ESTIMATION OF THE BASIC REPRODUCTIVE NUMBER AND NUMERICAL STABILITY OF SIMULATION DURING IMMUNE CONTROL OF EIAV WITH CELL MEDIATED IMMUNITY

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Abstract: In this paper, we introduce ordinary differential equation (ODE) models of the EIAV (Equine Infectious Anemia Virus) system designed for the study of the effects of lentivirus. EIAV is a retrovirus that establishes a persistent infection in lentivirus. We developed a model of EIAV infection dynamics that contains both Numerical simulation and cell-mediated immune responses. Analysis of the basic reproductive number yields results on steady states that would be necessary for an immune response to successfully control EIAV infection. We discussed linear stability states and Numerical simulation of the model to predict long term behavior in healthy and infected states. Numerical simulations are obtained to illustrate the results to immunological control measures for lentiviral infection.

Keywords: Basic reproduction number, Cytotoxic T Lymphocytes (CTLs), Numerical stability, ODE Model

Introduction: EIAV is an RNA virus, a member of the Retroviridae family and of the lentivirus genus infecting equids. The similarities between these two viruses make the study of the immune response to EIAV relevant to research on AIDS. Equine Infectious Anemia (EIA) was first described in France in 1843 by Ligne and was associated with infection with a "filterable agent" .This makes EIA the first animal disease to be assigned a viral etiology, preceding by several years the major discovery of the first tumor virus by Rous is mechanically transmitted by insect vectors or unsterile needles. The main route of transmission is by hematophagous insects of the Tabanida family. The virus is carried on the mouthparts of the horsefly. The receptor for EIAV on the cellular membrane remains unknown [1].

EIA is considered a worldwide disease but is, due to its transmission by insect vectors, predominant in warm climates. To control the spread of infection, horses are routinely tested at race tracks, shows, and rodeos, before breeding, and crossing borders. EIAV disease in horses is apparently related to an exclusive infection of monocytes and macrophages, making EIA a relevant model for studying lentiviral pathogenicity from macrophage infections without the complications of lymphocyte infections associated with the immunodeficiency lentiviruses.[2]

Infection with EIAV typically follows three stages: acute, chronic & asymptomatic [3] .The acute episode usually subsides within a few days, and then the animal enters the chronic stage of disease characterized by the recurrence of clinical cycles. After 6 to 12 months, the recurrent fevers cease and the animal enter the asymptomatic stage, which is associated with very low viral load & the absence of clinical symptoms.

EIAV infection results in a high – titer, infectious plasma viremia within 3 weeks post infection. Several lines of evidence suggest that both cellular EIAV-specific responses are needed to terminate the initial viremia [1]. All these studies suggest that during the course of EIAV infection, the host develops a highly effective and enduring immune response able to maintain viral replication below the entry level for disease induction (see [1 - 11]). The clearance of the primary infectious plasma viremia correlates with the emergence of EIAV-specific $CD8^+$cytotoxic T lymphocytes (CTL) and non – neutralizing EIAV-specific antibodies [5, 6]. Major histocompatibility complex (MHC) class I restricted viral – specific CD8+ CTL are important for lentivirus immune control of simian immunodeficiency virus (SIV) in infected rhesus monkeys is provided by in vivo depletion of CD8+ lymphocytes with monoclonal antibody. We study the roles of antibodies in limiting virus replication during HIV infection. Antibodies directed against HIV structural proteins are detected in the body within a few weeks following a natural infection [9]. EIAV is a naturally occurring lentivirus that remains a useful model to investigate correlates of immune control. Importantly, we recently reported the selection of a neutralization resistant EIAV variant in severe combined immune deficient foals following passive transfer of immune plasma with broad neutralizing activity [11].

The aim of this study is to create a mathematical model of EIAV and immune system dynamics in order to predict conditions that correlate with viral control, basic reproductive number & Numerical stability of simulations. We use a 5-equation model, and also we include an alternate equation for antibody dynamics that models antibody production in direct proportion to virus. Our analysis gives the characteristics of 3 scenarios: no infection, viral persistence without CTLs, and viral persistence with both CTL and antibody responses. We simulate the long term dynamics of viral infection, showing viral persistence in the context of antibodies alone or of both antibodies and CTLs [10, 11].

