Journal of Interdisciplinary Mathematics
ISSN: 0972-0502 (Print), ISSN: 2169-012X (Online)
Vol. 26 (2023), No. 4, pp. 733–745
DOI : 10.47974/JIM-1508

Mathematical model of evasion of immune system by virus

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Abstract

Virus needs to infect cells to spread the disease in the host and to achieve this, they have developed specific tactics to evade the immune system, which is in charge of trying to prevent any infection. In this way, we develop a mathematical model to represent the evasion of immune system by virus using a non-monotonic functional response describing an antipredator behavior, where the virus is the prey and the immune cells are the predator. We found four equilibrium points, the disease free equilibrium, immune evasion equilibrium and two immune activation equilibrium points. The disease free equilibrium is globally asymptotically stable if $R_0 \leq 1$, the immune evasion equilibrium and two immune activation equilibria are locally asymptotically stable if $R_0 > 1$. We conclude that in our model the evasion of immune system is always possible when there is a inoculation of virus in the host, but there is also a chance to control the infection or to activate the immune system when there are a cross-reactive antibodies.

Subject Classification: *92B05, 37N25, 65P40.*

Keywords: *Non-monotonic functional response, Defense group, Evasion of immune system, Virus, Mathematical model, Simplified Monod–Haldane function.*

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1. Introduction

The simplified Monod–Haldane or Holling type-IV function is

$$f(v) = p\frac{v}{v^2+a^2}; \tag{1}$$

where a, p are positive constants, which was proposed by Sokol and Howell [15] (see Figure 1), this function f represents a non-monotonic functional response describing an antipredator behavior called defense group formation [4, 16, 17, 13]. Defense group is a term which is used to describe the phenomenon whereby predators are diminished, or even avoided altogether, due to the increased ability of the prey to better defend themselves or cover the weaker ones when their numbers are sufficiently large. We take this idea to mimic the evasion of immune system by virus, where the immune cells will be the predator and the virus will be the prey. We know that when a virus enters the body, immune cells try to prevent its spread, sometimes this procedure is successful but in other cases the virus evades the immune cells and succeeds infecting a large number of cells [3, 8, 12, 10, 11, 14, 9]. In this way, we develop a mathematical model considering the target cells x, the infected cells y, the virus v and the immune cells z as follows:

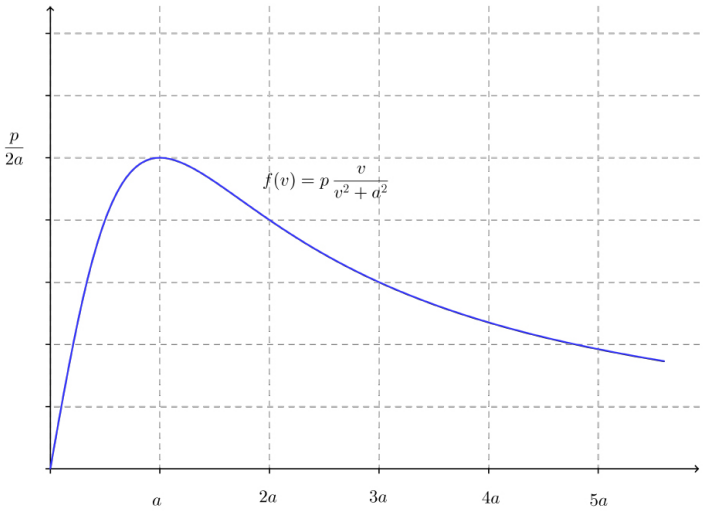


Figure 1

The figure shows the non-monotonic functional response (1)

$$\begin{aligned}
\frac{dx}{dt} &= k - \beta xv - \mu x \\
\frac{dy}{dt} &= \beta xv - \alpha yz - by \\
\frac{dv}{dt} &= ry - p\frac{zv}{v^2+a^2} - mv \\
\frac{dz}{dt} &= q\frac{zv}{v^2+a^2} - cz.
\end{aligned} \tag{2}$$

