Co-infection Models for the Development of AIDS

Wai-Ki Ching[a] Yang Cong[a] Tuen-Wai Ng[a] Zheng-Jian Bai[b]
[a]*Advanced Modeling and Applied Computing Laboratory,*
Department of Mathematics,
The University of Hong Kong, Hong Kong.
Email:{ wching, congyang}@hkusua.hku.hk, ntw@maths.hku.hk
Department of Information and Computational Mathematics,
Xiamen University, Xiamen 361005, People's Republic of China[b]
Email:zjbai@xmu.edu.cn
[*] *Corresponding Author. Email:congyang@hkusua.hku.hk*

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, Co-infection.

I. 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 their theory, they introduce the parameter a which reflects the average viral cytopathicity based on virus dynamics model proposed by Nowak and May [2]. They then extended the model to the case of co-infection.

The model can be briefly explained as follows. In the model, 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, the dynamics of the system is governed by the following system of differential equations:

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

In the model, we note that the uninfected cells have a reproduction rate of λ, a death rate of $dx(t)$, and an infection rate of $\beta x(t)y(t)$. While 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:

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

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 and Figures 1(b) and (c) in [1]. From now 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 disease 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.

Suppose infection occurs with a certain amount of virus particles. Thus the initial conditions are $x_0 = \lambda/d,\ y_0 = 0$. The system will eventually converge to the following equilibrium:

$$x^*(a) = \frac{a}{\beta'} = \frac{x_0}{R_0} \quad \text{and} \quad y^*(a) = \frac{\lambda}{a} - \frac{d}{\beta'} = (R_0 - 1)\frac{d}{\beta'}. \tag{5}$$

If the basic reproductive ratio of the virus is much larger 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.

We then followed from Wodarz and Levy's idea, we examined their result and extend the discussion to more biological meaningful variables, such as the extreme point of the numbers of uninfected and infected cells separately. Wodarz and Levy [1] presented a theory to explain under high virus load whether there would be development of AIDS or not. We then did similar discussions on a model involved virus load.

The rest of this paper is organized as follows. In Section 2, we give an analysis of the model (Model I) in [1], and then we calculated 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 give the 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.

II. The Analysis of Model I

In this section, we give an analysis of the model 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 infected cell in 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 and vice versa.

Here we consider R_0 as a function of a:

$$R_0(a) = \frac{\lambda\beta'}{da} = \frac{\lambda f a}{d(g + a^2)}. \tag{6}$$

In fact, we can find R_0 reaches its maximum

$$\max_{0\leq a}\{R_0\} = R_{0max} = \frac{\lambda f}{2d\sqrt{g}} \tag{7}$$

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 they argued that there is a minimum point, at which the value of a is defined as a_{path}. By calculating the positive root for

$$\frac{d}{da}(x^* + y^*) = 0$$

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 under 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 target cells (x^*+y^*), we also analyze the number of uninfected cells x^*. We consider $x^* = \frac{a}{\beta'}$, it can be shown that

$$a = \sqrt{g} = a_{path(x)},$$

x^* reaches its minimum and we have

$$\min_a\{x^*\} = x^*_{min} = \frac{2\sqrt{g}}{f}.$$

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 then give an analysis on the number of infected cells y^*. Here we consider the number of infected cells y^* as the number of target cells.

$$y^* = \frac{\lambda}{a} - \frac{d}{\beta'} = \frac{\lambda}{a} - \frac{d(g + a^2)}{fa^2}. \tag{8}$$

We can find that there is a maximum point of y^*, when

$$a = a_{point(y)} = \frac{2dg}{\lambda f}.$$

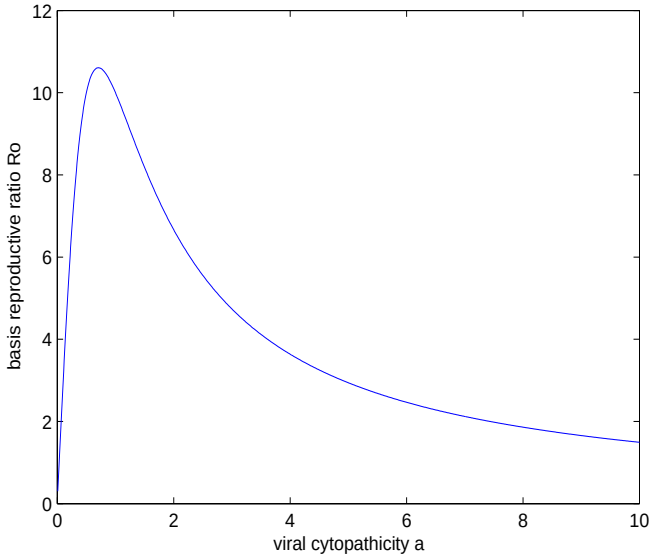

Fig. 1. The basic reproductive ratio of the virus.

