



Stability of pathogen dynamics models with viral and cellular infections and immune impairment



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Abstract

We study the global stability analysis of pathogen infection models with immune impairment. Both pathogen-to-susceptible and infected-to-susceptible transmissions have been considered. We drive the basic reproduction parameter \mathcal{R}_0 , which determines the global dynamics of models. Using the method of Lyapunov function, we established the global stability of the steady states of the models. Numerical simulations are used to confirm the theoretical results.

Keywords: Global stability, pathogen infection, immune impairment transfer, Lyapunov function, cell-to-cell transmission.

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1. Introduction

Mathematical models and their analysis can be used for better understanding the dynamical behavior of human pathogens and for providing helpful suggestions for clinical treatment. Great efforts have been done to construct and analyze models which describe the pathogen dynamics (see e.g. [3, 6–16, 26, 28, 29, 31, 36, 39, 42, 46, 47]). Cytotoxic T Lymphocyte (CTL) cells play central role of adaptive immune response. CTL cells attack and kill the infected cells [30]. The pathogen infection model with CTL immune response can be presented as:

$$\begin{aligned}\dot{s} &= \beta - \delta s - \eta sp, \\ \dot{y} &= \eta sp - \epsilon y - qyx, \\ \dot{p} &= \pi y - cp, \\ \dot{x} &= \phi(y, x) - mx.\end{aligned}$$

The variables s , y , p , and x denote the concentrations of susceptible cells, infected cells, pathogens, and

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CTL cells, respectively. The susceptible cells are generated at a constant rate β , die at rate δs and become infected at rate ηsp , where δ and η are the natural death and infection rate constants, respectively. The infected cells are attacked by CTL cells at rate qyx and die at rate εy , where ε and q are the natural death and killer rate constants, respectively. Parameters π and c represent, respectively, the generation and death rate constants of pathogens. The CTL cells are proliferated at $\phi(y, x)$ and die at rate mx . In the literature, CTL immune response has been incorporated into mathematical models of different pathogen infections (see e.g. [18, 24, 25, 27, 32, 33, 37, 38, 48]). The function $\phi(y, x)$ has been chosen in different forms such as: (i) constant, $\phi(y, x) = c_1$ [31]; (ii) linear, $\phi(y, x) = \rho y$ [1, 23, 44]; (iii) nonlinear $\phi(y, x) = c_2 yx$ (see e.g. [27, 30]). In these works, most pathogen infection models assume that the presence of the antigen can stimulate immunity and neglect the CTL immune impairment. However, when the concentration of some pathogens is high, the pathogens can suppress CTL immune response. In this case, the function ϕ can be given as $\phi(y, x) = \rho y - hyx$ [35]. Pathogen infection models with immune impairment have been studied in several works (see e.g. [2, 17, 19, 20, 35, 43]).

The works presented in [2, 17, 19, 20, 35, 43] assume that the susceptible cells become infected due to pathogen contacts. However, pathogen can also spread by direct infected-to-susceptible transmission. It has been reported in several papers that there are two ways of pathogen transmissions, pathogen-to-susceptible, and infected-to-susceptible (see [4, 5, 21, 22, 34, 40, 41, 45]). However, all of these papers neglected the effect of the immune impairment.

The aim of this paper is study the qualitative behavior of two pathogen dynamics model with immune impairment and with both cellular and viral infections. We consider bilinear incidence rate in the first model and saturated incidence rate in the second one. For each model we derive the basic reproduction number which determines the global dynamics of the pathogen infection model. Some numerical simulations is performed to confirm the theoretical results.

2. The model

We propose a pathogen dynamics model with pathogen-to-susceptible and infected-to-susceptible transmissions and immune impairment as:

$$\begin{aligned} \dot{s} &= \beta - \delta s - \eta_1 sp - \eta_2 sy, \\ \dot{y} &= \eta_1 sp + \eta_2 sy - \varepsilon y - qyx, \\ \dot{p} &= \pi y - cp, \\ \dot{x} &= \rho y - mx - hyx, \end{aligned} \tag{2.1}$$

where η_1 and η_2 are the pathogen-susceptible and infected-susceptible incidence rate constants. All the parameters are positive.

2.1. Basic properties

In this subsection we investigate the nonnegativity and boundedness of the solutions of system (2.1).

Lemma 2.1. *For system (2.1) there exists a positively invariant compact set*

$$\Omega = \{(s, y, p, x) \in \mathbb{R}_{\geq 0}^4 : 0 \leq s, y \leq n_1, 0 \leq p \leq n_2, 0 \leq x \leq n_3\}. \tag{2.2}$$

Proof. We have

$$\begin{aligned} \dot{s}|_{(s=0)} &= \beta > 0, \\ \dot{y}|_{(y=0)} &= \eta_1 sp \geq 0 \text{ for all } s, p \geq 0, \\ \dot{p}|_{(p=0)} &= \pi y \geq 0 \text{ for all } y \geq 0, \\ \dot{x}|_{(x=0)} &= \rho y \geq 0 \text{ for all } y \geq 0. \end{aligned}$$

This shows the positively invariant property of $\mathbb{R}_{\geq 0}^4$ with respect to system (2.1). Let $F = s + y + \frac{\epsilon}{2\pi}p + \frac{\epsilon}{4\rho}x$. Then

$$\begin{aligned} \dot{F} &= \beta - \delta s - \eta_1 sp - \eta_2 sy + \eta_1 sp + \eta_2 sy - \epsilon y - qyx \\ &\quad + \frac{\epsilon}{2\pi}(\pi y - cp) + \frac{\epsilon}{4\rho}(\rho y - mx - hyx) \\ &= \beta - \delta s - \frac{\epsilon}{4}y - \left(q + \frac{\epsilon h}{4\rho}\right)yx - \frac{\epsilon c}{2\pi}p - \frac{\epsilon m}{4\rho}x \\ &\leq \beta - \delta s - \frac{\epsilon}{4}y - \frac{\epsilon c}{2\pi}p - \frac{\epsilon m}{4\rho}x \\ &\leq \beta - \sigma \left(s + y + \frac{\epsilon}{2\pi}p + \frac{\epsilon}{4\rho}x\right) = \beta - \sigma F, \end{aligned}$$

where $\sigma = \min\{\delta, \frac{\epsilon}{4}, c, m\}$. Then

$$F(t) \leq e^{-\sigma t} \left(F(0) - \frac{\beta}{\sigma}\right) + \frac{\beta}{\sigma}.$$

