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HIV BLIPS MAY NOT BE ACCIDENTAL

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Abstract

We present a model consisting of five first order ODE's to model the progression of HIV from infection to AIDS. The model clarifies the role of protease inhibitors and reverse transcriptase inhibitors in this progression. We also show that, depending upon the viral activity, the solution may exhibit progression to an endemic state, or what appears to be a limit cycle around this state. In this model, the disease may be eradicated by sufficiently strong doses of protease inhibitors or reverse transcriptase inhibitors or a combination thereof. An attempt is made to understand the phenomenon of hiv blips. It is proposed that these blips occur because of change in the infection coefficient.

1. Introduction

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 keeps on coming down during this stage as well. HIV infection leads to low levels of CD4+ T-cells through three main mechanisms: firstly, direct viral killing of infected cells; secondly, increased rates of apoptosis in infected cells; and thirdly, killing of infected CD4+ T-cells by CD8 cytotoxic lymphocytes that recognize infected cells. When CD4+ T-cell

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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 about one in ten remain healthy for many years, with no noticeable symptoms [1, 2, 10].

It has been argued in the literature [9] 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 cells for HIV to attack and multiply inside these cells. Also, there are some CD4+ T-ce1ls 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 two 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. There are other inhibitors being developed by the drug companies, but none of them are on the market and we shall not consider them here.

In this paper, we develop an ODE model with five variables which will mimic this behaviour of CD+ 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. We take mm^3 as the unit of volume and one day as the unit of time and write

$$x_1'[t] = A_1 x_1 - A_2 x_1^2 - A_3 u_1 x_1 \tag{1a}$$

$$x_2'[t] = A_4 u_1 x_1 - A_5 x_2 + A_6 x_3 - A_{11} u_2 x_2 \tag{1b}$$

$$x_3'[t] = A_7 u_1 x_1 - A_8 x_3 \tag{1c}$$

$$u_1'[t] = A_9 x_2 - c_1 u_1 \tag{1d}$$

$$u_2'[t] = A_{10} u_1 - c_3 u_2, \tag{1e}$$

where

$x_1(t)$ = number of healthy 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

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

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

at any time t.

Also

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

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

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

$A_4u_1x_1$ = rate of increase of productively infected cells

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

A_5 = 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_8 = 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

c_1 = rate of clearance of virions

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

c_3 = rate of clearance of antibodies.

2. Values of the Parameters

We shall assume that all these coefficients 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 (any where from .1 [3] to 10 [7]) cells 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, so that such a term can be compensated for by a slight adjustment in the value of A_1. Since the values of all the parameters, including A_1, are highly uncertain, we feel that there is not much advantage in including one more parameter.

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 [7] to .0048 [3] per mm^3 per day. As another example, the values of c_1 in the literature vary from .081 to 5.191 per day [3]. 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 [3].

We shall 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 [3], so that any (positive) estimate of this value is almost equally reliable. Assuming this value to be 480 [6], 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 [3]. The point we wish to emphasize is that these values are highly variable from patient to patient and from time to time [1, 2].

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 shall take $A_4 = .4A_3$ and so on.

3. Positivity of the Solution

We shall prove that if $x_1(0) > 0$, $x_2(0) \geq 0$, $x_3(0) \geq 0$, $u_1(0) > 0$, and $u_2(0) \geq 0$, then these variables stay nonnegative in $t > 0$. Notice that if, at any time t, $x_1(t) = 0$, then $x_1'(t)$ is also equal to zero (as are the higher derivatives of $x_1(t)$). This shows that if, at any time t, the moving 'particle' $(x_1, x_2, x_3, u_1, u_2)$ hits $x_1(t) = 0$, then it cannot move away from it. Since $x_1(0) > 0$, this shows that $x(t)$ is nonnegative in $t \geq 0$, and that $x_1(t) > 0$ in some interval $0 \leq t < t_2$. Equations (1c), (1d), and (1e) 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 $0 \leq t \leq t_1$ and then from (2b) that $u_2(t) > 0$ in $0 \leq t \leq t_1$, and from (2c) that $x_3(t) > 0$ in $0 \leq t \leq t_1$. 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 $x_2(t) \geq 0$ in $t > 0$. But then $u_1(t) \geq 0$ in $t > 0$ and then $u_2(t) \geq 0$ and then $x_3(t) \geq 0$ in $t > 0$. This proves the nonnegativity of the solution in $t > 0$.

4. Boundedness of the Solution

Equations (1) give $(x_1 + x_2 + x_3)' = A_1x_1 - A_2x_1^2 - (A_3 - A_4 - A_7)u_1x_1 - A_5x_2 - (A_8 - A_6)x_3 - A_{11}x_2u_2$. Since x_1, x_2, x_3, u_1 and u_2 are known to be nonnegative, $A_3 \geq A_4 + A_7$, and $A_8 > A_6$ the right hand side can be seen to be negative for large enough values of $A_1x_1 + A_5x_2 + (A_8 - A_6)x_3$ $(> A_1^2/A_2)$. This implies that $x_1 + x_2 + x_3$ is decreasing for large enough values of $x_1 + x_2 + x_3$. This shows the boundedness of x_1, x_2, x_3 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, $P_1(0, 0, 0, 0, 0)$, $P_2(A_1/A_2, 0, 0, 0, 0)$, and $P_3(x_{13}, x_{23}, x_{33}, u_{13}, u_{23})$, where

