HIV Disease Progression Models

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Acknowledgement

I am greatly indebted to all the authors mentioned in the reference list. I am also greatly thankful to my course instructor Dr. Stephanie Portet for helping me in understanding the complex HIV disease progression dynamics. Section[2] and section[3] are completely dependent on the article [1]. All the figures in this article are generated by me except otherwise indicated. Besides following the materials mentioned in the reference list, I also used some open online sources like Wikipedia.

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1 Introduction

We start this article with the concepts of 'Virus' and 'Immune response'.

"A virus is usually 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. Different viruses have different genome(e.g. the viral genome of HIV is RNA). Eventually, newly generated virus particles leave the cell."

"Immune responses can be divided into two branches: (i) Innate or non-specific responses and (ii) specific, adaptive responses. Innate responses are unable to recognize the physical structure of a pathogen but they sense the presence of a virus and react accordingly. These responses interrupt the initial growth of a pathogen. On the other hand, specific immune cells can recognize the pathogen proteins and immediately start to divide and expand. They highly increase in number to efficiently fight the pathogen."

Here, we also provide the concepts of 'antigen' and 'epitope'. Antigen is a substance that is able to induce the generation of a specific immune response. However, the site of an antigen that is actually recognized by the immune cell receptor is known as an epitope. The same pathogen can have various epitopes, each of which is recognized by a distinct immune cell.

The dynamics between virus infections and immune system can be well understood by mathematical models. Mathematical models help us to originate new hypotheses and lead to their proper rational conclusions. In [1], a specific example of HIV infection has been described. The dynamics of HIV and immune system are much more complex compared to other virus-immune system dynamics.

In [1], the authors provide a three dimensional model of HIV-Immune system interactions and conclude the consequences of this interactions. In this article, we tried to simplify this model in two dimensions for the sake of phase-plane analysis of this complex dynamics. Here, we introduce two simplified versions of the model given in [1]. It is to be mentioned that these two models do not consider all the biological aspects of HIV-Immune system interactions. However, these models might be conducive to understand the first hand of the complex dynamics of HIV disease progression.

2 Basic virus model

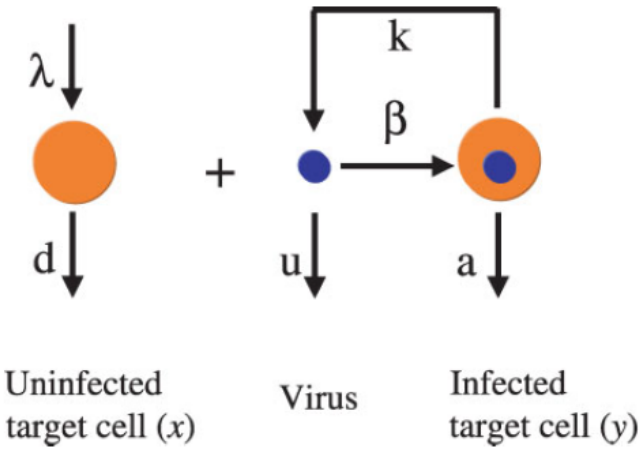


Figure 1: Virus-Cell reaction

The above picture(see [1]) illustrates the basic model of virus dynamics. Uninfected cells are produced at a constant rate λ; free virus particles infect uninfected cells at a rate β; new virus particles are produced from infected cells at a rate k. The death rates of uninfected cells, virus and infected cells are d, u and a respectively. The average life-time of an uninfected cell is $1/d$ and the average life-time of an infected cell is $1/a$. Also, the average life-time of a free virus particle is $1/u$. The total number of virus particles produced from one infected cell is given by k/a which is known as the "burst size".

When there is no infection, the host cell population dynamics is given by $x' = \lambda - dx$. So, in the absence of virus uninfected cells converges to the equilibrium value λ/d.

