Modeling of HIV mediated derangement of Immune System Dynamics

S. N. Sarbadhikari, A. K. Saha and M. Singh

Abstract- **Acquired Immuno-Deficiency Syndrome (AIDS) is a dreaded outcome of HIV (Human Immunodeficiency Virus) attack on the human immune system. The application of mathematical models to HIV data is resulting in a steady stream of studies, which are leading to better understanding and prediction of the behavior of the virus and the immune system, and are helping clinicians in making the very complex choices involved in treating HIV-infected patients. The aim of the present study is primarily focused on two aspects: (i) how does this complex mechanism work when there is a foreign particle (HIV antigen) inside the body and, (ii) what could happen if one or more components of the immune system do not function properly. Our model shows that HIV antigen triggers off the unstable state. However, since HIV itself is attaching to the CD4 cells, instead of a steady rise, there is actually a steady decline of CD4 cell count, moving the dynamics of the system towards the immunodeficient steady state. Our model is also capable of predicting the dynamics in abnormal performance of the system. HIV as an antigen stimulates more formation of CD4 cells. But, further rise in HIV count actually suppresses CD4, leading to progress of the diseased state to full blown AIDS. From our preliminary findings, we can justifiably look ahead in the following manner. There is a slow decline of CD4 cells in the latent infection stage. This can now be modeled by altering our parameters suitably to purvey insight into the factors responsible. These factors can then be taken care of by new groups of anti-HIV drugs, which may reduce the severity and speed of disease progression.**

Keywords- **Model, HIV, Immune System Dynamics.**

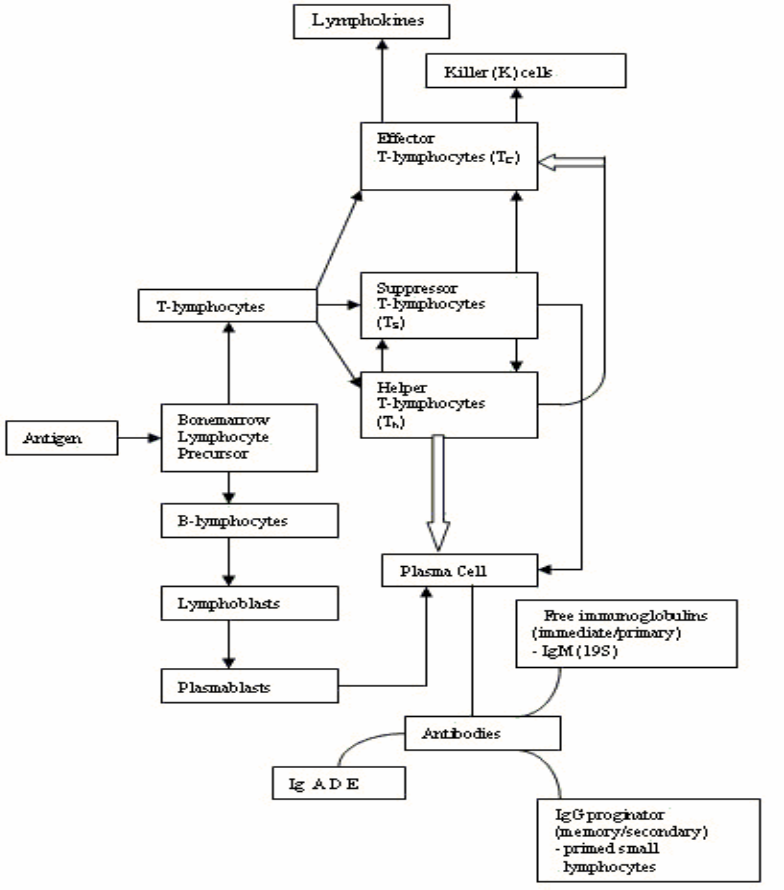

Fig. 1. Schematic diagram of the Immune System interaction.

I. Introduction

ACQUIRED Immuno-Deficiency Syndrome (AIDS) is a dreaded outcome of HIV (Human Immunodeficiency Virus) attack on the human immune system. A schematic view of the immune system is presented in Fig. 1 [1-3].

The application of mathematical models [4] to HIV data is resulting in a steady stream of studies, which are leading to better understanding and prediction of the behavior of the virus and the immune system, and are helping clinicians in making the very complex choices involved in treating HIV-infected patients. Our purpose is to understand what regulates the dynamics of the virus-target cell interaction; and, which factors are most important for the killing of infected cells. This will help in realizing under what conditions is it reasonable to assume that the infection has been cleared, and to attempt to discontinue drug therapy?

