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Full Length Research Paper

Solution to an HIV- immune dynamic system

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Some mathematical properties of nonlinear system associated with an HIV- Immune dynamic model will be given. The considered model will be solved numerically. The numerical method permits the examination of the behavior of the dynamic system on long -term. In the same time, it is easy to implement, fast convergent and has a very competitive stability results. Numerical results demonstrate the effect of improving the function of the thymus on the viral growth and T cell population.

Key words: Mathematical immunology, dynamic system, HIV, critical points, finite difference, convergence.

2000 Mathematical Subject Classifications: 92B05, 70K75, 65L12, 65L20.

INTRODUCTION

Acquired Immune Deficiency Syndrome (AIDS) is a viral disease. It suppresses the immune system and elimina-tes the body's ability to increase an immune response by killing helper T cells (its target). The T cells are able to fight this invasion for a period of time, but eventually cannot oppose the violently aggressive attack. As a re-sult, the immune system becomes less effective in fighting. As the disease progresses, the body becomes unable to defend itself against any infections such as pneumonia. The virus, which causes AIDS, is the human immunodeficiency (HIV) virus.

Recently, mathematical immunology has been advan-ced dramatically. The aim of mathematical immunology is to aid understanding of the complexities of the immune system response through mathematical modeling. Mathe-matical models enable us to verify the role of various interactions of individual elements within the frame of the function of the whole immune system. These models may be lead to different situations with different interpreta-tions, which can be helpful to clinicians.

This paper, consider the model that describes the population of HIV virus and its target T cells. It has been used extensively, see e.g., (Kirschner, 1996; Perelson et al., 1993; Prikrylova et al., 1992) and the including refe-rences. However most of these studies, appear to give no details about the utilized numerical methods

The examination of the long-term behavior of a dyna-mic system is necessary. While, using small time step size requires extra computing costs. So, it is essential to use a numerical method that allows the largest time steps.

This work considers an existing model (Kirschner,1996) concerned with the dynamics of HIV- Immune interaction, with slight modification. The solution of this model is uni-que, depends on the initial data. In the case of uninfected individual, there are no points of singularity and the criti-cal point is stable. While for the case of infected indivi-dual, the solution posses two critical points.

Four schemes are investigated to present a compara-tive study for solving HIV-immune dynamic model, name-ly linear implicit finite difference method, nonlinear implicit finite difference method, Euler method and Runge-Kutta method. The numerical comparisons were carried up to test the effect of time step size on the behavior of these methods. It was shown that the linear implicit finite differ-rence method is much better, in terms of numerical con-vergence, than the other methods. It permits the exami-nation of the behavior of the dynamic system on long-term. The novelty of the implicit difference scheme to be developed in this paper is that it is easy to implement, fast convergent and has a very competitive stability re-sults.

Numerical results demonstrate the effect of improving the function of the thymus on the viral growth and T cell population.

HIV-immune dynamic system [1, 3, 7 - 10]

The typical T-cell lymphocyte, originate from the hemo-poietic stem cells in the bone marrow. A population of lymphocytes then passes through the thymus gland to

take their T cell education. Then they become mature T cells. Most of them home to the lymph nodes and spleen, other circulate in the blood stream. Normally T cells are produced at a uniform rate. When the body detects a need for T cells to fight an infection, additional T cells are created by proliferation. Even after thymes involution the thymus remains functional (www.HealthyImmmunity.com; www.aidsinfonet.org). Increases in T cell count is considered as a sign of immune restoration in the case of damage done to the immune system by a foreign substance. T cells live only for a finite period of time.

The mechanism of HIV infection is as follows: Like most viruses, HIV is a very simple RNA virus. It binds to $CD^{+}4$ (marker of T cell) molecules on the surface of T cells. The virus then invades the cytoplasm of the T cell. By means of its reverse transcripts gene, the HIV virus synthesizes a homologous DNA copy and inserts itself into the host cell's DNA. The virus then produces copies of itself. So, the outcome of an HIV' infected patient is an interplay between load and rate of proliferation of HIV virus, rate of proliferation of T helper cells, rate of prolix-feration of infected T helper cells and other members of the immune system. As the disease progresses, the number of T helper cells declines and the body becomes unable to defend itself against any infections.

