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A Mathematical Model of HIV Infection with Cellular and Immune Delays

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Abstract: We propose an infection age HIV model that considers virus-to-cell and cell-to-cell infections and immune response. This new and more complex model combines and extends the models proposed in [4,9]. We prove that the solution to the associated initial-value problem is positive and bounded from above. Furthermore, we analyze the stability of the infection-free equilibrium.

Keywords: HIV infection; stability; cellular infections; immune response

1 Introduction

It is known that the human immunodeficiency virus (HIV) infects $CD4^+$ T helper cells, which are an important part of the immune system because they facilitate the body's response to many common but potentially fatal infections. Because of its lethality and quasi-incurability, HIV has become a major problem for human health; it is responsible for millions of infections and deaths so far. Without treatment with HIV medicines, HIV infection advances in stages, getting worse over time. The phase of primary infection is characterized by a strong viral replication, which is followed by a strong immune response. In the second phase of HIV infection, infected individuals display no symptoms, but have persistent viral replications, which eventually results in the development of AIDS [8], which is the final, most severe stage of HIV infection. Individuals are diagnosed with AIDS if they have a T cells count of less than 200 $cells/mm^3$ or if they have certain opportunistic infections. Without treatment, people with AIDS typically survive about 3 years.

Mathematical models have made substantial contributions to our understanding of HIV infection, immune responses, and anti-retroviral treatment (see [3,5,7,13,15,16], etc.). Time delays have also been incorporated into mathematical models to study virus dynamics; see for example [1,2,6,10,12,14,24], among many others. There have also been a variety of modifications of these models that have resulted from incorporating drug therapies. It is known that there is no perfect treatment for HIV infection, but HIV medicines can prevent HIV from advancing to AIDS. HIV medicines help people with HIV live longer, healthier lives. HIV medicines also reduce the risk of HIV transmission to other people. For examples of how mathematical models predict HIV treatment outcomes, see [17,18,19,20,21,22,23], and references therein.

In this paper, we introduce a new model based on the models presented and analyzed in [4] and [9], which our model combines and extends.

2 New Model and Properties

In [4], the authors consider the following viral model incorporating mitosis of the healthy target cells which is described by the logistic term, two routes of infection: virus-to-cell and cell-to-cell infection, and three time delays accounting, respectively, for a period of the chemical reaction in the virus-to-cell infection, an intracellular incubation period in the cell-to-cell infection, and a period of the immune lag incurred by antigenic activation and selection.

$$\frac{dT}{dt} = s - \mu_1 T(t) + rT(t)\left(1 - \frac{T(t)}{T_{max}}\right) - \beta_1 T(t)V(t) - \beta_2 T(t)I(t) \quad (1)$$

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$$\frac{dI}{dt} = \beta_1 e^{-a_1\tau_1} T(t-\tau_1)V(t-\tau_1) + \beta_2 e^{-a_2\tau_2} T(t-\tau_2)I(t-\tau_2) - \mu_2 I(t) - \delta E(t)I(t) \quad (2)$$

$$\frac{dV}{dt} = bI(t) - \mu_3 V(t) \quad (3)$$

$$\frac{dE}{dt} = ce^{-a_3\tau_3} I(t-\tau_3) - \mu_4 E(t) \quad (4)$$

Here, the four dynamic variables are the healthy target cells $T(t)$, the infected cells $I(t)$, the virus $V(t)$, and the effector cells $E(t)$. In the equation (1) for $T(t)$, s is the constant input rate, and β_1 and β_2 are the virus-to-cell and cell-to-cell infection rates, respectively. The mitosis of healthy target cells is described by the logistic term $rT(t)\left(1-\frac{T(t)}{T_{max}}\right)$, where r is the intrinsic mitosis rate and T_{max} is the carrying capacity of the target cell population. That is, if the T cells population ever reaches T_{max} (in the uninfected case) it should decrease. Thus, the constraint $s < \mu_1 T_{max}$ appears naturally. Furthermore, all cells have a natural lifespan; here μ_i, $i = 1,\dots,4$, denote the death rates of populations $T(t)$, $I(t)$, $V(t)$, and $E(t)$, respectively, and δ is the death rate of infected cells due to action of the immune response. The first two terms in the $I(t)$ equation (2) represent the delayed sources of infection by free virus and infected cells, respectively, and b in (3) denotes the average production rate of virus from an infected cell. The first term of the equation (4) quantifies the delayed production rate of the effector cells $E(t)$.