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

$$\lambda = 100, \quad d = 1.00, \quad f = 0.15, \quad g = 0.50. \tag{9}$$

Here the parameters are chosen for the purpose of illustration.

III. 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 the following

model:

$$\begin{cases} \dfrac{dx(t)}{dt} &= \lambda - dx(t) - \beta x(t)v(t), \\ \dfrac{dy(t)}{dt} &= \beta x(t)v(t) - ay(t), \\ \dfrac{dv(t)}{dv} &= ky(t) - uv(t). \end{cases} \tag{10}$$

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:

$$x^* = \frac{au}{k\beta'}, \quad y^* = \frac{\lambda}{a} - \frac{du}{k\beta'} \quad \text{and} \quad v^* = \frac{k\lambda}{au} - \frac{d}{\beta'}. \tag{11}$$

The basic reproductive ratio is given by

$$R_0 = \frac{\beta'\lambda k}{adu} = \frac{f\lambda ka}{ud(g + a^2)}. \tag{12}$$

Using similar argument as in previous section, one can establish the following result. When $a'_{fit} = \sqrt{g}$, R_0 reaches its global maximum point of R_0,

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

Now we consider the total number of the infected and uninfected cells $(x^* + y^*)$, and

$$x^* + y^* = \frac{\lambda}{a} + \frac{u(a - d)(g + a^2)}{fka^2}. \tag{13}$$

By applying the same analysis as in the previous section, one can obtain a similar result for $(x^* + y^*)$.

We can find there is a global minimum of the number of the uninfected cells

$$x^* = \frac{au}{k\beta'}$$

and

$$\min\{x^*\} = x^*_{min} = \frac{2u\sqrt{g}}{fk}$$

where $a'_{path(x)} = \sqrt{g}$. We then consider the total number of infected cells

$$y^* = \frac{\lambda}{a} - \frac{du}{k\beta'} = \frac{\lambda}{a} - \frac{du(g + a^2)}{kfa^2} \tag{14}$$

is a function of a. We can find that y^* only has a maximum point, where

$$a = a'_{path(y)} = \frac{2dug}{\lambda fk}. \tag{15}$$

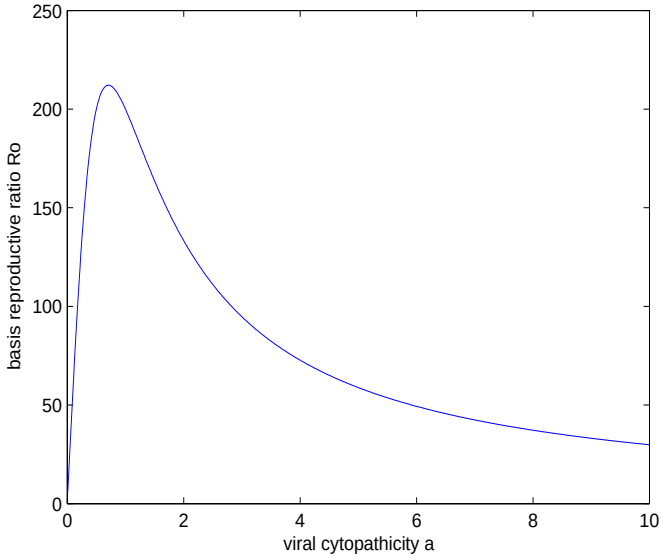

Fig. 2. the basic reproductive ratio R_0

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

$$v^* = \frac{k\lambda}{au} - \frac{d}{\beta'} = \frac{k\lambda}{au} - \frac{d(g+a^2)}{fa^2} \tag{16}$$

is a function of a. We note that v^* only has one critical point, where

$$a = a_{virus} = \frac{2dug}{\lambda fk}.$$

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

$$\lambda = 100, \quad d = 1, \quad k = 100, \quad u = 5, \quad f = 0.15, \quad g = 0.5. \tag{17}$$

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IV. Concluding Remarks

We conclude the paper by giving a summary of the results as follow:

1. We have

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

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.

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