Mathematical model

The present model (Elsady, 2002) considered as a slight modification of that (Kirschner, 1996). It represents the interaction of HIV and the immune system response. The model consists of three differential equations, which describe rate of changes in "T" the uninfected T helper cells population, "T^i" the infected T helper cells population, and "V" the virus population that lives freely in blood. The basic equations of the model are

$$\frac{dT(t)}{dt} = \alpha(t) - \beta_T T(t) + \gamma_T T(t)\left(1 - \frac{T(t)}{T_{\max}}\right) - k_V T(t)V(t) \quad (1)$$

$$\frac{dT^i(t)}{dt} = k_V T(t)V(t) - \beta_{T^i} T^i(t) - \gamma_{T^i} \frac{T^i(t)V(t)}{c + V(t)} \quad (2)$$

$$\frac{dV(t)}{dt} = n\gamma_{T^i} \frac{T^i(t)V(t)}{c + V(t)} - \beta_V V(t) + \frac{gV(t)}{b + V(t)} \quad (3)$$

with the initial conditions:

$$T(0) = T_0, T^i(0) = 0 \text{ and } V(0) = V_0. \quad (4)$$

In equation (1), (t) represents the rate of generation of new helper T cells from the thymus, bone marrow, or other sources in the presence of virus. The T cells have a finite life span with a death rate T, so the second term represents natural death of uninfected T cell. The third term represents normal proliferation process of T cells with rate T.

In equations (1) and (2), the term $k_V T(t)V(t)$ represents the rate that free virus infects new healthy T helper cells. After a T helper cell becomes infected, it becomes T^i cell and hence the $k_V T(t)V(t)$ term is subtracted from (1) and added to (2). k_V is the kinetic constant for the infection rate

While in equation (2), the infected T^i cells are assumed to have a death rate T^i or destroyed during the proliferation process according to Michaelis- Menten mechanism. T^i is the maximal proliferation rate and c is the half saturation constant of the proliferation process

Equation (3) models the free virus population. The first term on the right hand side is the source for virus population, where n is the average number of viruses released per infected cell before it dies. The second term represents partial clearance of virus from the blood by specific immune response, e.g., antibodies, natural killer T cells and cytotoxic T cells, where V is the rate of the process. The third term, represents release of virus from other infected cells (such as macrophage and other cells). The growth rate of this process is g, and the half saturation constant is b

Equations (1) - (3) together with the initial conditions (4) represent the initial value problem, which represents the dynamic interaction between HIV and the immune response.

ANALYSIS AND RESULTS

For convenience equation (1) will be rewritten in the form

$$\frac{dT(t)}{dt} = \alpha(t) + \beta T(t) - \gamma T^2(t) - k_V T(t)V(t) \quad (5)$$

where $\beta = \alpha(t) - \beta_T$, $\gamma = \frac{\gamma_T}{T_{\max}}$, $T_{\max}$ denotes T cells' maximum possible population, called equilibrium level, which cannot be exceeded by the organism.

The initial value problem, equations (2), (3), and (5) together with the initial conditions (4) can be written in compact form as

$$x' = f(t, x), \quad x(0) = x_0 \quad (6)$$

where

$$x = \begin{pmatrix} T(t) \\ T^i(t) \\ V(t) \end{pmatrix}, f(t,x) = \begin{pmatrix} f_1(t,T,T^i,V) \\ f_2(t,T,T^i,V) \\ f_3(t,T,T^i,V) \end{pmatrix}, x_0 = \begin{pmatrix} T_0 \\ T_0^i \\ V_0 \end{pmatrix}$$

and

$$f_1(t,T,T^i,V) = \alpha(t) + \beta T(t) - \gamma T^2(t) - k_V T(t)V(t)$$

$$f_2(t,T,T^i,V) = k_V T(t)V(t) - \beta_{T^i} T^i(t) - \gamma_T \frac{T^i(t)V(t)}{c+V(t)}$$

$$f_3(t,T,T^i,V) = n\gamma_{T^i} \frac{T^i(t)V(t)}{c+V(t)} - \beta_V V(t) + \frac{gV(t)}{b+V(t)}$$

with the initial conditions:

$T(0) = T_0$, $T^i(0) = 0$ *and* $V(0) = V_0$.

f and its Jacobian matrix:

$$J = \begin{bmatrix} \beta - 2\gamma T - k_V V & 0 & -k_V T \\ k_V T & -\beta_T - \frac{\gamma_{T^i} V}{c+V} & k_V T - \frac{\gamma_{T^i} cT^i}{(c+V)^2} \\ 0 & \frac{n\gamma_{T^i} V}{c+V} & \frac{n\gamma_{T^i} cT^i}{(c+V)^2} - \beta_V + \frac{gb}{(b+V)^2} \end{bmatrix}$$

are defined and continuous t 0. By standard results (Sundaram, 1996), problem (6) is well posed and posses unique, continuous, positive and uniform ally bounded solution. Therefore, the considered model is reasonable in the sense that no population goes negative and no population grows unboundedly. This solution dependent on the initial conditions.

Setting $\frac{dT}{dt} = \frac{dT^i}{dt} = \frac{dV}{dt} = 0$ yields a trivial critical point:

$$\left(T(t) \neq 0,\ T^i(t) = 0,\ V(t) = 0\right)$$

which is stable if $\beta_V > \frac{g}{b}$

Case of uninfected individual

Equation (1) can be rewritten in the form

$$\frac{dT}{dt} = f(t,T(t)), \qquad T(0) = T_0 \qquad (7)$$

where $f(t,T(t)) = \alpha + \beta T(t) - \gamma T^2(t)$ and the initial conditions $T(0) = T_0$.

This model gives realistic population dynamics (Perelson et al., 1993) under the assumptions:

$\alpha \geq 0$, $\beta_T T_{\max} > 0$ and the steady state population size T_s should be less than $T_{\max}$.

For t 0, problem (7) is well posed and has a unique solution

$$T(t) = \frac{\sqrt{\alpha}\left(e^{p(t+d)} - 1\right)}{c - be^{p(t+d)}}$$

where

$$b = \frac{\beta - \sqrt{\beta^2 + 4\alpha\gamma}}{2\sqrt{\alpha}},\ c = \frac{\beta + \sqrt{\beta^2 + 4\alpha\gamma}}{2\sqrt{\alpha}},\ d = \frac{1}{p}\frac{\sqrt{\alpha} + cT_0}{\sqrt{\alpha} + bT_0},\ p = \sqrt{\alpha}(c-b)$$

This solution depends on the initial conditions and has no point of singularity. While the solution

$$T_s = \frac{1}{2\gamma}\left(\beta + \sqrt{\beta^2 + 4\alpha\gamma}\right)$$

is a stable equilibrium solution.

For a healthy individual and in mm^3, the realistic value of the parameters is

$$\alpha = 10,\ \beta_T = 0.02/d,\ \gamma_T = 0.03/d,\ T_{\max} = 1700$$

Note that the fractionation, which is not accepted biologically, will be used to unify the unit of volume (mm^3).

Figure 1 shows that in the absence of any infection, the steady state concentration of T cells would be 1100 cells/ mm^3 after a period of 100 days for different initial count of T cells.

Numerical schemes and comparison (Elsady, 2002)

Let $\{x_n \mid n = 0, 1, 2, ...\}$ represents an approximate solution to x(t) solution of the non- linear ordinary differential equations of the model at a discrete set of points $\{t_n \mid n = 0, 1, 2, ...\}$ and is the time step size. The proposed two discretization methods of the non-linear ordinary differential equations is as follows:

Non-linear implicit method (NLIM)

$$T^{n+1} = T^n + \tau\left(\alpha + \beta T^{n+1} - \gamma\left(T^{n+1}\right)^2 - k_V T^{n+1} V^n\right)$$

$$T^{i,n+1} = T^{i,n} + \tau\left(k_V T^{n+1} V^n - \beta_{T^i} T^{i,n+1} - \gamma_{T^i} \frac{T^{i,n+1} V^n}{c+V^n}\right)$$

$$V^{n+1} = V^n + \tau\left(n\gamma_{T^i} \frac{T^{i,n+1} V^{n+1}}{c+V^{n+1}} - \beta_V V^{n+1} + \frac{gV^{n+1}}{b+V^{n+1}}\right)$$