Preliminaries: In this paper we present a 5-equation model [4]. Our model explicitly contains the dynamics of CTLs and antibodies, including an equation for antibody dynamics that models antibody production in direct proportion to virus. We then find the steady state solutions.

Notations:	Parameter	description
	λ	Production rate of susceptible host cell(x)
	dx	Death rate of susceptible host cell
	β	Infection rate
	a	Death rate of infected cells
	p	Rate of killing by CTLs
	k	Production rate of free virus
	u	Death rate of free virus
	q	Neutralization of virus by antibodies
	g	Production rate of Antibody
	h	Clearance rate of antibodies
	c	Proliferation rate of CTLs
	b	Death rate of CTLs
	Variable	**Description**
	x	Uninfected cells (monocytes/macrophages)
	y	Infected cells
	v	Virus
	w	Antibodies
	z	Cytotoxic T lymphocytes (CTLs)

Our deterministic model representing the 5-ordinary differential equations: $\dot{x} = \lambda - dx - \beta vx$,

$\dot{y} = \beta vx - ay - pyz$, $\dot{v} = ky - uv - qvw$,

$\dot{w} = gvw - hw$, $\dot{z} = cyz - bz$. (1)

where $x(0)=x_0, y(0)=y_0, v(0)=v_0, w(0)=w_0, z(0)=z_0$ *are given.*

In this model, the target cells of EIAV infection monocyte - derived tissue macrophages [3]. Susceptible hose cells (x) are produced at a rate λ, die at a rate dx and become infected by virus at a rate βvx. Infected cells die at a rate ay and are killed by the CTL response at a rate pyz. Free virus is produced by infected cells at a rate ky, decays at a rate uv and is neutralized by antibodies at a rate qvw. Antibodies develop in response to free virus at a rate gvw and decay at a rate hw. CTLs expand in response to viral antigen derived from infected cells at a rate cyz and decay in the absence of antigenic stimulation at a rate bz.

Steady State: The steady state of the model are found

$$\bar{x} = \frac{\lambda}{dx + \beta\bar{V}}, \quad \bar{y} = \frac{\beta\lambda\bar{V}}{a\left(dx + \beta\bar{V}\right)},$$

$$\bar{v}_1 = \frac{-(hua\beta + qgadx) + \sqrt{(hua\beta + qgadx)^2 - 4qga\beta h(audx - k\beta\lambda)}}{2qga\beta}$$

$$\bar{v}_2 = \frac{-(hua\beta + qgadx) - \sqrt{(hua\beta + qgadx)^2 - 4qga\beta h(audx - k\beta\lambda)}}{2qga\beta},$$

$$\bar{z} = 0, \quad \bar{w} = \frac{g\bar{v}}{h}. \quad (2)$$

We set the equation of the model to zero. The infection-free equilibrium is given by IFE = $\left(\tilde{x}, \tilde{y}, \tilde{v}, \tilde{z}, \tilde{w}\right) = \left(\frac{\lambda}{dx}, 0, 0, 0, 0\right)$. We obtain four other solution $\left(\bar{x}, \bar{y}, \bar{v}_{1,2}, \bar{z}, \bar{w}\right)$ & $\left(\tilde{x}, \tilde{y}, \tilde{v}_{1,2}, \tilde{z}, \tilde{w}\right)$, where

$$\tilde{x} = \frac{\lambda}{dx + \beta\tilde{V}}, \quad \tilde{y} = \frac{b}{c},$$

$$\tilde{v}_1 = \frac{-uhc + \sqrt{(huc)^2 + 4cqgkbh)}}{2qgc},$$

$$\tilde{v}_2 = \frac{-uhc - \sqrt{(huc)^2 + 4cqgkbh)}}{2qgc}, \quad \tilde{z} = \frac{c}{pb}\left(\frac{\beta\lambda\tilde{v}}{dx + \beta\tilde{v}} - \frac{ab}{c}\right), \quad \tilde{w} = \frac{g\tilde{v}}{h}.$$

(3)

Since $\bar{v}_2, \tilde{v}_2$ are less than zero, the steady states are not biological meaningful and therefore will not be discussed further.

