Analysis of A Virus Dynamics Model

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Abstract. In order to more accurately characterize the virus infection in the host, a virus dynamics model with latency and virulence is established and analyzed in this paper. The positivity and boundedness of the solution are proved. After obtaining the basic reproduction number and the existence of infected equilibrium, the Lyapunov method and the LaSalle invariance principle are used to determine the stability of the uninfected equilibrium and infected equilibrium by constructing appropriate Lyapunov functions. We prove that, when the basic reproduction number does not exceed 1, the uninfected equilibrium is globally stable, the virus can be cleared eventually; when the basic reproduction number is more than 1, the infected equilibrium is globally stable, the virus will persist in the host at a certain level. The effect of virulence and latency on infection is also discussed.

1. Introduction

In the study of viral infection dynamics, most scholars think that the death of infected target cells is caused by the release of progeny virus. But the recent medical experiments find that, in the process of virus infection, in addition to the disruption death, the death of infected target cells also depends on the virulence of virus[1]. Based on the fact that the intensity of virulence depends on the size of viral load, Regoes adopts virulence function αv[2]. Furthermore, the unified general function $g(v)$ is used to describe the virulence[3], However, when analyzing the stability of infected equilibrium, where the concentration of virus is v^*, the author gives plenty of restrictions:

$$\left(1-\frac{v}{v^*}\right)\left(1-\frac{g(v^*)}{g(v)}\right)<0,\left(\frac{g(v)}{g(v^*)}-\frac{v}{v^*}\right)\left(1-\frac{g(v^*)}{g(v)}\right)\le 0$$

The article does not give a reasonable biological interpretation of these conditions, which makes it difficult to meet in practical applications.

On the basis of above studies, we adopt an unified virulence function $g(v)$, only retaining condition $g(0)=0$ and $g'(v)>0$, which means that virulence effect disappears when there is no virus in the body; On the contrary, the higher the viral load is and the stronger the virulence is. Moreover, we also consider the influence of latency. A virus dynamics model is established:

$$\begin{cases} \dfrac{\mathrm{d}x}{\mathrm{d}t} = \lambda - dx - \beta xv \\ \dfrac{\mathrm{d}z}{\mathrm{d}t} = \mu\beta xv - (d+\varepsilon)z \\ \dfrac{\mathrm{d}y}{\mathrm{d}t} = (1-\mu)\beta xv + \varepsilon z - \left[g(v)+a\right]y \\ \dfrac{\mathrm{d}v}{\mathrm{d}t} = ky - \gamma v \end{cases} \tag{1.1}$$

where $x(t)$, $z(t)$, $y(t)$ and $v(t)$ denote the concentration of uninfected target cells, latently infected target cells, actively infected target cells and free virus at time t, respectively. λ is the recruitment rate of uninfected target cells. dx, dz and γv are the death rate of uninfected target cells, latently infected target cells and actively infected target cells, respectively. β is the infection rate coefficient. The fractions $\mu(0<\mu<1)$ and $1-\mu$ are the probability that upon infection, an uninfected target cell becomes latent or active. Latently infected target cells are converted to actively infected target cells with rate εz. Actively infected target cells, on the one hand, die directly at rate $g(v)y$ due to virulence; on the other hand, disrupt at rate ay, at the same time generating progeny virus at rate ky. According to the biological background, all parameters are positive and $a > d$.

Figure 1 describes the virus infection mechanism of model (1.1):

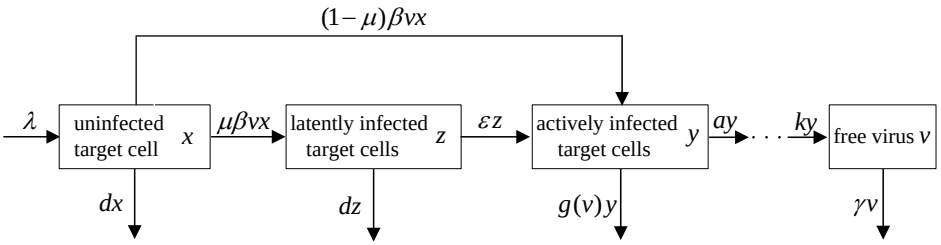

Figure 1: The virus infection diagram for model (1.1)

2. Positivity and boundedness of the solution

It is obvious that region $\Omega = \{(x,z,y,v): x>0, z\ge 0, y\ge 0, v\ge 0\}$ is a positively invariant for model (1.1). Summing up the first three equations in model (1.1), it follows that

$$(x+z+y)' = \lambda - dx - dz - \left[g(v)+a\right]y \le \lambda - d(x+z+y)$$

then $\lim_{t\to\infty}\sup(x+y+z)\le \lambda/d$. where $a>d$ and $g(v)\ge 0$ are used.