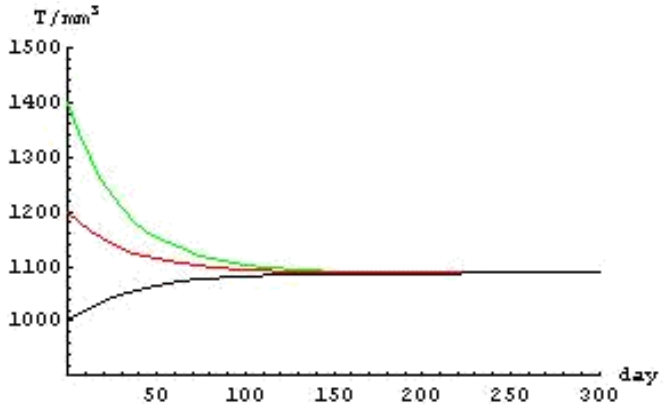

Figure 1. Steady state concentration of T-cells in the absence of any infection.

Table 1. Initial values

Dependent variables	Values
T_0 = initial count of T cells population	1000 cells /mm³
T_{ax} = maximum concentration	1700 cells /mm³
T^I_0 = initial count of infected T^I cells population	0 cells /mm³
V_0 = initial count of infection population	0.001 virus/mm³

Table 2. Parameters values

Parameters and constants	Values
S = source of new T cells	10 cells /day
T = death rate of uninfected T cells	0.02 / day
T^I = death rate of infected T cells	0.5 / day
T = death rate of virus due to other sources	7.4×10^{-4} / day
T =normal proliferation rate of helper T cells	0.003 / day
T^I = the maximal proliferation rate of infected cells	0.002 day
k_V = rate of T cell becomes infected by free virus	2.4×10^{-5}
n = number of virus produced by each infected cell	1000
c = half saturation constant of the proliferation process	100 viruses/mm³
g = growth rate of external viral source other than T cells	0.1/ day
b = half saturation constant of the viral source	15 viruses/mm³

Linear implicit method (LIM)

$$T^{n+1} = T^n + \tau\left(\alpha + \beta T^{n+1} - \gamma T^n T^{n+1} - k_V T^{n+1} V^n\right)$$

$$T^{i,n+1} \quad T^{i,n} \quad T^{n+1} \quad T^n \quad T^{i,n+1} \quad \frac{T^{i,n+1}V^n}{c+V}$$

$$T^{n+1} \quad T^n \quad \frac{T^{i,n+1}V^{n+1}}{c+V} \quad T^{n+1} \quad \frac{gV^{n+1}}{b+V}$$

The terms of the present model are similar to that of the model in (Kirschner, 1996). Therefore, the initial values for the dependent variables and the parameters are chosen to be as in Tables 1 and 2. Also, the fractionation, which is not accepted biologically, will be used to unify the unit of volume (mm³).

Comparison

Now, the numerical comparisons will be given to test the effect of time step size on the convergence of Euler, second order Runge-Kutta, NLIM and LIM methods. The results are summarized in Table 3 for different choice of time step .

The failure of Euler method and second order Runge-Kutta method occur when 1.2, and 2.5 respectively. While the successful of NLIM is up to = 37 and for the LIM for any step size. The failure of both Euler and RK2 methods is due to overflow in computation, while the failure of NLIM is due to Newton's method failed to converge to the prescribed accuracy after 15 iterations. Therefore, from Table 3, the LIM method has a much better behavior than the Euler method, Runge-Kutta method and the NLIM method. It permits the examination of the long- term behavior of a dynamic system by using a larger time steps. The LIM is easy to implement and fast convergent.

Effect of improving thymus on the count of T cells

It is assumed that there is a deterioration of these sources as the viral level increases during the course of HIV infection. By taking

$$\frac{1+\theta V(t)}{1+V(t)} S \le \alpha(t) \le S, \qquad 0 \le \theta \le 1$$

Figures 2 and 3 illustrate the effect of thymus on the quality of life for an infected individual. As the thymus function well, there is a longer period before the complete deterioration of the T cells.

