数理解析研究所講究録
第1547巻 2007年 191-199

A Viral Infection Model with Saturating Expansion and Immune Impairment*

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Abstract

The paper considers a viral infection model with saturating expansion and immune impairment. The model may exhibit a bistable behavior in some parameter regions, which means that infection will result in disease or immune control outcome, depending on the initial conditions. It is shown that the disease could change from a disease progression and tend to an immune control outcome if some phase of drug therapy is introduced, despite that the therapy is not necessarily lifelong.

Keywords: Virus dynamics; Immune impairment; Immune control; Stability; Permanence.

1 Introduction

Many models have been proposed to describe virus dynamics in different situations. In virus dynamics we usually examine which conditions are necessary for virus increasing or decreasing. This is important for studying the evolutionary process of disease and can be described well with models of differential equations.

Taking immune response into consideration, Nowak and May [1] presented several basic models, which differ mainly in terms of describing the expansion of the immune response. It is true that virus infections typically evoke immune responses composed of antibodies and CD8+ cytotoxic T cells, but several human pathgens have the ability to suppress immune responses, allowing themselves to establish a persistent and productive infection that eventually results in pathology. A potent strategy is to impair virus-specific CD4 T helper cell responses (directly or indirectly), because they are the central component orchestrating

*Supported by the National Natural Science Foundation of China (10571143).

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antiviral effector mechanisms. According to clinical data, the most prominent examples of this are HIV, hepatitis C virus (HCV), and hepatitis B virus (HBV) infections ([2, 3]).

In this paper, based on the previous models and considering both antigenic stimulation and immune impairment, we introduce a viral infection model, and then study its dynamics, especially the effect of immune impairment.

Let x, y, v and z represent the concentration of susceptible cells, productively infected cells, free virus particles and virus-specific CTL cells, respectively. The following equations represent the rate of change of these populations:

$$\begin{aligned} \frac{dx}{dt} &= \lambda - dx - \beta xv, \\ \frac{dy}{dt} &= \beta xv - \delta y - pyz, \\ \frac{dv}{dt} &= n\delta y - rv, \\ \frac{dz}{dt} &= f(y,z) - bz, \end{aligned} \tag{1.1}$$

The constant λ represents a source of susceptible cells, and d is their death rate. β is the infection rate constant, and infection is assumed to occur at a rate proportional to the product of the concentration of virus and target cells, an assumption which is valid for a well-mixed system with relatively high concentrations of each product. δ is the death rate of infected cells, p is the efficacy of the immune response in killing infected cells, n is the number of free viral particles produced during the average infected cell life span, and r is the death rate of the free virus. The function $f(y,z)$ represents the increasing of immune activity, and b is the decay rate of CTL cells.

Since the mechanism how immune cells are induced is largely unknown, there are many forms of $f(y,z)$ ([1]), such as $f(y,z) = c, f(y,z) = cy$ and $f(y,z) = cyz$, which describe self-regulating CTL-reaction, linear immune response and bilinear CTL-reaction, respectively. However, interactions between two populations are not always as simple as these, and the form of such expressions may change, among other ways, as the relative and absolute population sizes varying. Here, we take both antigenic stimulation and immune impairment into consideration, and consider the following form of $f(y,z)$:

$$f(y,z) = \frac{cyz}{1+\epsilon y} - qyz,$$

which is an example in [7] for describing the dynamics of the populations of virus and immune cells. Here the immune response expands at a rate $cyz/(\epsilon y + 1)$, i.e., expansion

is a saturating function of the amount of infected cells. The infected cells population also inhibits the immune response at a rate qyz.