All the parameters are positive constants. The target cells are produced at a constant rate k and its natural death rate is μ, the infected cells are produced from target cells and free virus at rate β, killed by immune cells at rate α and die at rate b, free virus is produced from infected cells at rate r, decay at rate m, the immune cells kills the virus with simplified Monodâ€"Haldane functional response $\frac{v}{v^2+a^2}$ acting as a predator at a capture rate p and continue to their activation or growth with activation rate q and decay at rate c. The summary of the parameters present in the model is shown in Table 1

The organization of this paper is as follows: In Section 2, we found four equilibrium points, the disease free equilibrium, immune evasion equilibrium and two immune activation equilibria. In Section 3, the stability analysis of disease free equilibrium point and immune evasion equilibrium is proved. In Section 4, numerical simulations are performed to study the evasion of immune systems and to show the stability of the two immune activation equilibria. In Section 5, we discuss our results.

2. Equilibrium points

The equilibrium points are found resolving the next system of equations:

$$k - \beta xv - \mu x = 0 \tag{3}$$

$$\beta xv - \alpha yz - by = 0 \tag{4}$$

$$ry - p\frac{zv}{v^2+a^2} - mv = 0 \tag{5}$$

$$q\frac{zv}{v^2+a^2} - cz = 0. \tag{6}$$

From the first equation of this system we have

$$x = \frac{k}{\beta v+\mu} \tag{7}$$

and from the equation (6), we have

$$z = 0 \tag{8}$$

or

$$\frac{qv}{v^2+a^2} = c. \tag{9}$$

- If $z = 0$ is substituted into equations (4) and (5), we have

$$\beta xv - by = 0 \tag{10}$$

$$ry - mv = 0, \tag{11}$$

from the last equation, we have $y = \frac{m}{r}v,$ substituting this equation and the equation (7) into (10), we get

$$\beta \frac{k}{\beta v+\mu} v - b\frac{m}{r}v = 0, \tag{12}$$

from which, we obtain, $v = 0$ or $v = \frac{\mu}{\beta}(R_0 - 1),$ where $R_0 = \frac{\beta k r}{bm\mu} > 1.$ Then we get two equilibrium points, $E_0 = \left(\frac{k}{\mu}, 0, 0, 0\right)$ and $E_1 = (x_1, y_1, v_1, 0),$ where $x_1 = \frac{k}{\mu R_0}$, $y_1 = \frac{k}{b}\left(1 - \frac{1}{R_0}\right)$, $v_1 = \frac{\mu}{\beta}(R_0 - 1)$ and $R_0 > 1.$ The point $E_0 = \left(\frac{k}{\mu}, 0, 0, 0\right)$ will be called the **disease free equilibrium** and the point $E_1 = (x_1, y_1, v_1, 0)$ the **immune evasion equilibrium**.

- If $\frac{qv}{v^2+a^2} = c,$ we get

$$v_{2,3} = \frac{q}{2c} \pm \frac{1}{2}\sqrt{\left(\frac{q}{c}\right)^2 - 4a^2}. \tag{13}$$

Which just has sense if $\frac{q}{c} > 2a.$ Taking the equation (13) into (5), we have

$$y_{2,3} = \frac{p}{r} z \frac{v_{2,3}}{v_{2,3}^2+a^2} + \frac{m}{r}v_{2,3} = \frac{p}{r} z \frac{c}{q} + \frac{m}{r}v_{2,3}. \tag{14}$$