In [9], the authors propose a model that incorporates both the cell-to-cell infection mechanism and the virus-to-cell infection mode, considering infection age as well (the notations are synchronized with the notations of the model (1)-(4)).

$$\frac{dT}{dt} = s - \mu_1 T(t) - \beta_1 T(t)V(t) - \beta_2 T(t)I(t) \quad (5)$$

$$\frac{dI}{dt} = \int_0^\infty [\beta_1 T(t-s)V(t-s) + \beta_2 T(t-s)I(t-s)]e^{-as} f(s)ds - \mu_2 I(t) \quad (6)$$

$$\frac{dV}{dt} = bI(t) - \mu_3 V(t) \quad (7)$$

Here, it is assumed that the infected cells may die or be cleared at a rate a before becoming productively infected, that is, only a proportion e^{-as} survives after a time period s. As explained in [9], the time for infected cells to become productively infected may vary from case to case; this explains the distribution function $f : [0,\infty) \to [0,\infty)$, which is nonnegative, has compact support, and satisfies $\int_0^\infty f(s)ds = 1$.

Based on (1)-(4) and (5)-(7), we propose the following model, whose dynamical variables and parameters are as in (1)-(4) and (5)-(7), and are self-explanatory.

$$\frac{dT}{dt} = s - \mu_1 T(t) + rT(t)\left(1-\frac{T(t)}{T_{max}}\right) - \beta_1 T(t)V(t) - \beta_2 T(t)I(t) \quad (8)$$

$$\frac{dI}{dt} = \int_0^\infty [\beta_1 T(t-s)V(t-s) - \mu_2 I(t) + \beta_2 T(t-s)I(t-s)]e^{-as} f(s)ds - \delta E(t)I(t) \quad (9)$$

$$\frac{dV}{dt} = bI(t) - \mu_3 V(t) \quad (10)$$

$$\frac{dE}{dt} = c\int_0^\infty I(t-s)e^{-as} f(s)ds - \mu_4 E(t) \quad (11)$$

In what follows, we study some properties of this newly introduced HIV mathematical model.

2.1 Positivity and boundedness of solutions

Since all dynamic variables are populations, only nonnegative, bounded initial conditions make sense for the delay system (8)-(11). With such initial conditions, our first result states that the solution to the evolution problem stays positive and bounded. One of the tools to be used in the proof is the classical Gronwall inequality, which states that if $y : [0,T] \to \mathbb{R}$ is differentiable and $y(t)$ satisfies the differential inequality

$$y'(t) \le h(t) + g(t)y(t),$$

with g continuous and h locally integrable, then

$$y(t) \le y(0)e^{G(t)} + \int_0^t e^{G(t)-G(s)} h(s)ds,$$

for $G(t) := \int_0^t g(r)dr$.

Theorem 1. Let $(T(t),I(t),V(t),E(t))$ be the solution of the system (8)-(11) with continuous, bounded initial conditions $T_0, I_0, V_0, E_0 : (-\infty,0] \to [0,\infty)$. Assume that either $I(t_0) > 0$ or $V_0(t_0) > 0$ for some $t_0 \in (-\infty,0]$ (i.e., infection occurs). Then $T(t)$, $I(t)$, $V(t)$, and $E(t)$ are all positive and bounded for $t > 0$.

Proof. First, let us prove that the solution of (8)-(11) is positive for all $t > 0$. Observe that $T(t)$, $I(t)$, $V(t)$, and $E(t)$ must be positive in a right-side neighborhood of $t = 0$. This follows from continuity (if either one is positive at zero, then it must be positive in a neighborhood of zero), or from the fact that the derivative at zero must be positive if either one is zero at $t = 0$. Arguing by contradiction, assume that there exists $t_1 > 0$ such that

$$\min\{T(t_1),I(t_1),V(t_1),E(t_1)\} = 0$$

for first time.

First, assume $T(t_1)=0$. Then, from (8) it follows that $T'(t_1)=s>0$, which is in contradiction with the positivity of $T(t)$ in a left-side neighborhood of t_1. In fact, exactly the same argument proves that $T(t)$ must be positive on the entire interval $[0,\infty)$, independently of the behavior of the other variables of the system. Next, we prove the positivity of $I(t)$. If $I(t_1)=0$, then, from (9), we get

$$I'(t_1)=\int_0^\infty [\beta_1 T(t_1-s)V(t_1-s) + \beta_2 T(t_1-s)I(t_1-s)]e^{-as}f(s)ds>0,$$

which contradicts the positivity of $I(t)$ in a left-side neighborhood of t_1. Similar arguments show that neither $V(t_1)$ nor $E(t_1)$ can be zero. In conclusion, the solution to (8)-(11) is positive for all $t>0$.

