T-cell Proliferation in a Mathematical Model of CTL Activity Through HIV-1 Infection

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Abstract—**HIV-1 infection degrading the human immune system and recent advances of drug therapies for the HIV-1 dynamics under the application of highly active anti-retroviral therapy (HAART) generated considerable research interest in this area. It is specially associated with virus - specific Cytotoxic T-Lymphocyte (CTL) response that declines with disease progression. Here we introduced a population model representing long term dynamics of HIV-1 infection in response to available drug therapies. We also considered that T-cells can be created by proliferation of existing CD4$^+$T cells in body. These models focus on the interactions of susceptible T-cells, virus producing cells and cytotoxic T-cells, that would be able to provide a complete understanding of the long term dynamics of the system. Some crucial system parameters may significantly collided the way in which HIV-1 infected AIDS patient are treated with potent antiretroviral drugs. Results from our analysis of the model are consistent with clinical observation.**

Keywords: Asymptotic Stability, CD4$^+$T cells, CTL, HAART, HIV-1, T-cell proliferation, Time Series Solutions.

1 Introduction

Over the last several years extensive research has been made in our understanding of the pathogenesis of HIV-1 infection. Though impressive amount of knowledge and information have been gathered till date regarding the implications of genetic variations of immune cells, HIV-1 pathogenesis and drugs which act either by blocking the integration of viral RNA into the host CD4$^+$T cells, or by inhibiting the proper cleavage of viral proteins inside an infected cell [1] - [4]. But still the fundamental questions remain unanswered. On that point of view HIV-1 infection is very much associated with an extremely vigorous virus specific Cytotoxic T- Lymphocyte (CTL) response that declines disease progression [2], [3], [5] - [7].

Retroviral therapy when began to a HIV-1 individual, the main clinical indicators of that HIV-1 positive patient are in the follow up both the viral load and the CD4$^+$T cells count in blood plasma [1], [8], [9]. Also it is to be mentioned that when therapy is started, make a portion to the immune cells to be toxic thereby introducing toxicity in the immune system of the individual. Thus qualitative aspects of the HIV-1 specific CTL response is to be an important determinants of the efficacy of these response in controlling viral replication. The main purpose of this study is to develop a mathematical framework that can be used to understand the various drug therapy in optimum controlled level for which it should be maximize the survival time of each infected individual and minimize the number of new infection [10] - [12].

It has been observed clinically that patients infected with immunodeficiency virus type-1 (HIV-1), if treated with a combination of inhibitor-drugs lamivudine and zidovudine shows a 10 to 100 fold reduction of viral load and nearly 25% increase in the healthy CD4$^+$T cells count. Sustenance of such drug receiving patients is observed to be more than one year [8], [9], [13].

In this paper we build on a mathematical model HIV-1 infection to CD4$^+$T cell as a host cell including the mentioned inhibitor drug. The system response to the drug stimulation by generating Cytotoxic T-Lymphocyte (CTL) and this CTL's in-turn attack the actively infected CD4$^+$T cells and kill them. We have also considered that the growth of CD4$^+$T cells is governed by a logistic equation. It is to be mentioned here that in the absence of limited population the average specific CD4$^+$T cells growth rate may be obtained. Our focus in this paper which deals specifically when that mentioned inhibitor drug is to be given to a HIV-1 patient, what will be the dynamical behavior of the human immune system through drug stimulation by generating CTL with maximum proliferation of T-cells and that T-cells population at which proliferation shuts off [8], [9], [14], [16], [17].

The model equation is analyzed in two different avenues, analytical and numerical. Different equilibria and boundedness of the system carried out through the conditions under which the system dynamics is permanent and asymptotically stable around the interior equilibrium

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point. It is also been checked that under which condition the system is globally asymptotically stable. Model has been solved numerically to find out the threshold values of the system parameters for which the diseases can be controlled. Numerical findings are in agreement with the results of theoretical analysis.

