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DO FREQUENT DOSES OF HAART BLOCK THE HIV BLIPS?

B. D. AGGARWALA and ROBERT J. SMITH?

Department of Mathematics and Statistics
University of Calgary
Calgary, Alberta, Canada

Department of Mathematics and Faculty of Medicine
The University of Ottawa
Ottawa, ONT, Canada

Abstract

We present a model consisting of six differential equations to show that sufficiently large doses of HAART tend to suppress the HIV blips that may otherwise occur because of change in the infection coefficient of the virus. We also show that large doses of HAART will eradicate the reservoir of latently infected CD4+ T cells in a patient.

1. Introduction

In this paper, we continue our study of HIV blips in HIV positive patients [1]. In the beginning, HIV infection appears in the body of a patient as mild fever and / or diarrhoea. Soon, these symptoms disappear and the patient stays asymptomatic for a number of years. The symptoms in the beginning are because of a sharp increase in the number of virions (virus particles) in the body after which this number comes down and the patient becomes asymptomatic. However, the number of CD4+ T cells decreases during this stage as well. HIV infection leads to low levels of CD4+ T cells through a number of mechanisms: firstly, direct viral killing

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of infected cells; secondly, increased rates of apoptosis in infected cells; thirdly, killing of infected CD4+ T cells by CD8 cytotoxic T lymphocytes that recognize infected cells. Sufficiently frequent doses of HIV inhibitors also create a number of (uninfected) inhibited cells which are not infected; reverse transcriptase inhibitors prevent the virus from infecting the host cell, whereas protease inhibitors prevent the cell from producing infectious virus. The inhibited cells, therefore, may be divided into a number of classes [13]. However, in this paper, we combine all these classes into one and take the clearance rate of drugs in our model as the average rate of clearance in all these cells. As pointed out below, the values of all the parameters in our model are extremely approximate anyway and, in most cases, represent averages. The combined treatment, consisting of both reverse transcriptase inhibitors and protease inhibitors, is called *HAART* in the HIV literature and it has been shown to be extremely effective in keeping such patients healthy and help them maintain their CD4+ T cell levels. When CD4+ T cell numbers decline below a critical level, cell-mediated immunity is lost, and the body becomes progressively more susceptible to opportunistic infections. Eventually, most HIV-infected individuals develop AIDS and die; however some remain healthy for many years, with no noticeable symptoms [2, 3, 11].

It has been argued in the literature [15] that during the asymptomatic period, the HIV activity in the body is anything but quiet. The life span of a virion producing T cell is approximately two days and as these cells die, more and more healthy cells are being produced in the body which provide a continuous source of susceptible cells for HIV to attack and multiply inside these cells. Also, there are some CD4+ T cells which are affected by virions but start producing more virions only at some later date. The life span of these latently affected cells is considerably longer since they are living as normal cells before they start producing virions. The virion producing activity in a 'sick' cell can be stopped at different stages, one to make the attack on the cell less effective and second to reduce the propensity of the cell to release virions. The corresponding drugs are called *reverse transcriptase inhibitors* and *protease inhibitors*, respectively.

In this paper, we develop an ODE model with six variables which will mimic this behaviour of CD4+ T cells and the virions and outline the effect of protease inhibitors and reverse transcriptase inhibitors in such a model. The model will also produce viral blips which have often been observed in HIV patients and show that frequent doses of HAART tend to suppress these viral blips. However, with change in infection coefficient due to evolution of the virus, these blips may reappear. We take mm^3 as the unit of volume and one day as the unit of time and write (all numbers are per unit volume)

$$x_1'[t] = A_1x_1 - A_2x_1^2 - A_3u_1x_1 + B_1x_4, \tag{1a}$$

$$x_2'[t] = A_4u_1x_1 - A_5x_2 + A_6x_3 - A_{11}u_2x_2, \tag{1b}$$

$$x_3'[t] = A_7u_1x_1 - A_8x_3, \tag{1c}$$

$$x_4'[t] = A_{12}x_1 - A_{13}x_4, \tag{1d}$$

$$u_1'[t] = A_9x_2 - c_1u_1, \tag{1e}$$

$$u_2'[t] = A_{10}u_1 - c_3u_2, \tag{1f}$$

where

$x_1(t)$ = number of healthy (susceptible) CD4+ T cells in the body

$x_2(t)$ = number of productively infected CD4+ T cells in the body

$x_3(t)$ = number of latently infected CD4+ T cells in the body

$x_4(t)$ = number of healthy (but not susceptible, because inhibited by HAART) cells in the body

$u_1(t)$ = number of virions in the body

$u_2(t)$ = number of antibodies in the body

at any time t.

Also

$A_1 = A_1^1 - A_{12}$

$A_1^1x_1$ = rate (per unit of time) of production of healthy cells in a healthy body near $x_1 = 0$

$A_2 = A_1^1/$ (maximum number of such cells in unit volume) in a healthy person

$A_3u_1x_1$ = rate of loss of healthy cells due to interaction with virions

B_1x_4 = rate at which HAART treated cells become susceptible to infection because of drug clearance

$A_4u_1x_1$ = rate of increase of productively infected cells

A_5x_2 = rate of clearance of infected cells due to apoptosis

A_6x_3 = rate at which latently infected cells become productive

$A_7u_1x_1$ = rate of production of latently infected cells as a response to virions

A_8x_3 = rate of clearance of latently infected cells either by becoming productively infected or by lysis.