Main Results: In this section we discuss the basic reproductive number, R_0, which arises from linear analysis around the infection-free equilibrium point. We provide stability condition for IFE in theorem 2, and we provide existence criteria for boundary equilibrium & endemic equilibrium in theorem3. In addition we provide a numerical stability analysis as well as numerical simulations that illustrate the stability of these equilibrium

points. The basic reproductive number, $R_0^{(1)}$, is a threshold that delineates whether an infection spreads or dies out when a single infected cell encounters a population of uninfected target cells [7]. If $R_0^{(1)} > 1$, then more than one cell becomes infected and the infection will spread; if $R_0^{(1)} < 1$, then less than one cell becomes infected and infection will not take hold [9].

Theorem 1. The basic reproductive number of the model is $R_0^{(1)} = \frac{\beta \bar{x} k}{au}$.

Proof: We find $R_0^{(1)}$ using next generation method. Consider the matrix of new infections, F, and the matrix of transfers, V, both evaluated at the infection-free equilibrium.

$$F(E_0) = \begin{bmatrix} 0 & \beta\bar{x} \\ 0 & 0 \end{bmatrix} \& V(E_0) = \begin{bmatrix} a & 0 \\ -k & u \end{bmatrix}, F(E_0).V(E_0)^{-1} = \begin{bmatrix} \frac{\beta\bar{x}k}{au} & \frac{\beta\bar{x}}{u} \\ 0 & 0 \end{bmatrix}. \quad (4)$$

The basic reproductive number is given by the spectral radius of $F(E_0).V(E_0)^{-1}$. From eqn. (4), we get

$$R_0^{(1)} = \frac{\beta \bar{x} k}{au}.$$

Theorem 2. The IFE $= (\bar{x}, 0, 0, 0, 0)$, of the model is linearly asymptotically stable and attracting for & $R_0^{(1)} < 1$ and unstable for $R_0^{(1)} > 1$.

Proof: The IFE is linearly asymptotically stable and attracting for $R_0^{(1)} > 1$but unstable for $R_0^{(1)} > 1$is an immediate consequence of the computations provided in Theorem 1. The equilibrium endemic equilibrium exists if $\tilde{z}$ is biologically relevant, i.e., $\tilde{z}$ >0. $\tilde{z}$ can be rewritten as $\tilde{z} = \frac{a}{p}\left(R_0^{(2)} - 1\right)$

Where $R_0^{(2)} = \frac{\tilde{v}_1 \beta \lambda c}{ab(dx + \beta \tilde{v}_1)}$.

Hence, endemic equilibrium exists if $R_0^{(2)}$.We will refer to boundary equilibrium .Which represents the case with the presence of antibodies and without CTLs. We will refer to endemic equilibrium, which represents the case with the presence of both antibodies and CTLs.

Theorem 3. If $R_0^{(2)} < R_0^{(1)} < 1$,then IFE is the only equilibrium point and is linearly stable. If $R_0^{(2)} < 1 < R_0^{(1)}$then IFE is unstable, and boundary equilibrium exists. If $1 < R_0^{(2)} < R_0^{(1)}$ then IFE is unstable, boundary equilibrium is unstable, and endemic equilibrium exists.

Proof: We obtain that $R_0^{(1)} > R_0^{(2)}$ from the inequalities

$$R_0^{(1)} = \frac{\beta \bar{x} k}{au} > \frac{\tilde{v}_1 \beta \bar{x} c}{ab} > \frac{\tilde{v}_1 \beta \bar{x} c}{ab\left(1 + \tilde{v}_1 \frac{\beta}{dx}\right)} = R_0^{(2)}$$

Since $\frac{kb}{uc} > \tilde{v}_1$. The later inequality is shown as follow.