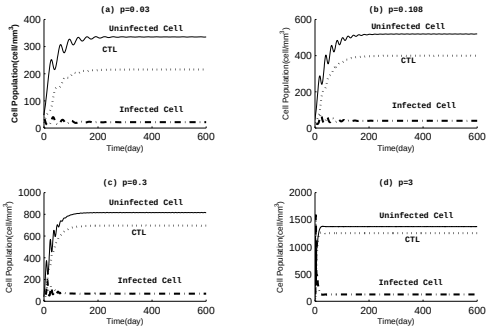

Figure 1: Population density of the uninfected, Infected cells and CTL converges to their equilibrium. Time series solution of the model variables for different values of the proliferation rate. Various model parameters are as in Table.1.

2 Formulation of HIV-1 Model

To generate a realistic model of HIV-1 infection to $CD4^+T$ cells, we consider $x(t)$ and $y(t)$ be the uninfected and infected (virus producing cells) portions of the hosts $CD4^+T$ immune cells at a time t. Uninfected $CD4^+T$ cells are produced at a constant rate λ and are removed on the system through the natural death rate d. A variable denoting free virus load in the system becomes relevant while considering short term viral dynamics. However when one is interested in drug induced changes at the steady state the variable corresponding to free virus can be omitted. At the steady state it is inherently assumed that the free virus populations is proportional to the virus-producing $CD4^+T$ cells which are already infected [3]. Note that infected $CD4^+T$ cells produce free virus by their replication through the process of cell lysis. The process of infection to the uninfected $CD4^+T$ cells follows the law of mass action under mixing homogeneity. This means that the number of new infection at the steady state is proportional to $x(t)y(t)$. Some immunocompetent T cells are produced by the lymphatic system. Over a shorter period of time, their production rate is constant and independent of the number of T cells. This constant rate of production denote as β. It is to be assumed that T cells may be created by proliferation of existing T cells and the total number of T cells cannot increase unboundedly. Here we represent the proliferation of T cells by a logistic fashion in which p is the maximum proliferation rate constant and it proliferate to a maximum given by T_m, mentioning that T cell population density at which proliferation shuts off. To formulate of our mathematical model we thus considered the logistic term in the form of $px(1-\frac{x}{T_m})$ [8], [9].

Based on the above assumption one can write down a simple model as

$$\begin{aligned}\frac{dx}{dt} &= \lambda + px(1-\tfrac{x}{T_m}) - dx - \beta xy \\ \frac{dy}{dt} &= \beta xy - ay\end{aligned} \tag{2.1}$$

Where the parameter a is the normal death rate of infected $CD4^+T$ cells. It can be seen in the literature that the rate at which uninfected $CD4^+T$ cells are converted into virus producing (infected) portion is smaller than β, we consider here the rate to be same as β. The argument in support of such enforcement goes at steady state under the condition of mixing homogeneity and the law of mass action holds perfectly.

Whenever a HIV-1 infected patient is subjected to RTI (Reverse Transcriptase Inhibitors) drug or HAART (Highly Active Anti-Retroviral Therapy), the virus replications within the virus producing T-cells faces a reduction. Such effect may be incorporated in the two variable simple viral dynamics model by reducing the numerical value of the parameter β (rate of infection). However, mere reduction of β in the basic viral dynamics model fails to explain the strong suppression of equilibrium virus load observed during long term drug therapy. Therefore it is imperative to include another variable in the basic viral dynamics model (2.1), in order to make the long term immune response of the model at per with those observed in reality. We include a variable z to represent the density of the Cytotoxic-T-Lymphocyte (CTL) responses against virus infected cells. The basic viral dynamics model with this inclusion becomes

$$\begin{aligned}\frac{dx}{dt} &= \lambda + px(1-\tfrac{x}{T_m}) - dx - \beta xy \\ \frac{dy}{dt} &= \beta xy - ay - kyz \\ \frac{dz}{dt} &= sy - bz.\end{aligned} \tag{2.2}$$