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Some models [5], based on Monte Carlo simulations, focus on primary infection and the latent stage of infection of HIV. This is an area of the HIV infection in which more modeling is needed. The latent stage of infection and why there is a slow decline of $CD4^+$ T cells are an unanswered questions and ones in which modeling, both stochastic and deterministic, are needed. The stochastic models purvey a very nice simulation to what is seen clinically but there is not much stress as to what the model predicts about the causative agents or how the model analysis has lead to an improvement in the science. The emergence of mutation and of drug resistance is a critical event in HIV. Stochastic models could play a role with both of these biological phenomena and it would be nice to see more of a combination of modeling efforts that include both stochastic effects and deterministic models.

The aim of the present study is primarily focused on two aspects: (i) how does this complex mechanism work when there is a foreign particle (HIV antigen) inside the body and, (ii) what could happen if one or more components of the immune system do not function properly.

II. MATHEMATICAL MODEL

As shown in Fig. 1, T_C, T_S, T_H, P and Antigen (H_V) represent the Effector T-cells, Suppressor T-cells, Helper T-cells, Plasma cells and HIV respectively. The role of Suppressor T-cells is to give feedback inhibition to the rate of formation of Effector T-cells, Helper T-cells and Plasma cells. On the other hand Helper T-cells give some positive feedback and enhance the growth rates of Effector T-cells and Plasma cells, but it behave opposite with Suppressor T-cells. This is an overview of a normal immune system [3].

When HIV invades the body, it utilizes $CD4^+$ T-cells (a by product of Helper T-cells) for its own replications, eventually, forced Helper T-cells to stay away from its normal functional activities within the system dynamics.

The detailed mathematical model can be denoted as:

$$\begin{aligned}
\frac{dT_c}{d\tau} &= \frac{\alpha_1 T_h}{K^m + T_s^m} - \beta_1 T_c \\
\frac{dT_s}{d\tau} &= \frac{\alpha_2}{K^n + T_h^n} - \beta_2 T_s \\
\frac{dT_h}{d\tau} &= \frac{\alpha_3}{K^p + T_s^p} - \beta_3 T_h - \xi T_h H_v \\
\frac{dP}{d\tau} &= \frac{\alpha_4 T_h}{K^q + T_s^q} - \beta_4 P \\
\frac{dH_v}{d\tau} &= \Re\, \xi T_h H_v - \beta_5 H_v
\end{aligned} \tag{2.1}$$

where, $\alpha_i > 0, (i = 1,...,4)$ are normal growth rates and $\beta_j > 0, (j = 1,...,5)$ are normal decay rates of respective immune components and HIV. $K > 0$, $m > 0, n > 0, p > 0$ and $q > 0$ are system parameters, $\xi > 0$ is the rate at which HIV utilizes Helper T-cells for its own replication, $\Re > 0$ number of new viruses born using one Helper T-cell as template.

In absence of HIV, the above system looks like equ.1 of [3]:

$$\begin{aligned}
\frac{dT_c}{d\tau} &= \frac{\alpha_1 T_h}{K^m + T_s^m} - \beta_1 T_c \\
\frac{dT_s}{d\tau} &= \frac{\alpha_2}{K^n + T_h^n} - \beta_2 T_s \\
\frac{dT_h}{d\tau} &= \frac{\alpha_3}{K^p + T_s^p} - \beta_3 T_h \\
\frac{dP}{d\tau} &= \frac{\alpha_4 T_h}{K^q + T_s^q} - \beta_4 P
\end{aligned} \tag{2.2}$$

One thing we have to keep in mind is that the system (2.1) is operative when there is presence of HIV, while the system (2.2) is active when there is presence of any antigen in the system other than HIV.

The dimensionless form of system (2.1) is as follows:

$$\begin{aligned}
\frac{dx}{dt} &= \frac{Az}{1 + y^m} - \gamma_1 x \\
\frac{dy}{dt} &= \frac{B}{1 + z^n} - \gamma_2 y \\
\frac{dz}{dt} &= \frac{C}{1 + y^p} - \gamma_3 z - \delta z v \\
\frac{dw}{dt} &= \frac{Dz}{1 + y^q} - \gamma_4 w \\
\frac{dv}{dt} &= \Re\, \delta z v - \gamma_5 v
\end{aligned} \tag{2.3}$$

where,

$$\begin{aligned}
&x = T_c K^{-1}, y = T_s K^{-1}, z = T_h K^{-1}, w = P K^{-1}, v = H_v K^{-1}, t = T K^{-1} \\
&A = \alpha_1 K^{-m+1}, B = \alpha_2 K^{-n}, C = \alpha_3 K^{-p}, D = \alpha_4 K^{-q+1}, \delta = \xi K^{-2} \\
&\gamma_1 = \beta_1 K, \gamma_2 = \beta_2 K, \gamma_3 = \beta_3 K, \gamma_4 = \beta_4 K, \gamma_5 = \beta_5 K
\end{aligned} \tag{2.4}$$