A_9 = rate of production of virions per productively infected cell

$A_{10}u_1$ = rate of production of antibodies in response to virions in the body

$A_{11}u_2x_2$ = rate of loss of productively infected cells due to interaction with antibodies per unit of time

$A_{12}x_1$ = rate at which susceptible cells are becoming inhibited to infection due to drugs being administered

$A_{13}x_4$ = rate at which inhibited cells are being cleared either because of apoptosis or by becoming susceptible due to drug clearance

B_1 = rate at which inhibited cells become susceptible due to drug degeneration

c_1 = rate of clearance of virions

c_3 = rate of clearance of antibodies.

2. Values of the Parameters

We assume that all these coefficients (including A_1) are positive unless stated otherwise. Many authors have postulated a source of production of T cells in the body other than the one we have and inserted a constant term in equation (1a). However, the magnitude of this term has been estimated to be quite small number of cells (anywhere from .1 [4] to 10 [9]) per day and it would become important in the model only near $x_1 = 0$. This does not happen in the body where values of x_1 even in an AIDS patient are of the order of $200/\text{mm}^3$, so that such a term can be compensated by a slight adjustment in the value of A_1.

The values of other parameters must be chosen on the basis of medical studies. However, such values obtained in these studies are wildly different. Thus the most critical parameter, A_3, has been estimated anywhere from .000024 [9] to .0048 [4] per mm^3 per day. As another example, the values of c_1 in the literature vary from .081 to 5.191 per day [4]. We must also keep in mind that HIV virus is extremely prone to evolutionary change. The mechanism that changes the virus from its RNA coding to align it with the DNA of the host cell is not perfect and the 'mistakes' keep on multiplying. The values of these parameters, therefore, are changing with time in most patients. Our object in this paper is to see how the solutions of our equations behave for various values of the parameters and we have given the results for the values as listed in the various figures.

An important parameter is the value of A_9. This parameter measures the number of virions released per day per cell as productively infected cells disintegrate. This value has been estimated in the literature anywhere from 98.08 to 7080 in different patients [4].

We also write N = Number of virions released when a productively infected cell is destroyed and then write $A_9 = NA_5$. The value of N has been estimated in the literature as 1861.53 with a standard deviation of 185915 [4], so that any (positive) estimate of this value is almost equally reliable. Assuming this value to be 480 [8], if a productively infected cell

lives for approximately two days then $A_5 = .5$ so that the value of A_9 in the absence of any protease inhibitor becomes 240. In a recent study, the value of N varied from 160.26 to 591851.00 in different patients [4]. The point we wish to emphasize is that these values are highly variable from patient to patient and from time to time [2, 3].

The parameter A_4 is an indicator of the amount of reverse transcriptase inhibitor in the drug being administered to the patient. So that if 80% of the infected cells become productively infected and the reverse transcriptase inhibitor is 50% effective, then we take $A_4 = .4A_3$ and so on.

3. Positivity of the Solution

We prove that if $x_1(0) > 0$, $x_2(0) \geq 0$, $x_3(0) \geq 0$, $x_4(0) = 0$, $u_1(0) > 0$, and $u_2(0) \geq 0$, then these variables stay non-negative in $t > 0$. Notice that at $t = 0$, $x_4'[t] > 0$, so that $x_4 > 0$ in some interval $0 < t < t_3$, and at $t = t_3$, the value of x_1 will be greater than it would have been with $B_1 = 0$, and therefore positive [1]. Let t_3 be the first moment such that $x_4[t] > 0$ in $0 < t < t_3$. Since at $t = t_3$, $x_4[t_3] = 0$ and $x_1[t_3] > 0$, therefore $x_4'[t_3] > 0$. This shows that if, at any time t_3, the moving 'particle' $(x_1, x_2, x_3, x_4, u_1, u_2)$ hits $x_4(t) = 0$, then it bounces back into the region $x_4[t] > 0$. This shows that $x_4[t] > 0$ in $t > 0$. But then, $x_1[t]$ must always be greater than it would have been with $B_1 = 0$ and therefore, positive [1]. Equations (1c), (1e), and (1f) imply that

$$u_1(t) = e^{-c_1 t}u_1(0) + e^{-c_1 t}\int_0^t e^{c_1 t}A_9 x_2(t)dt, \tag{2a}$$

$$u_2(t) = e^{-c_3 t}u_2(0) + e^{-c_3 t}\int_0^t e^{c_3 t}A_{10}u_1(t)dt, \tag{2b}$$

$$x_3(t) = e^{-A_8 t}x_3(0) + e^{-A_8 t}\int_0^t e^{A_8 t}A_7 x_1(t)u_1(t)dt. \tag{2c}$$

Now at $x_2(t) = 0$, we have $x_2'(t) = A_4u_1(t)x_1(t) + A_6x_3(t)$. Since $x_2(0) > 0$, there is a first time $t = t_1 > 0$, when $x_2(t)$ hits $x_2(t) = 0$, (if $x_2(0) = 0$, then $x_2'(0) > 0$ and the same argument applies). This means that $x_2(t) > 0$ in $0 < t < t_1$. This implies from (2a) that $u_1(t) > 0$ in $0 \le t \le t_1$ and then from (2b) that $u_2(t) > 0$ in $0 \le t \le t_1$, and from (2c) that $x_3(t) > 0$ in $0 \le t \le t_1$. But then $x_2'(t_1) > 0$ which means that if the particle hits $x_2(t) = 0$ at $t = t_1$, then it must bounce back into $x_2(t) > 0$ space. This implies that $x_2(t) \ge 0$ in $t > 0$. But then $u_1(t) \ge 0$ in $t > 0$ and then $u_2(t) \ge 0$ and then $x_3(t) \ge 0$ in $t > 0$. This proves the non-negativity of the solution in $t > 0$.