Substituting the equation (14) into (4) we obtain

$$\beta x_{2,3} v_{2,3} - \alpha\left(\frac{p}{r} z \frac{c}{q} + \frac{m}{r}v_{2,3}\right) z - b \frac{p}{r} z \frac{c}{q} - b\frac{m}{r}v_{2,3} = 0 \tag{15}$$

$$z^2 + \left(\frac{m}{p}\frac{q}{c}v_{2,3} + \frac{b}{\alpha}\right) z + \frac{b}{\alpha}\frac{m}{p}\frac{q}{c}v_{2,3} - \frac{\beta}{\alpha}\frac{r}{p}\frac{q}{c}x_{2,3}v_{2,3} = 0, \tag{16}$$

from which we obtain,

$$z_{2,3} = \frac{-\left(\frac{m}{p}\frac{q}{c}v_{2,3} + \frac{b}{\alpha}\right) \pm \sqrt{\left(\frac{m}{p}\frac{q}{c}v_{2,3} + \frac{b}{\alpha}\right)^2 - 4\left(\frac{b}{\alpha}\frac{m}{p}\frac{q}{c}v_{2,3} - \frac{\beta}{\alpha}\frac{r}{p}\frac{q}{c}x_{2,3}v_{2,3}\right)}}{2}. \tag{17}$$

$$\beta x_{2,3} v_{2,3} - \alpha\left(\frac{p}{r} z \frac{c}{q} + \frac{m}{r} v_{2,3}\right) z - b \frac{p}{r} z \frac{c}{q} - b \frac{m}{r} v_{2,3} = 0 \tag{15}$$

$$z^2 + \left(\frac{m}{p}\frac{q}{c} v_{2,3} + \frac{b}{\alpha}\right) z + \frac{b}{\alpha}\frac{m}{p}\frac{q}{c} v_{2,3} - \frac{\beta}{\alpha}\frac{r}{p}\frac{q}{c} x_{2,3} v_{2,3} = 0, \tag{16}$$

from which we obtain,

$$z_{2,3} = \frac{-\left(\frac{m}{p}\frac{q}{c} v_{2,3} + \frac{b}{\alpha}\right) \pm \sqrt{\left(\frac{m}{p}\frac{q}{c} v_{2,3} + \frac{b}{\alpha}\right)^2 - 4\left(\frac{b}{\alpha}\frac{m}{p}\frac{q}{c} v_{2,3} - \frac{\beta}{\alpha}\frac{r}{p}\frac{q}{c} x_{2,3} v_{2,3}\right)}}{2}. \tag{17}$$

From this equation, we can infer that:

- If $\frac{b}{\alpha}\frac{m}{p}\frac{q}{c} v_{2,3} - \frac{\beta}{\alpha}\frac{r}{p}\frac{q}{c} x_{2,3} v_{2,3} > 0$, there are not feasible points for z, i.e. $z < 0$.
- If $\frac{b}{\alpha}\frac{m}{p}\frac{q}{c} v_{2,3} - \frac{\beta}{\alpha}\frac{r}{p}\frac{q}{c} x_{2,3} v_{2,3} < 0$, there are feasible points $z_{2,3}$. Now, we verify when this inequality is true,

$$\frac{b}{\alpha}\frac{m}{p}\frac{q}{c} v_{2,3} - \frac{\beta}{\alpha}\frac{r}{p}\frac{q}{c} x_{2,3} v_{2,3} = \frac{1}{\alpha}\frac{1}{p}\frac{q}{c} v_{2,3}(bm - r\beta x_{2,3}) < 0, \Leftrightarrow$$

$$bm - r\beta x_{2,3} < 0$$

$$x_{2,3} > \frac{bm}{r\beta},$$

from equation (7), we have

$$\frac{k}{\beta v_{2,3} + \mu} > \frac{bm}{r\beta} \Leftrightarrow$$

$$\frac{k}{\beta v_{2,3} + \mu} > \frac{1}{\frac{r\beta}{bm}} \Leftrightarrow$$

$$\frac{1}{\beta v_{2,3} + \mu} > \frac{1}{\mu \frac{r\beta k}{bm\mu}} = \frac{1}{\mu R_0} \Leftrightarrow$$