Where k is the killing rate of virus producing cells by CTL, s is the rate of stimulation (production) of CTL and b be the base line mortality rate of CTL. The system (2.2) needs to analyzed with the following initial condition: $x(0) > 0,\ y(0) > 0,\ z(0) > 0$ and we denote

$$R^3_+ = \{(x,y,z) \in R^3,\ \ x \geq 0,\ \ y \geq 0,\ \ z \geq 0\} \tag{2.3}$$

3 Equilibria and Local Stability

In this section, we only consider positive equilibriums (Including positive equilibriums) of the system and there stability. The system (2.2) with the initial condition (2.3) possesses the following positive equilibrium $E_0(x_0, 0, 0)$ and $E^*(x^*, y^*, z^*)$ where,

$$x_0 = \tfrac{T_m}{2p}[(p-d) + \sqrt{(p-d)^2 + 4\tfrac{p\lambda}{T_m}}] \tag{3.1}$$

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and

$$\begin{aligned} x^* &= \frac{(\frac{ab\beta}{sk}+p-d)+\sqrt{(\frac{ab\beta}{sk}+p-d)^2+4\lambda(\frac{b\beta^2}{sk}+\frac{p}{T_m})}}{2(\frac{b\beta^2}{sk}+\frac{p}{T_m})} \\ y^* &= \frac{b}{sk}(\beta x^* - a) \\ z^* &= \frac{\beta x^* - a}{k} \end{aligned} \tag{3.2}$$

satisfy the following inequalities

$$p > d \quad \text{and} \quad x^* > \frac{a}{\beta} \tag{3.3}$$

To study the stability of the following equilibrium let us introduce the basic reproduction ratio R_0 defined as $R_0 = \frac{x_0}{x^*}$ of the system (2.2). This represents the average number of secondary infection caused by the single infected $CD4^+T$ cells in an uninfected T cells population in the infection period for the long period of time.

Since x_0 and x^* satisfy

$$\begin{aligned} \lambda + px_0(1-\tfrac{x_0}{T_m}) - dx_0 &= 0 \\ \lambda + px^*(1-\tfrac{x^*}{T_m}) - dx^* &= \tfrac{b\beta}{sk}(\beta x^{*2} - ax^*) \end{aligned}$$

so that we can get

$$\begin{aligned} & x^* > \tfrac{a}{\beta} \Rightarrow x_0 > x^* \\ \text{and} \quad & x^* < \tfrac{a}{\beta} \Rightarrow x_0 < x^* \end{aligned} \tag{3.4}$$

i.e if $R_0 > 1$, then the positive equilibrium $E^*(x^*, y^*, z^*)$ exists.

Now the Jacobian matrix of the system (2.2) is

$$\begin{pmatrix} p - d - \frac{2px}{T_m} - \beta y & -\beta x & 0 \\ \beta y & \beta x - a - kz & -ky \\ 0 & s & -b \end{pmatrix} \tag{3.5}$$

For the equilibrium $E_0(x_0, 0, 0)$, the characteristic equation becomes

$$(\rho - p + d + \tfrac{2px_0}{T_m})(\rho + a - \beta x_0)(\rho + b) = 0 \tag{3.6}$$

whose eigen values are

$$\begin{aligned} &\rho_1 = p - d - \tfrac{2px_0}{T_m} = -(\tfrac{px_0}{T_m} + \tfrac{\lambda}{x_0}) < 0, \\ &\rho_2 = \beta x_0 - a > 0 \\ &\text{and} \quad \rho_3 = -b < 0 \end{aligned} \tag{3.7}$$

Hence $E_0(x_0, 0, 0)$ is locally asymptotically stable if $R_0 < 1$ and it is saddle with $dimW^s(E_0) = 2$, $dimW^u(E_0) = 1$ for $R_0 > 1$. Thus we can establish the theorem.