This yields, $0 \leq F(t) \leq n_1$ for all $t \geq 0$ if $F(0) \leq n_1$, where $n_1 = \frac{\beta}{\sigma}$. It follows that $0 \leq s(t), y(t) \leq n_1, 0 \leq p(t) \leq n_2$ and $0 \leq x(t) \leq n_3$ for all $t \geq 0$ if $s(0) + y(0) + \frac{\epsilon}{2\pi}p(0) + \frac{\epsilon}{4\rho}x(0) \leq n_1$, where $n_2 = \frac{2\pi\beta}{\epsilon\sigma}$ and $n_3 = \frac{4\rho\beta}{\epsilon\sigma}$. This guarantees the boundedness of $s(t), y(t), p(t)$, and $x(t)$. \square

The existence of the steady state of the model (2.1) will be shown in the next lemma.

Lemma 2.2. For system (2.1), there exists a threshold parameter $\mathcal{R}_0 > 0$ such that (i) if $\mathcal{R}_0 \leq 1$, then there exists only one steady state Π_0 ; and (ii) if $\mathcal{R}_0 > 1$, then there exist two steady states Π_0 and Π_1 .

Proof. Let (s, y, p, x) be any steady state satisfying

$$\begin{aligned} 0 &= \beta - \delta s - \eta_1 sp - \eta_2 sy, \\ 0 &= \eta_1 sp + \eta_2 sy - \epsilon y - qyx, \\ 0 &= \pi y - cp, \\ 0 &= \rho y - mx - hyx. \end{aligned} \tag{2.3}$$

Solving Eqs. (2.3), we find that the system has two steady states, disease-free steady state $\Pi_0 = (s_0, 0, 0, 0)$, where $s_0 = \frac{\beta}{\delta}$ and unique endemic steady state $\Pi_1(s_1, y_1, p_1, x_1)$, where

$$\begin{aligned} s_1 &= \frac{\beta c}{\eta_1 \pi y_1 + \eta_2 c y_1 + c \delta}, & p_1 &= \frac{\pi y_1}{c}, \\ x_1 &= \frac{\rho y_1}{h y_1 + m}, & y_1 &= \frac{-B + \sqrt{B^2 - 4AC}}{2A}, \end{aligned}$$

and

$$\begin{aligned} A &= (\eta_1 \pi + \eta_2 c)(\epsilon h + \rho q), \\ B &= (\eta_1 \pi + \eta_2 c)(m\epsilon - \beta h) + (\epsilon h + \rho q)\delta c, \\ C &= \delta \epsilon c m \left(1 - \frac{s_0}{\epsilon c}(\eta_1 \pi + \eta_2 c)\right). \end{aligned}$$

The equilibrium Π_1 exists when $\frac{s_0}{\epsilon c}(\eta_1 \pi + \eta_2 c) > 1$. Let us define

$$\mathcal{R}_0 = \frac{s_0}{\epsilon c}(\eta_1 \pi + \eta_2 c), \tag{2.4}$$

where, \mathcal{R}_0 represents the basic infection reproduction number. \square

2.2. Global properties

The following theorems investigate the global stability of the steady states of system (2.1). Let us define the function $g : (0, \infty) \rightarrow [0, \infty)$ as $g(\ell) = \ell - 1 - \ln \ell$.

Theorem 2.3. For system (2.1), if $\mathcal{R}_0 < 1$, then Π_0 is globally asymptotically stable (GAS) and it is unstable if $\mathcal{R}_0 > 1$.

Proof. Let $\mathcal{R}_0 < 1$ and construct a function $L_0(s, y, p, x)$ as:

$$L_0(s, y, p, x) = s_0 g\left(\frac{s}{s_0}\right) + y + \frac{\eta_1 s_0}{c} p + \frac{\varepsilon(1 - \mathcal{R}_0)}{\rho} x.$$

Clearly, $L_0(s, y, p, x) > 0$ for all $s, y, p, x > 0$ and $L_0(s_0, 0, 0, 0) = 0$. Calculating $\frac{dL_0}{dt}$ along the system (2.1), we get

$$\begin{aligned} \frac{dL_0}{dt} &= \left(1 - \frac{s_0}{s}\right) (\beta - \delta s - \eta_1 s p - \eta_2 s y) \\ &\quad + \eta_1 s p + \eta_2 s y - \varepsilon y - q y x + \frac{\eta_1 s_0}{c} (\pi y - c p) + \frac{\varepsilon(1 - \mathcal{R}_0)}{\rho} (\rho y - m x - h y x) \\ &= \delta \left(1 - \frac{s_0}{s}\right) (s_0 - s) + \varepsilon \left(\frac{\eta_1 s_0 \pi}{\varepsilon c} + \frac{\eta_2 s_0}{\varepsilon} - \mathcal{R}_0\right) y - \left(q + h \frac{\varepsilon(1 - \mathcal{R}_0)}{\rho}\right) y x - \frac{\varepsilon(1 - \mathcal{R}_0) m}{\rho} x \\ &= -\delta \frac{(s - s_0)^2}{s} - \left(q + h \frac{\varepsilon(1 - \mathcal{R}_0)}{\rho}\right) y x - \frac{\varepsilon(1 - \mathcal{R}_0) m}{\rho} x. \end{aligned}$$

Since $\mathcal{R}_0 < 1$, then $\frac{dL_0}{dt} \leq 0$ for all $s, y, p, x > 0$. One can easily show that $\frac{dL_0}{dt} = 0$ at Π_0 . Applying LaSalle’s invariance principle (LIP), we get that Π_0 is GAS.