Furthermore, we assume that the turnover of free virus is much faster than that of infected cells (see [4]), and study a simplified system by assuming that v is at a steady state given by $\dot{v} = 0$, which implies $v = n\delta y/r$. Let $k = \beta\delta n/r$, and these assumptions lead to

$$\begin{aligned} \frac{dx}{dt} &= \lambda - dx - kxy, \\ \frac{dy}{dt} &= kxy - \delta y - pyz, \\ \frac{dz}{dt} &= \frac{cyz}{1+\epsilon y} - qyz - bz. \end{aligned} \tag{1.2}$$

Our purpose is to investigate the effect of immune impairment via mathematical analysis of (1.2). The equilibria and their stability are discussed in Section 2, and the permanence of the system is given in Section 3. In the final section, we will discuss our results.

2 Equilibria and their stability

Firstly, from the epidemiological point of view, we point out that there should be some positive ranges of y such that $z' > 0$, . Therefore, from

$$\frac{cy}{1+\epsilon y} - qy - b = \frac{-\epsilon q y^2 + (c - \epsilon b - q)y - b}{1+\epsilon y},$$

we obtain that $c - \epsilon b - q > 0$ and $(c - \epsilon b - q)^2 - 4b\epsilon q > 0$ should always hold. Under this assumption, there are two roots of equation $cy/(1+\epsilon y) - qy - b = 0$:

$$y^*_{1,2} = \frac{c - \epsilon b - q \mp \sqrt{(c - \epsilon b - q)^2 - 4b\epsilon q}}{2\epsilon q},$$

where $0 < y^*_1 < y^*_2$. Define

$$h(y) \triangleq \left(\frac{cy}{1+\epsilon y} - qy - b\right)' = \frac{c}{(1+\epsilon y)^2} - q,$$

then it is easy to check that $h(y^*_1) > 0$ and $h(y^*_2) > 0$.

Furthermore, the basic reproductive ratio of the virus is given by $R_0 = \lambda k/\delta d$, which describes the average number of newly infected cells generated from one infected cell at the beginning of the infectious process.

System (1.2) has four equilibria. The first one is $E_0 = (x_0, 0, 0) = (\lambda/d, 0, 0)$, and it represents the state in which there is no infection and no immune response. The second is

$$E_1 = (x_1, y_1, 0) = (\frac{\delta}{k}, \frac{\lambda}{\delta} - \frac{d}{k}, 0) = (\frac{\delta}{k}, \frac{d}{k}(R_0 - 1), 0),$$

which has epidemiological meaning if $R_0 > 1$. E_1 represents the state that the virus can establish an infection in the absence of immune response. We will refer to it as the virus equilibrium. The third is

$$E_1^* = (x_1^*, y_1^*, z_1^*) = (\frac{\lambda}{d + ky_1^*}, y_1^*, \frac{kx_1^* - \delta}{p}),$$

which lies in the interior of the first quadrant if $R_0 > 1 + ky_1^*/d$. E_1^* is the state that the virus can establish an infection that is controlled by an immune response, we refer to this outcome as the immune control equilibrium. The last is

$$E_2^* = (x_2^*, y_2^*, z_2^*) = (\frac{\lambda}{d + ky_2^*}, y_2^*, \frac{kx_2^* - \delta}{p}),$$

which lies in the interior of the first quadrant if $R_0 > 1 + ky_2^*/d$. E_2^* is always unstable (Theorem 2.4) and therefore it is epidemiologically irrelevant.

Now we will study the local and global stability of these equilibria, via the method of Lyapunov function and Routh-Hurwitz criterion.

Theorem 2.1. *E_0 is globally asymptotically stable when $R_0 < 1$.*

Proof. Define a Lyapunov function,

$$V_0 = x - x_0 - x_0 \ln\frac{x}{x_0} + y + \frac{pz}{c},$$

Along the trajectories of system (1.2), we have

$$\begin{aligned} V_0' &= x' - \tfrac{x_0}{x}x' + y' + \tfrac{pz'}{c} \\ &= -\tfrac{1}{dx}(\lambda - dx)^2 - \delta(1 - R_0)y - \tfrac{pz}{c}(\tfrac{c\epsilon y^2}{1+\epsilon y} + qy + b). \end{aligned}$$