4. Boundedness of the Solution

Equations (1) give

$$(x_1 + x_2 + x_3 + x_4)' = A_1x_1 - A_2x_1^2 - (A_3 - A_4 - A_7)u_1x_1 - A_5x_2 - (A_8 - A_6)x_3 - A_{11}x_2u_2 - (A_{13} - B_1)x_4 + A_{12}x_1.$$

Since x_1, x_2, x_3, x_4, u_1 and u_2 are known to be non-negative, $A_3 \ge A_4 + A_7$, $A_8 > A_6$ and $A_{13} > B_1$ the right hand side can be seen to be negative for large enough values of $(A_1 + A_{12})x_1 + A_5x_2 + (A_8 - A_6)x_3 + (A_{13} - B_1)x_4 (> (A_1 + A_{12})^2/A_2)$. This implies that $x_1 + x_2 + x_3 + x_4$ is decreasing for large enough values of $x_1 + x_2 + x_3 + x_4$. Combined with positivity, this shows the boundedness of x_1, x_2, x_3, x_4 and then of u_1 and u_2 as well from equations (2a) and (2b).

5. The Equilibrium Points

There are three equilibrium points of the system,

$$P_1(x_{11}, x_{21}, x_{31}, x_{41}, u_{11}, u_{21})$$
$$= (0, 0, 0, 0, 0, 0), P_2(x_{12}, x_{22}, x_{32}, x_{42}, u_{12}, u_{22})$$
$$= ((A_1A_{13} + A_{12}B_1)/(A_{13}A_2), 0, 0, (A_{12}(A_1A_{13} + A_{12}B_1))/(A_{13}^2A_2), 0, 0),$$

and

$$P_3(x_{13}, x_{23}, x_{33}, x_{43}, u_{13}, u_{23}),$$

where

$$x_{13} = (A_8c_1(A_{10}A_{11}(A_1A_{13} + A_{12}B_1) + A_{13}A_3A_5c_3))/$$
$$(A_{13}(A_{10}A_{11}A_2A_8c_1 + A_3(A_6A_7 + A_4A_8)A_9c_3)),$$

$$x_{23} = (c_1((A_6A_7 + A_4A_8)A_9(A_1A_{13} + A_{12}\,B_1) - A_{13}A_2A_5A_8c_1)c_3)/$$
$$(A_{13}A_9(A_{10}A_{11}A_2A_8c_1 + A_3(A_6A_7 + A_4A_8)A_9c_3)),$$

$$x_{33} = (A_7c_1((A_6A_7 + A_4A_8)A_9(A_1A_{13} + A_{12}B_1) - A_{13}A_2A_5A_8c_1)c_3$$
$$(A_{10}A_{11}(A_1A_{13} + A_{12}B_1) + A_{13}A_3A_5c_3))/$$
$$(A_{13}^2(A_{10}A_{11}A_2A_8c_1 + A_3(A_6A_7 + A_4A_8)A_9c_3)^2),$$

$$x_{43} = (A_{12}A_8c_1(A_{10}A_{11}(A_1A_{13} + A_{12}B_1) + A_{13}A_3A_5c_3))/$$
$$(A_{13}^2(A_{10}A_{11}A_2A_8c_1 + A_3(A_6A_7 + A_4A_8)A_9c_3)),$$

$$u_{13} = (((A_6A_7 + A_4A_8)A_9(A_1A_{13} + A_{12}B_1) - A_{13}A_2A_5A_8c_1)c_3)/$$
$$(A_{13}(A_{10}A_{11}A_2A_8c_1 + A_3(A_6A_7 + A_4A_8)A_9c_3)), \text{ and}$$

$$u_{23} = (A_{10}((A_6A_7 + A_4A_8)A_9(A_1A_{13} + A_{12}B_1) - A_{13}A_2A_5A_8c_1))/$$
$$(A_{13}(A_{10}A_{11}A_2A_8c_1 + A_3(A_6A_7 + A_4A_8)A_9c_3)).$$

6. Stability of the Equilibrium Points

It is to be noticed that x_{13} and x_{43} are always non-negative and x_{23}, x_{33}, u_{13} and u_{23} are either all positive, all zero or all negative together. Also if u_{13} is positive then $x_{13} + x_{43} < x_{12} + x_{42}$. This says that if HIV is attacking the body, if there is virus in the body, then, in the equilibrium state, the number of healthy (whether susceptible or not) CD4+ T cells is less than their value when there is no virus, which makes

physical sense. It is to be noticed that if $u_{13} = 0$, then P_2 and P_3 coincide. We show that if $u_{13} < 0$, then P_2 is the only stable equilibrium point, while if u_{13} is positive, then P_1 and P_2 are both unstable and P_3 can be either stable or unstable. If P_3 is stable, then this is the only stable equilibrium point and since the solutions are bounded, all solutions go to it while if P_3 is unstable, then there are no stable points and the solutions seem to go to a limit cycle. Also notice that since

$$(A_1A_{13} + A_{12}B_1)/(A_{13}A_2) = (A_1^1A_{13} - A_{12}(A_{13} - B_1))/(A_{13}A_2) \qquad (3)$$

and since $A_{13} > B_1$, the right hand side will become small as A_{12} increases (smaller values of B_1 will help, see equation (5)), which will imply that u_{13} (and therefore x_{23}, x_{33} and u_{23} as well) will tend to become zero ($u_{13} = 0$ at a certain (positive) value of $A_1A_{13} + A_{12}B_1$, see the expression for u_{13}) and also that P_2 and P_3 will tend to coincide. We conclude that large values of A_{12} drive the equilibrium values of x_2 (the infected cells) and x_3 (the latently infected cells) to zero. In impulsive loading, large values of A_{12} correspond to frequent dosing of inhibitors [12, 13, 14], so that we have