In determining the equilibrium points endemic equilibrium, the values $\tilde{v}_1 \& \tilde{v}_2$ were found as the roots of quadratic function

$$G(v) = cqgv^2 + uhcv - kbh. \quad (5)$$

Since the leading coefficient of $G(v)$ is positive, & $G\left(\frac{bk}{uc}\right)$>0, then the positive root $\tilde{v}_1$ lies to the left of the positive value $\left(\frac{bk}{uc}\right)$. i.e. $\tilde{v}_1 < \left(\frac{kb}{uc}\right)$. We now consider the existence of the equilibrium points boundary equilibrium & IFE . This is determined by the sign of the root of the quadratic function

$$H(v) = qga\beta v^2 + (hua\beta + qgadx)v + h(ua\rho dx - k\beta\lambda) \quad (6)$$

Since $h(uadx - k\beta\lambda) = huadx\left(1 - R_0^{(1)}\right)$, then if $R_0^{(1)} < 1$, we get the new inequality

$$\sqrt{(hua\beta + qgadx)^2 - 4qga\beta h(uadx - k\beta\lambda)} < hua\beta + qgadx$$

, which implies that $\bar{v}_1 < 0 \& \bar{v}_2 < 0$ .Hence, the equilibrium points IFE & boundary equilibrium are not biologically possible. If $R^{(1)}{}_0 > 1$, we find

$$\sqrt{(hua\beta + qgadx)^2 - 4qga\beta h(uadx - k\beta\lambda)} > hua + qgadx$$

, which implies that $\bar{v}_1 > 0 \& \bar{v}_2 < 0$ This shows that IFE is an existing equilibrium. The endemic equilibrium exists only if $\tilde{z} > 0$ .Since $\tilde{z} = \frac{a}{p}\left(R_0^{(2)} - 1\right)$, endemic equilibrium is biologically possible only if. We note that $R_0^{(2)}$ is a threshold that delineates the boundary equilibrium from the endemic equilibrium.

Numerical simulations of EIAV: In the previous sections we found the steady states of the model and determined thresholds for their linear stability. The biologically plausible steady states IFE, boundary equilibrium & endemic equilibrium represent the scenarios of the infection-free equilibrium the boundary equilibrium with no CTLs, & the endemic equilibrium

with both CTL and antibody function.

We performed a linear stability analysis of the equilibrium of the model by using numerical values for the parameters and determining the Eigen values of the Jacobian matrices evaluated at each steady state. Negative real parts of all the Eigen values indicated stability of the steady state. We present the results using three representative parameter sets. Our results are summarized in Table1. Parameter sets 1 to 10 were selected because they predict equilibrium IFE, boundary equilibrium & endemic equilibrium respectively. We now illustrate the results on linear stability with numerical simulations using each of the parameter sets.

In the IFE, the infection dies out. All populations approach zero except the number of uninfected cells, which approaches its uninfected steady state level. The time course of infection showing each of the populations over 100 days is shown in figure 1.