Thus $V_0' \leq 0$ when $R_0 < 1$, and the result follows from LaSalle's invariance principle. □

Theorem 2.2. *E_1 is globally asymptotically stable if $1 < R_0 < 1 + ky_1^*/d$, and is locally asymptotically stable if $R_0 > 1 + ky_2^*/d$.*

Proof. Define a function,

$$V_1 = (x - x_1 - x_1 \ln \frac{x}{x_1}) + (y - y_1 - y_1 \ln \frac{y}{y_1}) + \frac{p}{h(y_1^*)} z.$$

Along the trajectories of system (1.2), we have

$$\begin{aligned} V_1' &= x' - \tfrac{x_1}{x} x' + y' - \tfrac{y_1}{y} y' + \tfrac{p}{h(y_1^*)} z' \\ &= -\tfrac{\lambda}{k\delta x}(\delta - kx)^2 - \tfrac{1}{h(y_1^*)} pz[h(y_1^*)(y - y_1) - (\tfrac{cy}{1+\epsilon y} - qy - b)]. \end{aligned}$$

Let $g(y) = cy/(1+\epsilon y) - qy - b$, then $h(y) = g'(y) = c/(1+\epsilon y)^2 - q$, and $g''(y) = -2c\epsilon/(1+\epsilon y)^3 < 0$. Then by intermediate value theorem, there is ξ_1 between y and y_1^* such that

$$g(y) = g(y) - g(y_1^*) = h(y_1^*)(y - y_1^*) + \frac{1}{2} g''(\xi_1)(y - y_1^*)^2. \tag{2.1}$$

(a) If $1 < R_0 < 1 + ky_1^*/d$, which is equivalent to $0 < y_1 < y_1^*$, from (2.1), we have

$$g(y) \le h(y_1^*)(y - y_1^*) < h(y_1^*)(y - y_1),$$

for all $y > 0$. Thus, $V_1' \le 0$, and therefore, V_1 is a global Lyapunov function.

(b) If $R_0 > 1 + ky_2^*/d$, which is equivalent to $y_1 > y_2^*$, we have

$$g(y) < h(y_1^*)(y - y_1) \tag{2.2}$$

for $y > y_1$, since $g(y) < 0$, but $h(y_1^*)(y - y_1) > 0$. It is clear that (2.2) still holds for all $y > y_1 - \xi_2$, where $\xi_2 > 0$ is sufficiently small. Thus, $V_1' \le 0$, and therefore, V_1 is a local Lyapunov function near E_1.

The result follows from LaSalle's invariance principle. □

Theorem 2.3. *E_1^* is locally asymptotically stable if it exists.*

Proof. The characteristic equation of the Jacobin matrix at E_1^* is

$$s^3 + a_1 s^2 + a_2 s + a_3 = 0, \tag{2.3}$$

where

$$\begin{aligned} &a_1 = d + ky_1^* > 0, \\ &a_2 = py_1^* z_1^* h(y_1^*) + k^2 y_1^* x_1^*, \\ &a_3 = py_1^* z_1^* h(y_1^*)(d + ky_1^*) > 0, \\ &a_1 a_2 - a_3 = k^2 y_1^* x_1^* (d + ky_1^*) > 0. \end{aligned}$$

The result follows from Routh-Hurwitz criterion. □

The stability of the last equilibrium is given in the following theorem without proof, because it is similar to the above one, except that $h(y_2^*) < 0$.

Theorem 2.4. *E_2^* is unstable if it exists.*

3 Permanence

Firstly, we show that system (1.2) is uniformly bounded above.