Lemma 1. *Frequent dosing of inhibitors in HAART drive the values of the infected cells and the latently infected cells to zero.*

This result should be compared with the corresponding result in [13] which says that "if RTI's are taken with sufficient frequency, then 'all other cells' approach zero". 'All other cells' are the cells other than those inhibited by RTI's or inhibited by both RTI's and PI's. Compare also with the title of [13] which asks "Can the reservoir of latently infected CD4 + T cells be eradicated with antiretroviral HIV drugs?" Our answer is "yes".

We now look at the characteristic matrix of the system (1) at P_2 and find that its determinant is equal to

$$(1/(A_{13}^2A_2))(c_3 + \lambda)(A_1A_{13}(A_{13} + \lambda) + A_{13}\lambda(A_{13} + \lambda) + A_{12}B_1(A_{13} + 2\lambda))EE,$$

where

$$EE = a_0 + a_1\lambda + a_2\lambda^2 + a_3\lambda^3,$$

and where

$$a_0 = -A_1A_{13}A_6A_7A_9 - A_1A_{13}A_4A_8A_9 - A_{12}A_6A_7A_9B_1 - A_{12}A_4A_8A_9B_1 + A_{13}A_2A_5A_8c_1,$$

$$a_1 = A_{13}A_2A_5A_8 - A_{13}A_1A_4A_9 - A_{12}A_4A_9B_1 + A_{13}A_2A_5c_1 + A_{13}A_2A_8c_1,$$

$$a_2 = A_{13}(A_2A_5 + A_2A_8 + A_2c_1),$$

$$a_3 = A_{13}A_2, \text{ and}$$

$$a_1a_2 - a_0a_3 = A_2(A_2(A_5 + A_8)(A_5 + c_1)(A_8 + c_1) - A_1A_9(-A_6A_7 + A_4(A_5 + c_1))).$$

For P_2 to be stable, we need a_0, a_1 and a_3 to be of the same sign and if they are positive, we also need $a_1a_2 - a_0a_3$ to be positive. Since a_3 is positive, we need a_0 to be positive, which demands that u_{13} must be negative. We also need a_1 to be positive, which demands that

$$A_4A_9(A_{13}A_1 + A_{12}B_1) < A_{13}A_2(A_5A_8 + A_5c_1 + A_8c_1). \tag{A}$$

It is easy to see that if condition (A) is satisfied, then $a_1a_2 - a_0a_3$ is also positive. We conclude that if u_{13} is negative, and condition (A) is satisfied, then P_2 is a stable point. Writing $A_4 = \alpha(1 - n_{rt})A_3$, and $A_9 = (1 - n_p)NA_5$, where n_{rt} and n_p denote the effectiveness of reverse transcriptase inhibitor and protease inhibitor, respectively, N is the number of virions released by one productively infected T cell, and α is the fraction of productively infected T cells being produced, we notice that this condition implies that

$$(1 - n_{rt})(1 - n_p) < (A_5A_8 + (A_5 + A_8)c_1)A_{13}A_2/(\alpha N(A_1A_{13} + A_{12}B_1)A_3A_5). \tag{B}$$

As an example, for $c_1 = 3$; $A_5 = .5$; $A_9 = 240$; $A_2 = A_1/1000$; $A_1 = .6$; $A_3 = .00003$; $A_4 = .8A_3$; $A_6 = .05$; $A_7 = .2A_3$; $A_8 = .5$; $aN = 480$; $A_{13} = .5$;

$A_{12} = .22$; $B_1 = .2$; and $\alpha = .8$; the right hand side of this inequality is .492066, so that if only one treatment is applied, then this treatment must be approximately 51% effective (for P_2 to be stable), while if both are applied, they both need to be only more than 30% effective [3]. A similar result has been noted by Murray [8].

Now suppose that condition (A) is not satisfied, so that $A_4A_9(A_1A_{13} + A_{12}B_1) = (A_5A_8 + A_5c_1 + A_8c_1)A_2A_{13} + \varepsilon$, where $\varepsilon \geq 0$. It is then easy to see that u_{13} is also positive, so that if $u_{13} \leq 0$, then condition (A) must be satisfied. It follows that P_2 is stable if and only if $u_{13} \leq 0$. Absence of drugs is implied by $A_{12} = 0$, $n_{rt} = 0$, and $n_p = 0$, in which case condition (A) reduces to

$$A_4A_9A_1 < A_2(A_5A_8 + A_5c_1 + A_8c_1). \tag{C}$$

Because of large value of A_1/A_2 (of the order of 10^3), and small values of the death rates, this condition is extremely unlikely to be satisfied, so that we have [13].