Let us now prove that the solution is bounded from above. To prove the boundedness of $T(t)$, observe that

$$\frac{dT}{dt}\le s-\mu_1 T(t)+rT(t)\Big(1-\frac{T(t)}{T_{max}}\Big),$$

which when coupled with the constraint $s<\mu_1 T_{max}$ shows that $T\le T_{max}$ for all time $t>0$, because $T'(t)<0$ wherever $T(t)=T_{max}$.

Let m be the maximum value of the function $g(y):=s+ry(1-y/T_{max})$, that is $m:=s+rT_{max}/4$. Consider the function

$$H(t):=\int_0^\infty T(t-s)e^{-as}f(s)ds+I(t),$$

and observe that

$$\begin{aligned}\frac{dH}{dt}&=\int_0^\infty g(T(t-s))e^{-as}f(s)ds\\&\quad-\mu_1\int_0^\infty T(t-s)e^{-as}f(s)ds\\&\quad-\mu_2 I(t)-\delta E(t)I(t)\\&\le m-\mu H(t),\end{aligned}$$

where $\mu:=\min\{\mu_1,\mu_2\}$. From Gronwall's inequality, it follows that

$$\begin{aligned}H(t)&\le H(0)e^{-\mu t}\\&\quad+\int_0^t e^{-\mu t+\mu s}m ds\le H(0)e^{-\mu t}+\frac{m}{\mu}\\&\le T_{max}+I(0)+\frac{m}{\mu}\ \text{ for } t\ge 0.\end{aligned}$$

Hence, $H(t)$ is bounded by $M:=T_{max}+I(0)+m/\mu$, which in turn implies the boundedness of $I(t)$.

From equations (10) and (11), together with Gronwall's inequality, one can obtain the following upper bounds for $V(t)$ and $E(t)$ for $t\ge 0$

$$\begin{aligned}V(t)&\le V(0)e^{-\mu_3 t}+\frac{bM}{\mu_3}(1-e^{-\mu_3 t})\\&\le V(0)+\frac{bM}{\mu_3},\\E(t)&\le E(0)e^{-\mu_4 t}+\frac{cM_I}{\mu_4}(1-e^{-\mu_4 t})\\&\le E(0)+\frac{cM_I}{\mu_4},\end{aligned}$$

where M_I is an upper bound of $I(t)$ on $(-\infty,\infty)$ (possibly greater than M). □.

2.2 Stability of the Infection-free Equilibrium Solution

System (8)-(11) admits an infection-free equilibrium $E_0=(\bar{T},0,0,0)$, with

$$\bar{T}:=\frac{T_{max}}{2r}\Big(r-\mu_1+\sqrt{(r-\mu_1)^2+\frac{4rs}{T_{max}}}\Big).$$

Define the basic reproduction number $\mathscr{R}_0$ by

$$\mathscr{R}_0:=\frac{b\beta_1\bar{T}\mathscr{L}_f(a)}{\mu_2\mu_3}+\frac{\beta_2\bar{T}\mathscr{L}_f(a)}{\mu_2},$$

where $\mathscr{L}_f(a):=\int_0^\infty e^{-as}f(s)ds$ is the Laplace transform of f at a. Observe that $\mathscr{R}_0$ depends on the delays related to infections but not on the delay related to the effector cells production. As explained in [4], the first term in the definition of $\mathscr{R}_0$, $\mathscr{R}_{01}:=b\beta_1\bar{T}\mathscr{L}_f(a)\mu_2^{-1}\mu_3^{-1}$, measures the average number of secondary infected generation caused by an existing free virus, while the second term, $\mathscr{R}_{02}:=\beta_2\bar{T}\mathscr{L}_f(a)\mu_2^{-1}$, measures the average number of secondary infected generation caused by an infected cell.

The following result shows that $\mathscr{R}_0$ is a measure of whether or not an infection caused by a small inoculation of virus can persist.

Theorem 2. Consider the system (8)-(11) with continuous, bounded initial conditions. The infection-free equilibrium E_0 is locally asymptotically stable if $\mathscr{R}_0<1$, and unstable if $\mathscr{R}_0>1$.