We combine the dynamics of host cells and virus infection to obtain the basic virus model:

$$\begin{cases} \dfrac{dx}{dt} = \lambda - dx - \beta xv \\ \dfrac{dy}{dt} = \beta xv - ay \\ \dfrac{dv}{dt} = ky - uv \end{cases} \tag{2.0.1}$$

Before infection, the abundance of uninfected cells is λ/d and $y = 0$ and

$v = 0$. Suppose that, infection occurs at time $t = 0$ with v_0 virus particles. So the initial conditions are $(x_0, y_0, v_0) = (\lambda/d, 0, v_0)$. Now, the question is whether or not virus can grow and cause an infection. The answer to this question depends on the basic reproduction number $\mathcal{R}_0$, which is defined as the number of newly infected cells that emerge from any one infected cell when almost all cells are still uninfected. Therefore, $\mathcal{R}_0$ is obtained as $\mathcal{R}_0 = \frac{k}{a} \times \frac{1}{u} \times \beta \times x = \frac{\beta\lambda k}{adu}$ [since $x = \lambda/d$].

If $\mathcal{R}_0 < 1$, then one cell on average produces less than one newly infected cell. As a result, the virus population cannot spread and the system goes to the infection free equilibrium $(\lambda/d, 0, 0)$.

On the other hand, if $\mathcal{R}_0 > 1$ then one cell on average produces more than one newly infected cell and the system goes to the positive equilibrium $(\bar{x}, \bar{y}, \bar{v})$. This equilibrium is obtained by setting $\frac{dx}{dt}, \frac{dy}{dt}, \frac{dv}{dt}$ equal to zero respectively.

$$\frac{dx}{dt} = 0 = \lambda - dx - \beta xv$$
$$\implies x = \frac{\lambda}{d + \beta v} \tag{2.0.2}$$

$$\frac{dy}{dt} = 0 = \beta xv - ay$$
$$\implies y = \frac{\beta xv}{a} \tag{2.0.3}$$

and

$$\frac{dv}{dt} = 0 = ky - uv$$
$$\implies v = \frac{ky}{u} \tag{2.0.4}$$

From equations (2.0.3) and (2.0.4) we get,

$$\bar{v} = \frac{\beta\lambda k - aud}{au\beta}$$
$$\implies \bar{v} = \frac{(\mathcal{R}_0 - 1)d}{\beta} \tag{2.0.5}$$

Using $\bar{v}$ in equation (2.0.2), we find $\bar{x} = \frac{\lambda}{d\mathcal{R}_0}$ and using both $\bar{v}$ and $\bar{x}$ in

equation (2.0.3) we get $\bar{y} = \dfrac{(\mathcal{R}_0 - 1)du}{\beta k}$.

3 Virus evolution and disease progression in individual patients

HIV is not latent during the symptomless phase of the infection, rather it continuously replicates with a high turn-over rate. This helps the virus to develop at a fast rate.

HIV disease progression is much more complex compared to other virus induced diseases. Typically, patients take on 10 years to progress from infection to AIDS. It has been observed that some HIV infected patients died within 2 years of infection and on the other hand some patients remained AIDS free for more than 15 years.

Usually, the HIV population are somewhat homogeneous during the early stages of infection and gradually it becomes diversified with respect to numerous aspects.

The main reason behind the ability of HIV to grow fast and cause disease is the variety of immune cells that it can infect. The cell types a virus can infect are collectively called cell tropism. The immune cells are generally CD4 T helper cells, macrophages and microglial cells. Macrophages and CD4 T helper cells are considered to be significant as far as the disease progression is concerned. The entry of HIV to macrophages and CD4 T cells is mediated through the co-receptors present on the cells. Two coreceptors are considered most important in this connection. One of them is CCR5 coreceptor(present on macrophages and CD4 T cells). The other one is CXCR4(present mostly on CD4 cells). Some HIV variants may specialize on CCR5(R5 tropic strains) or CXCR4(X4 tropic strains). Other HIV variants are dual tropic. The CCR5 coreceptor is used by almost all primary HIV isolates in any case of viral genetic subtype. In fact macrophages appear to be the first cells infected by HIV and most likely the source of HIV production when CD4 become depleted in a patient. In 50% of patients, emergence of X4 virus triggers the development of AIDS. The evolution of X4 tropic strains is generally promoted by the escape from immune responses.