Since $x(t)>0$ and $z(t)\ge 0$, then $\lim_{t\to\infty}\sup y(t)\le \lambda/d$. When t is large enough, from the last equation of model (1.1),we obtain $\lim_{t\to\infty}\sup y(t)\le \lambda/d$, then $\lim_{t\to\infty}\sup v(t)\le \lambda k/\gamma d$. So the region $\Omega = \{(x,z,y,v): 0<x+z+y\le \lambda/d, 0\le v\le \lambda k/\gamma d\}$ is a positively invariant set of model (1.1).

3. Basic reproduction number and the existence of equilibrium

Model (1.1) always has an uninfected equilibrium $E_0(\lambda/d,0,0,0)$. According to the method of next generation[4], the basic reproduction number of model (1.1) is:

$$R_0 = \frac{\lambda\beta k\left[(1-\mu)d+\varepsilon\right]}{\gamma a d(d+\varepsilon)}$$

Let the right-hand side of equalities in model (1.1) be 0. Then calculating the corresponding equation straightforwardly, we have following theorem:

Theorem 1. *When* $R_0 > 1$, *model (1.1) has also a unique infected equilibrium* $E^*(x^*, z^*, y^*, v^*)$ *besides* E_0, *where*

$$x^* = \frac{\lambda}{d+\beta v^*}, z^* = \frac{\lambda\beta\mu v^*}{(d+\varepsilon)(d+\beta v^*)}, y^* = \frac{\gamma v^*}{k}$$

and v^* *is the only positive root of the equation* $\gamma(d+\varepsilon)\left[g(v)+a\right]/\left[(1-\mu)d+\varepsilon\right] = \lambda\beta k/(d+\beta v)$ *in the interval* $(0, \lambda k/\gamma d)$.

4. The global stability

Theorem 2. *When* $R_0 \le 1$, *the uninfected equilibrium* $E_0(\lambda/d, 0, 0, 0)$ *is globally stable on* Ω.

Proof. Let

$$L_1 = x - x_0 - x_0 \ln\frac{x}{x_0} + \frac{\lambda\beta k\varepsilon}{\gamma ad(d+\varepsilon)} z + \frac{\lambda\beta k}{\gamma ad} y + \frac{\lambda\beta}{\gamma d} v$$

Then the derivative of L_1 along solution of model (1.1) is

$$L_1' = \left(1-\frac{x_0}{x}\right)(\lambda - dx - \beta vx) + \frac{\lambda\beta k\varepsilon}{\gamma ad(d+\varepsilon)}\left[\mu\beta vx - (d+\varepsilon)z\right]$$
$$+ \frac{\lambda\beta k}{\gamma ad}\left[(1-\mu)\beta vx + \varepsilon z - g(v)y - ay\right] + \frac{\lambda\beta}{\gamma d}(ky - \gamma v)$$

Since $d = \lambda/x_0$, then

$$L_1' = \lambda\left(1-\frac{x_0}{x}\right)\left(1-\frac{x}{x_0}\right) - (1-R_0)\beta vx - \frac{\lambda\beta k}{\gamma ad} g(v)y$$

where $\lambda\left(1-\frac{x_0}{x}\right)\left(1-\frac{x}{x_0}\right) = \lambda\left(2-\frac{x}{x_0}-\frac{x_0}{x}\right) \le 0$.

When $R_0 \le 1$, it is obvious that $L_1' \le 0$. We can derive that the maximum invariant set in $\left\{(x,z,y,v) \in \Omega : L_1' = 0\right\}$ is the singleton $\left\{E_0\right\}$. According to the LaSalle's invariance principle[5], Theorem 2 holds.

Theorem 3. *When* $R_0 > 1$, *the infected equilibrium* $E^*(x^*, z^*, y^*, v^*)$ *is globally stable in* Ω.

Proof. Define functions

$$L_2 = \int_{x^*}^{x} \frac{\theta - x^*}{\theta} d\theta + m\int_{z^*}^{z} \frac{\theta - z^*}{\theta} d\theta + n\int_{y^*}^{y} \frac{\theta - y^*}{\theta} d\theta + p\int_{v^*}^{v} \frac{\theta - v^*}{\theta} d\theta + q\int_{v^*}^{v} \left[g(\theta) - g(v^*)\right] d\theta$$

where

$$m = \frac{\varepsilon z^*}{\mu\left[\varepsilon z^* + (1-\mu)\beta x^* v^*\right]}, n = \frac{\beta x^* v^*}{\varepsilon z^* + (1-\mu)\beta x^* v^*}$$

and

$$p = \frac{\beta x^*}{\gamma}, q = \frac{\beta x^* v^*}{k\left[\varepsilon z^* + (1-\mu)\beta x^* v^*\right]}$$