On the other hand, the characteristic equation at Π_0 is given by

$$(\lambda + \delta)(\lambda + m) [\delta \lambda^2 + (\delta c + \varepsilon \delta - \eta_2 \beta) \lambda + (\varepsilon \delta c - \eta_1 \pi \beta - \eta_2 c \beta)] = 0.$$

Define a function ψ_1 on $[0, \infty)$ by

$$\psi_1(\lambda) = \delta \lambda^2 + (\delta c + \varepsilon \delta - \eta_2 \beta) \lambda + (\varepsilon \delta c - \eta_1 \pi \beta - \eta_2 c \beta) = 0.$$

We have $\psi_1(0) = \varepsilon \delta c - \eta_1 \pi \beta - \eta_2 c \beta = \varepsilon \delta c(1 - \mathcal{R}_0) < 0$ when $\mathcal{R}_0 > 1$ and $\lim_{\lambda \rightarrow \infty} \psi_1(\lambda) = \infty$, which implies that ψ_1 has a positive real root. Consequently, Π_0 is unstable for $\mathcal{R}_0 > 1$. \square

Theorem 2.4. For system (2.1), if $\mathcal{R}_0 > 1$, then Π_1 is GAS.

Proof. Let a function $L_1(s, y, p, x)$ be defined as:

$$L_1 = s_1 g\left(\frac{s}{s_1}\right) + y_1 g\left(\frac{y}{y_1}\right) + \frac{\eta_1 s_1}{c} p_1 g\left(\frac{p}{p_1}\right) + \frac{q}{2(\rho - h x_1)} (x - x_1)^2.$$

Clearly, $L_1(s, y, p, x) > 0$ for all $s, y, p, x > 0$, and $L_1(s_1, y_1, p_1, x_1) = 0$. Calculating $\frac{dL_1}{dt}$ along the trajectories of (2.1), we get

$$\begin{aligned} \frac{dL_1}{dt} &= \left(1 - \frac{s_1}{s}\right) (\beta - \delta s - \eta_1 s p - \eta_2 s y) + \left(1 - \frac{y_1}{y}\right) (\eta_1 s p + \eta_2 s y - \varepsilon y - q y x) \\ &\quad + \frac{\eta_1 s_1}{c} \left(1 - \frac{p_1}{p}\right) (\pi y - c p) + \frac{q}{\rho - h x_1} (x - x_1) (\rho y - m x - h y x) \\ &= \left(1 - \frac{s_1}{s}\right) (\beta - \delta s) + \eta_2 s_1 y - \varepsilon y - q y x - \eta_1 s p \frac{y_1}{y} - \eta_2 s y_1 + \varepsilon y_1 \\ &\quad + q y_1 x + \frac{\eta_1 s_1}{c} \pi y - \frac{\pi \eta_1 s_1}{c} \frac{p_1}{p} y + \eta_1 s_1 p_1 + \frac{q}{\rho - h x_1} (x - x_1) (\rho y - m x - h y x). \end{aligned} \tag{2.5}$$

Simplifying Eq. (2.5) and applying the following conditions for Π_1 :

$$\beta - \delta s_1 = \eta_1 s_1 p_1 + \eta_2 s_1 y_1 = \varepsilon y_1 + q y_1 x_1, \quad \pi y_1 = c p_1, \quad \rho y_1 = m x_1 + h y_1 x_1,$$

we get

$$\begin{aligned} \frac{dL_1}{dt} &= -\delta \frac{(s - s_1)^2}{s} + \left(1 - \frac{s_1}{s}\right) (\eta_1 s_1 p_1 + \eta_2 s_1 y_1) + \eta_2 s_1 y - \eta_1 s p \frac{y_1}{y} - \eta_2 s y_1 \\ &\quad - \varepsilon (y - y_1) - q (y - y_1) x + q (y - y_1) x_1 - q (y - y_1) x_1 + \frac{\eta_1 s_1}{c} \pi y - \frac{\pi \eta_1 s_1}{c} \frac{p_1}{p} y \\ &\quad + \eta_1 s_1 p_1 + \frac{q}{\rho - h x_1} (x - x_1) (\rho y - m x - h y x - \rho y_1 + m x_1 + h y_1 x_1 + h y x_1 - h y x_1) \\ &= -\delta \frac{(s - s_1)^2}{s} + \left(1 - \frac{s_1}{s}\right) (\eta_1 s_1 p_1 + \eta_2 s_1 y_1) + \eta_2 s_1 y \tag{2.6} \\ &\quad - \eta_1 s p \frac{y_1}{y} - \eta_2 s y_1 - (\varepsilon y_1 + q y_1 x_1) \left(\frac{y}{y_1} - 1\right) - q (y - y_1) (x - x_1) \\ &\quad + \frac{\eta_1 s_1}{c} \pi y - \frac{\eta_1 s_1}{c} \frac{p_1}{p} \pi y + \eta_1 s_1 p_1 + \frac{q \rho}{\rho - h x_1} (x - x_1) (y - y_1) \\ &\quad - \frac{q m}{\rho - h x_1} (x - x_1)^2 - \frac{q h}{\rho - h x_1} (x - x_1)^2 y - \frac{q h}{\rho - h x_1} x_1 (x - x_1) (y - y_1). \end{aligned}$$

Eq. (2.6) can be simplified as:

$$\begin{aligned} \frac{dL_1}{dt} &= -\delta \frac{(s - s_1)^2}{s} + \left(1 - \frac{s_1}{s}\right) (\eta_1 s_1 p_1 + \eta_2 s_1 y_1) + \eta_2 s_1 y \\ &\quad - \eta_1 s p \frac{y_1}{y} - \eta_2 s y_1 - (\eta_1 s_1 p_1 + \eta_2 s_1 y_1) \left(\frac{y}{y_1} - 1\right) - q (y - y_1) (x - x_1) \\ &\quad + \frac{\eta_1 s_1}{c} \pi y - \frac{\eta_1 s_1}{c} \frac{p_1}{p} \pi y + \eta_1 s_1 p_1 + q (x - x_1) (y - y_1) - q \left(\frac{m + h y}{\rho - h x_1}\right) (x - x_1)^2 \\ &= -(\delta + \eta_2 y_1) \frac{(s - s_1)^2}{s} + \eta_1 s_1 p_1 \left(3 - \frac{s_1}{s} - \frac{s p y_1}{s_1 p_1 y} - \frac{p_1 y}{p y_1}\right) - q \left(\frac{m + h y}{\rho - h x_1}\right) (x - x_1)^2. \end{aligned}$$