The antigenic escape dynamics can be described by the following model.

$$\begin{cases} \dfrac{dv_i}{dt} = v_i(r - px_i - sz), \quad i = 1 \cdots n \\ \dfrac{dx_i}{dt} = kv_i - bx_i - uvx_i, \quad i = 1, \cdots n \\ \dfrac{dz}{dt} = k'v - bz - uvz \end{cases} \tag{3.0.1}$$

Here, v_i represents the number of population of virus mutant labeled i; x_i represents the immune response specifically directed against the virus strain i; and z represents the group-specific immune response directed against all types of virus mutants. The overall number of virus strains is given by n and the mutation process occurs throughout the infection period. The entire virus population is given by $v = \sum v_i$.

The model contains seven parameters. They are namely, r, p, s, k, k', b and u. The parameter r denotes the average rate of replication of all different virus strains. p denotes the efficacy of the strain specific immune responses and k denotes the rate at which they are evoked. Likewise s denotes the efficacy of the group specific immune responses and k' denotes the rate at which they are evoked. The immune response decays at a slow rate b in the nonexistence of further stimulation. Lentiviruses(Lentivirus is a genus of retroviruses that cause chronic and deadly diseases and have a long incubation period) have the ability to deteriorate immune responses, either by directly killing infected $CD4^+$ cells or by indirect mechanisms. These effects are described in the loss terms, $-uvx_i$ and $-uvz$. Consequently, the parameter u specifies the ability of the virus to deteriorate immune responses. By deteriorating CD4 cell function, the virus also destroys B cell and cytotoxic T cell mediated immune responses indirectly.

The above model is a representation of simplified concept of virus-immune system interactions. The individual virus strains are considered as being different in terms of strain-specific immune responses. In reality, every virus has few different epitopes(the part of a bio-molecule that is the target of an immune response) that can be recognized by an immune response. Some virus mutants may differ in one epitope but coincide in others. This implies that a specific immune response may have capability of recognizing a number of different virus strains, but unable to recognize others. There are various types of group-specific and strain-specific immune responses. Two

utmost possibilities of completely group-specific and strain-specific immune responses are considered in this model.

It is also assumed that all the parameters r, p, s, k, k' and u are the same for all the different virus strains. The reason behind this simplification is, it makes the mathematical analysis more obvious.

From equation (3.0.1), we find that x_i converges to their steady-state levels ${x_i}^* = \dfrac{kv_i}{b+uv}$ and z converges to $z^* = \dfrac{k'v}{b+uv}$. The rate at which the total virus population changes is obtained as follows.

$$\frac{dv}{dt} = v\big(r - \frac{pkv}{b+uv}D - \frac{sk'v}{b+uv}\big) \tag{3.0.2}$$

Here, $D = \sum(\frac{v_i}{v})^2$ denotes the Simpson index, which is an inverse measure for viral diversity. If there is only one virus strain present then $D = 1$. If there are n strains present, all of them in same abundance, then $D = 1/n$. In fact D is the probability that two viruses chosen at random belong to the same strain and it is always between 0 and 1. In this model, virus strain v_i is simply a sub-population of viruses that are all recognized by the same strain-specific immune responses, x_i.

By setting $\dfrac{dv}{dt} = 0$ from equation (3.0.2), we find that v converges towards the steady-state

$$v^* = \frac{rb}{sk' + pkD - ru} \tag{3.0.3}$$

The product sk' denotes the efficacy of group-specific immune responses, such as antibodies or CTLs directed at epitopes that are preserved between different virus strains. The product pkD specifies the strain-specific immune responses, such as antibodies or CTLs directed at variable regions. The antigenic diversity of the virus population controls the efficacy of these strain-specific immune responses. From equation (1.3) , we see that increasing diversity(i.e. decreasing D) increases the total virus population size and as a result governs disease progression. This model has three parameter regions, which correspond to three qualitatively different courses of infection. They are discussed below.

If $ru > sk' + pk$, there is no symptomless phase and the virus population instantly replicates to high levels. In this case, the combined action of strain-specific and group-specific immune responses fails to control the virus replication.

If $sk' > ru$, there is chronic infection, but no disease. In this case, the virus population can be controlled solely by the group-specific immune responses.

