Boundedness and Positivity of a Mathematical Model of the Immune Response to HIV Infection

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Abstract
Antiretroviral drugs (ARV's) have been in use in controlling Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS). The elimination of the disease depends on prognostic pointers which include HIV viral load and CD4+ cell count. A Mathematical model using differential equations was formulated to describe the interaction of the Immune system with HIV germs. Positivity and boundedness of the model was analyzed epidemiologically and demographic parameters of HIV/AIDS and immune response data analyzed showed that the viral infection is seen to reduce the T-cell population such that at the onset of the disease at time $t = 0$, the T-cell population is more or equal to the total cell population and that for initial population, values grow approaching the carrying capacity, K.

1. Introduction

A mathematical model ideally reflects as many salient features of the real life systems as much as possible. There exist multiple scales at which models can focus, typically associated with the scale of infection, within host, between individuals or within populations[1]. A good Mathematical model, therefore, only retains those features or characteristics that are relevant and significant from the point of view of the goal.

The emergence of epidemics such as HIV has led researchers to focus more deeply on the understanding of the dynamics of the causative virus and the corresponding response by the immune system[2]. This understanding will lead to formulation of more control strategies.

Although an infection may not show its effects on the body immediately, many mathematical models do not take into account variables such as disease gestation times, incubation periods, intracellular lags, pharmaceutical delays, body reaction times, latency periods and other biological processes that take time between the action and reaction time[3]. There are basically seven stages of the HIV life cycle[4].

Stage I Binding: HIV binds (attaches itself) to molecules on the surface of the CD4+ T lymphocyte.

Stage II: Fusion: The HIV viral envelope fuses with the CD4+ cell membrane. Fusion allows the HIV to enter the CD4 T cell.

Stage III: Reverse Transcription. Once HIV is inside the CD4+ cell, it releases and uses reverse transcriptase to convert its genetic material- HIV RNA into HIV DNA. This process enables the HIV to enter the CD4+ cell nucleus and mingle with the genetic material of the cell.

Stage IV: Integration: Here HIV, uses integrase, an HIV enzyme, to insert (integrate) its viral DNA into DNA of the host cell.

Stage V: Replication. Here the HIV starts to use the CD4+ cell's machinery to create long chains of HIV proteins which are building blocks for more HIV.

Stage VI: Assembly. At this stage, new HIV RNA and HIV proteins made by the host CD4+ cell move to the surface of the cell and pull together into an immature or noninfectious HIV.

Stage VII: Budding. At this stage, immature (noninfectious) HIV pushes itself out (buds) of the CD4+ cell and the new copies of HIV can now move on to infect other cells.. Noninfectious HIV cannot infect another CD4+ cell. When one has one or several of these diseases and few CD4+ T cells, one is said to have AIDS. AIDS is clinically diagnosed when the CD4+ T cells are less than 200 cells per microliter(μl), out of the normal range of between 1000 cells per microliter of plasma to 1300 cells per microliter of plasma[7]. The immune response represents a complex defense system against invading pathogens. There are two types of immune responses, namely innate immunity (inborn) and adaptive immunity (acquired). Innate immune system is the first line of defense against invading microbes.

2. Equations, Definition of Variables and Parameters

A model with variables and parameters to describe the immune response to HIV infection has been developed[5].

Letting T denote the population of activated CD4+ cells, E to denote the population of effector cells and V to denote the population of the viral material, the model equations are given by,

$$\frac{dT}{dt} = s + rT\left(1 - \frac{T}{k}\right) - \mu_T T - (I - e)\beta TV$$

(1) $$\frac{dE}{dt} = N(1-e)\beta TV - \mu_e E$$

(2)

$$\frac{dV}{dt} = M(1-e)\beta TV - \mu_V V \qquad (3)$$

The following variables and parameters were used in describing the population and interaction dynamics of the immune response to pathogenic invasion. Letting $T(t)$ denote the population of naïve T cells, $E(t)$ denotes the population of activated effector cells. These are differentiated and specific to the antigen presented by APC. Some of these cells multiply to become memory cells, which are then reactivated at a faster rate by the presence of the antigen to form effector cells which respond to eliminate antigens present, the population of the antigen is denoted by the variable $V(t)$. The following parameters were used to describe the flow rates of individuals from one compartment to the other;

s is the constant recruitment of naive CD4+T cells

r is the growth rate of CD4+T cells

K is the carrying rate of naive CD4+T cells

μ_T is the death (natural) rate of naive CD4+T cells

β is the force of infection of CD4+T cells by the virus i.e. the probability of activated macrophages coming in contact with naive CD4+T cells sufficient to cause infection and activate the cells to differentiate into effector cells.

e is the efficiency of the effectors cells to kill infected CD4+T cells

N is the proliferation rate of the infected or activated cells. This is usually equal to $N = 2$, unless in the presence of immune boosters or therapy.