We have if $\mathcal{R}_0 > 1$, then $s_1, y_1, p_1, x_1 > 0$. The geometrical and arithmetical means relationship implies that

$$3 \leq \frac{s_1}{s} + \frac{s p y_1}{s_1 p_1 y} + \frac{p_1 y}{p y_1}.$$

Thus, $\frac{dL_1}{dt} \leq 0$ for all $s, y, p, x > 0$ and $\frac{dL_1}{dt} = 0$ when $s = s_1, y = y_1, p = p_1$, and $x = x_1$. Using LIP we obtain that Π_1 is GAS when $\mathcal{R}_0 > 1$. □

3. Model with saturated incidence rate

Model (2.1) has considered bilinear form for pathogen-susceptible and infected-susceptible incidence. However, when the concentration of the pathogens and infected cells are high, then this bilinear form may not describe the pathogen dynamics accurately [13]. In this section, we propose a pathogen dynamics model with saturated pathogen-susceptible and infected-susceptible incidence as follows:

$$\begin{aligned} \dot{s} &= \beta - \delta s - \frac{\eta_1 s p}{1 + \alpha_1 p} - \frac{\eta_2 s y}{1 + \alpha_2 y}, \\ \dot{y} &= \frac{\eta_1 s p}{1 + \alpha_1 p} + \frac{\eta_2 s y}{1 + \alpha_2 y} - \varepsilon y - q y x, \\ \dot{p} &= \pi y - c p, \\ \dot{x} &= \rho y - m x - h y x, \end{aligned} \tag{3.1}$$

where $\alpha_1 \geq 0$ and $\alpha_2 \geq 0$ are saturation constants.

3.1. Basic properties

We note that the compact set Ω defined in (2.2) is also positively invariant for system (3.1). The existence of the steady state of the model (3.1) will be shown in the next lemma.

Lemma 3.1. *For system (3.1), there exists a threshold parameter $\mathcal{R}_0 > 0$ such that*

- (i) *if $\mathcal{R}_0 \leq 1$, then there exists only one steady state Π_0 , and*
- (ii) *if $\mathcal{R}_0 > 1$, then there exist two steady states Π_0 and Π_1 .*

Proof. Let

$$\begin{aligned} 0 &= \beta - \delta s - \frac{\eta_1 s p}{1 + \alpha_1 p} - \frac{\eta_2 s y}{1 + \alpha_2 y}, \\ 0 &= \frac{\eta_1 s p}{1 + \alpha_1 p} + \frac{\eta_2 s y}{1 + \alpha_2 y} - \varepsilon y - qyx, \\ 0 &= \pi y - cp, \\ 0 &= \rho y - mx - hyx. \end{aligned} \tag{3.2}$$

Solving Eqs. (3.2) we find that the system has a disease-free steady state $\Pi_0 = (s_0, 0, 0, 0)$, where $s_0 = \frac{\beta}{\delta}$. Moreover, the system has another steady state given as:

$$\begin{aligned} s &= \frac{\beta(\alpha_1 \pi y + c)(\alpha_2 y + 1)}{(\alpha_1 \alpha_2 \delta \pi + \eta_1 \alpha_2 \pi + \eta_2 \alpha_1 \pi) y^2 + (\alpha_1 \delta \pi + \alpha_2 c \delta + \eta_1 \pi + \eta_2 c) y + c \delta}, \\ p &= \frac{\pi y}{c}, \quad x = \frac{\rho y}{hy + m}, \end{aligned} \tag{3.3}$$

and y satisfying the following equation:

$$Ay^3 + By^2 + Cy + D = 0,$$

where

$$\begin{aligned} A &= ((q\rho + \varepsilon h)(\alpha_1 \alpha_2 \delta + \alpha_2 \eta_1 + \alpha_1 \eta_2)) \pi, \\ B &= -(\eta_2 \alpha_1 + \eta_1 \alpha_2) h \pi \beta + ((q\rho + \varepsilon \alpha_2 m + \varepsilon h)(\alpha_1 \delta + \eta_1) + \varepsilon \eta_2 \alpha_1 m) \pi + (q\rho + \varepsilon h)(\alpha_2 c \delta + c \eta_2), \\ C &= -(((h + \alpha_2) \eta_1 + \eta_2 \alpha_1) m \pi - \eta_2 c h) \beta + (\delta \alpha_1 + \eta_1) \varepsilon m \pi + (q\rho + \varepsilon \alpha_2 m + \varepsilon h) c \delta + \varepsilon \eta_2 c m, \\ D &= (\varepsilon \delta c - \eta_1 \pi \beta - \eta_2 c \beta) m = \varepsilon \delta c m (1 - \mathcal{R}_0), \end{aligned}$$

and \mathcal{R}_0 is defined by Eq. (2.4). Define a function ψ_2 on $[0, \infty)$ by

$$\psi_2(y) = Ay^3 + By^2 + Cy + D = 0.$$

We have $\psi_2(0) = \varepsilon \delta c m (1 - \mathcal{R}_0) < 0$ when $\mathcal{R}_0 > 1$ and $\lim_{y \rightarrow \infty} \psi_2(y) = \infty$, which implies that there exists $y_1 \in (0, \infty)$ such that $\psi_2(y_1) = 0$. Therefore, from Eqs. (3.3) we get that s_1, p_1 , and x_1 are all positive. It follows that, an endemic steady state $\Pi_1(s_1, y_1, p_1, x_1)$ exists when $\mathcal{R}_0 > 1$. \square

3.2. Global properties

In the following we prove the global stability of Π_0 and Π_1 of system (3.1) by constructing suitable Lyapunov functions.

