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Homotopy perturbation Method For Solving A Model For EIAV Infection

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Abstract : In this article, Equine Infectious Anemia Virus (EIAV) is a retrovirus that establishes a persistent infection in horses and ponies. The virus is in the same lentivirus subgroup that includes human immunodeficiency virus (HIV).Two strains, referred to as the sensitive strain and the resistant strain, have been isolated from an experimentally infected pony. The sensitive strain is vulnerable to neutralization by antibodies whereas the resistant strain is neutralization-insensitive. The sensitive strain mutates to the resistant strain. **Methods/ Statistical Analysis:** Homotopy perturbation method (HPM) is implemented to give approximate and analytical solutions of nonlinear ordinary differential equation systems suchas a model for EIAV infection. **Findings:** This method yields solutions in convergent series forms with easily computable terms. The result shows that this method is very convenient and can be applied to large class of problems. It is worth mentioning that the techniques and ideas presented in this paper can be extended for finding the analytic solution of the nonlinear differential equations. **Applications/Improvements:** This paper is aimed to provide a compact platform for researchers, especially the beginners, in understanding the phenomenon and diagnosing new research problems as well as finding solutions to the existing.

Keywords : EIAV; HPM; Within-host model; virus dynamics.

1. INTRODUCTION

EIAV is a retrovirus of the genus lentivirus that infects equids such as horses and ponies. EIAV is spread between horses through biting flies. Horse flies, primarily of the family Tabanidae, feed on acutely infected horses and spread the virus through a subsequent blood meal on an uninfected equid.

EIA is considered a worldwide disease but is, due to its transmission by insect vectors, predominant in warm climates [3]. 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 [1].

Infection with EIAV typically follows three stages: acute, chronic & asymptomatic. 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].

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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].

Once the initial infection is brought under control, antigenic variants escape thee immunological control and cause the increases in viral load and fevers associated with the chronic stage. After six to twelve months, the recurrent fevers cease and the animal enter the asymptomatic stage, which is associated with very low viral load and the absence of clinical symptoms. We investigate a model of viral infection at the within-host level that includes two modes of viral transmission, free virus and direct cell-to-cell transmission.

In EIAV, a neutralization-resistant variant emerged over time in an experimentally- infected pony. The process of cell-to-cell viral transfer is coordinated to maximize vectorial transfer of virus into uninfected cells [5]. Lentiviruses such as EIAV and HIV are characterized by co-infection by multiple strains. Therefore it is critical to consider multiple strain competition, and emergence of resistance.

The current work provides the study of EIAV viral dynamics by considering the effect of cell-to-cell transmission [2]. Our aim is to provide a mathematical analysis of within-host viral infection for EIAV using both modes of transmission to determine conditions that allow one or both strains to persist and to provide an analysis for infection clearance [4]. We used ordinary differential equations for the mutation from the sensitive strain to the resistant strain and for the proportion of cell-to-cell versus free virus transmission. EIAV targets monocyte-derived macrophages in several tissues of infected equids, including spleen, liver, lungs, and bone marrow [8-13].

These tissues serve as reservoirs for infection for the remainder of the animal's life. Virus enters a prolonged period of clinical quiescence associated with the presence of cytotoxic T cells and broadly neutralizing antibody. Infected animals are typically able to control the viral infection throughout their lifetimes, with control mediated by antibody and cellular immune responses. In cell-to-cell transmission, viruses are transferred from infected cells to uninfected cells. The new within-host model with two viral strains and with free-virus and cell-to-cell transmission is formulated. We used ordinary differential equations for the mutation from the sensitive strain to the resistant strain and for the proportion of cell-to-cell versus free virus transmission.

2. MATHEMATICAL MODELING

Our model is applicable to EIAV, as it displays both modes of transmission. The within-host nonlinear ordinary differential equations include two viral variants transmitted via free viral entry into a cell or direct cell-to-cell transmission [10]. Models used to study EIAV infection have involved the concentration of the five variables in this model are denoted ϕ_1 = target cell ϕ_2 = target cells infected with sensitive strain, ϕ_3= target cells infected with resistant strain, ϕ_4 = free virions of the sensitive strain, and ϕ_5= free virions of the resistant strain. The terms $\beta_{fi}VT$ and $\beta_{ci}IT$ represent transmission rates of free-virus and cell-to-cell, respectively, from either the sensitive $i = 1$ or the resistant viral strain $i = 2$.