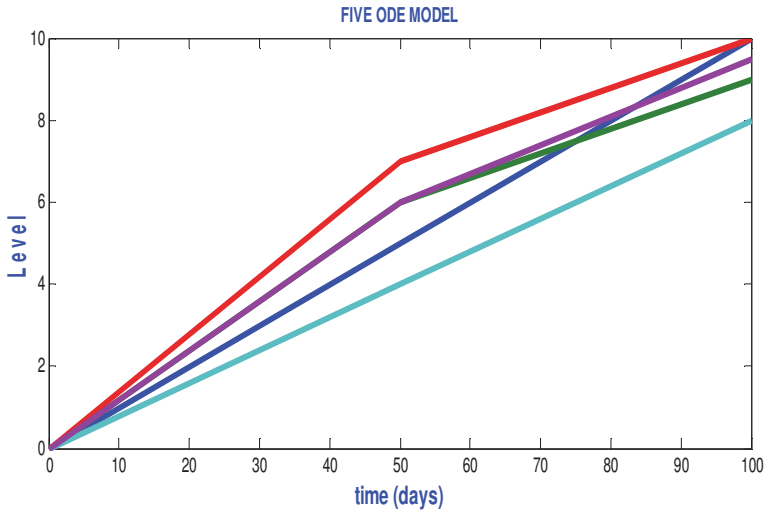
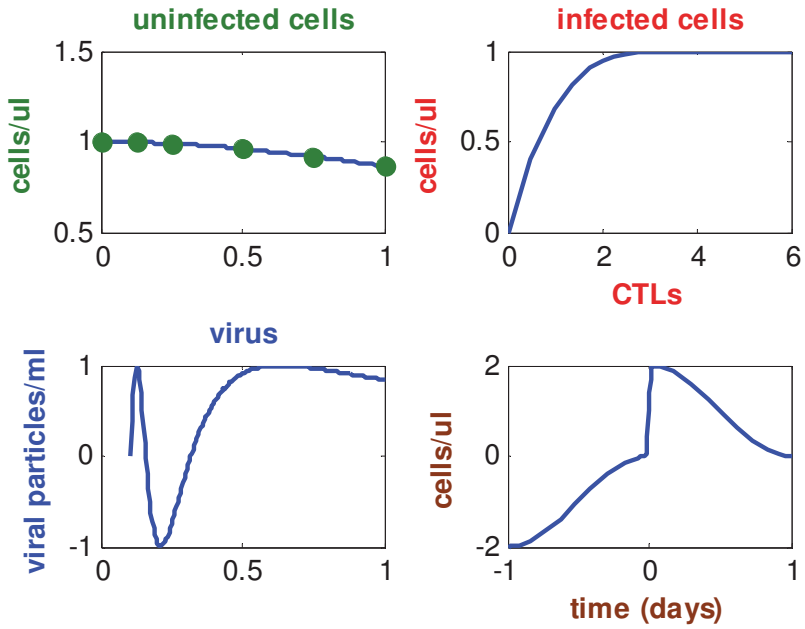


Figure 1. A populations over 100 days for a parameter set representing the infection-free equilibrium (IFE).

Figure 2. A populations over 100 days for a parameter set representing the boundary equilibrium. Parameters are as in Figure 1 except $\lambda = 1$.

Here, ($R_0^{(1)} > R_0^{(2)}$)



The boundary equilibrium represents the case with antibodies but no CTLs.

Here $R_0^{(1)} > 1$ & $R_0^{(2)} < 1$ the long term dynamics show that all populations reach a positive steady state except CTLs, which decay to zero. The time course of infection showing each of the populations over 100 days is shown in figure 2.

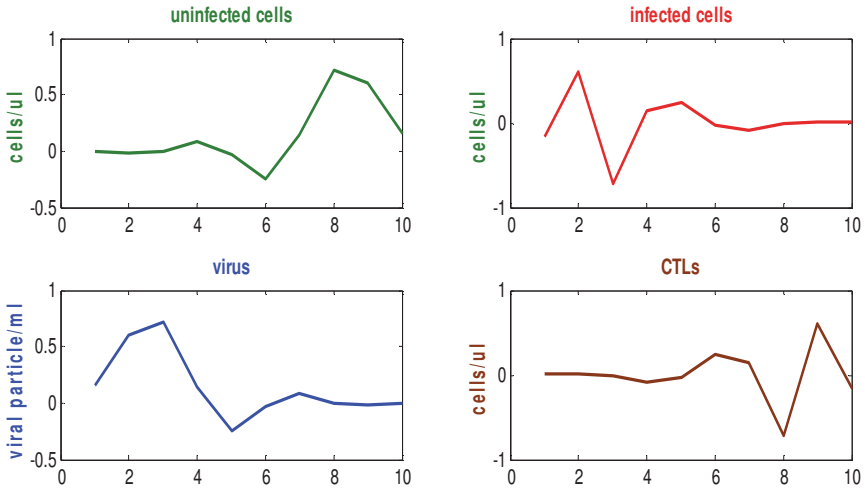


Figure 3. A populations over 100 days for a parameter set representing the endemic equilibrium. Parameters are as in Figure 2 except λ = 2. Here, $R_0^{(1)} < R_0^{(2)}$

The endemic equilibrium shows the case with both antibodies and CTLs. We observe nonnegative steady state values for all populations. In this case, days, is shown in figure 3. This is the case that correlates with clinical infection of EIAV.