Finally, an interesting situation arises when $sk'+pk > ru > sk'$, i.e. when the combined effects of group-specific and strain-specific immune responses are able to control the virus replication(of the individual strains) but the group-specific immune responses alone cannot do so. The entire virus population size is governed to some equilibrium value if the virus diversity is low(i.e. large D). On the other hand, the virus population size becomes very large if the viral diversity is high(small D). The critical transition occurs when

$$D = \frac{ru - sk'}{pk} \tag{3.0.4}$$

Beyond this point, the entire virus population explodes. The diversity threshold is given by equation (3.0.4). As soon as this threshold is surpassed, the virus population escapes from the control by the immune responses and tends to arbitrarily high densities. Development of immunodeficiency disease which is characterized by high virus counts and depletion of $CD4^+$ cells may be described by this process. During the symptomless phase, though the viral diversity increases, the immune system is able to control viral densities and to maintain $CD4$ cell levels.

4 Two dimensional HIV disease progression model-1

Let us assume, there is only one virus strain is present and the overall immune response instead of strain-specific and group-specific immune responses. The following model reflects these assumptions.

$$\begin{cases} \dfrac{dv}{dt} = vr - \alpha vy = f(v, y) \\ \dfrac{dy}{dt} = \beta v - \gamma y - \mu vy = g(v, y) \end{cases} \tag{4.0.1}$$

This model has two types of variables. Here, v represents the population size of virus and y represents the immune response directed against the virus population. The model also contains five different parameters. The parameter r represents the rate of replication of the virus strain; α denotes the

efficacy of immune response and β denotes the the rate at which it is evoked. The immune response decays at a rate γ, in the absence of further stimulation. The parameter μ specifies the ability of virus to impair the immune response.

The term vr denotes the exponential growth of virus population and αvy is the loss term that reflects the cleaning up by immune response. The deterioration of immune response is summarized by the term μvy.

4.1 Mathematical analysis of the model-1

For the system (4.0.1), if we start at any positive initial point in the vy-plane, the solution remains positive for all time. So the positivity of solution 0f the system holds. Since both $f(v, y)$ and $g(v, y)$ are continuous and their partial derivatives are continuous, there exists a unique solution for the system.

We find the steady states of the system by setting $\frac{dy}{dt} = 0$ and $\frac{dv}{dt} = 0$.

$$\begin{aligned} \frac{dy}{dt} &= 0 = \beta v - \gamma y - \mu vy \\ \implies y &= \frac{\beta v}{\gamma + \mu v} \end{aligned} \tag{4.1.1}$$

and

$$\frac{dv}{dt} = 0 = vr - \alpha vy \tag{4.1.2}$$

Solving equation (4.1.1) and (4.2.2), we find two equilibrium points. They are namely $E_1 = (v_1, y_1) = (0, 0)$ and $E_2 = (v_2, y_2) = \Big(\frac{r\gamma}{\alpha\beta - r\mu}, \frac{r}{\alpha}\Big)$. If the system is initially in one of these two steady states, it remains unchanged forever. We notice that if $\alpha\beta < r\mu$ i.e. $\frac{\beta}{\mu} < \frac{r}{\alpha}$ the the equilibrium point E_2 becomes negative which is not of our interest. Therefore, if this condition holds then we have only one equilibrium point E_1. On the other hand, if $\frac{\beta}{\mu} > \frac{r}{\alpha}$ then E_2 exists and we have two equilibriums.

To study the behavior of this system near the equilibrium points, we linearize the system. The Jacobian matrix of the system is given by,

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

Now we evaluate the Jacobian at the first equilibrium point.