Then the derivatives of L_2 along the solution of model (1.1) is

$$L_2' = \left(1-\frac{x^*}{x}\right)x' + m\left(1-\frac{z^*}{z}\right)z' + n\left(1-\frac{y^*}{y}\right)y' + p\left(1-\frac{v^*}{v}\right)v' + q\left[g(v) - g(v^*)\right]v'$$

It is easy to derive that

$$\lambda = dx^* + \beta x^* v^*, d + \varepsilon = \frac{\mu\beta x^* v^*}{z^*}, a = \frac{(1-\mu)\beta x^* v^* + \varepsilon z^*}{y^*} - g(v^*), k = \frac{\gamma v^*}{y^*} \qquad (4.1)$$

substituting equation (1.1) and (4.1) into L_2', then

$$\begin{aligned} L_2' &= \left(1-\frac{x^*}{x}\right)(dx^* + \beta x^* v^* - dx - \beta xv) + m\left(1-\frac{z^*}{z}\right)\left(\mu\beta xv - \mu\beta x^* v^* \frac{z}{z^*}\right) \\ &\quad + n\left(1-\frac{y^*}{y}\right)\left[(1-\mu)\beta xv + \varepsilon z - g(v)y - (1-\mu)\beta x^* v^* \frac{y}{y^*} - \varepsilon z^* \frac{y}{y^*} + g(v^*)y\right] \\ &\quad + p\left(1-\frac{v^*}{v}\right)(ky - \gamma v) + q(ky - \gamma v)\left[g(v) - g(v^*)\right] \\ &= dx^*\left(1-\frac{x^*}{x}\right)\left(1-\frac{x}{x^*}\right) + n(y^* - y)\left[g(v) - g(v^*)\right] + q\left(\gamma v^* \frac{y}{y^*} - \gamma v\right)\left[g(v) - g(v^*)\right] + l_2' \end{aligned}$$

where

$$\begin{aligned} l_2' &= n\left\{(1-\mu)\beta(xv + x^* v^*) + \varepsilon(z + z^*) - \left[(1-\mu)\beta x^* v^* + \varepsilon z^*\right]\frac{y}{y^*} - \left[(1-\mu)\beta xv + \varepsilon z\right]\frac{y^*}{y}\right\} \\ &\quad + \left(\beta x^* v^* + \beta x^* v - \beta xv - \frac{\beta v^* x^{*2}}{x}\right) + p\left(\gamma v^* - \gamma v + \frac{\gamma v^* y}{y^*} - \frac{\gamma y v^{*2}}{y^* v}\right) \\ &\quad + m\left(\mu\beta xv + \mu\beta x^* v^* - \frac{\mu\beta x^* v^* z}{z^*} - \frac{\mu\beta xvz^*}{z}\right) \end{aligned}$$

substituting m, n, p and q into l_2', we obtain

$$l_2' = n\left[(1-\mu)\beta x^* v^*\left(3 - \frac{x^*}{x} - \frac{yv^*}{y^* v} - \frac{xy^* v}{x^* y v^*}\right) + \varepsilon z^*\left(4 - \frac{x^*}{x} - \frac{zy^*}{z^* y} - \frac{yv^*}{y^* v} - \frac{xz^* v}{x^* z v^*}\right)\right] \le 0$$

It is obvious that

$$dx^*\left(1-\frac{x^*}{x}\right)\left(1-\frac{x}{x^*}\right) = dx^*\left(2 - \frac{x}{x^*} - \frac{x^*}{x}\right) \le 0$$

substituting n and q into the two intermediate items of L_2', we have

$$n(y^* - y)\left[g(v) - g(v^*)\right] + q\left(\frac{\gamma v^* y}{y^*} - \gamma v\right)\left[g(v) - g(v^*)\right] = -q\gamma(v - v^*)\left[g(v) - g(v^*)\right] \le 0$$

where $g'(v) > 0$ is used. Then

$$\begin{aligned} L_2' &= n\left[(1-\mu)\beta x^* v^*\left(3 - \frac{x^*}{x} - \frac{yv^*}{y^* v} - \frac{xy^* v}{x^* y v^*}\right) + \varepsilon z^*\left(4 - \frac{x^*}{x} - \frac{zy^*}{z^* y} - \frac{yv^*}{y^* v} - \frac{xz^* v}{x^* z v^*}\right)\right] \\ &\quad + dx^*\left(2 - \frac{x}{x^*} - \frac{x^*}{x}\right) - q\gamma\left[g(v) - g(v^*)\right](v - v^*) \le 0 \end{aligned}$$

Since $n > 0$ and $q > 0$, then $L_2' = 0$ is equivalent to $x = x^*$, $z = z^*$, $y = y^*$ and $v = v^*$. By the Lyapunov asymptotic stability theorem[6], Theorem 3 holds.