Equilibrium values are seen clearly in simulations run over the days, The boundary equilibrium over the interval is shown in Table 1.The endemic equilibrium over the days is shown figure 2.We observe that final values for x, y, v, w, z greater in endemic equilibrium than in boundary equilibrium, but this is likely due to the larger value for λ in this parameter set. For parameter set 1 representing the IFE, all populations except x reach over particular days.

The conditions for the outcome of the dynamics are as follows:

i. Virus1 wins if $R_0^{(1)} > 1$ & $R_0^{(2)} < 1$

ii. Virus 2 wins if $R_0^{(2)} > 1$ & $R_0^{(1)} < 1$.

iii. Coexistence is observed if $R_0^{(1)} > 1$ & $R_0^{(2)} < 1$.

As expected, if the CTL response is higher, the basic reproductive ratio of the invading strain is reduced. How much viral cytopathicity influences this measure depends on the magnitude of the rate of virus-induced cell death, u, relative to the rate of CTL-induced cell killing. The rate of virus-induced cell killing, in turn, is given by $\beta\dot{x}$-dx-u . Where $\dot{x}$ the equilibrium number of uninfected host is cells in the presence of the established $R_0^{(1)} > 1$ & $R_0^{(2)} > 1$. The time course of infection, showing each of the populations over 100 virus strain and is given by $\dot{x} = \frac{\lambda c}{dxc + pz\beta}$. Whether cytopathicity is an important determinant of the ability of a virus to invade or not is therefore dictated by the relative magnitudes of the parameters u & $\beta\dot{x}$. The basic reproductive ratios given above can be written as

$$R_0^{(1)} = \frac{\beta_1 x^{(2)}}{\beta_2 x^{(2)} - u_2 + u_1} \text{ and}$$

$$R_0^{(2)} = \frac{\beta_2 x^{(1)}}{\beta_1 x^{(1)} - u_1 + u_2} \text{ [7].}$$

Discussion: In summary, we constructed a mathematical model of EIAV infection that takes into account the dynamics of cell-mediated and immune responses. We presented equations for the basic reproductive number $R_0^{(1)}$ as well as second thresholds, $R_0^{(2)}$ .We showed that $R_0^{(1)}$ distinguishes IFE from the boundary equilibrium boundary equilibrium and the endemic equilibrium and that $R_0^{(2)}$ distinguishes boundary equilibrium from endemic equilibrium. Finally, we presented parameter sets that correlate with the results of the linear stability analysis. Estimation of $R_0^{(1)}$ from viral load data obtained from 10 primary infection patient,

again identified within a few weeks of infection[8].
The steady states each describe a scenario with a different virological and immunological profile: viral clearance IFE, control of infection with antibodies and no CTLs boundary equilibrium, and control of infection with both antibodies and CTLs endemic equilibrium. Biologically, two of these scenarios are seen: viral clearance IFE and control of infection with both antibodies and CTLs endemic equilibrium. Since coexistence is what is observed in clinical EIAV infection, knowledge of the characteristics of this steady state may be useful both for understanding fundamental mechanisms of immune control as well as for developing therapeutic strategies to bring about the control of viral infection without disease.

Table 1. Stability analysis of Numerical Intervals

Parameter set	$R_0^{(1)}$	$R_0^{(2)}$	Equilibrium stability	Interpretation
1	(-∞,1)	(-∞,1)	Infection free equilibrium stable	Uninfected cell
2	(1,∞)	(-∞,1)	Boundary equilibrium stable,	CTLs does not exist
3	(1,∞)	(1,∞)	Endemic equilibrium stable	Antibody & CTLs exist
4	(-∞,1)	(1,∞)	IFE, BE &EE does not exist	NA
5	(-∞,1)	(-∞,1)	Boundary equilibrium unstable	Uninfected cell
6	(-∞,1)	(-∞,1)	Endemic equilibrium unstable	Uninfected cell
7	(1,∞)	(-∞,1)	Infection free equilibrium unstable	CTLs does not exist
8	(1,∞)	(1,∞)	Boundary Equilibrium unstable	Antibody & CTLs exist
9	(1,∞)	(-∞,1)	Endemic equilibrium unstable	CTLs does not exist
10	(1,∞)	(1,∞)	Infection free equilibrium unstable	Antibody & CTLs exist