$$\mu R_0 > \beta v_{2,3} + \mu$$

$$\mu R_0 - \mu > \beta v_{2,3}$$

$$\frac{\mu}{\beta}(R_0 - 1) > v_{2,3}.$$

Remembering the equation for v_1, we have

$$v_1 > v_{2,3}.$$

Then if $v_1 > v_{2,3}$ we get the equilibrium points $E_2 = (x_2, y_2, v_2, z_2)$, which is feasible $(z_2 > 0)$ if $v_1 > v_2$ and $E_3 = (x_3, y_3, v_3, z_3)$, which is feasible $(z_3 > 0)$ if $v_1 > v_3$, where

$$x_2 = \frac{k}{\beta v_2 + \mu},\ y_2 = \frac{p}{r}\frac{c}{q}z_2 + \frac{m}{r}v_2,\ v_2 = \frac{q}{2c} + \frac{1}{2}\sqrt{\left(\frac{q}{c}\right)^2 - 4a^2},$$

$$z_2 = \frac{-\left(\frac{m}{p}\frac{q}{c}v_2 + \frac{b}{\alpha}\right) + \sqrt{\left(\frac{m}{p}\frac{q}{c}v_2 + \frac{b}{\alpha}\right)^2 - 4\left(\frac{b}{\alpha}\frac{m}{p}\frac{q}{c}v_2 - \frac{\beta}{\alpha}\frac{r}{p}\frac{q}{c}x_2 v_2\right)}}{2},$$

$$x_3 = \frac{k}{\beta v_3 + \mu},\ y_3 = \frac{p}{r}\frac{c}{q}z_3 + \frac{m}{r}v_3, v_3 = \frac{q}{2c} - \frac{1}{2}\sqrt{\left(\frac{q}{c}\right)^2 - 4a^2} \text{ and}$$

$$z_3 = \frac{-\left(\frac{m}{p}\frac{q}{c}v_3 + \frac{b}{\alpha}\right) + \sqrt{\left(\frac{m}{p}\frac{q}{c}v_3 + \frac{b}{\alpha}\right)^2 - 4\left(\frac{b}{\alpha}\frac{m}{p}\frac{q}{c}v_3 - \frac{\beta}{\alpha}\frac{r}{p}\frac{q}{c}x_3 v_3\right)}}{2}$$

The points E_2 and E_3 will be called the **immune activation equilibria**

Remark 1 : Observe that, $z_i > 0$, for $i = 2,3$, if $v_1 > v_i$. Then, since we know that $v_2 > v_3$, we have that E_2 and E_3 are feasible points when $v_1 > v_2$, whereas if $v_2 > v_1 > v_3$, existence is only guaranteed for E_3. On the other hand E_2 and E_3 are not feasible when $v_1 < v_3 < v_2$.

3. Stability Analysis

Theorem 1 (The Point E_0 is GAS) : *If* $R_0 \leq 1$, *the point* E_0 *is globally asymptotically stable*

Proof: Let be L the function defined by

$$L = \left(x - \frac{k}{\mu} - \frac{k}{\mu}\ln\frac{\mu x}{k}\right) + y + \frac{b}{r}v + \frac{bp}{rq}z.$$

Taking the derivative of function L along trajectories of system (2), we have

$$\dot{L} = \left(1 - \frac{k}{\mu x}\right)\dot{x} + \dot{y} + \frac{b}{r}\dot{v} + \frac{bp}{rq}\dot{z}.$$

Which is equivalent to

$$\dot{L} = \left(1 - \frac{k}{\mu x}\right)(k - \beta xv - \mu x) + \beta xv - \alpha yz - by + \frac{b}{r}\left(ry - p\frac{zv}{v^2 + a^2} - mv\right) + \frac{bp}{rq}\left(q\frac{zv}{v^2 + a^2} - cz\right),$$

this can be written as:

$$\dot{L} = -\mu x\left(1 - \frac{k}{\mu x}\right)^2 + \beta\frac{k}{\mu}v - \alpha yz - m\frac{b}{r}v - c\frac{bp}{rq}z,$$

or

$$\dot{L} = -\mu x\left(1-\frac{k}{\mu x}\right)^2 + mv(R_0-1) - \alpha yz - c\frac{bp}{rq}z.$$

Then $\dot{L}(E_0)=0$ or $\dot{L}<0$ otherwise. Therefore the point E_0 is globally asymptotically stable for $R_0 \le 1$.