Theorem 3.2. *For system (3.1), if $\mathcal{R}_0 < 1$, then Π_0 is GAS and it is unstable if $\mathcal{R}_0 > 1$.*

Proof. Define $U_0(s, y, p, x)$ as:

$$U_0 = s_0 g\left(\frac{s}{s_0}\right) + y + \frac{\eta_1 s_0}{c} p + \frac{\varepsilon(1 - \mathcal{R}_0)}{\rho} x.$$

Then

$$\begin{aligned} \frac{dU_0}{dt} &= \left(1 - \frac{s_0}{s}\right) \left(\beta - \delta s - \frac{\eta_1 s p}{1 + \alpha_1 p} - \frac{\eta_2 s y}{1 + \alpha_2 y}\right) + \frac{\eta_1 s p}{1 + \alpha_1 p} + \frac{\eta_2 s y}{1 + \alpha_2 y} \\ &\quad - \varepsilon y - q y x + \frac{\eta_1 s_0}{c} (\pi y - c p) + \frac{\varepsilon(1 - \mathcal{R}_0)}{\rho} (\rho y - m x - h y x) \\ &= \delta \left(1 - \frac{s_0}{s}\right) (s_0 - s) + \frac{\eta_1 s_0 p}{1 + \alpha_1 p} + \frac{\eta_2 s_0 y}{1 + \alpha_2 y} - \varepsilon y - q y x \\ &\quad + \frac{\eta_1 s_0}{c} (\pi y - c p) + \frac{\varepsilon(1 - \mathcal{R}_0)}{\rho} (\rho y - m x - h y x) \\ &= -\delta \frac{(s - s_0)^2}{s} - \frac{\alpha_1 \eta_1 s_0 p^2}{1 + \alpha_1 p} - \frac{\alpha_2 \eta_2 s_0 y^2}{1 + \alpha_2 y} - \left(q + \frac{\varepsilon h(1 - \mathcal{R}_0)}{\rho}\right) y x - \frac{\varepsilon(1 - \mathcal{R}_0) m}{\rho} x \\ &= -\delta \frac{(s - s_0)^2}{s} - \frac{\alpha_1 \eta_1 s_0 p^2}{1 + \alpha_1 p} - \frac{\alpha_2 \eta_2 s_0 y^2}{1 + \alpha_2 y} - \left(q + \frac{\varepsilon h(1 - \mathcal{R}_0)}{\rho}\right) y x - \frac{\varepsilon m(1 - \mathcal{R}_0)}{\rho} x. \end{aligned}$$

Clearly if $\mathcal{R}_0 < 1$, then $\frac{dU_0}{dt} \leq 0$ for all $s, y, p, x > 0$, moreover $\frac{dU_0}{dt} = 0$ if and only if $s = s_0, y = 0, p = 0$, and $x = 0$. LIP implies that Π_0 is GAS when $\mathcal{R}_0 < 1$.

On the other hand, the characteristic equation at Π_0 is given by

$$(\lambda + \delta)(\lambda + m) [\delta \lambda^2 + (\delta c + \varepsilon \delta - \eta_2 \beta) \lambda + (\varepsilon \delta c - \eta_1 \pi \beta - \eta_2 c \beta)] = 0.$$

Define a function ψ_3 on $[0, \infty)$ by

$$\psi_3(\lambda) = \delta \lambda^2 + (\delta c + \varepsilon \delta - \eta_2 \beta) \lambda + (\varepsilon \delta c - \eta_1 \pi \beta - \eta_2 c \beta) = 0.$$

We have $\psi_3(0) = \varepsilon \delta c - \eta_1 \pi \beta - \eta_2 c \beta = \varepsilon \delta c(1 - \mathcal{R}_0) < 0$ when $\mathcal{R}_0 > 1$ and $\lim_{\lambda \rightarrow \infty} \psi_3(\lambda) = \infty$, which implies that ψ_3 has a positive real root. Consequently, Π_0 is unstable for $\mathcal{R}_0 > 1$. \square

Theorem 3.3. For system (3.1), if $\mathcal{R}_0 > 1$, then Π_1 is GAS.

Proof. Construct a function $U_1(s, y, p, x)$ as:

$$U_1 = s_1 g\left(\frac{s}{s_1}\right) + y_1 g\left(\frac{y}{y_1}\right) + \frac{\eta_1 s_1}{c(1 + \alpha_1 p_1)} p_1 g\left(\frac{p}{p_1}\right) + \frac{q}{2(\rho - h x_1)} (x - x_1)^2.$$

Then

$$\begin{aligned} \frac{dU_1}{dt} &= \left(1 - \frac{s_1}{s}\right) \left(\beta - \delta s - \frac{\eta_1 s p}{1 + \alpha_1 p} - \frac{\eta_2 s y}{1 + \alpha_2 y}\right) \\ &\quad + \left(1 - \frac{y_1}{y}\right) \left(\frac{\eta_1 s p}{1 + \alpha_1 p} + \frac{\eta_2 s y}{1 + \alpha_2 y} - \varepsilon y - q y x\right) \\ &\quad + \frac{\eta_1 s_1}{c(1 + \alpha_1 p_1)} \left(1 - \frac{p_1}{p}\right) (\pi y - c p) + \frac{q}{\rho - h x_1} (x - x_1) (\rho y - m x - h y x) \\ &= \left(1 - \frac{s_1}{s}\right) (\beta - \delta s) + \frac{\eta_1 s_1 p}{1 + \alpha_1 p} + \frac{\eta_2 s_1 y}{1 + \alpha_2 y} - \varepsilon y - q y x - \frac{\eta_1 s p}{1 + \alpha_1 p} \frac{y_1}{y} \\ &\quad - \frac{\eta_2 s y_1}{1 + \alpha_2 y} + \varepsilon y_1 + q y_1 x + \frac{\pi \eta_1 s_1}{c(1 + \alpha_1 p_1)} y - \frac{\eta_1 s_1 p}{1 + \alpha_1 p_1} - \frac{\pi \eta_1 s_1}{c(1 + \alpha_1 p_1)} \frac{p_1}{p} y \end{aligned}$$

$$+ \frac{\eta_1 s_1 p_1}{1 + \alpha_1 p_1} + \frac{q}{\rho - hx_1} (x - x_1) (\rho y - mx - hyx).$$