5. The effect of virulence on the infection

In this section, we adopt a specific virulence function $g(v)=bv/(1+mv)(b>0,m>0)$ to analyze the effect of virulence in the process of infection. It is easy to derive that $g(0)=0$, $g'(v)=b/(1+mv)^2>0$ and $\lim_{t\to\infty} g(v)=b/m$, which is biologically meaningful. Based on the analysis of a HIV-1 model containing latency[7], we choose the following parameters: $\lambda=10^4\,\mathrm{ml^{-1}\,d^{-1}}$, $1/d=100\,\mathrm{d}$, $\beta=2.4\times10^{-8}\,\mathrm{ml\,d^{-1}}$, $\mu=0.5$, $\varepsilon=0.3\mathrm{d^{-1}}$, $1/a=1\mathrm{d}$, $k=4000\mathrm{d^{-1}}$, $\gamma=23\mathrm{d^{-1}}$. We fix the initial concentration at $(1.2\times10^6,15,25,100)$.

Firstly, we fix $m=1.2$ and choose three group numbers of b; secondly, we fix $b=2$ and choose three group numbers of m. By numerical simulations, we obtain

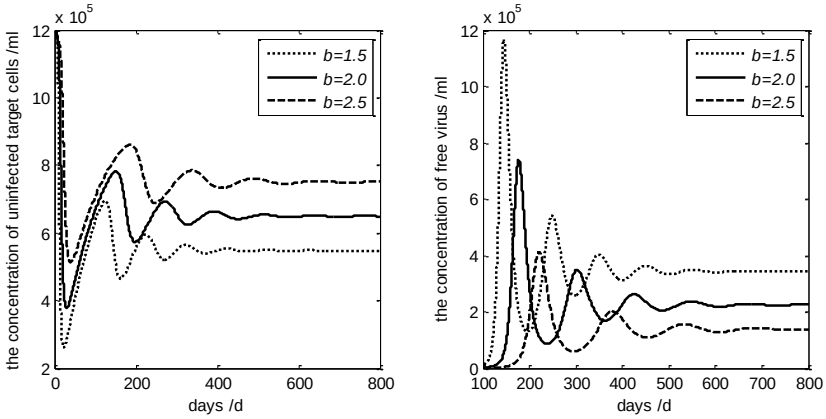

Figure 2: The number of $x(t)$ and $v(t)$ when b changes

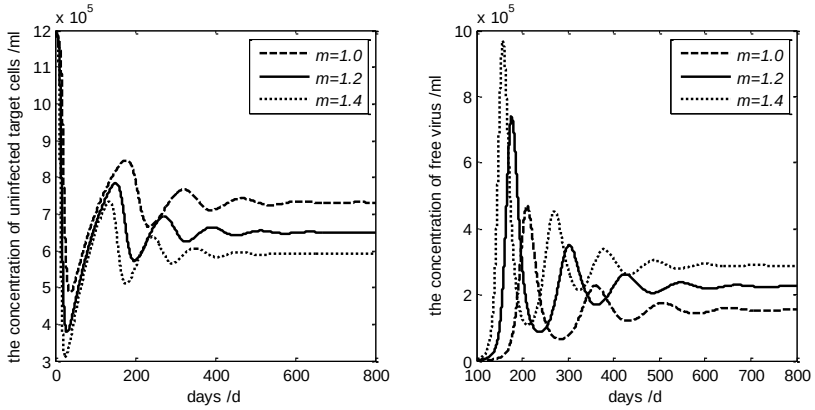

Figure 3: The number of $x(t)$ and $v(t)$ when m changes

From Figure 2 and Figure 3, we can conclude that: the bigger the parameter b is and the smaller the m is, which represents the stronger the virulence is, then the higher the number of uninfected target cells and the lower the concentration of free virus are. This phenomenon is easy to understand: when the virulence becomes stronger, the infected target cells decreases, then free virus declines, thus the probability of uninfected target cells becoming infected is reduced, the number of uninfected target cells increases. Finnally, the degree of infection becomes lighter.

6. Conclusion

In this paper, we have considered a virus dynamics model with latency and virulence depending on the viral load. We adopt an unified general virulence function $g(v)$. Based on the release of virus, we partition the infected cells into the latency and the activity. The basic reproduction number determines the dynamics behavior of this model. Finally, we discuss the effect of virulence on the infection: the stronger the virulence is, and the lighter the degree of infection is.

Furthermore, from the expression of R_0 and E^*, it is easy to find that parameters μ and ε can influence R_0 and the position of E^*, so we can also change the infection results by corresponding drug therapy.

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