Theorem 3.1 : If $R_0 < 1$ then E_0 is locally asymptotically stable, if $R_0 > 1$ then E_0 is unstable. Now for the equilibrium $E^*(x^*, y^*, z^*)$ the characteristic equation is as follows,

$$\rho^3 + A\rho^2 + B\rho + C = 0 \tag{3.8}$$

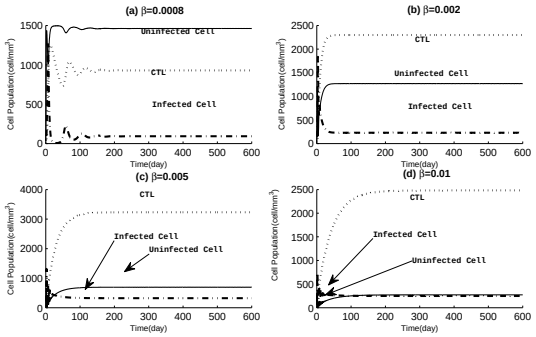

Figure 2: Time series solution of the model variables for different values of β. Various model parameters are as in Table.1.

where,

$$\begin{aligned} &(i) \;\; A = \tfrac{px^*}{T_m} + \tfrac{\lambda}{x^*} + b > 0, \\ &(ii) \;\; B = b(\tfrac{px^*}{T_m} + \tfrac{\lambda}{x^*}) + sky^* + \beta^2 x^* y^* > 0, \\ &(iii) \;\; C = sky^*(\tfrac{px^*}{T_m} + \tfrac{\lambda}{x^*}) + b\beta^2 x^* y^* > 0 \end{aligned} \tag{3.9}$$

From the Routh-Hurwitz criterion, the necessary and sufficient condition for locally asymptotic stability of the steady state is

$$\begin{aligned} &AB - C > 0 \quad \text{i.e} \\ &(\tfrac{px^*}{T_m} + \tfrac{\lambda}{x^*} + b)[b(\tfrac{px^*}{T_m} + \tfrac{\lambda}{x^*}) + sky^* + \beta^2 x^* y^*] \\ &-[sky^*(\tfrac{px^*}{T_m} + \tfrac{\lambda}{x^*}) + b\beta^2 x^* y^*] > 0 \end{aligned} \tag{3.10}$$

and the system locally asymptotically stable around the positive interior equilibrium if,

$$\begin{aligned} &(i) \quad x^* > \tfrac{a}{\beta} \quad (ii) \quad d > \beta, \quad (iii) \quad p > \tfrac{(ad-\lambda)\beta^2 T_m}{a(\beta T_m - a)}, \\ &(iv) \quad \tfrac{b\beta^2}{sk} + \tfrac{p}{T_m} > 0, \quad (v) \quad p > d\beta - \tfrac{ab\beta}{sk}, \\ &(vi) \quad \beta > \tfrac{-apT_m + \sqrt{(apT_m)^2 + 4(a^2 - \frac{1}{T_m})[T_m(\lambda - ad) + \frac{b}{sk}]p}}{2[T_m(\lambda - ad) + \frac{b}{sk}]} \end{aligned} \tag{3.11}$$

Then we can establish the theorem

Theorem 3.2: If (i)$R_0 > 1$ and (ii) $AB - C > 0$ then the positive equilibrium $E^*(x^*, y^*, z^*)$ is locally asymptotically stable.

4 Boundedness and Permanence of the system

To discuss the permanence of the system (2.2) we assume $R_3{}^+ = \{(x(t), y(t), z(t)) | x(t) > 0, y(t) > 0, z(t) > 0\}$ a positively invariant set. Also we assume that $x(t)$, $y(t)$, and $z(t)$ are random positive solution of the system with initial values. To prove the permanence of the system we first prove the boundedness by using some theorem given below.