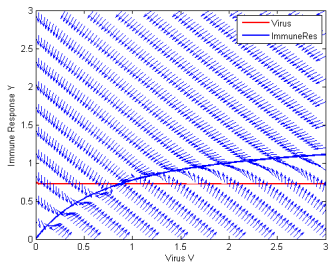
$$J|_{E_1=(0,0)} = \begin{bmatrix} r & 0 \\ \beta & -\gamma \end{bmatrix}$$

There are two eigenvalues namely $\lambda_1 = r > 0$ and $\lambda_2 = -\gamma < 0$. Therefore $(0, 0)$ is a saddle point and hence unstable. Evaluating the Jacobian at E_2 we obtain,

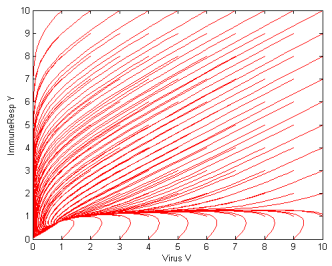
$$J|_{E_2=\left(\frac{r\gamma}{\alpha\beta - r\mu}, \frac{r}{\alpha}\right)} = \begin{bmatrix} 0 & -\dfrac{\alpha r\gamma}{\alpha\beta - r\mu} \\ \beta - \dfrac{\mu r}{\alpha} & -\dfrac{\alpha\beta\gamma}{\alpha\beta - r\mu} \end{bmatrix}$$

The determinant of this matrix is $Det(J|_{E_2}) = r\gamma$, which is always positive (> 0). The trace is, $Tr(J|_{E_2}) = -\dfrac{\alpha\beta\gamma}{\alpha\beta - r\mu}$. The condition for stability of E_2 is $Tr(J|_{E_2}) < 0$ which implies $\dfrac{\beta}{\mu} > \dfrac{r}{\alpha}$. This condition is essentially the condition for existence of E_2. This condition can be interpreted as the ratio of the rate at which immune responses are evoked and the ability of virus to deteriorate immune responses is greater than the ratio of the rate of replication of virus population and the efficacy of immune responses. Therefore, it is obvious that if E_2 exists, then it is locally asymptotically stable(L.A.S).

The following figures has been obtained for the parameter values, $r = 0.65, \alpha = 0.9, \beta = 0.85, \gamma = 0.5, \mu = 0.60$. Here, the values of α, β are larger than the values of r, μ.



(a) Phase portrait



(b) Basin of attraction

Figure 2: Local asymptotic stability of E_2

Again, the following figure has been obtained for the parameter values, $r = 0.90$, $\alpha = 0.60$, $\beta = 0.85$, $\gamma = 0.5$, $\mu = 0.80$.

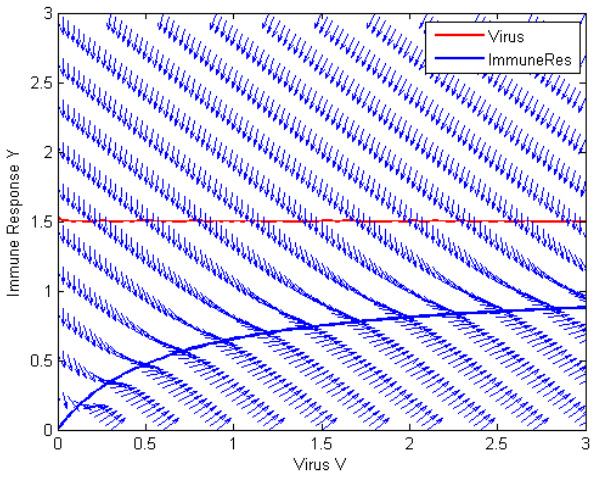


Figure 3: Phase Portrait

We can see that the equilibrium point E_2 does not exist in this case.

5 Two dimensional HIV disease progression model-2

Like the previous model, we assume that there is only one virus strain is present. In addition to that, we assume the virus strain grows logistically.

As we know virus grows inside a living cell, (for example)it can be thought of that a cell can provide nesting space to a certain number of virus population. So the cell has a carrying capacity. Here, we denote it by k. Also, let us suppose that there is an overall immune response instead of two different types of immune responses. These assumptions are captured in the following model.

$$\begin{cases} \dfrac{dv}{dt} = v\Big[r\big(1-\dfrac{v}{k}\big)\Big] - \alpha vy = Q(v,y) \\ \dfrac{dy}{dt} = \beta v - \gamma y - \mu vy = R(v,y) \end{cases} \tag{5.0.1}$$

Here, v denotes the virus population and y denotes the overall immune responses. The parameters have the same meanings mentioned in model (4.0.1).