Summary

In the absence of any infection, there is steady state concentration of T-cells depends on the initial count of T-cells in the body. By using the same mathematical model, the graphical pattern of other cellular members of the immune system (using the corresponding empirical numbers values of the immune cells studied) can be getting. The effect of thymus on the quality of life for an infected individual is clear. The numerical method permits the examination of the behavior of the dynamic system on long-term. In the same time, it is easy to implement, fast convergent and has a very competitive stability result.

Table 3. Effect of time step on the successful of the method.

	Euler	RK2	NMIM	LIM
0.1	Convergence	Convergence	Convergence	Convergence
1.0	Convergence	Convergence	Convergence	Convergence
1.1	Convergence	Convergence	Convergence	Convergence
1.2	Failure	Convergence	Convergence	Convergence
2.5	Failure	Failure	Convergence	Convergence
37	Failure	Failure	Failure	Convergence
100	Failure	Failure	Failure	Convergence
1000	Failure	Failure	Failure	Convergence

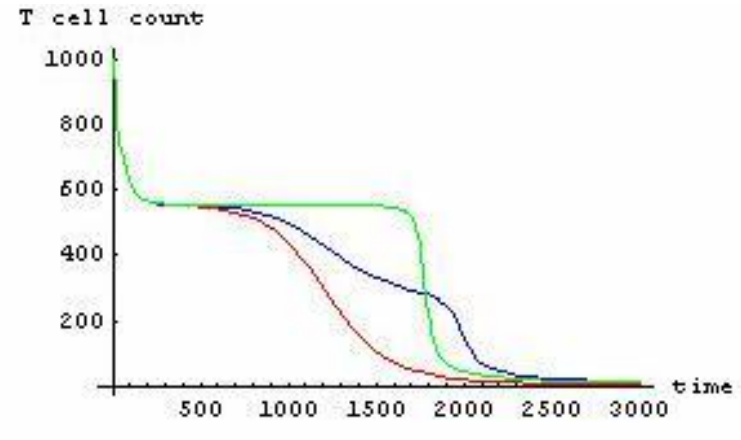

Figure 2. Count of T cells for = 0, 0.5, 1 is in red, blue, and green respectively, where $\frac{1+\theta V(t)}{1+V(t)} S$. Decrease in the population of normal T cells may be due to secretion of soluble substances by the virus that decrease the proliferation process of normal T helper cells.

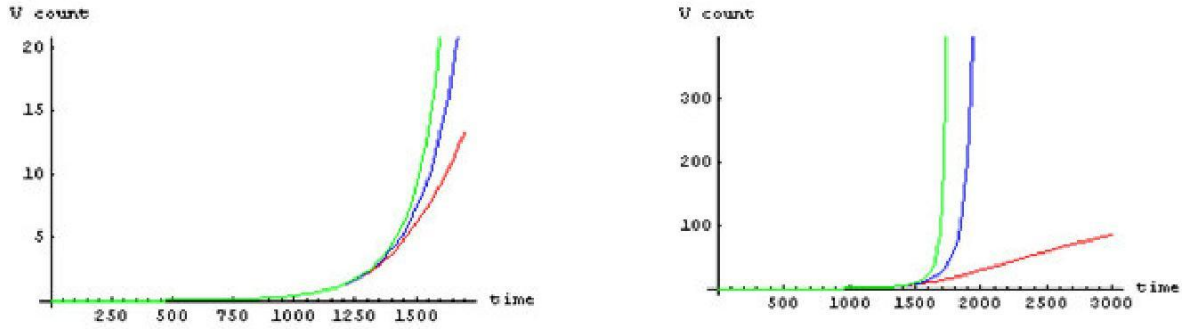

Figure 3. Number of HIV virus for = 0, 0.5, 1 is in red, blue, and green respectively, where $\frac{1+\theta V(t)}{1+V(t)} S$.

Aggressive proliferation of the virus as the progress with time in the case of strong immune system.

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