Theorem 4.1: There is $M > 0$ such that, for any positive $x(t)$, $y(t)$, and $z(t)$ of system (2.2), $x(t) \leq M$, $y(t) \leq M$, and $z(t) \leq M$ for

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large t

Proof: let $L(t) = x(t) + y(t)$ According the system (2.2) we can find $\frac{dL}{dt} \leq -hL + M_0$ where

$$M_0 = \frac{p^2 T_m + 4\lambda p}{4p} \tag{4.1}$$

Then there exist $M_1 > 0$ depending upon the parameter of the system (2.2) such that $L(t) \leq M_1$ for large $t \geq T$. Hence $x(t)$ and $y(t)$ are bounded above. From the third equation of the system (2.2), $z(t)$ is also bounded above. Therefore for large $t \geq T$, there exist M such that $x(t) \leq M$, $y(t) \leq M$, and $z(t) \leq M$. Hence it is proved that the system is bounded above.

Theorem 4.2: The system (2.2) satisfy the initial condition (2.3) and there exist m such that $x(t) \geq m$, $y(t) \geq m$, $z(t) \geq m$ for large $t \geq T$.

Proof: To prove the following lemma we choose large $t \geq T$ such that,

$$\begin{array}{l} \frac{dy}{dt} = y(\beta x - a - kz) \geq y(\beta x - a - kM) \geq 0 \text{ and} \\ \frac{dz}{dt} = sy - bz \geq sy - bM \geq 0 \\ \text{for} \quad x \geq m_1 \quad \text{and} \quad y \geq m_2 \\ \text{where} \quad m_1 = \frac{a+kM}{\beta} \quad \text{and} \quad m_2 = \frac{Mb}{s} \end{array} \tag{4.2}$$

Then $z(t)$ is also bounded below i.e $z(t) \geq m_3$ where $m_3 = \frac{s}{b\beta}[\frac{\lambda\beta}{a+MK} + p(1 - \frac{a+Mk}{T_m\beta}) - a]$. Then there exists $m = max(m_1, m_2, m_3)$ such that $x(t) \geq m$, $y(t) \geq m$, and $z(t) \geq m$ for large $t \geq T$. Hence it is proved that the system is bounded below.

Now we can define
$D = \{x(t), y(t), z(t) | m \leq x(t) \leq M,\ m \leq y(t) \leq M,\ m \leq z(t) \leq M\}$ where D is ultimately bounded set of the system (2.2) where each solution of the system with positive initial value will be enter the compact region D and remain it finally. Thus we have the following persistence theorem.

Theorem 4.3: The positive invariant solution of the system (2.2) with boundedness is permanent.

5 Global Stability of System

If the system (2.2) together with the initial condition (2.3) holds the inequalities (3.11), then at the equilibrium point $E^*(x^*, y^*, z^*)$ the system is locally asymptotically stable.

We construct the Liapunov function

$$V(x,y,z) = w_1(x - x^* - x^* \ln \tfrac{x}{x^*}) + w_2(y - y^* - y^* \ln \tfrac{y}{y^*}) + \tfrac{w_3}{2}(z - z^*)^2$$

Calculating the upper right derivative of $V(x, y, z)$ along

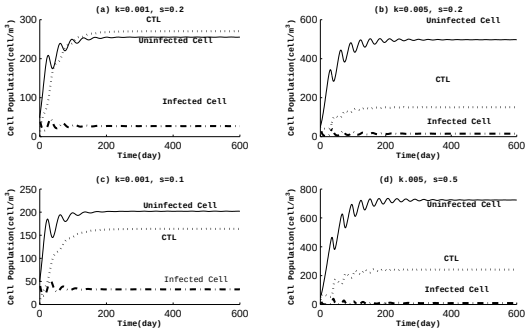

Figure 3: Time series solution of the model variables for different values of k and s, keeping others parameters are as in Table.1.

