The Second International Symposium on Optimization and Systems Biology (OSB'08)
Lijiang, China, October 31– November 3, 2008

Some Infection Models for the Development of AIDS

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Abstract The co-infection of HIV viruses can affect the viral evolution *in vivo*. Wodarz and Levy 2007 [1] study the effect of HIV co-infection by investigating the values of the virus cytopathicity when the basic reproductive ratio of the virus and the total number of the target cells reach their extreme point respectively. Here based on their ideas, we further extended the discussion to a more general model.

Keywords HIV Dynamics; Mathematical Models

1 Introduction

The assumption that a cell can be infected by only one virus particle is well accepted, as cells down-regulate the CD4 receptor shortly after becoming infected by Human immunodeficiency virus (HIV). And most theoretical studies about the evolution of HIV *in vivo* and disease progression have been made with mathematical models under this assumption. However, experimental data (Jung *et al.* 2002 [3]; Dang *et al.* 2004 [4]; Levy *et al.* 2004 [5]; Chen *et al.* 2005 [6]) indicate that a cell can be infected with multiple virus particles, which is defined as co-infection. Because it usually takes a couple of days or so to make the CD4 receptor eventually down-regulated, and this provides a large enough time window for multiple viruses to infect the cell. Thus one can expect that virus competition and evolution to be changed in the context of co-infection. Wodarz and Levy 2007 [1] examined the effect of co-infection on viral evolution *in vivo*, and presented a theory that might explain how viral evolution can lead to two alternative outcomes:

(i) high virus load with the development of AIDS; and
(ii) high virus load without the development of AIDS.

In [1], Wodarz and Levy first considered a simple model containing the parameter a which reflects the average viral cytopathicity. This model is based on virus dynamics

model proposed by Nowak and May [2]. They then extended the model to the case of co-infection.

The simple model proposed in [1] can be briefly explained as follows, denoted as Model I. In Model I, it includes the following variables: $x(t)$ uninfected cells at time t and $y(t)$ infected cells at time t. Assuming that the population of free viruses turns over with a relatively fast rate and is in a quasi-steady state, then one can obtain the Model I :

$$\begin{cases} \dfrac{dx(t)}{dt} &= \lambda - dx(t) - \beta x(t)y(t) \\ \dfrac{dy(t)}{dt} &= \beta x(t)y(t) - ay(t). \end{cases} \tag{1}$$

In the model, at time t the uninfected cells have a reproduction rate of λ, a death rate of $dx(t)$, and an infection rate of $\beta x(t)y(t)$. The infected cells have a death rate of $ay(t)$, (we note that here a reflects the average viral cytopathicity). Since we assume that the virus population is in a quasi-steady state, the parameter β summarizes the overall rate of viral replication, including the rate of virus production, the rate of infection and the death rate of free viruses. It is assumed that the increase in the viral cytopathicity is correlated asymptotically to a higher rate of virus production, and thus with a larger value of β. There are at least two different forms of β:

$$\beta_1 = \beta_1(a) = \frac{fa}{g+a} \quad \text{and} \quad \beta_2 = \beta_2(a) = \frac{fa^2}{g+a^2}$$

where f and g are some constants.

In [1], the authors adopted β_1. Here we would like to point out that, if β_1 is adopted, one may not be able to obtain the results (Figures 1(b) and 1(c)) in [1]. From now on we take

$$\beta'(a) = \frac{fa^2}{g+a^2}. \tag{2}$$

The basic reproductive ratio of the virus is given by [2]:

$$R_0(a) = \frac{\lambda \beta'}{da}. \tag{3}$$

The model always has an equilibrium point. However if $R_0 < 1$, the infection will not spread, otherwise if $R_0 > 1$, an infection will be spread in the host.

The system will eventually converge to the following equilibrium:

$$x^*(a) = \frac{a}{\beta'} \quad \text{and} \quad y^*(a) = \frac{\lambda}{a} - \frac{d}{\beta'}. \tag{4}$$

The total number of target cells at the equilibrium, $(x^* + y^*)$, is a measure of the degree of pathology caused by the virus.