Applying the steady state conditions for Π_1 :

$$\beta - \delta s_1 = \frac{\eta_1 s_1 p_1}{1 + \alpha_1 p_1} + \frac{\eta_2 s_1 y_1}{1 + \alpha_2 y_1} = \varepsilon y_1 + q y_1 x_1, \quad \pi y_1 = c p_1, \quad \rho y_1 = m x_1 + h y_1 x_1,$$

we get

$$\begin{aligned} \frac{dU_1}{dt} &= -\delta \frac{(s - s_1)^2}{s} + \left(1 - \frac{s_1}{s}\right) \left(\frac{\eta_1 s_1 p_1}{1 + \alpha_1 p_1} + \frac{\eta_2 s_1 y_1}{1 + \alpha_2 y_1}\right) + \frac{\eta_1 s_1 p}{1 + \alpha_1 p} + \frac{\eta_2 s_1 y}{1 + \alpha_2 y} \\ &\quad - \varepsilon (y - y_1) - q x_1 (y - y_1) + q x_1 (y - y_1) - q x (y - y_1) - \frac{\eta_1 s p}{1 + \alpha_1 p} \frac{y_1}{y} - \frac{\eta_2 s y_1}{1 + \alpha_2 y} \\ &\quad + \frac{\pi \eta_1 s_1}{c(1 + \alpha_1 p_1)} y - \frac{\eta_1 s_1 p}{1 + \alpha_1 p_1} - \frac{\pi \eta_1 s_1}{c(1 + \alpha_1 p_1)} \frac{p_1}{p} y + \frac{\eta_1 s_1 p_1}{1 + \alpha_1 p_1} \\ &\quad + \frac{q}{\rho - hx_1} (x - x_1) (\rho y - mx - hyx - \rho y_1 + m x_1 + h y_1 x_1 + h y x_1 - h y x_1) \\ &= -\delta \frac{(s - s_1)^2}{s} + \left(1 - \frac{s_1}{s}\right) \left(\frac{\eta_1 s_1 p_1}{1 + \alpha_1 p_1} + \frac{\eta_2 s_1 y_1}{1 + \alpha_2 y_1}\right) + \frac{\eta_1 s_1 p}{1 + \alpha_1 p} + \frac{\eta_2 s_1 y}{1 + \alpha_2 y} \\ &\quad - (\varepsilon y_1 + q y_1 x_1) \left(\frac{y}{y_1} - 1\right) - q (y - y_1) (x - x_1) - \frac{\eta_1 s p}{1 + \alpha_1 p} \frac{y_1}{y} - \frac{\eta_2 s y_1}{1 + \alpha_2 y} \\ &\quad + \frac{\pi \eta_1 s_1}{c(1 + \alpha_1 p_1)} y - \frac{\eta_1 s_1 p}{1 + \alpha_1 p_1} - \frac{\pi \eta_1 s_1}{c(1 + \alpha_1 p_1)} \frac{p_1}{p} y + \frac{\eta_1 s_1 p_1}{1 + \alpha_1 p_1} - \frac{q m}{\rho - hx_1} (x - x_1)^2 \\ &\quad - \frac{q h}{\rho - hx_1} (x - x_1)^2 y - \frac{q h}{\rho - hx_1} x_1 (x - x_1) (y - y_1) + \frac{q \rho}{\rho - hx_1} (x - x_1) (y - y_1). \end{aligned} \tag{3.4}$$

Eq. (3.4) can be simplified as:

$$\begin{aligned} \frac{dU_1}{dt} &= -\delta \frac{(s - s_1)^2}{s} + \left(1 - \frac{s_1}{s}\right) \left(\frac{\eta_1 s_1 p_1}{1 + \alpha_1 p_1} + \frac{\eta_2 s_1 y_1}{1 + \alpha_2 y_1}\right) + \frac{\eta_1 s_1 p}{1 + \alpha_1 p} + \frac{\eta_2 s_1 y}{1 + \alpha_2 y} \\ &\quad - \frac{\eta_1 s p}{1 + \alpha_1 p} \frac{y_1}{y} - \frac{\eta_2 s y_1}{1 + \alpha_2 y} - \left(\frac{\eta_1 s_1 p_1}{1 + \alpha_1 p_1} + \frac{\eta_2 s_1 y_1}{1 + \alpha_2 y_1}\right) \left(\frac{y}{y_1} - 1\right) \\ &\quad + \frac{\pi \eta_1 s_1}{c(1 + \alpha_1 p_1)} y - \frac{\eta_1 s_1 p}{1 + \alpha_1 p_1} - \frac{\pi \eta_1 s_1}{c(1 + \alpha_1 p_1)} \frac{p_1}{p} y + \frac{\eta_1 s_1 p_1}{1 + \alpha_1 p_1} \\ &\quad - \frac{q m}{\rho - hx_1} (x - x_1)^2 - \frac{q h}{\rho - hx_1} (x - x_1)^2 y \\ &= -\delta \frac{(s - s_1)^2}{s} + \frac{\eta_1 s_1 p_1}{1 + \alpha_1 p_1} \left(\frac{p(1 + \alpha_1 p_1)}{p_1(1 + \alpha_1 p)} - \frac{p}{p_1}\right) \\ &\quad + \frac{\eta_1 s_1 p_1}{1 + \alpha_1 p_1} \left(3 - \frac{s_1}{s} - \frac{s p y_1 (1 + \alpha_1 p_1)}{s_1 p_1 y (1 + \alpha_1 p)} - \frac{y p_1}{y_1 p}\right) + \frac{\eta_2 s_1 y_1}{1 + \alpha_2 y_1} \left(\frac{y(1 + \alpha_2 y_1)}{y_1(1 + \alpha_2 y)} - \frac{y}{y_1}\right) \\ &\quad + \frac{\eta_2 s_1 y_1}{1 + \alpha_2 y_1} \left(2 - \frac{s_1}{s} - \frac{s(1 + \alpha_2 y_1)}{s_1(1 + \alpha_2 y)}\right) - q \left(\frac{m + h y}{\rho - hx_1}\right) (x - x_1)^2 \\ &= -\delta \frac{(s - s_1)^2}{s} - \frac{\eta_1 s_1 p_1}{1 + \alpha_1 p_1} \left(\frac{\alpha_1 (p - p_1)^2}{p_1(1 + \alpha_1 p)(1 + \alpha_1 p_1)}\right) \\ &\quad + \frac{\eta_1 s_1 p_1}{1 + \alpha_1 p_1} \left(4 - \frac{s_1}{s} - \frac{s p y_1 (1 + \alpha_1 p_1)}{s_1 p_1 y (1 + \alpha_1 p)} - \frac{y p_1}{y_1 p} - \frac{1 + \alpha_1 p}{1 + \alpha_1 p_1}\right) \\ &\quad - \frac{\eta_2 s_1 y_1}{1 + \alpha_2 y_1} \left(\frac{\alpha_2 (y - y_1)^2}{y_1(1 + \alpha_2 y)(1 + \alpha_2 y_1)}\right) \\ &\quad + \frac{\eta_2 s_1 y_1}{1 + \alpha_2 y_1} \left(3 - \frac{s_1}{s} - \frac{s(1 + \alpha_2 y_1)}{s_1(1 + \alpha_2 y)} - \frac{1 + \alpha_2 y}{1 + \alpha_2 y_1}\right) - q \left(\frac{m + h y}{\rho - hx_1}\right) (x - x_1)^2. \end{aligned}$$