Theorem 3.1. *There exists an $M > 0$ such that all the solutions of system (1.2) satisfy $x(t), y(t), z(t) \leq M$ for all large t.*

Proof. It is easy to check that all solutions of (1.2) are nonnegative for $t > 0$. Furthermore, we have

$$\begin{aligned} x' + y' + \tfrac{p}{c}z' &= \lambda - dx - \delta y - pyz + \tfrac{p}{c}(\tfrac{cyz}{1+\epsilon y} - qyz - bz) \\ &\leq \lambda - \alpha(x + y + \tfrac{p}{c}z), \end{aligned}$$

where $\alpha = \min\{d, \delta, b\}$. Hence by comparison theory of differential equations, it is easy to verify that there exists $t_1 > 0$ such that $x(t)+y(t)+pz(t)/c \leq M \triangleq \max\{1, c/p\}\lambda/\alpha+\varepsilon_0, t > t_1$ for $\varepsilon_0 > 0$. The proof is complete. □

Theorem 3.2. *If $1 + ky_1^*/d < R_0 < 1 + ky_2^*/d$, then system (1.2) is uniformly persistent, i.e., there exists an $\varepsilon > 0$ such that $\liminf_{t\to+\infty} x(t) \geq \varepsilon, \liminf_{t\to+\infty} y(t) \geq \varepsilon$, and $\liminf_{t\to+\infty} z(t) \geq \varepsilon$.*

Proof. By Theorem 3.1, there exists an $M > 0$ such that $y(t) < M$ for all $t > t_1$, Thus we have

$$x' = \lambda - dx - kxy \geq \lambda - (d + kM)x,$$

for all $t > t_1$, and the result for x follows immediately. Therefore, it suffices to prove that $\liminf_{t\to+\infty} y(t) \geq \varepsilon$, and $\liminf_{t\to+\infty} z(t) \geq \varepsilon$, which follows from an application of Theorem 4.6 in [5], with $X_1 = \text{int}(R^3_+)$ and $X_2 = \text{bd}(R^3_+)$. The left of the proof is to verify that E_0 and E_1 are weak repellers for X_1, and we omit it here since it is similar to that of [6, Theorem 3.2]. □

Theorems 3.1 and 3.2 imply that (1.2) is permanent provided that $1 + ky_1^*/d < R_0 < 1 + ky_2^*/d$.

From the results in Sections 2 and 3, we can summarize the stability of the equilibria and the behaviors of system (1.2) in the following table:

Equilibria	(i) $R_0 < 1$	(ii) $1 < R_0 < R_1$	(iii) $R_1 < R_0 < R_2$	(iv) $R_0 > R_2$
$E_0(x_0, 0, 0)$	GAS	US	US	US
$E_1(x_1, y_1, 0)$	–	GAS	US	LAS
$E_1^*(x_1^*, y_1^*, z_1^*)$	–	–	LAS	LAS
$E_2^*(x_2^*, y_2^*, z_2^*)$	–	–	–	US
System (1.2)	Tends to E_0	Tends to E_1	Permanent	Bistable

Table 1: The stability of the equilibria and the behaviors of system (1.2). Here $R_1 = 1 + ky_1^*/d$, $R_2 = 1 + ky_2^*/d$, 'GAS', 'LAS', 'US' and '–' represent that the equilibrium is globally asymptotically stable, locally asymptotically stable, unstable and nonexistent, respectively.

4 Discussion

As what Komarova *et al.* [7] suggested, E_1 describes the failure of long-term control in the model and can correspond to an *in vivo* scenario where suboptimal immune responses are temporarily maintained and subsequently collapse. Such suboptimal responses are not explicitly included in the model but can be assumed to be implicit in parameters determining virus load (such as the replication rate and the death rate). To use specific examples, the immune control outcome (E_1^*) in the model can correspond to the state of long-term nonprogression in HIV infection ([8]), whereas failure of long-term control in the model (E_1) corresponds to typical HIV disease progression. A similar difference can be seen in HCV infection: a small fraction of patients control the virus (or clear virus from blood) and establish long-term immunity (E_1^*), whereas most patients fail to do so and eventually may develop disease (E_1) ([9]).

We seek to understand the stability of these equilibria as R_0 increases from low to high, because it is influenced by drug therapy. These results suggest that

(i) If R_0 is very small, the virus cannot infect the host, and the system converges to E_0.