Lemma 2. P_2 (*the disease-free equilibrium*) *is unstable in the absence of drugs*.

It should be noticed that

$$\begin{aligned} & x_{13} - x_{43} \\ &= -((A_{12} - A_{13})A_8c_1(A_1A_{10}A_{11} + A_3A_5c_3))/ \\ & \quad (A_{13}(A_{10}A_{11}A_2A_8c_1 + A_3(A_6A_7 + A_4A_8)A_9c_3)) \end{aligned}$$

so that if $A_{12} > A_{13}$, i.e., if the inhibited cells are being created faster than they are disappearing (due to the drugs being cleared out of the system and / or due to apoptosis), then $x_{43} > x_{13}$, i.e., the equilibrium value of inhibited cells is more than that of susceptible cells (for large values of A_{12}). We now have

Lemma 3. *As* $A_{13}/A_{12} \to 0$, $x_{13}/x_{43} \to 0$.

Proof. At an equilibrium point, $x_{13}/x_{43} = A_{13}/A_{12}$.

In administration of HAART, large values of A_{12} are associated with frequent dosing [13, 14], so that we may say that frequent dosing tends to increase the number of inhibited cells and decrease the number of susceptible cells. This conclusion should be compared with a similar conclusion in a previous paper where it is concluded that for large values of A_{12}, x_{13} approaches zero [13]. It should be pointed out that the system in [13] is seen to be very close to the system in this paper if we write $x_1 = T_s + T_{pn}$, $x_2 = T_i + T_{pi}$, $x_3 = T_L$, and $x_4 = T_R + T_{RP}$ (where the notation for T's is taken from that paper) and write three more equations for the three additional variables.

The above discussion allows for the possibility that condition (A) may be satisfied and P_2 may still be unstable, i.e., the disease may not be eradicated. A look at u_{13} suggests that even if $A_4 = 0$, so that condition (A) is satisfied, u_{13} may still be positive while if $A_9 = 0$, u_{13} is certainly negative and P_2 is stable. This says that a hundred percent effective protease inhibitor will certainly eradicate the disease while a hundred percent effective reverse transcriptase inhibitor may or may not. It should be noted that this result only holds for $A_6 > 0$ and $A_7 > 0$. If $A_6 = A_7 = 0$, then the results concur with those of [12]. It follows that accounting for latent infection may potentially sustain the disease in the presence of 100% effective reverse transcriptase inhibitor. However, see [13] for reasons that this is unlikely to be the case.

We can now write

$$R_0 = (A_6A_7 + A_4A_8)A_9(A_1A_{13} + A_{12}B_1)/(A_{13}A_2A_5A_8c_1)$$

and conclude that the disease is endemic if and only if $R_0 > 1$, so that R_0 is the basic reproduction number [5]. It should be noticed that R_0 will increase as A_9 increases and/or c_1 decreases, both of which imply a higher rate of increase of virions. It is interesting to look at the magnitudes of some of the terms in R_0. Taking mm^3 as the unit of volume, we notice that, A_1/A_2 is of the order of 10^3, A_4 is $O(10^{-5})$, A_9 is

$O(10^2)$, A_{13} is $O(10^{-1})$, A_5c_1 is $O(1)$, $A_{13}A_1 \gg A_{12}B_1$ and $A_4A_8 \gg A_6A_7$, so that R_0 is of the order of one. Because of the large variability of these coefficients, it follows that the inequality $R_0 < 1$ will be satisfied in the case of some patients and not so in the case of others. If this inequality is satisfied in a patient, then P_2 is stable and that patient will not show signs of AIDS even after he has been infected by the HIV virus. It is well known that this does happen in the case of some patients [11].

The above result provides a very large number of choices for studying the treatment of HIV. In a previous paper [1], we have discussed the behaviour of solutions for $A_{12} = 0$. With $A_{12} = 0$, we noticed the presence of HIV blips and argued that these blips were caused by such phenomenon exhibited by our solution and were not 'statistical quirks' as argued by some people [6]. It now transpires that, keeping all other values the same, a large value of A_{12} tends to suppress these blips. We give an example. In Figure 1, we exhibit a situation where, we get blips (caused by a limiting solution) with $A_{12} = 0$ with five equations in our model (there are no inhibited cells).

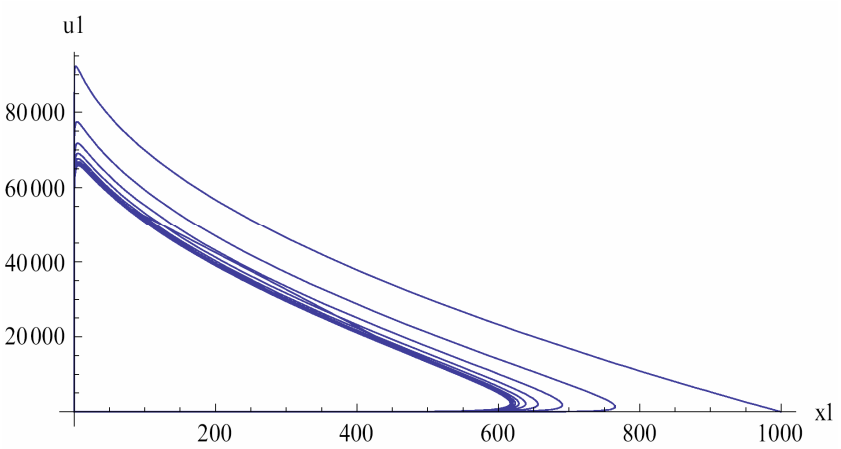

Figure 1. Solution in our model with five equations with no inhibited cells. The values of other variables are $A_1 = .6$; $A_2 = A_1/1000$; $A_3 = .0001$; $A_4 = .8A_3$; $A_5 = .5$; $A_6 = .05$; $A_7 = .2A_3$; $A_8 = .5$; $A_9 = 480$; $A_{10} = .01$; $A_{11} = .0001$; $c_1 = 3$; $c_3 = .5$.

