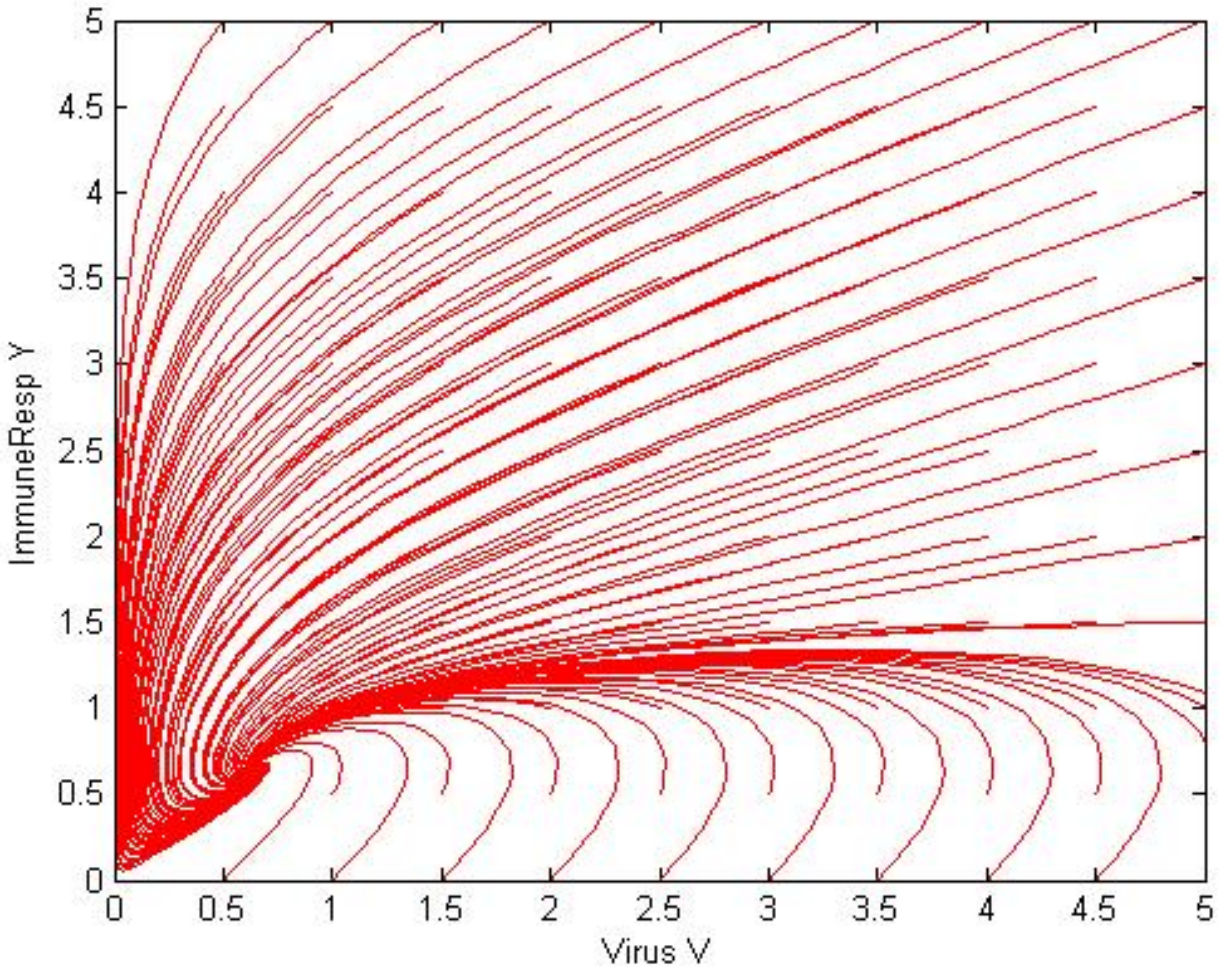


Figure: Vector fields

2-D HIV model-1 continued



2-D HIV model-1 continued

Case-II:

If $\frac{\beta}{\mu} < \frac{r}{\alpha}$, then the equilibrium point (v_1, y_1) is unstable.

2-D HIV Model-2

Assumptions:

- There is only one virus strain present.
- Virus population grow logistically
- Consider there is one type of immune response instead of group-specific and strain-specific immune responses.

2-D HIV Model-2 Continued

The Model:

$$\begin{cases} \dfrac{dv}{dt} = v\left(r\left(1-\dfrac{v}{k}\right)\right) - \alpha vy \\ \dfrac{dy}{dt} = \beta v - \gamma y - \mu vy \end{cases} \tag{7}$$

Here,

$v =$ the total virus population

$y =$ the immune response

$k =$ the carrying capacity of a cell

References

- Dominik Wodarz and Martin A. Nowak, *Mathematical models of HIV pathogenesis and treatment*. BioEssays 24:1178-1187, 2002
- Dominik Wodarz, *Killer Cell Dynamics: Mathematical and Computational Approaches to Immunology*. Springer
- Open sources on Internet.

Thank You for Your Attention