Theorem 2 (The Point E_1 is LAS): *If* $R_0 > 1$ *and* $v_1 > v_2$ *or* $v_1 < v_3$, *the point* E_1 *is locally asymptotically stable and unstable for* $v_3 < v_1 < v_2$.

Proof: The jacobian matrix evaluated in E_1 is

$$J(E_1) = \begin{pmatrix} -\beta v_1 - \mu & 0 & -\beta x_1 & 0 \\ \beta v_1 & -b & \beta x_1 & -\alpha y_1 \\ 0 & r & -m & -p\frac{v_1}{v_1^2+a^2} \\ 0 & 0 & 0 & q\frac{v_1}{v_1^2+a^2} - c \end{pmatrix}.$$

The polynomial characteristic of this matrix is

$$P(\lambda) = \left(\lambda - q\frac{v_1}{v_1^2+a^2} + c\right)[\lambda^3 + (\mu R_0 + m + b)\lambda^2 + (m+b)\mu R_0\lambda + mb\mu(R_0-1)].$$

The polynomial of degree three has roots with negative real part (Ruth-Hurwitz criterium) when

$$(\mu R_0 + m + b)(m+b)\mu R_0 > mb\mu(R_0-1). \tag{18}$$

Let's verify this inequality

$$(\mu R_0 + m + b)(m+b)\mu R_0 = \mu^2 R_0^2(m+b) + (m^2 + 2mb + b^2)\mu R_0 > mb\mu R_0 > mb\mu(R_0-1).$$

From last expression, we can infer that the inequality (18) it is always true for $R_0 > 1$, which rules out the possibility of pure complex roots. Which could exist if $(\mu R_0 + m + b)(m+b)\mu R_0 = mb\mu(R_0-1)$.

Now, we just need to verify that $-q\frac{v_1}{v_1^2+a^2} + c > 0$ and the equilibrium E_1 will be LAS. In fact

$$-q\frac{v_1}{v_1^2+a^2} + c = \frac{cv_1^2 - qv_1 + a^2c}{v_1^2+a^2} > 0. \tag{19}$$

If and only if

$$\left(v_1 - \frac{q}{2c} - \frac{1}{2}\sqrt{\left(\frac{q}{c}\right)^2 - 4a^2}\right)\left(v_1 - \frac{q}{2c} + \frac{1}{2}\sqrt{\left(\frac{q}{c}\right)^2 - 4a^2}\right) > 0,$$

which is equivalent to

$$(v_1 - v_2)(v_1 - v_3) > 0.$$

For $v_2 > v_3$, if $v_1 > v_2$ then $(v_1 - v_2)(v_1 - v_3) > 0$, and if $v_1 < v_3$, then $(v_1 - v_2)(v_1 - v_3) > 0$, while $v_3 < v_1 < v_2$, we have $(v_1 - v_2)(v_1 - v_3) < 0$ and the theorem follows.

Remark 2 : When $v_1 > v_2$ the points E_2 and E_3 coexists, it means that there is a chance of activation of immune system, while that if $v_1 < v_3$, these points are no feasible; it means that the evasion is effective with not chance of activation of immune system, but could be a possibility to eliminate the infection (see 4). When $v_3 < v_1 < v_2$, just the point E_3 will be feasible and the evasion of immune system (E_1) will be unstable.