(ii) If R_0 crosses a threshold, an infection can be established, but the amount of antigenic stimulation is too low to trigger sustained immunity. The system converges to E_1.

(iii) If R_0 is higher and crosses another threshold, levels of antigen are sufficient to trigger sustained immunity. The system converges to the equilibrium describing long-term immunological control, E_1^*.

(iv) If R_0 is still higher and crosses a final threshold, the immune response can be significantly impaired. In this parameter region, both the immune control (E_1^*) and the

virus equilibrium (E_1) are stable, and the outcome of infection depends on the initial conditions.

Now we assume that the patient is in the bistable parameter region (iv). Thus, infection will result in disease or immune control outcome, depending on the initial conditions, i.e., which region does $(x(0), y(0), z(0))$ belong to, the basin of attraction for E_1 or E_1^*? However, the model suggests that therapeutic intervention may shift the dynamics toward the immune control outcome. During therapy, R_0 is reduced in the model and the amount of reduction corresponds to the efficacy of the drugs. On cessation of therapy, R_0 is reset to its pretreatment value. If therapy is efficient enough to reduce R_0 at least from parameter region (iv) to region (iii), then after one phase (or several phases) of therapy, the system may enter the basin of attraction for E_1. Then the therapy could be stopped, since R_0 has been reset to region (iv), thus the system may result in the immune control outcome, E_1^*.

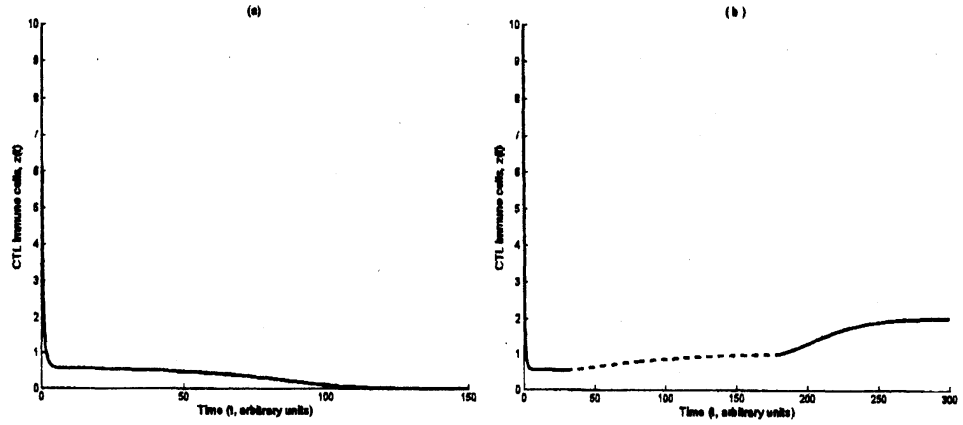

Figure 1: Time series of z. The phase of treatment is indicated by dash line. (a) Without therapy, $z(t)$ tends to zero. (b) After a phase of therapy, which begins at $t = 30$, the system will tend to immune control outcome, although the treatment has been stopped at $t = 180$. Parameter values are chosen as follows: $\lambda = 1, d = 0.05, k = 0.5, p = 0.3, c = 0.6, \epsilon = 0.5, q = 0.2, b = 0.2, \delta = 0.3$. During therapy, $\delta = 0.6$.

An simulation is shown in Fig. 1. The initial values of the two trajectories are the same $(20, 10, 10)$, but there is a phase of therapy (from $t = 30$ to 180) in the right one. The results are obviously different, i.e., the phase of the therapy leads to an immunological control, instead of the disease outcome in the left one.

Theoretically, the optimal timing of when therapy should be stopped and/or restarted can be determined by monitoring the dynamics of the system.

Finally, we point out that the bistable behavior as described in this paper hinges on the assumption that the virus impairs specific immune responses. Therapy can therefore shift the patient from a disease progression to a control outcome. With viruses that do not impair immunity, there is no bistability.

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