μ_v is the natural death rate of antigens.

M is the multiples of identical daughter viral materials produced by each activated or infected CD4+T cells which eludes the immune response.

μ_e is the natural death rate of effector T cells

We begin by establishing some basic properties of solutions to the system 1, 2, 3.

These properties are summarized as follows:

- Given positive initial data, the solutions remain positive for all time, t
- Solutions are uniformly bounded regardless of initial data.
- That their steady states, stability and sensitivity shall be determined.

In order to do the analysis above, it is necessary to define the initial conditions and the space we operate in $T(0) = T_0 \geq 0, V(0) = V_0 \geq 0, E(0) = E_0 \geq 0$. The solution is evaluated in the Banach Space defined as $\mathbb{R}_{+0} = \{(T, V, E) | (T \geq 0, V \geq 0, E \geq 0)\}$ and $\mathbb{R}_{+0} = \{(T, V, E) \mid (T > 0, V > 0, E > 0)\}$

3. Positivity and Boundedness of Solutions

Model equations 1,2, 3 describe human cell population and therefore it is very important to prove that all the state variables $T(t)$, $V(t)$ and $E(t)$ are non-negative for all time t. This analysis ensures that the model is well posed and that it is realistic in representing the cell populations with no negative values. A Mathematical problem is well posed if it has a solution, that the solution is unique and that the solution depends continuously on data and parameters[6].

We prove that all solutions of system equations 1, 2 and 3 with positive initial data will remain positive for time $t > 0$ and are bounded in $\mathbb{R} = \mathbb{R}_{+0} + \mathbb{R}_{+}$.

Proposition

Let the initial data be $T_{(S)} = T_0(s) \geq 0$, $V_{(S)} = V_0(s) \geq 0$, $E_{(S)} = E_0(s) \geq 0$ with

$T_0(o) > 0$,$V_0(o) > 0$, $E_0(o) > 0$

Then the solution T (t), V (t) and E (t) of system 1, 2 and 3 are positive for all $t > 0$

For the model system 1, 2, 3, the region $\mathbb{R}$ is positively invariant and all solutions starting in $\mathbb{R}_{+0}$ or $\mathbb{R}_{+}$ approach, enter or stay in $\mathbb{R}$.

4. Results and Discussions

Proof

Under the given initial conditions, it is possible to prove that the components T (t), V (t), and E (t) of systems 1, 2, 3 respectively are positive for $t > 0$

If not we assume a contradiction that there exists a first time t_o such that $T(t_o) = 0$,

$T'(t_o) \leq 0$ and $T(t) > 0$, for $0 \leq t \leq t_o$.

Consider the equation 1 with these assumptions, it follows that when we evaluate at t_o we have;

$$\frac{dT(t_o)}{dt} = s + rT(t_o)\left(1 - \frac{T(t_o)}{K}\right) - \mu_T T(t_o) - (1 - e)\beta V(t_o)T(t_o) = s > 0 \qquad (4)$$

This is a contradiction.

Note that $$\frac{dT(t_o)}{dt} = s > 0, \quad t \in (t - \varepsilon, to) \qquad (5)$$

implies that for $t\epsilon\,(t - \varepsilon, t_o)$, we have $T(t) < 0$ for sufficiently small $\varepsilon > 0$, which is also a contradiction, thus there exists no such first time and thus $T(t) > 0$ for all $t \geq 0$■

The second equation in system 1,2 and 3 is also analyzed for positivity, thus

$$\frac{dE}{dt} = N(1-e)\beta TV - \mu_e E \qquad (6)$$

If we assume that there is also a first time t_o such that $E(t_0) = 0, E'(t_0) \leq 0$ and $E(t) > 0$