4. Numerical simulations

In the next figures, we use the parameters in Table 1 to show some scenarios to represent the evasion of immune system by virus and when there is no chance to escape of the immune system. The point E_0 represents the virus free equilibrium, while the point E_1 represents the evasion of immune system by virus and the points E_2, E_3 are the responses of immune system to virus. We analyzed the case when there is a inoculation of virus in the body, i.e. the initial point was $(k/\mu, 0, v_0, 0)$ or when there is a previous activation of immune system or cross-reactive antibodies, i.e. $(k/\mu, 0, v_0, z_0)$.

Table 1

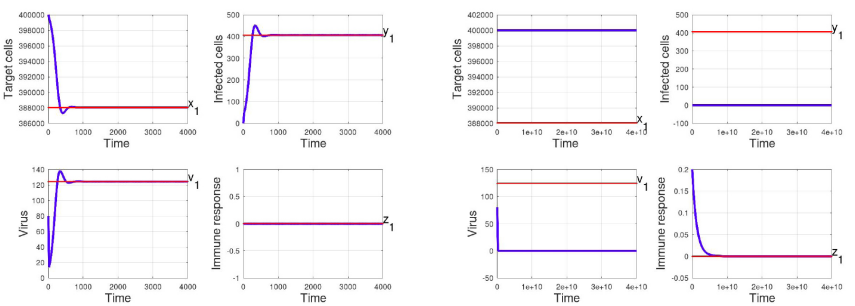
Model parameters. $^\bullet$ When $v_1 < v_3 < v_2$, * when $v_1 > v_2 > v_3$, and * when $v_2 > v_1 > v_3$.

Parameter	Definition	Value	Reference
k	Target cells production rate	6.8×10^3	[2, 1]
β	The infection rate of target cells	4.21×10^{-6}	Assumed
μ	Natural mortality rate of target cells	0.017	[2, 7, 6]

Contd...

b	Apoptosis rate of infected cells	0.5	Assumed
α	Lysis rate of infected cells	0.1	[7, 6]
r	The release rate of viral particles	$1.6\times10^{3*}$ $1.01^{\bullet}$ $6.2\times10^{2\star}$	Assumed
p	The capture rate	20	Assumed
a	maximum capture saturation	$3.7\times10^{4\bullet}$ $3\times10^{4*,\star}$	Assumed
m	Decrease rate of virus	3.3	[7, 6, 5]
q	The rate of immune cell activation	5×10^{-3}	Assumed
c	Natural mortality rate of immune cells	8×10^{-10}	Assumed

1. If $v_1 < v_3 < v_2$, E_1 is locally asymptotically stable while do not have existence for E_2 and E_3, so in this scenario we have a inhibition of immune system or not progression of infection (asymptotically convergence to E_0). See Figure 2.



(a) Initial condition here was $(4\times10^5, 0, 80, 0)$.

(b) Initial condition here was $(4\times10^5, 0, 80, 0.2)$.

Figure 2

In 2a Evasion of immune system when there is initial inoculation of virus in the body and 2b the control of infection by previous activation of immune system.

In this simulation R_0 was 1.0308. Besides, these figures shows that the stability of E_1 is just local.

2. If $v_1 > v_2 > v_3$, E_1 is locally asymptotically stable and we have the existence of E_2 and E_3. In this scenario we have the evasion of immune system or the activation of immune system (asymptotic convergence to E_2 or E_3) but not the control of the infection. See Figure 3