If the basic reproductive ratio of the virus is much bigger than one (which means $R_0 > 1$), then compared to x_0, x^* will be greatly reduced. This means that during infection, the number of the uninfected cells at the equilibrium is much smaller than that before infection. Thus, the above model cannot explain the situation that almost all infected

cells remain uninfected ($x^* \approx x_0$) under a persistent virus infection. AIDS develops when the CD4 T-cell count drops from normal levels (1000 cells μl^{-1} blood) to an average of 200 cells μl^{-1} blood. Target cell depletion and virus cytopathicity a are interrelated. If a is too small, HIV virus is unable to induce target cell depletion. If a is too large, HIV spread is compromised by the short lifespan of virus producing infected cells. In [1], Wodarz and Levy developed their co-infection theory based on the discussion of the relation of a_{path} and a_{fit}, where a_{path} and a_{fit} stand for the values of a when target cells and basic reproductive ratio reach their extreme separately. They drew the conclusion that if $a_{fit} > a_{path}$ satisfies, the virus cytopathicity is too low that HIV cannot grow, the virus can grow only if $a_{fit} < a_{path}$. They then considered the effect of co-infection on the basic of a co-infection model based on their above conclusion. Their co-infection model is extended from Model I, as follows.

$$\begin{cases} \dfrac{dx}{dt} = \lambda - dx - \beta_1' x(y_1 + y_{12}) - \beta_2' x(y_2 + y_{12}), \\ \dfrac{dy_1}{dt} = \beta_1' x(y_1 + y_{12}) - a_1 y_1 - \beta_2' y_1(y_2 + y_{12}) - p y_1 z, \\ \dfrac{dy_2}{dt} = \beta_2' x(y_2 + y_{12}) - a_2 y_2 - \beta_1' y_2(y_1 + y_{12}) - p y_2 z, \\ \dfrac{dy_{12}}{dt} = \beta_1' y_2(y_1 + y_{12}) + \beta_2' y_1(y_2 + y_{12}) - a_2 y_{12} - p y_{12} z, \\ \dfrac{dz}{dt} = F(z, y_1 + y_2 + y_{12}) - bz. \end{cases}$$

The variables y_1, y_2, y_{12} and x stand for the populations of cells infected only by virus 1, only by virus 2, by both viruses, uninfected. And z denotes a specific immune responses, which kills infected cells with a rate p. Represented by $F = c(y_1 + y_2 + y_{12})$, immune responses expand upon exposure to all types of infected cells. Immune cells die with a rate b. Other parameters hold the similar meaning as Model I. Cells infected with both viruses die with a rate a_2, because virus 2 is assumed to be more cytopathic than virus 1. Here we would explain Wodarz and Levy's idea, examine their results and then extend the discussion to more biological meaningful variables, such as the extreme point of the numbers of uninfected and infected cells.

The rest of this paper is organized as follows. In Section 2, we give a further analysis of the model (Model I) in [1], and then we calculate the value of the the virus cytopathicity a when the number of uninfected cells and infected cells reach their extreme point separately. In Section 3, we introduce a model involving virus load (Model II), to discuss the value of a when the basic reproductive ratio, the total number of infected and uninfected cells, the number of uninfected cells, the number of infected cells and the virus load reach their critical points separately. Finally, concluding remarks are given in Section 4.

2 The Analysis of Model I

In this section, we give an analysis of Model I in [1]. The basic reproductive ratio of the virus R_0 stands for the average number of infected cells which derives from any one of the infected cells at the beginning of the infection. If on average every infected cell produces less than one newly infected cell, i.e., $R_0 < 1$, then the infection will not take off.

Here we consider R_0 as a function of a:

$$R_0(a) = \frac{\lambda\beta'}{da} = \frac{\lambda f a}{d(g+a^2)}. \tag{5}$$

In fact, we can find R_0 reaches its maximum

$$\max_{0\le a}\{R_0\} = R_{0max} = \frac{\lambda f}{2d\sqrt{g}} \tag{6}$$

when $a = \sqrt{g}$, which is defined as a_{fit} in [1].

We first give an analysis of the number of target cells $(x^* + y^*)$. In [1], the number $(x^* + y^*)$ is defined as the total number of target cells, and it was argued that there is a minimum point for R_0, at which the value of a is defined as a_{path}. By considering the positive root for the equation $\frac{d}{da}(x^* + y^*) = 0$, one can obtain the following three different cases of a_{path}.