The parameter p_i represents the proportion of transmission from the free virus and $1 - p_i$ the proportion that is cell-to-cell, for either the sensitive ($i = 1$) or the resistant ($i = 2$) strain. The proportion of cells infected with the sensitive virus that mutates to the resistant strain is μ. Healthy target cells are produced at a constant rate

Λ. Parameters d_T, d_1 and d_2 are the death rates of healthy or infected target cells, either sensitive or resistant. The parameters c_1 and c_2 are the clearance rates of the sensitive and resistant viral strains. The parameter N_1 and N_2 is referred to as the burst number, the number of free viruses produced by either a sensitive or a resistant infected cell. With these assumptions, the ODE models take the following form :

$$
\begin{aligned}
\frac{d\phi_1}{dt} &= \Lambda - \sigma\phi_1 - p_1\beta_1\phi_4\phi_1 - p_2\beta_2\phi_5\phi_1 - \theta_1\beta_3\phi_2\phi_1 - \theta_2\beta_4\phi_3\phi_1 \\
\frac{d\phi_2}{dt} &= p_1\theta_3\beta_1\phi_4\phi_1 + \theta_1\theta_3\beta_3\phi_2\phi_1 - a\phi_2 \\
\frac{d\phi_3}{dt} &= p_2\beta_2\phi_5\phi_1 + \theta_2\beta_4\phi_3\phi_1 + p_1\mu\beta_1\phi_4 + \theta_1\mu\beta_3\phi_2\phi_1 - b\phi_3 \\
\frac{d\phi_4}{dt} &= ap_1\mathrm{N}_1\phi_2 - c_1\phi_4 - p_1\beta_1\phi_4\mathrm{T} \\
\frac{d\phi_5}{dt} &= bp_2\mathrm{N}_2\phi_2 - c_2\phi_5 - p_1\beta_2\phi_5\phi_1
\end{aligned} \tag{1}
$$

Where $1-p_s = \theta_1, 1-p_r = \theta_2, 1-\mu = \theta_3,$

$d_{\mathrm{T}} = \sigma,\ d_1 = a, d_2 = b,$

$\beta_{fs} = \beta_1, \beta_{cs} = \beta_2, \beta_{fr} = \beta_3, \beta_{cr} = \beta_4$

$\Lambda = 2019,\ \sigma = 0.048,\ a = 0.048,\ b = 0.048$

$c_1 = c_2 = 6.73, \mathrm{N}_1 = \mathrm{N}_2 = 5302.5$

Initial and boundary conditions are

$\phi_1(0) = 42,390, \phi_2(0) = 0,$

$\phi_3(0) = 0, \phi_4(0) = 233, \phi_5(0) = 1,$

$\phi_i(j) = 0,\ i = 1, 22, \ldots 5,\ j = 1 \text{ to } \infty.$

Table 1. Parameter Values For EIAV Corresponding To Model Eqn. (1)

Parameter	***Units***	***Definition***	***Value***	***Reference***
Λ	Cells/(ml D)	Reproduction rate T	2019	Calculated
σ	D^{-1}	Death rate T	1/21	[13]
β_1	ml/(virions D)	FVT1	6.50x10-7	[2]
β_3	ml/(virions D)	FVT2	1.44x10-7	[14]
β_2	ml/(cells D)	CCT1	5.13x10-4	[14]
β_4	ml/(cells D)	CCT2	5.13x10-4	[14]
μ	$(\text{base cycle})^{-1}$	Mutation rate	3x10-5	[9]
a	D^{-1}	Death rate I1	1/21	[13]
b	D^{-1}	Death rate I2	1/21	[13]
N_1	Virions/cell	Burst number for sensitive virus	5302.5	[13]
N_2	Virions/cell	Burst number for resistant virus	5302.5	[13]
c_1	D^{-1}	Clearance rate sensitive virus	6.73	[13]
c_2	D^{-1}	Clearance rate resistant virus	6.73	[13]

Table 2. Initial Value For EIAV Corresponding To Model Eqn. (1)

Initial Value	*Units*	*Value*	*Reference*
$\phi_1(0)$	Cells/ml	42,390	[4]
$\phi_2(0)$	Cells/ml	0	–
$\phi_3(0)$	Cells/ml	0	–
$\phi_4(0)$	Virions/ml	233	[8]
$\phi_5(0)$	Virions/ml	Varies	–

3. HOMOTOPY PERTURBATION METHOD

Before To illustrate the homotopy perturbation method (HPM) for solving non-linear differential equations, He (1998, 2000) [15] considered the following non-linear differential equation:

$$\begin{aligned} \mathrm{A}(u) &= f(r), \\ r &\in \Omega \end{aligned} \tag{2}$$