The next figure gives the solution with six equations but with a low value of A_{12}.

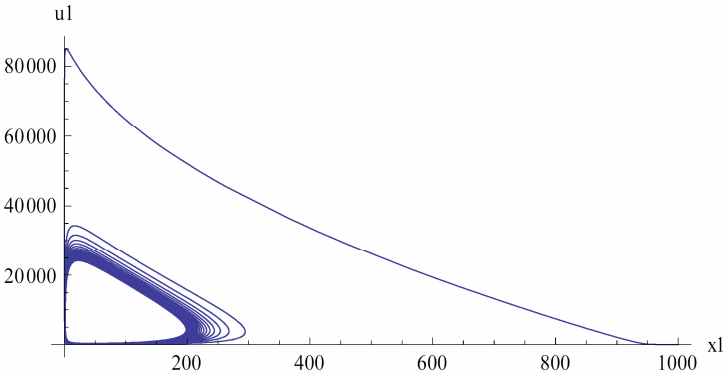

Figure 2. Solution in our model with $A_1^1 = .6$; $A_1 = A_1^1/(1 + B)$; $A_2 = A_1^1/1000$; $A_3 = .0001$; $A_4 = .8A_3$; $A_5 = .5$; $A_6 = .05$; $A_7 = .2A_3$; $A_8 = .5$; $A_9 = 480$; $A_{10} = .01$; $A_{11} = .0001$; $A_{12} = BA_1$; $A_{13} = .1A_{12}$; $B_1 = .1A_{13}$; $c_1 = 3$; $c_3 = .5$; $B = .1$.

Notice the limiting solution with reduced amplitude.

In the next figure, we exhibit the same situation but with an increased value of A_{12}. Notice that P_3 is no longer unstable.

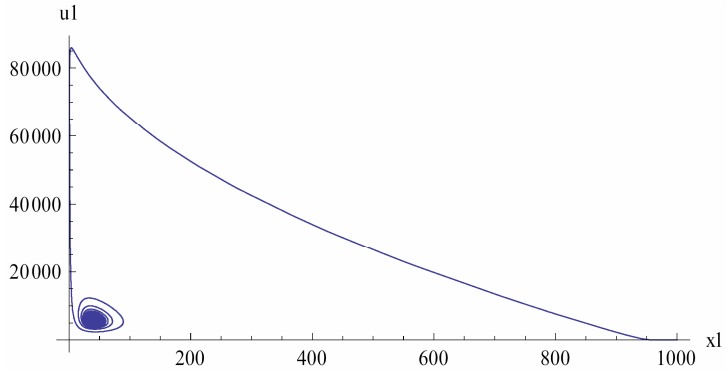

Figure 3. Solution in our model with the same values of variables as in Figure 2 and with $A_{12} = .95A_1$; $A_{13} = .1A_{12}$; $B_1 = .1A_{13}$; Notice that the limiting solution is no more oscillatory (see below where it is shown that for this case, P_3 is stable for $A_{12} > .805152A_1$).

7. Viral Blips

These limit cycles could help explain the "viral blips" that are often observed in patients who are being treated with HAART [10]. HAART may reduce the viral load of a patient below the detection level (approximately 50 copies/ml) of today and keep it like that for a while, and then suddenly examination will show a heightened level of viral count which will disappear and reappear. This phenomenon has been called *viral blips* and it has been speculated that this may signal emergence of a drug resistant viral strain of HIV [6]. However, it is obvious that these limit cycles will also produce these blips. In the previous section, we have given one example of such blips in our model. It is obvious from this figure that unless you take the sample (of blood) at very specific times, you are likely to miss the blip. It should be pointed out that these blips occur because the solution is revolving around P_3 because of insufficient medicine. These blips seem to appear approximately once every fifteen days (or less often) in our example and last for a very short time. This fact points to the great advantage of the reverse transcriptase and protease inhibitor drugs in that even with an insufficient amount of medicine, the patient is infectious only for a fraction of the time and his viral load is below the detection level, and he/she is probably non-infectious, most of the time.

8. The Stability of P_3

In this case, the determinant of the characteristic matrix turns out to be

$$a_0 + a_1\lambda + a_2\lambda^2 + a_3\lambda^3 + a_4\lambda^4 + a_5\lambda^5 + a_6\lambda^6 = 0, \tag{4}$$

where the a_i's are appropriate constants. The expressions of these a_i's in terms of the parameters in our equations (the A_i's, the B_i's, and the c_i's) are just too long to be reproduced in this paper. In the example we have taken, all these coefficients are seen to be positive for all values of A_{12} and with all other parameters as given in the example.