with the system (2.2) we obtain,

$$\begin{aligned} D^+V(x,y,z) &= w_1(\tfrac{x-x^*}{x})\tfrac{dx}{dt} + w_2(\tfrac{y-y^*}{y})\tfrac{dy}{dt} \\ &\quad + w_3(z - z^*)\tfrac{dz}{dt} \\ &= -w_1(\tfrac{\lambda}{x^*}(x - x^*)^2 + \tfrac{p}{T_m}) - w_3 b(z - z^*)^2 \\ &+ (x - x^*)(y - y^*)(w_2\beta - w_1\beta) + (y - y^*)(w_3 s - w_2 k) \end{aligned} \tag{5.1}$$

Thus if $w_1 = w_2 = sw$ and $w_3 = kw$, then we have ,

$$\begin{aligned} D^+V(t) &= -[w_1(\tfrac{\lambda}{xx^*} + \tfrac{p}{T_m})(x - x^*)^2 + w_3 b(z - z^*)^2] \\ &< 0 \end{aligned} \tag{5.2}$$

Therefore, we have the following theorem according to the Liapunov function.

Theorem 5: If the system (2.2) satisfy (2.3) and the inequalities of (3.11), then at the interior equilibrium point $E^*(x^*, y^*, z^*)$, system is globally asymptotically stable.

6 Numerical solutions of the model Equations

Theoretical analysis of the model is done to explore equilibria and their stability of the solutions. It has been proved that the positive invariant solution of the system with boundedness is permanent. Our analytical solutions also reveal that the system moves to globally stable regime. But for physical realization of the time evolution of different populations with varying model parameters, we consider numerical solutions of the set of equations (2.2). This enables us to visualize the dynamical behaviors of variables x, y, and z. Initially we choose the default values of the parameter from their reported range in various article [3], [9], [12], [17]. Numerical solution of the model equations (2.2) are done with the basic model parameters set to their standard values as in Table.1. At $t = 0$, values of model variables are considered as $x(0) = 50$, $y(0) = 50$, and $z(0) = 2$.

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Table.1. Values of parameters used for models dynamics calculations.

Parameter	Definition	Default Value
λ	Constant rate of production of CD4$^+$T	10.0 $mm^{-3}day^{-1}$ [12], [9]
p	Proliferation rate constant	0.03 day^{-1} [17], [9]
T_m	Maximum proliferation of $CD4^+T$ cells	1500 mm^{-3} [17], [9]
d	Death rate of Uninfected $CD4^+T$ cells	0.01 day^{-1} [9]
β	Rate of contact between x and y	0.002 $mm^{-3}day^{-1}$ [3]
a	Death rate of virus producing cells	0.24 day^{-1} [12]
k	Killing rate of Virus producing cells	0.001 $mm^{-3}day^{-1}$ [3]
s	Rate of simulation of CTL	0.2 day^{-1} [3]
b	Death rate of CTL	0.02 day^{-1} [3]

In the first panel (left side) of Fig.1 we find an interior equilibrium point $E^*(591.19, 7.4903, 188.62)$ which is asymptotically stable with the default parameter values given in the Table.1.

Here we are interested to see the effect of the dynamical system due to the change in parametric values of the model. In Fig.1 we also plot a time series of the model variables for different values of proliferation rate as shown in the figure. Changes in the time series solution with increase of p are apparent from the figure.

Fig.2 is a plot of a time series solution for the model variables x, y, and z for different values of β . In the above figure we see that if β increases from 0.0008 to 0.01 the uninfected cell population decreases fast and the virus producing cell population as well as the CTL population increases slowly.

In Fig.3 we simulated the system for $k = 0.001$ to 0.005 and $s = 0.01$ to 0.05 separately, keeping all other parameters fixed. It is observed that when k increase from 0.001 to 0.005 the activated CD4$^+$T together with CTL population increases whereas the infected cell population decreases.

If s increases from 0.1 to 0.5 similar qualitative features observe as shown for for k. Note that in the Fig.3 the variation of s and k is also restricted by the condition $\frac{sk}{b} \sim 0.01 - 0.05$.