And with the above assumptions it follows that when we evaluate at t_o, we have

$$\frac{dE(t_o)}{dt} = N(1-e)\beta T(t_0)V(t_o) - \mu_e E(t_0)$$
$$= N(1-e)\beta T(t_0)V(t_o) > 0 \qquad (7)$$

which is a contradiction, thus there exists no such first time t_o and thus $E(t) > 0$ for all $t \geq 0$■

Equation 3 is analyzed for positivity as,

$$\frac{dV}{dt} = M(1-e)\beta TV - \mu_V V \text{ or } \frac{dV}{dt} = [M(1-e)\beta TV - \mu_v]V. \qquad (8)$$

Note that equation 8 is a separable equation, whose solution by integration yields,

$$V(t) = V_0 e^{[M(1-e)\beta TV - \mu_v]t} \qquad (9)$$

Which is a contradiction, thus there exists no such first time, t_o, and therefore V (t) >0 for all t≥0.

Next we show that positive solutions of system 1, 2 and 3 are ultimately bounded for $t \geq 0$.

In equation 1 of the system, the viral infection is seen to reduce the T-cell population, so that at the onset of the disease $t = 0$, the T-cell population must be more or equal to the total cell population at $t > 0$

In the absence of the disease, the equations 2 and 3 reduce to zero and we remain with the equation governing the T-cell growth and since this is a logistic equation, the cell population is governed by the property of logistic equations, thus

$$T(t) = \frac{T_0 K e^{rt}}{[K + T_0(e^{rt} - 1)]} \qquad (10)$$

For initial population, values below the carrying capacity K, the population grows approaching K from below at $t \to \infty$ as shown in equation 11.

$$\lim_{t\to\infty} T(t) = \lim_{t\to\infty} \frac{T_0 K e^{rt}}{[K + T_0(e^{rt} - 1)]}$$

$$= \lim_{t\to\infty} \frac{T_0 K e^{rt}}{e^{rt}[Ke^{-rt} + T_0(1 - e^{-rt})]}$$

$$= \lim_{t\to\infty} \frac{T_0 K e^{rt}}{e^{rt}[Ke^{-rt} + T_0(1 - e^{-rt})]} = \lim_{t\to\infty} \frac{T_0 K}{[Ke^{-rt} + T_0(1 - e^{-rt})]}$$

$$= \lim_{t\to\infty} \frac{T_0 K}{[0 + T_0(1 - 0)]} = \lim_{t\to\infty} \frac{T_0 K}{T_0}$$

$$= K \qquad (11)$$

For population values greater than K, the death rate is greater than the supply rate, and the population will decrease towards the carrying capacity.

For this assumption to hold and ensure that the model gives realistic population dynamics, we assume that $s > 0$ and the steady state population T_0 should be less than K so that T-Cell population will increase when stimulated. If the population reaches the carrying capacity, it should decrease. Thus the system 1, 2, 3 is bounded above by K and below by 0. This is illustrated by the logistic graph given in Figure 1, below.

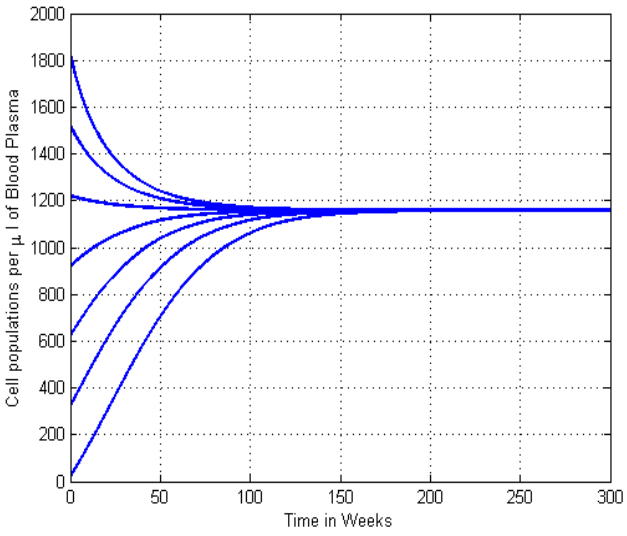

Figure 1 Graph of cell population per μl of blood against time

5. Conclusion

The viral infection is seen to reduce the T-cell population such that at the onset of the disease at time $t = 0$, the T-cell population is more or equal to the total cell population and that for initial population, values grow approaching the carrying capacity, K. Thus, the systems 1, 2 and 3 can be used to design a mathematical model to depict the immune response to HIV infection.

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