5.1 Mathematical analysis of the model-2

The positivity of solution holds for this model. Since both $Q(v,y)$ and $R(v,y)$ are continuous and their partial derivatives are continuous, there exists a unique solution for the system.

Now, we find the steady states of the system by setting $\dfrac{dy}{dt} = 0$ and $\dfrac{dv}{dt} = 0$.

$$\frac{dv}{dt} = 0 = v\Big[r\big(1-\frac{v}{k}\big) - \alpha y\Big]$$

Therefore, either $v = 0$ or,

$$y = \frac{r}{\alpha}\Big(1-\frac{v}{k}\Big) \tag{5.1.1}$$

and

$$\begin{aligned} \frac{dy}{dt} = 0 &= \beta v - \gamma y - \mu vy \\ \implies y &= \frac{\beta v}{\gamma + \mu v} \end{aligned} \tag{5.1.2}$$

Solving equations (5.1.1) and (5.1.2) we get,

$$\begin{aligned} \frac{r}{\alpha}\Big(1-\frac{v}{k}\Big) &= \frac{\beta v}{\gamma+\mu v} \\ \implies r\mu v^2 + v(r\gamma + k\alpha\beta - kr\mu) - kr\gamma &= 0 \\ \implies v = \frac{-(r\gamma + k\alpha\beta - kr\mu) \pm \sqrt{(r\gamma + k\alpha\beta - kr\mu)^2 + 4r^2\mu k\gamma}}{2r\mu} & \qquad (5.1.3) \end{aligned}$$

Now let us denote $A = (r\gamma + k\alpha\beta - kr\mu)$ and $B = 4r^2\mu k\gamma$. Then equation (5.1.3) takes the following form.

$$v = \frac{-A \pm \sqrt{A^2+B}}{2r\mu} \qquad (5.1.4)$$

We notice that $\sqrt{A^2+B} > 0$ always and $\sqrt{A^2+B} > A$. If $A > 0$, then $v = \dfrac{-A+\sqrt{A^2+B}}{2r\mu}$ is positive and $v = \dfrac{-A-\sqrt{A^2+B}}{2r\mu}$ is negative.

But we only consider the positive value of v, since we are looking for the positive equilibrium point. Plug in the positive value of v in equation (5.1.1) or (5.1.2) to get the positive value of y which is given by,

$$y = \frac{(r\gamma + k\alpha\beta + kr\mu) + \sqrt{(r\gamma + k\alpha\beta - kr\mu)^2 + 4r^2\mu k\gamma}}{2k\mu\alpha} > 0 \qquad (5.1.5)$$

Let $C = r\gamma + k\alpha\beta + kr\mu$. Then (5.1.5) becomes, $y = \dfrac{C+\sqrt{A^2+B}}{2k\mu\alpha} > 0$. Therefore, we find two equilibrium points. They are, $E_1 = (v_1, y_1) = (0,0)$ and $E_2 = (v_2, y_2) = \left(\dfrac{-A+\sqrt{A^2+B}}{2r\mu}, \dfrac{C+\sqrt{A^2+B}}{2k\mu\alpha}\right) = (a,b)$ (say).

To study the stability of the equilibrium points we find the Jacobian matrix of the system which is given by,

$$J = \begin{bmatrix} r - \dfrac{2vr}{k} - \alpha y & -\alpha v \\ \\ \beta - \mu y & -\gamma - \mu v \end{bmatrix}$$

Now we evaluate the Jacobian at the first equilibrium point.

$$J|_{E_1=(0,0)} = \begin{bmatrix} r & 0 \\ \\ \beta & -\gamma \end{bmatrix}$$

The two eigenvalues are $\lambda_1 = r > 0$ and $\lambda_2 = -\gamma < 0$. Therefore, $(0, 0)$ is a saddle point and hence unstable. Evaluating J at the second equilibrium point E_2 we obtain,

$$J|_{E_2=(a,b)} = \begin{bmatrix} r - \dfrac{2ar}{k} - \alpha b & -\alpha a \\ \\ \beta - \mu b & -\gamma - \mu a \end{bmatrix}$$