However, the other requirements for stability in this case, (called the *Hurwitz conditions*) may or may not be satisfied. Depending upon the values of the coefficients, some of these conditions may be satisfied and some may not. If all the six roots of equation (4) are real and negative, the approach to P_3 is non oscillatory and HIV blips will not appear. If two (or four) roots are negative and the other four (or two) are complex with negative real parts, P_3 is stable, approach to P_3 is oscillatory and HIV blips of decreasing magnitude will appear while if two (or four) of the roots are complex with positive real parts, P_3 is unstable, limit cycle should result and persistent HIV blips should appear. This is the situation we have exhibited in our examples above. Because of the large number of parameters involved, it is not easy to demarcate the manifolds of stability and instability of P_3. However, it is still possible to numerically demarcate the values of one of the variables, given the values of others, giving the relevant values of this variable for which P_3 would be stable and all solutions will approach this point. As an example for the case of $A_1 = .6$; $A_2 = A_1/1000$; $A_3 = .0001$; $A_4 = .8A_3$; $A_5 = .5$; $A_6 = .05$; $A_7 = .2A_3$; $A_8 = .5$; $A_9 = 480$; $A_{10} = .01$; $A_{11} = .0001$; $A_{13} = .1A_{12}$; $B_1 = .1A_{13}$; $c_1 = 3$; and $c_3 = .5$, all the stability conditions are not satisfied and therefore P_3 is unstable for all values of $A_{12} < .483091 = .805152A_1$. For higher values of A_{12}, these conditions are satisfied, P_3 is stable and blips disappear indicating that high values of reverse transcriptase inhibitor and/or protease inhibitor tend to suppress the blips. We therefore propose a

Hypothesis. High values of the reverse transcriptase inhibitor and/or protease inhibitor tend to suppress the HIV blips.

Comment. $u_{13} = 0$ will certainly suppress the HIV blips. This equation requires that

$$A_{12} = \alpha A_1^1,$$

where

$$\alpha = (A_{13}/(A_{13} - B_1))(1 - (A_5A_8c_1)/(MM(A_6A_7 + A_4A_8)A_9)). \qquad (5)$$

Since $A_{12} < A_1^1$, we need $\alpha < 1$. Since MM (the maximum number of cells in a unit volume) is very large, we need B_1 to be very small, i.e., the drugs to be very long lasting for this to happen, which makes physical sense. However, we do not need quite such a strong condition for the HIV blips to vanish, but our point is made.

9. A_3 Changing with Time

Just as the increasing values of A_{12} help to subside the blips, the increasing values of A_3 tend to promote them. This is perhaps because large values of A_3 produce large number of infected cells which in turn produce large number of virions which results in blips. These blips are generally measured with ml as the unit of volume presumably because the virus is undetectable these days in patients at the level of about 50/ml. Correspondingly, we take ml as the unit of volume in this section and arrive at the following solution in a particular case.

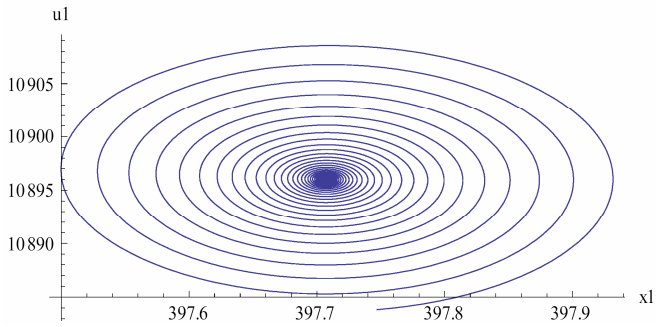

Figure 4. Solution of our equations (values of x_1 and u_1) for $A_1 = .1$; $A_2 = A_1/1000000$; $A_3 = .00001$; $A_4 = .8A_3$; $A_5 = .5$; $A_6 = .05$; $A_7 = .2A_3$; $A_8 = .5$; $A_9 = 480$; $A_{10} = .01$; $A_{11} = .0001$; $A_{12} = .9A_1$; $A_{13} = .1A_{12}$; $B_1 = .1A_{13}$; $c_1 = 3$; $c_3 = .5$.

In this case P_3 is a stable point and there are no blips.

We now take $A_3 = .00005$ keeping the values of all other parameters the same as in the above example. The solution is given in the next figure.

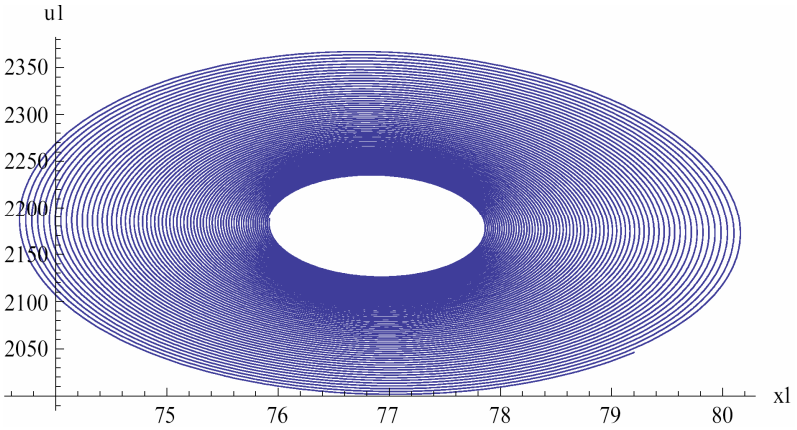

Figure 5. Solution of our equations for the same values of the variables as in Figure 5 but with $A_3 = .00005$.

P_3 is now unstable and blips result. These blips are shown again in the next figure.

