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Modeling the intracellular pathogen-immune interaction with cure rate

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ABSTRACT

Many common and emergent infectious diseases like Influenza, SARS, Hepatitis, Ebola etc. are caused by viral pathogens. These infections can be controlled or prevented by understanding the dynamics of pathogen-immune interaction in vivo. In this paper, interaction of pathogens with uninfected and infected cells in presence or absence of immune response are considered in four different cases. In the first case, the model considers the saturated nonlinear infection rate and linear cure rate without absorption of pathogens into uninfected cells and without immune response. The next model considers the effect of absorption of pathogens into uninfected cells while all other terms are same as in the first case. The third model incorporates innate immune response, humoral immune response and Cytotoxic T lymphocytes (CTL) mediated immune response with cure rate and without absorption of pathogens into uninfected cells. The last model is an extension of the third model in which the effect of absorption of pathogens into uninfected cells has been considered. Positivity and boundedness of solutions are established to ensure the well-posedness of the problem. It has been found that all the four models have two equilibria, namely, pathogen-free equilibrium point and pathogen-present equilibrium point. In each case, stability analysis of each equilibrium point is investigated. Pathogen-free equilibrium is globally asymptotically stable when basic reproduction number is less or equal to unity. This implies that control or prevention of infection is independent of initial concentration of uninfected cells, infected cells, pathogens and immune responses in the body. The proposed models show that introduction of immune response and cure rate strongly affects the stability behavior of the system. Further, on computing basic reproduction number, it has been found to be minimum for the fourth model vis-a-vis other models. The analytical findings of each model have been exemplified by numerical simulations.

1. Introduction

Many devastating diseases are caused by intracellular viral pathogens within a human cell. These pathogens use the host's machinery for its own growth and reproduction. When pathogen enters the body, this encounter the first line of defense mechanism which is largely the innate/natural immune response subsequently the acquired or specific immune

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response develops. This includes the cell mediated (Cytotoxic T cell mediated) immune response and humoral (antibody mediated) immune response. The presence of immune response along with the absorption/uptake of pathogens into uninfected cells and the presence of appropriate treatment modality play a significant role in determining the outcome and stability of the given system.

In the last few decades some mathematical models have been developed to understand the dynamics of interactions of pathogens with host's immune response in vivo [1–11]. This has helped us to predict reduction of viral load or eradication of infection and to get a better insight of spread of infection within the body. The mechanisms of immune response and pathogen interaction are discussed by Denise [3] and the references cited therein. The loss of pathogens or effect of absorption has not been considered in pathogen-immune interaction models [1–7]. Murase et al. [8] proposed a mathematical model with immune response and absorption of pathogens into uninfected cells. They studied the local stability of equilibria to get an insight of the persistence of infection and considered different cases in their models. Firstly they considered the basic virus dynamics model and then in the next model, they incorporated immune response and ignored the effect of absorption. Further, in third case they incorporated the effect of absorption of pathogens into uninfected cells and found that absorption of pathogens may disturb the stability of interior equilibrium point. Further, authors [9–12] considered the virus dynamics model with loss of pathogens into uninfected cells and extended their models to incorporate immune responses. For instance, Tian and Xu [11] studied the delayed model with CTL immune response and saturated infection rate considering the effect of absorption to describe the dynamics of HIV-1 infection. They have shown that infection becomes chronic in both cases (i) when CTL immune response is absent and (ii) when CTL immune response is present. Nuning et al. [9] studied a viral infection model for Dengue virus. They assumed that the inclusion of immune response may eradicate the infection and virus load decreases with increase in immune response. Wang et al. [12] studied viral dynamics model considering CTL immune response and antiretroviral therapy together with loss of virus into uninfected cells. They argued that the inclusion of absorption of virus term is important to get the better insight of the infection in-host.

In recent viral dynamics models, authors [13–19] developed an innovative approach to cure the infected cells using non-cytolytic processes (the removal of virus without destruction of infected cell). It is assumed and biologically proved that instead of killing, the infected cells can be cured or recovered into uninfected cells. Cuipe et al. [13] have shown in their model that in case of hepatitis B virus infection the covalently closed circular (ccc) DNA can be removed from the nucleus of infected cells and in turn the cell become uninfected cell. The detailed mechanism of the non-cytolytic process can be explored from [13,20] and the references cited therein. Zhou et al. [14] considered in their HIV dynamics model that the infected cells can be removed by two ways, either through death (mostly immune-mediated killing) or via cure (loss of cccDNA). The approach of inclusion of both cytolytic and non-cytolytic mechanisms of infected cell loss is more realistic and accurate. After that, Srivastava et al. [15] argued that the infected cells revert back to uninfected cells class due to non-completion of reverse transcription process i.e drug will not be 100% effective.

Getting motivated from the work of [8,14], we proposed a class of mathematical models to study the effect of non-cytolytic cure process without and with absorption of pathogens into uninfected cells in absence of immune response. Further, we extend our model to study aforesaid effect in presence of immune response. We incorporated the biological features in above models step by step to understand that which biological term effects prominently the behavior of infection. Besides this, we have also considered the infection rate as saturated infection rate, which is more realistic approach for modeling the dynamics of the system under consideration.

2. The mathematical model

Let $x(t)$ be the concentration of uninfected cells, $y(t)$ be the concentration of infected cells, $p(t)$ be the concentration of pathogens in blood cells.

We assume that the uninfected cells are recruited at a constant rate λ from the source within the body such as bone marrow and has a natural life expectancy of $\frac{1}{\delta_0}$ days. In general, the interaction of pathogens with uninfected cells are considered to be as "mass-action" which suggests that rate of infection is directly proportional to the product of concentrations of uninfected cells and pathogens. But this principle is not always true in real life. For example, the law of mass-action will not be followed if the concentration of pathogens is greater than that of concentration of uninfected cells. In such case, increase in concentration of pathogens will not increase infection. Taking this into consideration, we suggest that infection rate can be taken as nonlinear infection rate. Here in the proposed model we have considered saturated infection rate, also known as Holling type II infection rate and represented by the term $\frac{\beta xp}{1+\alpha p}$; $\beta > 0$, $\alpha \geq 0$. We assumed that infected cells die out at a rate δ_1 and r is the total number of pathogens produced by an infected cell due to its death. Let ρ be the cure rate of pathogens using the non-cytolytic processes. If we ignore the loss of pathogens due to absorption [2,6], then the dynamics of uninfected cells, infected cells and pathogens can be governed by the following system of ordinary differential equations:

$$\begin{cases} \dot{x} = \lambda - \delta_0 x - \dfrac{\beta xp}{1+\alpha p} + \rho y, \\ \dot{y} = \dfrac{\beta xp}{1+\alpha p} - \delta_1 y - \rho y, \\ \dot{p} = r\delta_1 y - \delta_2 p, \\ x(0) > 0, y(0) \geq 0, p(0) \geq 0. \end{cases} \tag{1}$$