Case 1: $a_{path} = (dg)^{1/3}$. Especially, if

$$(dg)^{1/3} = a_{fit} = \sqrt{g}, g = d^2,$$

then for the same a, the basic reproductive ratio of the virus R_0 reaches its maximum $\frac{\lambda f}{2d\sqrt{g}}$, and the total number of target cells $(x^* + y^*)$ reaches its minimum.
Case 2: there is no positive real root.
Case 3: there is no general form of the largest positive root.

Apart from the number of the target cells $(x^* + y^*)$, we also analyze when the number of uninfected cells $x^* = \frac{a}{\beta'}$ attains its extreme. Let $a_{path(x)}$ be the value of a when x^* reaches its extreme. It can be shown that $a_{path(x)} = \sqrt{g}$, and x^* reaches its minimum $\min_a\{x^*\} = x^*_{min} = \frac{2\sqrt{g}}{f}$.

We note that $a_{path(x)} = a_{fit} = \sqrt{g}$. Therefore, when $a = \sqrt{g}$ the basic reproductive ratio of the virus R_0 reaches its maximum $\frac{\lambda f}{2d\sqrt{g}}$ and the number of target cells x^* reaches its minimum $\frac{2\sqrt{g}}{f}$.

We now give a similar analysis on the number of infected cells y^*. Here we consider the number of infected cells y^* as the number of target cells.

$$y^* = \frac{\lambda}{a} - \frac{d}{\beta'} = \frac{\lambda}{a} - \frac{d(g+a^2)}{fa^2}. \tag{7}$$

We can find that there is a maximum point of y^*. Let $a_{path(y)}$ be the value of a when y^* reaches its maximum. It can be shown that $a = a_{point(y)} = \dfrac{2dg}{\lambda f}$.

We end this section by a numerical example on the basic reproductive ratio of the virus. Figure 1 reports the basic reproductive ratio R_0 with the following parameters

$$\lambda = 100, \quad d = 1.00, \quad f = 0.15, \quad g = 0.50. \tag{8}$$

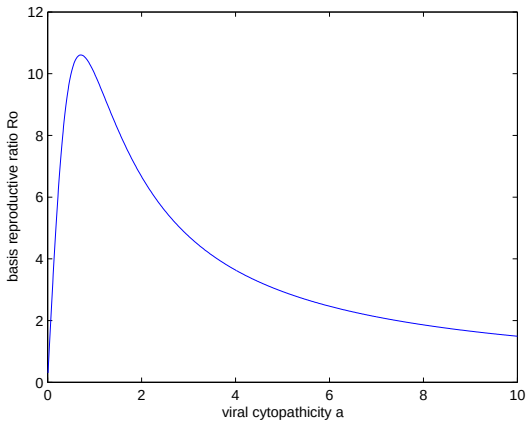

Figure 1: The basic reproductive ratio of the virus.

3 The Analysis of Model II

We now consider a more general model (Model II) which includes the free virus particles (Nowak and May 2000) [2] into consideration. Model II has three variables: the population sizes of uninfected cells, $x(t)$; infected cells, $y(t)$; and free virus particles, $v(t)$. The mechanism of the HIV infection is given as follows. Free virus particles infect uninfected cells at a rate of $\beta x(t)v(t)$. Here the rate constant, β, states the efficacy of the process, including the rate at which virus particles find uninfected cells, the rate of virus entry, and the rate and probability of successful infection. Infected cells produce free virus by $ky(t)$. Infected cells die at a rate $ay(t)$, and free virus particles are removed from the system at a rate $uv(t)$. Moreover, we assume that uninfected cells are produced at a constant rate, λ, and die at a rate $dx(t)$. Combining the above assumptions and the HIV infection mechanism, we can obtain Model II:

$$\begin{cases} \dfrac{dx(t)}{dt} &= \lambda - dx(t) - \beta x(t)v(t), \\ \dfrac{dy(t)}{dt} &= \beta x(t)v(t) - ay(t), \\ \dfrac{dv(t)}{dv} &= ky(t) - uv(t). \end{cases} \tag{9}$$

Here we again adopted $\beta' = fa^2/(g+a^2)$ as in (2).