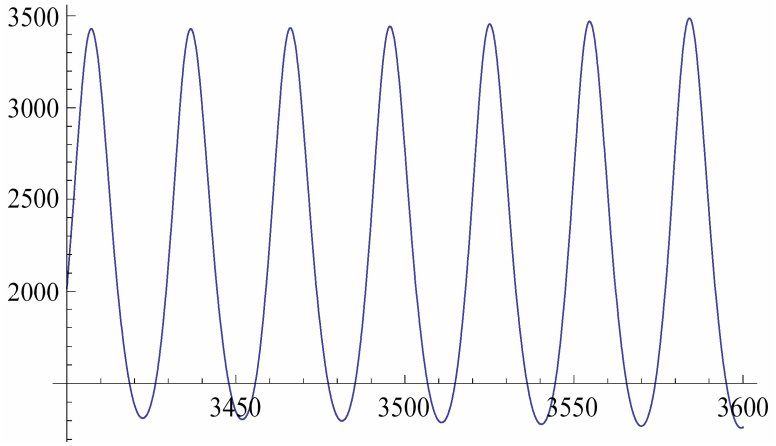

Figure 6. Blips in our solution shown in Figure 5.

We next investigated the case with all other parameters at the same value as before but with $A_3 = .00065$, a very high value indeed. We again found some oscillations, however as above, these were not of the correct order of magnitude and we shall not present them here. We now present a case where the blips are of the correct order of magnitude and occur at approximately the same intervals as observed in patients on HAART.

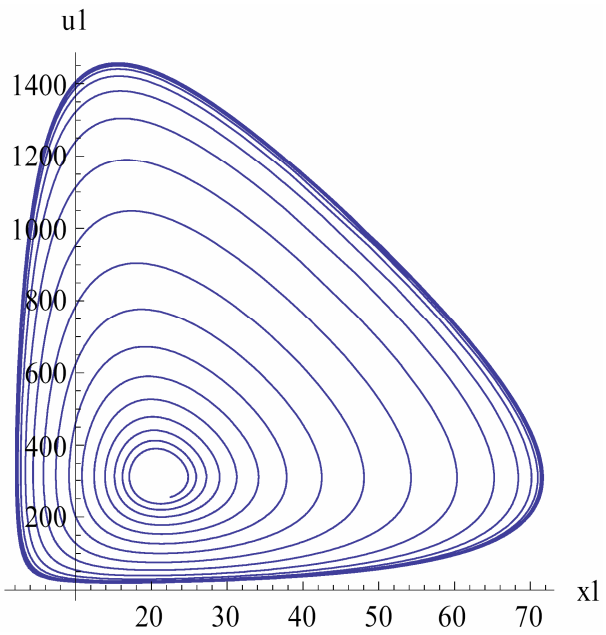

Figure 7. Solution of our equations for $A_1 = .2$; $A_2 = A_1/1000000$; $A_3 = .00065$; $A_4 = .24A_3$; $A_5 = .4$; $A_6 = .005$; $A_7 = .01A_3$; $A_8 = .01$; $A_9 = 240$; $A_{10} = .0001$; $A_{11} = .0001$; $A_{12} = .1A_1$; $A_{13} = .1A_{12}$; $B_1 = .1A_{13}$; $c_1 = 2$; $c_3 = .05$ and $N = 480$.

The HIV blips in this solution are shown in the next figure.

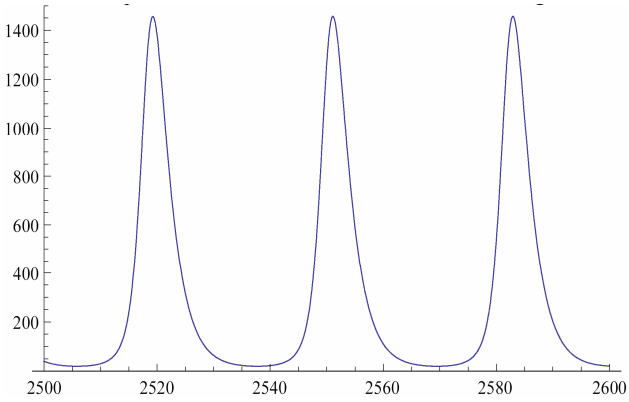

Figure 8. HIV blips in the above solution. Notice that the blips occur every 32 days and virus goes from a low of about twenty to a high of about 1454.

We observe that our blips are of the correct order of magnitude (about 1500/ml) and they appear at approximately the same interval as observed in the patients. According to one study [10], "Nearly half of all HIV-infected patients in the United States develop resistance to one or more classes of treatment medications". This development of resistance to antiretroviral drugs in as many as half the patients strongly points to a value of A_3 which is changing rapidly with time. We should also point out that the value of A_3, as well as the values of other parameters in our model, is strongly variable from patient to patient. Since both the intensity and the period of these blips depend upon the values of these parameters, they should vary from patient to patient. It is therefore extremely difficult to find any pattern in these blips as we measure them in different patients in a clinical study. This would explain the "lack of any consistency among the tests performed on blood samples" which many researchers think "confirms that there is no danger from these blips in viral load" [6].

Conclusion

We have tried to demonstrate how the solutions of our equations behave for certain chosen values of the parameters in our equations (1) and how they may behave for others. The statements that P_2 is unstable if and only if P_3 is 'reachable', (i.e., if the disease is endemic) and that P_2 is unstable in the absence of drugs seem to be intuitively correct lending credibility to our model.

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