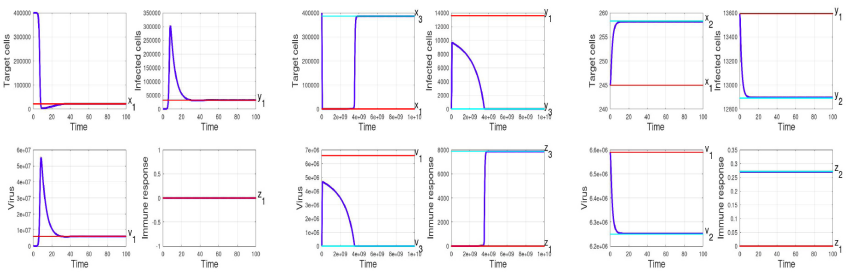


Figure 3

At 3a evasion of immune system when there is a initial inoculation of virus in the body. The initial condition was $(4\times10^5, 0, 80, 0)$. 3b the activation of immune system and the convergence to the equilibrium point E_3. The Initial condition was $(4\times10^5, 0, 80, 2)$. 3c convergence to the equilibrium point E_2. The initial condition here was $(x_1 - ep, y_1 - ep, v_1 - ep, z_2 - ep)$, where $ep = 2\times10^{-3}$

In this scenario, we see that when there is no evasion of immune system, the system converge to the lowest concentration of viral load (v_3) and the infected cells (y_3), but could be a convergence to the point E_2 too. Besides, the figures show that the points E_2 and E_3 are locally asymptotically stable when $v_1 > v_2 > v_3$.

3. If $v_2 > v_1 > v_3$, E_1 is unstable and we have the existence just for E_3. See Figure 4.

In these figures we show that the evasion of immune system is always possible even when the equilibrium point E_1 is unstable. The convergence to the point E_3 could be interpreted as activation of immune system or a kind of control of viremia.

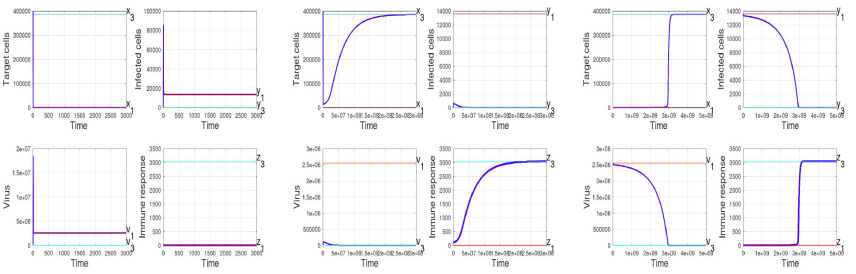


Figure 4

At 4a evasion of immune system when there is an initial inoculation of virus in the body. The initial condition was $(4\times10^5,0,80,0)$. **4b activation of immune system and the asymptotic convergence to** E_3. **The initial condition was** $(4\times10^5,0,80,100)$. **In 4c the convergence to the equilibrium point** E_3. **The initial condition was** $(x_1-ep, y_1-ep, v_1-ep, ep)$, **where** $ep=1\times10^{-1}$

5. Discussion

In this paper, we developed a mathematical model to represent a evasion of immune system by virus using a Hollig type-IV function known as the simplified Monod–Haldane. We found four equilibrium points that we called: the free equilibrium disease E_0, the evasion of immune system equilibrium E_1 and the activation of immune system equilibriums E_2 and E_3. The evasion to the immune system by virus in our model was possible when $R_0>1$ and there was a inoculation of virus even when the point E_1 was unstable. When the points E_2 and E_3 are not feasible, there are two possibilities or the system converges to evasion of immune system equilibrium E_1 or there is a control of the infection, i.e. the system converge to the free equilibrium disease E_0. When the points E_2 or/and E_3 are feasible, we have a similar behavior or the system converges to evasion of immune system equilibrium or converges to some of the immune system activation equilibria.

Mathematical model adequately represents when the virus evades the immune system when there a initial inoculation of virus, but it also shows that when there is activation of the immune system due to immunologic memory or a cross-reactive antibodies, there is not a chance to evade the immune system, in these cases there is activation of immune system that we can read as a low viral load and infected cells.

Conflict of Interest

The authors declare there is no conflict of interest.

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Received August, 2021

Revised February 2022