One can easily show that Π_1 is GAS. □

Remark 3.4. We mention that when $\alpha_1 = \alpha_2 = 0$, then model (3.1) leads to model (2.1) and the stability results for both systems are the same. Since $\alpha_1 \geq 0$ and $\alpha_2 \geq 0$, then all the results of Section 3 are still valid for the cases $\alpha_1 \neq 0$ and $\alpha_2 = 0$ or $\alpha_1 = 0$ and $\alpha_2 \neq 0$.

4. Numerical simulations

In this section, we will perform numerical simulations for system (3.1) with parameter values given in Table 1. Without loss of generality we take $\alpha = \alpha_1 = \alpha_2$. We choose three initial conditions as:

IC1: $s(0) = 900, y(0) = 10, p(0) = 50, x(0) = 6,$

IC2: $s(0) = 600, y(0) = 20, p(0) = 35, x(0) = 4,$

IC3: $s(0) = 300, y(0) = 30, p(0) = 20, x(0) = 2.$

Case (1): Effect of η_1 on stability of steady states.

We choose $\alpha = 0.01, h = 0.1$ and η_1 is varied as:

- (i) $\eta_1 = 0.0005$, then we compute $\mathcal{R}_0 = 0.7583 < 1$. From Lemma 3.1 we have that the system has one equilibrium Π_0 . Figure 1 shows that, for IC1-IC3, the concentration of susceptible cells is increasing and tends its healthy value $s_0 = 1300$, while the concentrations of infected cells, pathogens and CTL cells are decaying and approaching zero. It means that, Π_0 is GAS and the pathogen will be cleared. This confirms the result of Theorem 3.2.
- (ii) $\eta_1 = 0.005$, then $\mathcal{R}_0 = 2.9033 > 1$. Lemma 3.1 states that the system has two steady states Π_0 and Π_1 . It is clear from Figure 1, the numerical results confirm theoretical results of Theorem 3.3. It is seen that, the solutions of the system converge to the equilibrium $\Pi_1 = (656.7340, 24.7780, 45.4263, 4.8060)$ for all IC1-IC3.

Case (2): Effect of the saturation infection on the pathogen dynamics.

In this case, we choose $\eta_1 = 0.005, h = 0.1$, and α is varied. Also we consider the initial condition IC2. Figure 2 shows the effect of saturation infection. We observe that, as α is increased, both pathogen-susceptible and infected-susceptible infection rates are decreased and then the concentration of the susceptible cells is increased, while the the concentration of infected cells, pathogens, and CTL cells are decreased. We observe that \mathcal{R}_0 does not depend on α , therefore the saturation does not change the stability properties of the equilibria.

Case(3): Effect of h on the pathogen dynamics.

In this case, we choose $\eta_1 = 0.005, \alpha = 0.01$ and h is varied. We consider the following initial condition:

IC4: $s(0) = 700, y(0) = 20, p(0) = 35, x(0) = 20.$

Figure 3 shows that as h is increased, the concentration of CTL cells is decreased, and then the concentration of infected cells and free pathogen are increased, while the concentrations of the susceptible cells are decreased. We note that \mathcal{R}_0 does not depend on the parameter h , therefore h does not change the stability properties of steady states.

Table 1: The data of model (3.1).

Parameter	Value	Parameter	Value	Parameter	Value
β	260	η_2	0.002	c	3
δ	0.2	ϵ	5	ρ	0.5
η_1	varied	q	0.04	m	0.2
α_1, α_2	varied	π	5.5	h	varied