Subject to the boundary condition

$$\begin{aligned} \mathrm{B}\left(u, \frac{\partial u}{\partial t}\right) &= 0, \\ r &\in \Gamma \end{aligned} \tag{3}$$

Where A is a general differential operator, B is a boundary operator, $f(r)$ is known analytic function, Γ is the boundary of the domain Ω and $\frac{\partial}{\partial n}$ denotes differentiation along the normal vector drawn outwards from Ω. The operator A can generally be divided into two parts M and N. Therefore, (2) can be rewritten as

He (1999, 2000) (16) constructed a homotopy which satisfies Which is equivalent to

$$\begin{aligned} \mathrm{M}(u) + \mathrm{N}(u) &= f(r), \\ r &\in \Omega \end{aligned} \tag{4}$$

He (1999, 2000) constructed a homotopy $v(r, p) : \Omega \times [0,1] \to \Re$ which satisfies

$$\mathrm{H}(v, p) = (1-p)[\mathrm{M}(v) - \mathrm{M}(u_0)] + p[\mathrm{A}(v) - f(r)] = 0, \tag{5}$$

Which is equivalent to

$$\mathrm{H}(v, p) = \mathrm{M}(v) - \mathrm{M}(u_0) + p\mathrm{M}(v_0) + p[\mathrm{N}(v) - f(r)] = 0 \tag{6}$$

Where $p \in [0,1]$ is an embedding parameter, and u_0 is an initial approximation of (6) obviously, we have

$$\mathrm{H}(v, 0) = \mathrm{M}(v) - \mathrm{M}(u_0) = 0, \mathrm{H}(v, 1) = \mathrm{A}(v) - f(r) = 0. \tag{7}$$

The changing process of p from zero to unity is just that of $\mathrm{H}(v, p)$ from $\mathrm{M}(v) - \mathrm{M}(v_0)$ to $\mathrm{A}(v) - f(r)$. In topology, this is called deformation and $\mathrm{M}(v) - \mathrm{M}(v_0)$ and $\mathrm{A}(v) - f(r)$ are called homotopic. According to the homotopy perturbation method, the parameter p is used as a small parameter, and the solution of (5) can be expressed as a series in p in the form

$$v = v_0 + pv_1 + p^2 v_2 + p^3 v_3 + \ldots \tag{8}$$

When $p \to 1$, Eq. (5) corresponds to the original one, Eqs. (4) and (8) become the approximate solution of Eq.(11),

i.e.,

$$u = \lim_{p \to 1} v = v_0 + v_1 + v_2 + v_3 + \ldots \tag{9}$$

The convergence of the series in Eq.(9) is discussed by He(1999 and 2000).

4. HOMOTOPY PERTURBATION METHOD TO A MODEL FOR EIAV INFECTION

In this section, we will apply the homotopy perturbation method to nonlinear ordinary differential systems (1). According to homotopy perturbation method [15-18], we derive a correct functional as follows:

$$\begin{aligned}
\frac{d\phi_1}{dt} - \Lambda - \sigma\phi_1 + p_1\beta_1\phi_4\phi_1 + p_2\beta_2\phi_5\phi_1 + \theta_1\beta_3\phi_2\phi_1 + \theta_2\beta_4\phi_3\phi_1 &= 0 \\
\frac{d\phi_2}{dt} - p_1 - \theta_3\beta_1\phi_4\phi_1 - \theta_1\theta_3\beta_3\phi_2\phi_1 + a\phi_2 &= 0 \\
\frac{d\phi_3}{dt} - p_2\beta_2\phi_5\phi_1 - \theta_2\beta_4\phi_3\phi_1 - p_1\mu\theta_1\beta_1\phi_4 - \theta_1\mu\beta_3\phi_2\phi_1 + b\phi_3 &= 0 \\
\frac{d\phi_4}{dt} - ap_1\mathrm{N}_1\phi_2 + c_1\phi_4 + p_1\beta_1\phi_4\mathrm{T} &= 0 \\
\frac{d\phi_5}{dt} - bp_2\mathrm{N}_2\phi_2 + c_2\phi_5 + p_1\beta_2\phi_5\phi_1 &= 0
\end{aligned} \tag{10}$$