Proof. In order to analyze the stability of the infection-free equilibrium E_0, we calculate the linearization of system (8)-(11) about E_0. That is, we consider small perturbations of the components of E_0: $T(t)=\bar{T}+u_1(t)$, $I(t)=0+u_2(t)$, $V(t)=0+u_3(t)$, and $E(t)=0+u_4(t)$ in (8)-(11). Dropping the second order

terms gives

$$\frac{du_1}{dt} = -\sqrt{(r-\mu_1)^2+\frac{4rs}{T_{max}}}u_1 - \beta_1\bar{T}u_3 - \beta_2\bar{T}u_2, \quad (12)$$

$$\frac{du_2}{dt} = \int_0^\infty [\beta_1\bar{T}u_3(t-s)+\beta_2\bar{T}u_2(t-s)]e^{-as}f(s)ds - \mu_2u_2, \quad (13)$$

$$\frac{du_3}{dt} = bu_2 - \mu_3u_3, \quad (14)$$

$$\frac{du_4}{dt} = c\int_0^\infty u_2(t-s)e^{-as}f(s)ds - \mu_4u_4. \quad (15)$$

The characteristic equation of the linear system (12)-(15) is

$$(\lambda+\mu_4)\Big(\lambda+\sqrt{(r-\mu_1)^2+\frac{4rs}{T_{max}}}\Big) [(\lambda+\mu_3)(\lambda+\mu_2-\eta_a(\lambda)\beta_2\bar{T}) - b\eta_a(\lambda)\beta_1\bar{T}] = 0, \quad (16)$$

where $\eta_a(\lambda) := \int_0^\infty e^{-(a+\lambda)s}f(s)ds$. Observe that (16) has two negative eigenvalues, namely, $\lambda_1 = -\mu_4$ and $\lambda_2 = -\sqrt{(r-\mu_1)^2+4rs/T_{max}}$. Any other eigenvalue must be a root of the equation

$$(\lambda+\mu_3)(\lambda+\mu_2-\eta_a(\lambda)\beta_2\bar{T}) - b\eta_a(\lambda)\beta_1\bar{T} = 0. \quad (17)$$

Taking into account that $b\beta_1\bar{T} = \mu_2\mu_3\mathscr{R}_{01}/\mathscr{L}_f(a)$, $\beta_2\bar{T} = \mu_2\mathscr{R}_{02}/\mathscr{L}_f(a)$, and $\mathscr{R}_0 = \mathscr{R}_{01}+\mathscr{R}_{02}$, the equation (17) can be written as

$$\begin{aligned}(\lambda+\mu_3)(\lambda+\mu_2) &= (\lambda+\mu_3)\eta_a(\lambda)\beta_2\bar{T} + b\eta_a(\lambda)\beta_1\bar{T}\\ &= \eta_a(\lambda)(\lambda\beta_2\bar{T}+\mu_3\beta_2\bar{T}+b\beta_1\bar{T})\\ &= \eta_a(\lambda)\Big(\frac{\lambda\mu_2}{\mathscr{L}_f(a)}\mathscr{R}_{02}+\frac{\mu_2\mu_3}{\mathscr{L}_f(a)}\mathscr{R}_{02} + \frac{\mu_2\mu_3}{\mathscr{L}_f(a)}\mathscr{R}_{01}\Big)\\ &= \mu_2\frac{\eta_a(\lambda)}{\mathscr{L}_f(a)}(\lambda\mathscr{R}_{02}+\mu_3\mathscr{R}_0)\\ &= \mu_2\frac{\eta_a(\lambda)}{\mathscr{L}_f(a)}\Big(\lambda\frac{\mathscr{R}_{02}}{\mathscr{R}_0}+\mu_3\Big)\mathscr{R}_0\end{aligned}$$

Solving for $\mathscr{R}_0$, one obtains

$$\mathscr{R}_0 = \frac{\lambda+\mu_3}{\lambda(\mathscr{R}_{02}/\mathscr{R}_0)+\mu_3}\cdot\frac{\mathscr{L}_f(a)}{\eta_a(\lambda)}\cdot\Big(\frac{\lambda}{\mu_2}+1\Big). \quad (18)$$

Let us prove that all roots of (17) must have negative real parts when $\mathscr{R}_0 < 1$. Arguing by contradiction, assume that $\lambda = x+iy$ is a complex root of (17) with $x \geq 0$. Then, the modulus of each of the three factors on the right-hand side of equation (18) must be greater than or equal to 1, that is

$$\Big|\frac{\lambda+\mu_3}{\lambda(\mathscr{R}_{02}/\mathscr{R}_0)+\mu_3}\Big| \geq 1, \ \Big|\frac{\mathscr{L}_f(a)}{\eta_a(\lambda)}\Big| \geq 1, \text{ and } \Big|\frac{\lambda}{\mu_2}+1\Big| \geq 1,$$

which would imply $\mathscr{R}_0 \geq 1$. Thus, the real part of any solution λ to (17) must be negative if $\mathscr{R}_0 < 1$, and so E_0 is locally asymptotically stable in this case.