The trace is, $Tr(J|_{E_2}) = r - \dfrac{2ar}{k} - \alpha b - \gamma - \mu v$ and the determinant is, $Det(J|_{E_2}) = -r\gamma - r\mu a + \dfrac{2r\gamma a}{k} + \dfrac{2r\mu a^2}{k} + \alpha\gamma b + \alpha\beta a$. The steady state E_2 is locally asymptotically stable if $Tr(J|_{E_2}) < 0$ i.e.

$$\frac{r}{\alpha}\Big(1 - \frac{2a}{k} - \frac{\mu a}{r}\Big) < b + \gamma \tag{5.1.6}$$

and $Det(J|_{E_2}) > 0$ i.e.

$$\frac{r}{\alpha}\Big(\frac{2\gamma a}{k\mu} + \frac{2a^2}{k} - a\Big) > \frac{\beta}{\mu}\Big(\frac{r\gamma}{\alpha\beta} + \frac{\gamma b}{\beta} - a\Big) \tag{5.1.7}$$

If the conditions (5.1.6) and (5.1.7) are not satisfied then E_2 is unstable.

6 Conclusion

The model (3.0.1) considers various virus strains and two types of immune responses. On the other hand, the proposed models (4.0.1) and (5.0.1) consider a single virus strain and overall immune response. The first two models consider the exponential growth of the virus population, whereas the third model considers logistic growth of the virus population.

With the help of Matlab, we can check the behavior of virus population, strain-specific and group-specific immune responses for a particular mutation in model (3.0.1). The following figure has been obtained for some specific parameter values.

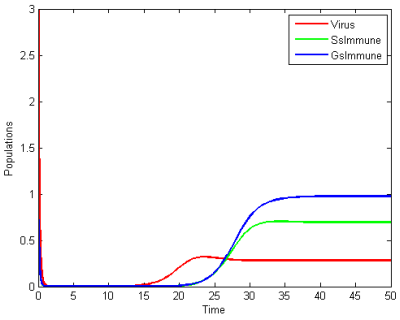


Figure 4: Solution Curves

The above figure shows that the solution curves eventually go to the equilibrium.

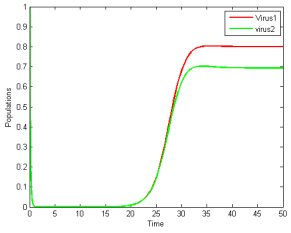
The models (4.0.1) and (5.0.1) can be generalized to a single model as follows.

$$\begin{cases} \dfrac{dv}{dt} = v\Big[r\big(1-\kappa v\big)\Big] - \alpha vy \\ \dfrac{dy}{dt} = \beta v - \gamma y - \mu vy \end{cases} \tag{6.0.1}$$

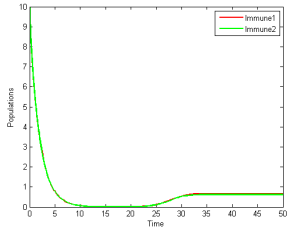
Where, κ is the rate of intraspecific competition. If $\kappa = 0$, then we have the model (4.0.1). Again, if $\kappa > 0$, then we have the model (5.0.1).

Using Matlab, we can see how the virus population and immune responses change over time of both models. The following (comparison) figures have been obtained for same initial condition.

N.B: The red curve has been used for model (4.0.1) and the green curve is for model (5.0.1).



(a) Virus Population



(b) Immune Responses

Figure 5: Comparison of Virus and Immune responses

We can see, initially the virus population of both models decreases at the same pace. But as the time progresses, virus population in model (4.0.1) tends to grow slightly faster. On the other hand, the immune responses are more or less remain at the same pace. Eventually, the virus population and the immune responses approach the equilibrium.

Also, if we assume that the intraspecific competition actually helps the growth of virus population then the term $-\kappa v$ is replaced by κv in the above model and we end up with a new model. This assumption may be irrelevant from the biological perspective. Then the same comparison strategy can be applied.

(a) Virus Population (b) Immune Responses

Figure 6: Comparison of Virus and Immune responses

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