We obtain the solution of (10) we first construct a Homotopy as follows :

$$\begin{aligned}
(1-p)\left[\frac{d\phi_1}{dt} - \Lambda + \sigma\phi_1\right] + p\left[\begin{array}{l}\frac{d\phi_1}{dt} - \Lambda + \sigma\phi_1 + p_1\beta_1\phi_4\phi_1 \\ + p_2\beta_2\phi_5\phi_1 + \theta_1\beta_3\phi_2\phi_1 + \theta_2\beta_4\phi_3\phi_1\end{array}\right] &= 0 \\
(1-p)\left[\frac{d\phi_2}{dt} + a\phi_2\right] + p\left[\frac{d\phi_2}{dt} + a\phi_2 - p_1\theta_3\beta_1\phi_4\phi_1 - \theta_1\theta_3\beta_3\phi_2\phi_1\right] &= 0 \\
(1-p)\left[\frac{d\phi_3}{dt} + b\phi_3\right] + p\left[\begin{array}{l}\frac{d\phi_3}{dt} + b\phi_3 - p_2\beta_2\phi_5\phi_1 - \theta_2\beta_4\phi_3\phi_1 \\ - p_1\mu\beta_1\phi_4\phi_1 - \theta_1\mu\beta_3\phi_2\phi_1\end{array}\right] &= 0 \\
(1-p)\left[\frac{d\phi_4}{dt} + c_1\phi_4\right] + p\left[\frac{d\phi_4}{dt} + c_1\phi_4 - ap_1\mathrm{N}_1\phi_1\right] &= 0 \\
(1-p)\left[\frac{d\phi_5}{dt} + c_2\phi_5\right] + p\left[\frac{d\phi_5}{dt} + c_2\phi_5 - bp_2\mathrm{N}_2\phi_2 + p_2\beta_2\phi_5\phi_1\right] &= 0
\end{aligned} \tag{11}$$

Let

$$\begin{aligned}
\phi_1 &= \phi_{10} + p\phi_{11} + p^2\phi_{12} + \ldots \\
\phi_2 &= \phi_{20} + p\phi_{21} + p^2\phi_{22} + \ldots \\
\phi_3 &= \phi_{30} + p\phi_{31} + p^2\phi_{32} + \ldots \\
\phi_4 &= \phi_{40} + p\phi_{41} + p^2\phi_{42} + \ldots \\
\phi_5 &= \phi_{50} + p\phi_{51} + p^2\phi_{52} + \ldots
\end{aligned} \tag{12}$$

$\boldsymbol{p^0}$ **:**

$$\begin{aligned}
\frac{d\phi_{10}}{dt} - \Lambda + \sigma\phi_{10} &= 0 \\
\frac{d\phi_{20}}{dt} + a\phi_{20} &= 0 \\
\frac{d\phi_{30}}{dt} + b\phi_{30} &= 0 \\
\frac{d\phi_{40}}{dt} + c_1\phi_{40} &= 0 \\
\frac{d\phi_{50}}{dt} + c_2\phi_{50} &= 0
\end{aligned} \tag{13}$$

$\boldsymbol{p^1}$ **:**

$$\frac{d\phi_{11}}{dt}+\sigma\phi_{11}+p_1\beta_1\phi_{40}\phi_{10}+p_2\beta_2\phi_{50}\phi_{10}+\theta_1\beta_3\phi_{20}\phi_{10}+\phi_2\beta_4\phi_{30}\phi_{10} = 0$$

$$\frac{d\phi_{21}}{dt}+a\phi_{21}-p_1\theta_3\beta_1\phi_{40}\phi_{10}-\theta_1\theta_3\beta_3\phi_{20}\phi_{10} = 0$$

$$\frac{d\phi_{31}}{dt}+b\phi_{31}-p_2\beta_2\phi_{50}\phi_{10}-\theta_2\beta_4\phi_{30}\phi_{10}-p_1\mu\beta_1\phi_{40}\phi_{10}-\theta_1\mu\beta_3\phi_{20}\phi_{10} = 0 \quad (14)$$

$$\frac{d\phi_{41}}{dt}+c_1\phi_{41}-ap_1\mathrm{N}_1\phi_{10} = 0$$

$$\frac{d\phi_{51}}{dt}+c_2\phi_{51}-bp_2\mathrm{N}_2\phi_{20}+p_1\beta_2\phi_{50}\phi_{10} = 0$$

(13) Implies

$$\phi_{10} = \frac{\Lambda}{\sigma}+\left(42390-\frac{\Lambda}{\sigma}\right)e^{-\sigma t}$$

$$\phi_{20} = 0$$

$$\phi_{30} = 0$$

$$\phi_{40} = 233e^{-c_1t}$$

$$\phi_{50} = e^{-c_2t}$$

(14) Implies

$$\phi_{11} = \frac{\mathrm{D}_1}{c_1-\sigma}(e^{-c_1t}-e^{-\sigma t})+\frac{\mathrm{D}_2}{c_1}e^{-c_1t}+\frac{\mathrm{D}_3}{c_2-\sigma}(e^{-c_2t}-e^{-\sigma t})+\frac{\mathrm{D}_4}{c_2}e^{-c_2t}$$