Using similar analysis, when $R_0 > 1$, the system converges to the following equilibrium:

$$x^* = \frac{au}{k\beta'}, \quad y^* = \frac{\lambda}{a} - \frac{du}{k\beta'} \quad \text{and} \quad v^* = \frac{k\lambda}{au} - \frac{d}{\beta'}. \tag{10}$$

The basic reproductive ratio is given by

$$R_0 = \frac{\beta'\lambda k}{adu} = \frac{f\lambda ka}{ud(g+a^2)}. \tag{11}$$

Using similar argument as in previous section, one can establish the following result. We define a'_{fit} as the value of a when R_0 reaches its extreme. One can find that $a'_{fit} = \sqrt{g}$, and R_0 reaches its global maximum point

$$\max_a\{R_0\} = R_{0max} = \frac{\lambda fk}{2ud\sqrt{g}}.$$

Now we consider the total number of the infected and uninfected cells, which is

$$x^* + y^* = \frac{\lambda}{a} + \frac{u(a-d)(g+a^2)}{fka^2}. \tag{12}$$

. Let a'_{path} be the value of a when $x^* + y^*$ reaches its extreme. By applying the same analysis to $x^* + y^*$ as in the previous section, one can also obtain three similar cases for a'_{path}.

Similarly we find that there is a global minimum of the number of the uninfected cells $x^* = \frac{au}{k\beta'}$. Let $a'_{path(x)}$ be the value of a when x^* reaches its minimum. We find that

$$a'_{path(x)} = \sqrt{g} \quad \text{and} \quad \min\{x^*\} = x^*_{min} = \frac{2u\sqrt{g}}{fk}.$$

We then consider the total number of infected cells

$$y^* = \frac{\lambda}{a} - \frac{du}{k\beta'} = \frac{\lambda}{a} - \frac{du(g+a^2)}{kfa^2} \tag{13}$$

.

We can find that y^* only has a maximum point, and define the value of a at this point as $a'_{path(y)}$. One can get that $a = a'_{path(y)} = \frac{2dug}{\lambda fk}$.

We give an analysis on the virus load v^* where

$$v^* = \frac{k\lambda}{au} - \frac{d}{\beta'} = \frac{k\lambda}{au} - \frac{d(g+a^2)}{fa^2} \tag{14}$$

is a function of a. We note that v^* only has one critical point, where we define the value of a as a_{virus}. One can find that $a = a_{virus} = \frac{2dug}{\lambda fk}$.

Finally we give a numerical example on the basic reproductive ratio R_0. Figure 2 reports the basic reproductive ratio R_0 with the following parameters

$$\lambda = 100, \quad d = 1, \quad k = 100, \quad u = 5, \quad f = 0.15, \quad g = 0.5. \tag{15}$$

4 Concluding Remarks for Model II

We conclude the paper by giving a summary of the results for Model II as follows:

1. We have

$$a'_{fit} = a'_{path} = \sqrt{g},$$

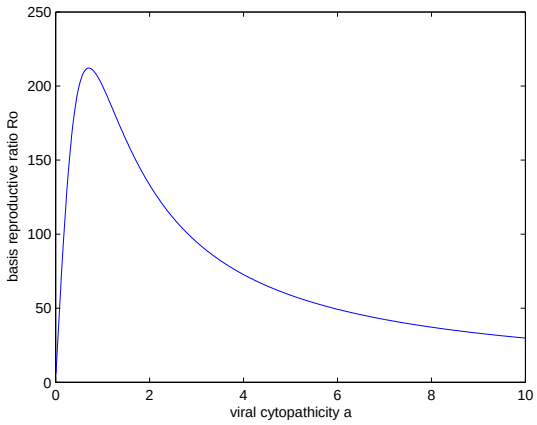

Figure 2: the basic reproductive ratio R_0

thus under the same value of the virus cytopathicity $a = \sqrt{g}$, the basic reproductive ratio reaches its maximum and the number of uninfected cells reaches its minimum.

2. We obtained

$$a'_{path(y)} = a_{virus} = \frac{2dug}{\lambda fk},$$

and thus under the same value of the virus cytopathicity

$$a = \frac{2dug}{\lambda fk},$$

both the virus load and the number of infected cells reach their maximum point separately.

Acknowledges

Research support in part by HKRGC Grant 7017/07P and HKU CRCG Grants and HKU strategic theme grant on computational sciences.

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