Table 2. Estimation of basic Reproductive numbers [8]

Patient ID	$R_0^{(1)}$	$R_0^{(2)}$
P1	4.53	NA
P2	16.02	NA
P3	10.69	NA
P4	3.23	NA
P5	10.70	7.10
P6	16.27	20.99
P7	2.78	NA
P8	19.13	14.45
P9	8.04	9.35
P10	7.30	16.85

Conclusion: Rapid progression & the clear demarcation of the disease in EIAV- infection in equids offers a unique model with which to characterize natural immunological control of lentivirus replication. We provide the estimation for basic reproductive number & numerical analysis of simulations. Development of an efficacious vaccine against lentiviruses, such HIV is a major challenge of this century.

References:

1. C. Leroux, J.L. Cadore, R.C. Montelaro. Equine Infections Anemia Virus (EIAV): What has HIV's country cousin got to tell us? Vet Res. Vol. 35, 2004, pp. 485-512.
2. B. Zhang, C. Sun, S. Jin, M. Cascio, R.C. Montelaro. Mapping of equine lentivirus receptor1 residues critical for equine infectious anemia virus envelop binding. Journal of Virology, 2008, pp. 1204-1213.
3. E.J. Schwartz, K.A. Pawelek, K. Harrington, R. Cangelosi, S. Madrid. Immune control of equine infectious anemia virus infection by cell mediated and humoral responses. Applied Mathematics, Vol. 4, 2013, pp. 171-177.
4. N. Yousfi, K. Hattaf, N. Rachik. Analysis of a HCV model with CTL and Antibody responses. Applied Mathematical sciences, Vol. 57, 2009, pp. 2835-2816.

5. R.H. Mealey, A. Sharif, S.A. Ellis, M.H. Littke, S.R. Leib, T.C. McGuire. Early detection of dominant Env specific and subdominant Gag specific CD8+ lymphocytes in equine infectious anemia virus infected horses using major histocompatibility complex class 1/ peptide tetrameric complexes. Virology, Vol. 339, 2005, pp. 110-126.
6. K.A. Pawelek, G.T. Huynh, M. Quinlivan, A. Cullinane, L. Rong, A.S. Perelson. Modeling within host dynamics of influenza virus infection including imuune responses. Plos Computational biology, vol. 8, No. 6, 2012, article ID: e1002588.
7. D. Wodarz. On the relative fitness of early and late stage simian immunodeficiency virus isolates. Theor Popul Biol, Vol. 72(3), 2007, pp. 426-435.
8. R.M. Ribeiro, L. Qin, L.L. Chavez, D. Li, S.G. Self, A.S. Perelson. Estimation of initial viral growth rate and basic reproductive number during acute HIV-1 infection. Journal of Virology, 2010, pp. 6096-6102.
9. S.M. Ciupe, P. De Leenheer, T.B. Kepler. Paradoxical suppression of poly specific broadly neutralizing antibodies in the presence of strain specific neutralizing antibodies following HIV infection. Journal of theoretical Biology, Vol. 277, 2011, pp. 55-66.
10. S.M. Ciupe, R.M. Ribeiro, P.W. Nelson, A.S. Perelson. Modeling the mechanisms of acute hepatitis B Virus infection. J Theor Biol, Vol. 247 (1), 2007, pp. 23-35.
11. S.D. Taylor, S.R. Leib, W. Wu, R. Nelson, S. Carpenter, R.H. Mealey. Protective Effects of Broadly Neutralizing Immunoglobulin against Homologous and Heterologous Equine Infectious Anemia Virus infection in Horses with Severe Combined immunodeficiency. Journal of Virology, Vol. 85(13), 2011, pp. 6814-6818.

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