Where,

$$\mathrm{D}_1 = p_1\beta_1 233\frac{\Lambda}{\sigma},\mathrm{D}_2 = p_1\beta_1 233(42390-\frac{\Lambda}{\sigma}),$$

$$\mathrm{D}_3 = p_2\beta_2\frac{\Lambda}{\sigma},\mathrm{D}_4 = p_2\beta_2(42390-\frac{\Lambda}{\sigma})$$

$$\phi_{21} = \frac{\mathrm{B}_1}{c_1-a}\left[e^{-at}-e^{-c_1t}\right]+\frac{\mathrm{B}_2}{\sigma-a}\left[e^{-at}-e^{-\sigma t}\right]$$

Where,

$$\mathrm{B}_1 = p_1\theta_3\beta_1 233\frac{\Lambda}{\sigma},\mathrm{B}_2 = p_1\theta_3\beta_1 233(42390-\frac{\Lambda}{\sigma})$$

$$\phi_{31} = \frac{\mathrm{A}_2}{b-c_2}(e^{-c_2t}-e^{-bt})+\frac{\mathrm{A}_3}{b-\sigma-c_2}(e^{-t(\sigma+c_2)}-e^{-bt})$$

$$+\frac{\mathrm{A}_4}{b-c_1}(e^{-c_1t}-e^{-bt})+\frac{\mathrm{A}_5}{b-\sigma-c_1}(e^{-t(\sigma+c_2)}-e^{-bt})$$

Where,

$$\mathrm{A}_2 = p_2\beta_2\frac{\Lambda}{\sigma},\mathrm{A}_3 = p_2\beta_2(42390-\frac{\Lambda}{\sigma}),$$

$$\mathrm{A}_4 = p_1\mu\beta_1 233\frac{\Lambda}{\sigma},\mathrm{A}_5 = p_1\mu\beta_1 233(42390-\frac{\Lambda}{\sigma})$$

$$\phi_{41} = \frac{\mathrm{B}_2}{c_1}(1-e^{-c_1t})+\frac{\mathrm{B}_3}{c_1-\sigma}(e^{-t\sigma}-e^{-c_1t})$$

Where,

$$\mathrm{B}_2 = ap_1\mathrm{N}_1\frac{\Lambda}{\sigma},\mathrm{B}_3 = ap_1\mathrm{N}_1(42390-\frac{\Lambda}{\sigma})$$

$$\phi_{51} = \frac{-\mathrm{A}_2}{\sigma}e^{-c_2t}-t\,\mathrm{A}_1e^{-c_2t}+\frac{\mathrm{A}_2}{\sigma}e^{-t(\sigma+c_2)} \quad (16)$$

Where, $$A_1 = p_2\beta_2 \frac{\Lambda}{\sigma} A_2 = p_2\beta_2(42390 - \frac{\Lambda}{\sigma})$$

Therefore the approximate analytical solutions of nonlinear differential equations systems are

Therefore the approximate analytical solutions of nonlinear differential equations systems are

$$\begin{aligned} \phi_1 &= \phi_{10} + \phi_{11}. \\ \phi_2 &= \phi_{20} + \phi_{21}. \\ \phi_3 &= \phi_{30} + \phi_{31}. \\ \phi_4 &= \phi_{40} + \phi_{41}. \\ \phi_5 &= \phi_{50} + \phi_{51}. \end{aligned} \tag{17}$$

Therefore the solutions are

$$\begin{aligned} \phi_1 &= 16772669.622\,e^{-6.732t} - 8588417.1841e^{-0.048t} \\ \phi_2 &= 412750.36665(e^{-0.048t} - e^{-6.73t}) \\ \phi_3 &= 25748935.179e^{-0.048t} - 25549883e^{-6.73t} - 1990528e^{-6.778t} \\ \phi_4 &= 233e^{-6.73t} + 1431675(1 - e^{-6.73t}) + 11227.143070(e^{-0.048t} - e^{-6.73t}) \\ \phi_5 &= e^{-6.73t} - 54513te^{-6.73t} + 371937656.25\,e^{-0.048t} \end{aligned}$$

5. CONCLUSIONS

In this paper, homotopy perturbation method was used for finding the solution of nonlinear ordinary differential equation systems such as a model for EIAV infection. We demonstrate the accuracy and efficiency of these methods by solving some ordinary differential equation systems. We apply He's homotopy perturbation method to calculate certain integrals. It is easy and very beneficial tool for calculating certain difficult integrals or in deriving new integration formula.

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