The non-trivial steady state of (2.1) is as follows:

$$x_0 = \frac{A\left(\frac{\gamma_5}{\Re\delta}\right)\left[1 + \left(\frac{\gamma_5}{\Re\delta}\right)^n\right]}{\gamma_1\left[1 + \left(\frac{B}{\gamma_2}\right) + \left(\frac{\gamma_5}{\Re\delta}\right)^n\right]}, \qquad y_0 = \frac{\left(\frac{B}{\gamma_2}\right)}{1 + \left(\frac{\gamma_5}{\Re\delta}\right)^n},$$

$$z_0 = \left(\frac{\gamma_5}{\Re\delta}\right), \tag{2.5}$$

$$w_0 = \frac{D\left(\frac{\gamma_5}{\Re\delta}\right)\left[1+\left(\frac{\gamma_5}{\Re\delta}\right)^n\right]}{\gamma_4\left[1+\left(\frac{B}{\gamma_2}\right)+\left(\frac{\gamma_5}{\Re\delta}\right)^n\right]},$$

$$v_0 = \frac{\Re}{\gamma_5}\left\{\frac{C\left[1+\left(\frac{\gamma_5}{\Re\delta}\right)^n\right]}{\left[1+\left(\frac{B}{\gamma_2}\right)+\left(\frac{\gamma_5}{\Re\delta}\right)^n\right]}-\frac{\gamma_3\gamma_5}{\Re\delta}\right\}$$

Compared to system (2.1), the system (2.2) has three possible steady states, two of them are stable and one is unstable. The stable steady states describe two extreme situations of immune system, (i) Autoimmune disorders like Rheumatoid Arthritis and (ii) immunodeficient states like AIDS. The unstable steady state is the one which can trigger off to eliminate the antigen from the system, if there is any. For details see [3].

III. PARAMETER CHOICE

As mentioned, system (2.1) is operative when there is a presence of antigen in the system. Clinically observed data pattern suggests [3] that antigen and corresponding antibody activities of any disease share a common property, both are unimodal and similar to the curve represents by the following mathematical formulations:

$$\chi = \psi e^{-\sigma\psi} \qquad (2.6)$$

where, $\sigma > 0$

For simplicity, we choose our parameters according to (2.8),

$$\begin{aligned}\alpha_1 &= M - f(\varpi)e^{-\theta_1 f(\varpi)}\\ \alpha_2 &= f(\varpi)e^{-\theta_2 f(\varpi)}\\ \alpha_3 &= \frac{1}{f(\varpi)}e^{-\theta_2 f(\varpi)}\\ \alpha_4 &= f(\varpi)e^{-\theta_1 f(\varpi)}\end{aligned} \qquad (2.7)$$

where, $\alpha_2\alpha_3 = 1$ (indicates an inverse relationship between Suppressor T-cells and Helper T-cells) and $\alpha_1 + \alpha_4 = M$ (indicates a linear relationship between Effector T-cell and Plasma cells) and, $\theta_1, \theta_2 > 0$ and $f(\varpi)$ represents number of weeks. α_i is maximum when $f(\varpi) = \frac{1}{\theta_i}$. Now, θ can be approximate from the number of weeks at which the antigen activity level will be at peak. *M* can be approximated from the time of a particular antibody actively engaged to defend a particular antigen.

Most of the parameters in our model system (2.1) are chosen based on normal human being white blood corpuscles [3], the parameters ξ, β_5 and $\Re$ are directly related to HIV-antigen, at this stage we estimate them arbitrarily.

IV. RESULTS AND DISCUSSION

After substituting the parameter magnitudes in the above equations, we obtain the following three graphs.

The first graph (Fig. 2) shows that the concentrations of Effector T-cells and Plasma cells are decreasing gradually with respect to time in presence of HIV-antigen. From biological point of view we can see both temporal and humoral responses of the immune system are declining in presence of HIV-antigen.