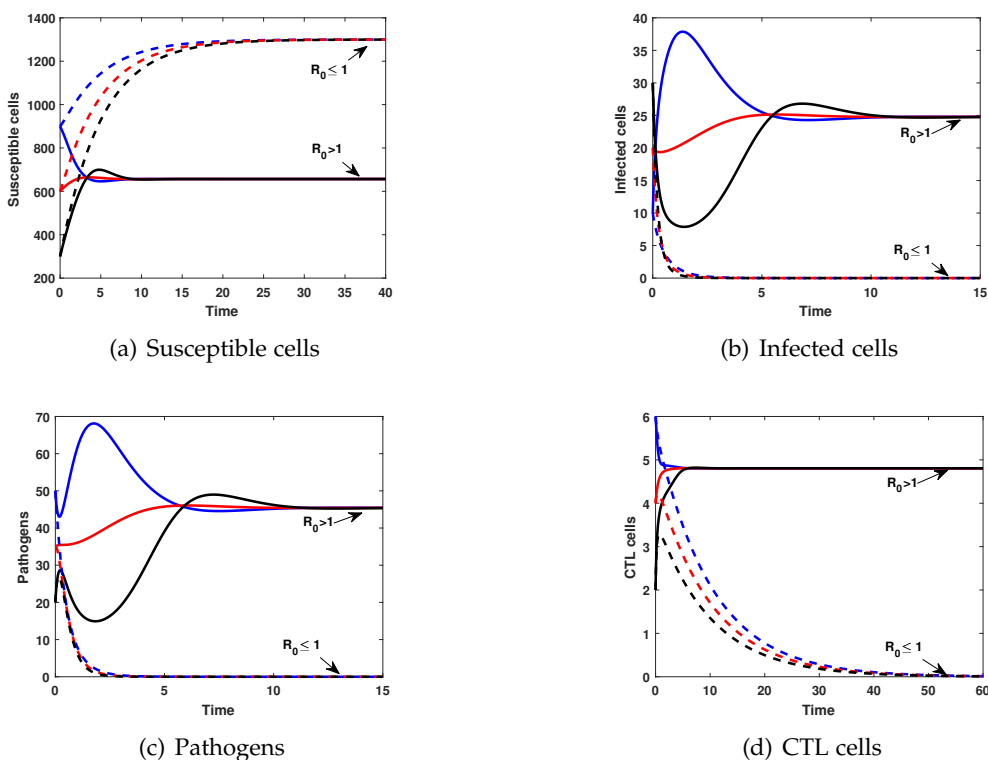


Figure 1: The simulation of trajectories of system (3.1) with IC1-IC3.

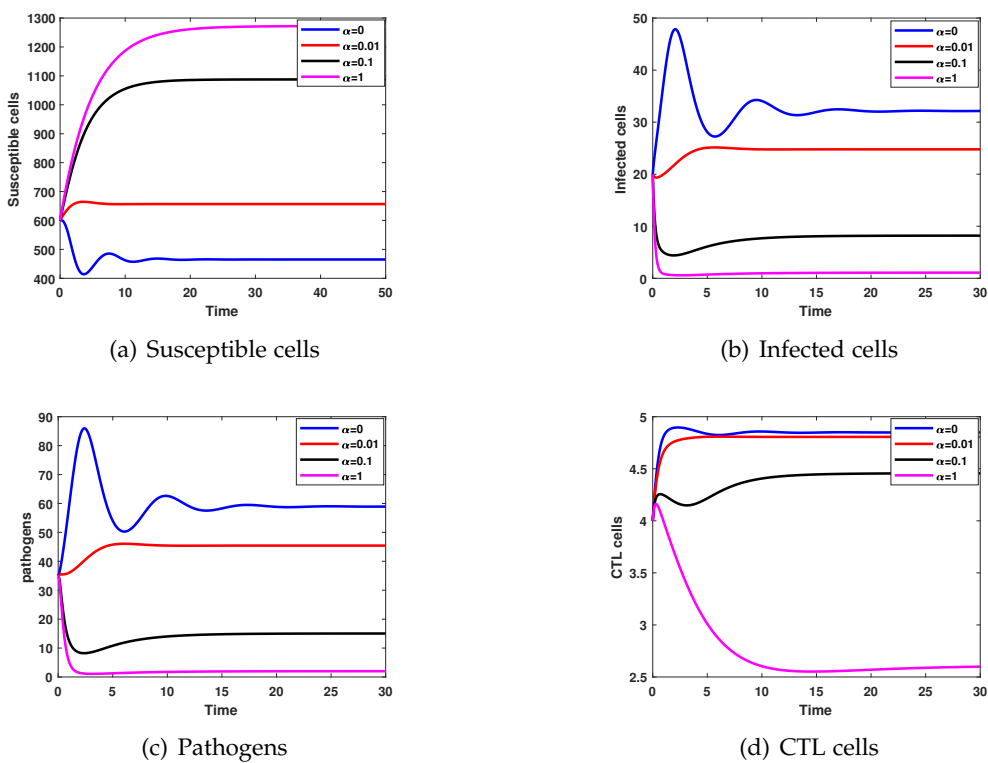


Figure 2: The simulation of trajectories of system (3.1) with different values of α .

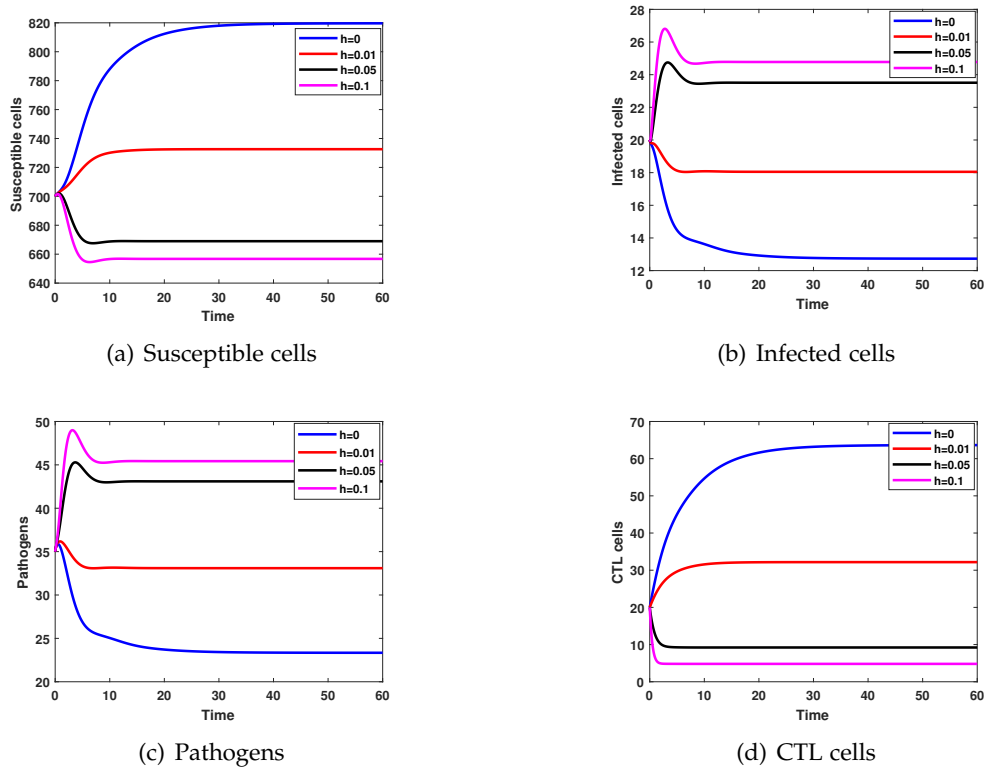


Figure 3: The simulation of trajectories of system (3.1) with with different values of h .

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