Next, let us prove that E_0 is unstable if $\mathscr{R}_0 > 1$. Consider the function

$$F(\lambda) := \frac{\lambda+\mu_3}{\lambda(\mathscr{R}_{02}/\mathscr{R}_0)+\mu_3}\cdot\frac{\mathscr{L}_f(a)}{\eta_a(\lambda)}\cdot\Big(\frac{\lambda}{\mu_2}+1\Big) - \mathscr{R}_0.$$

Observe that $F(0) = 1-\mathscr{R}_0 < 0$ if $\mathscr{R}_0 > 1$. On the other hand, $\lim_{\lambda\to\infty}F(\lambda) = \infty$. Therefore, there exists a positive root of $F(\lambda)$ and so, the characteristic equation of the linear system (12)-(15) has a positive eigenvalue. Hence, E_0 is unstable. □

*Remark.*The system (8)-(11) also admits an infected equilibrium $E_0^* = (T^*, I^*, V^*, E^*)$, where

$$\begin{aligned}T^* &= \frac{r-\mu_1+\theta\left(\frac{b\beta_1}{\mu_3}+\beta_2\right)+\sqrt{\Delta}}{2\left[\frac{r}{T_{max}}+\alpha\left(\frac{b\beta_1}{\mu_3}+\beta_2\right)\right]},\\ I^* &= \alpha T^* - \theta,\\ V^* &= \frac{b}{\mu_3}I^*,\\ E^* &= \frac{c\mathscr{L}_f(a)}{\mu_4}I^*,\end{aligned}$$

with

$$\theta = \frac{\mu_2\mu_3}{c\delta\mathscr{L}_f(a)} \text{ and } \alpha = \frac{\theta}{\bar{T}}\mathscr{R}_0$$

and

$$\Delta = \left[r-\mu_1+\theta\left(\frac{b\beta_1}{\mu_3}+\beta_2\right)\right]^2 + 4s\left[\frac{r}{T_{max}}+\alpha\left(\frac{b\beta_1}{\mu_3}+\beta_2\right)\right],$$

whenever $T^* > \bar{T}/\mathscr{R}_0$.

The necessary and sufficient condition for the existence of the infected equilibrium E_0^* is that $\mathscr{R}_0 > 1$. The proof uses the same ideas and techniques as in [4]; we include it here for reader's convenience. Let $h(x) := s-\mu_1x+rx(1-x/T_{max})-(\beta_1b\mu_3^{-1}+\beta_2)(\alpha x^2-\theta x)$. Observe that $h(T^*) = 0$, $h(x) > 0$ for $0 \leq x < T^*$, and $h(x) < 0$ for $T^* < x < \infty$. A simple calculation shows that

$$h\Big(\frac{\bar{T}}{\mathscr{R}_0}\Big) = \Big(1-\frac{1}{\mathscr{R}_0}\Big)\Big(s+\frac{r\bar{T}^2}{T_{max}\mathscr{R}_0}\Big),$$

which implies that $T^* > \bar{T}/\mathscr{R}_0$ if and only if $\mathscr{R}_0 > 1$.

Determining the stability and other properties of the infected equilibrium E_0^* requires further work, and will be the subject of a forthcoming paper. For example, local asymptotic stability is expected if $\mathscr{R}_0 > 1$ (as for the source models presented in [4] and [9]) and determining the global convergence to the infected equilibrium or uniform persistence of solutions would represent interesting directions of study.

3 Conclusion

In this paper, we have proposed and analyzed a new mathematical model for an HIV virus transmission process that takes into account mitosis of healthy target cells and three infection age time delays in the way of virus-to-cell and cell-to-cell infections and immune response. The delays indicate the times for processing chemical reaction in virus-to-cell infection, intracellular incubation period in cell-to-cell infection, and the time lag in immune response to active viruses. First, we showed that the solution of the initial-value problem associated to the system is positive and bounded; a necessary condition for the model's well-posedness. Then, we proved that the infection-free equilibrium is locally asymptotically stable if and only if the basic reproduction number is strictly less than one.

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