7 Discussion and Conclusions

Here we introduced a population model representing long term dynamics of HIV-1 infection in response to available drug therapies. Basically in this paper we have formulated a basic mathematical model of HIV-1 infection in $CD4^+T$ cells with CTL response. In the proposed model we introduced the proliferation of T cells by a logistic fashion in which we considered proliferation growth rate of $CD4^+T$ cells together with constant rate of proliferation. The set of differential equations of the model are solved both analytically and numerically. Our main focus is to find out the threshold values of the system parameters for which the diseases can be controlled. In our analytical study it shows that for the positive equilibrium of the system, the proliferation rate is always greater than the death rate of uninfected cells. It implies that the disease free system can not be obtained for no such threshold values of the system parameters. In our stability analysis we have shown that if the basic reproduction ratio $R_0 < 1$, then the infected free equilibrium $E_0(x_0, 0, 0)$ is locally asymptotically stable. If $R_0 > 1$ then the E_0 is unstable. We also obtained the stability condition under (3.11) and hence we get the Theorem 3.2 for the positive equilibrium $E^*(x^*, y^*, z^*)$. From the condition (3.11) we can find that there exist a definite parametric regions for which the equilibrium E^* is locally asymptotically stable. To investigate the boundedness of the system we thus formulate a compact region of D in which the the positive invariant solution of the system (2.2) with boundedness is permanent. It has also been shown that under the condition of (3.11), in which E^* is globally asymptotically stable.

Complete numerical solutions of the model equations for the parameters as in Table.1, yield results which are consistent with the parametric conditions obtained analytically. Also in this case we put emphasis on how the model dynamics evolve with threshold values of the system parameters for which the diseases can be controlled. In our numerical simulation we plot different figure to see the effect of parameter on the system. In Fig.1 we see that if proliferation rate constant p increases with its reported range then the uninfected cell increases fast but the infected and CTL population increases slowly. We also see that if p is small then there is an oscillation in early stage, but for the large value of p the system moves towards its equilibrium point with short period of time. In Fig.2 we see that if the parameter β (the force of infection) increases then the numerical value of infected cell and CTL population increases whereas uninfected cell population decreases. In Fig.3 we change the parameter of killing rate of virus producing cells (k) and the rate of simulation of CTL (s) separately restricting the condition $\frac{sk}{b} \sim 0.01 - 0.05$. Notice that in both the cases with the increases of k or s, the uninfected cell population increases fast whereas the infected cell population moves

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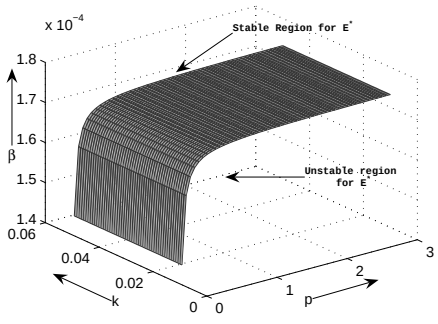

Figure 4: Shows graphically the stability criteria of E^* in p, k, and β parametric space, within the range $0.01 \leq s \leq 0.05$ and $0.03 \leq p \leq 3$.

towards extinction.

From our discussion of the results it is clear that the system competes with the killing rate of infected T-cells as well as stimulation rate of CTL. It is thus imperative for increasing of proliferation rate and for k or s, we can control the force of infection β. If this force of infection is restricted then disease can be controlled. In support of our analytical and numerical results we plot a mesh diagram ($Fig.4$) between proliferation rate constant p, killing rate of virus producing cells k, and force of infection β. In this figure we see that if p and k increases then the threshold value 0.000158 of β as reflected in ($Fig.4$), from where it is clearly manifested that the decease can be controlled. Moreover, shift of the system to globally stable regime carry along with it the assurance of eradication of toxic T-cells from the immune system naturally, as represented in our analysis.

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