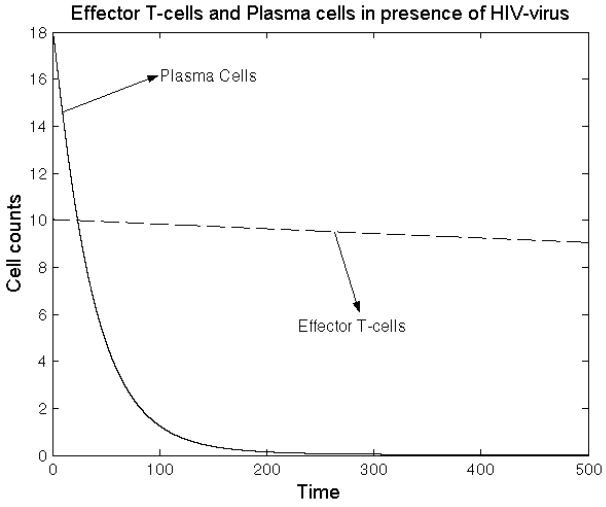

Fig. 2. Plasma cells and Effector T-cells in presence of HIV-virus in the Immune System, model parameters are estimated from normal white blood corpuscle counts [3]. Initially, only one virus is introduced into the system. It is assumed arbitrarily that one HIV-virus can replicate into 100 viruses by using only one CD4+ cell.

In the next graph (Fig. 3) we will justify the control mechanism of the immune system due to the presence of HIV-antigen. Here, in presence of HIV-antigen the concentration of the Suppressor T-cells is increasing whereas that of Helper T-cells is decreasing with respect to time. From biological point of view we can say that immune system is heading towards a stable steady state [3] where the Helper T-cells concentration is very low and the Suppressor T-cells concentration is very high. By stable steady state we mean a state from where immune system cannot trigger off to fight against any foreign antigen.

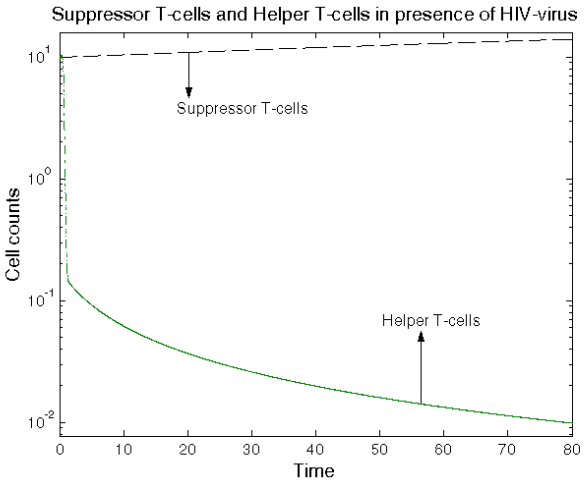

Fig. 3. Suppressor T-cells (CD8) and Helper T-cells (CD4) in presence of HIV-virus in the Immune System, model parameters are estimated as in Fig. 2.

Finally, the virus growth can be represented by Fig. 4. Here the virus population within the host is growing very rapidly with respect to time.

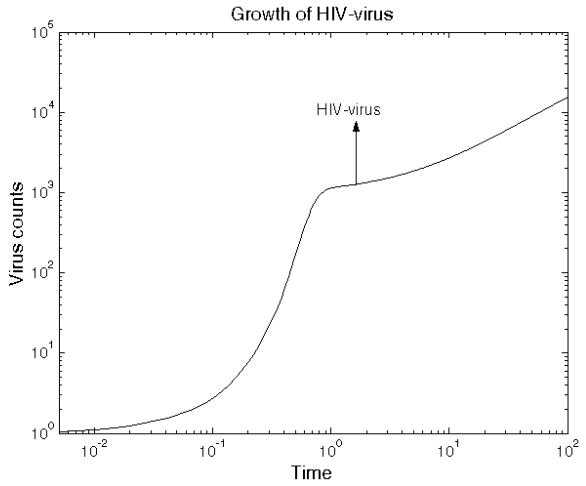

Fig. 4. Growth of HIV-virus in the human body, model parameters are estimated as in Fig. 2.

The first aim of our study is achieved since the model shows that HIV antigen triggers off the unstable state of the normal immune system [3], but within a period of time the total immune system moves towards another steady state which is perfectly stable, as shown in Fig. 3. Hence, at this point of time, the immune system appears to have lost control to fight against any foreign antigen, no matter what type of antigen it is. However, since HIV itself is attaching to the CD4 cells, instead of a steady rise, there is actually a steady decline of CD4 cell count, moving the dynamics of the system towards the immunodeficient steady state.

The second aim, of predicting the dynamics in abnormal performance of the system is also demonstrated by our model. HIV as an antigen stimulates more formation of CD4+ cells. However, further rise in HIV count, actually suppresses CD4+, leading to progress of the diseased state to full blown AIDS.

V. CONCLUSIONS & FUTURE PLANS

From our preliminary findings, we can justifiably look ahead in the following manner. As explained in the Introduction, there is a slow decline of CD4 cells in the latent infection stage. This can now be modeled by altering our parameters suitably to purvey insight into the factors responsible. These factors can then be taken care of by new groups of anti-HIV drugs, which may reduce the severity and speed of disease progression.

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