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

$$x_{23} = \frac{c_1(A_1(A_6A_7 + A_4A_8)A_9 - A_2A_5A_8c_1)c_3}{A_9(A_{10}A_{11}A_2A_8c_1 + A_3(A_6A_7 + A_4A_8)A_9c_3)},$$

$$x_{33} = \frac{(A_7c_1(A_1(A_6A_7 + A_4A_8)A_9 - A_2A_5A_8c_1)c_3(A_1A_{10}A_{11} + A_3A_5c_3))}{(A_{10}A_{11}A_2A_8c_1 + A_3(A_6A_7 + A_4A_8)A_9c_3)^2}$$

$$u_{13} = \frac{(A_1(A_6A_7 + A_4A_8)A_9 - A_2A_5A_8c_1)c_3}{A_{10}A_{11}A_2A_8c_1 + A_3(A_6A_7 + A_4A_8)A_9c_3},$$

and

$$u_{23} = \frac{A_{10}(A_1(A_6A_7 + A_4A_8)A_9 - A_2A_5A_8c_1)}{A_{10}A_{11}A_2A_8c_1 + A_3(A_6A_7 + A_4A_8)A_9c_3}.$$

6. Stability of the Equilibrium Points

It is to be noticed that x_{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 $x_{13} < A_1/A_2$. This says that if HIV is attacking the body, if there are virions in the body, then, in the equilibrium state, the number of healthy CD4+ T-cells is less than the maximum, which makes physical sense. It is to be noticed that if $u_{13} = 0$, then P_2 and P_3 coincide. We shall 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. We look at the characteristic matrix of the system (1) at P_2 and find that minus $A_2(A_1 + \lambda)(c_3 + \lambda)$ times its determinant is equal to $a_0 + a_1\lambda + a_2\lambda^2 + a_3\lambda^3$, where

$$\begin{aligned} a_0 &= -A_1(A_6A_7 + A_4A_8)A_9 + A_2A_5A_8c_1, \\ a_1 &= -A_1A_4A_9 + A_2(A_8c_1 + A_5(A_8 + c_1)), \\ a_2 &= A_2(A_5 + A_8 + c_1), \\ a_3 &= A_2, \end{aligned}$$

and

$$\begin{aligned} a_1a_2 - a_0a_3 = A_2(&A_2(A_5 + A_8)(A_5 + c_1)(A_8 + c_1) \\ &-A_1A_9(-A_6A_7 + A_4(A_5 + c_1))). \end{aligned}$$

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

$$A_4A_9 < (A_5A_8 + A_5c_1 + A_8c_1)A_2/A_1. \qquad (A)$$

It is easy to see that if condition (A) is satisfied, then $a_1a_2 - a_0a_3$ is also positive and P_2 is stable. 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,

$$(1 - n_{rt})(1 - n_p) < (A_5A_8 + (A_5 + A_8)c_1)A_2/(\alpha NA_1A_3A_5). \tag{B}$$

As an example, for $c_1 = 3$; $A_5 = .5$; $A_9 = 240$; $A_2 = A_1/1000$; $A_1 = .6$; $A_3 = .00003$; $A_4 = .8A_3$; $A_6 = .05$; $A_7 = .2A_3$; $A_8 = .5$; and $N = 480$; $\alpha = .8$, the right hand side of this inequality is .564236, so that if only one treatment is applied, then this treatment must be more than 44% effective (for P_2 to be stable), while if both are applied, they both need be only more than 25% effective [1]. A similar result has been noted by Murray [6].

Now suppose that condition (A) is not satisfied, so that $A_1A_4A_9 = (A_5A_8 + A_5c_1 + A_8c_1)A_2 + \varepsilon$, where $\varepsilon \geq 0$. This implies that

$$u_{13}(A_{10}A_{11}A_2A_8c_1 + A_3(A_6A_7 + A_4A_8)A_9c_3)$$
$$= (A_1A_6A_7A_9c_3 + A_8c_3(A_5A_8A_2 + A_8c_1A_2 + \varepsilon)) > 0,$$

which implies that $u_{13} > 0$, so that if $u_{13} \leq 0$, then condition (A) must be satisfied. It follows that P_2 is stable if and only if $u_{13} \leq 0$.

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. However, it should be noticed that the reverse transcriptase inhibitor works on A_6 in the same manner as it works on A_4, so that we should write $A_6 = (1 - n_{rt})A_6'$, where $A_6'x_3$ is the number of latently infected

cells that get activated. Now if A_4 is zero because of hundred percent effective reverse transcriptase inhibitor, so is A_6 and then $u_{13} \leq 0$ and P_2 is stable [1].

We can now write

$$R_0 = (A_1A_9(A_6A_7 + A_4A_8))/(A_2A_5A_8c_1)$$

and conclude that the disease is endemic if and only if $R_0 > 1$, so that R_0 is the basic reproduction number.

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 $O(10^2)$, and A_5c_1 is $O(1)$, and A_6A_7 is of the same order of magnitude as A_4A_8, 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 known that this happens in the case of about 10% of the patients [10].

The above result provides a very large number of choices for studying the treatment of HIV. It may happen that even if we employ both the protease inhibitor and the reverse transcriptase inhibitor, they are not sufficient to suppress the virus, though the number of virions decreases substantially while the number of T-cells goes up significantly because of the treatment. On the other hand, if the amount of reverse transcriptase inhibitor and protease inhibitor are sufficient, P_2 will be stable. Here is an example in which this happens.

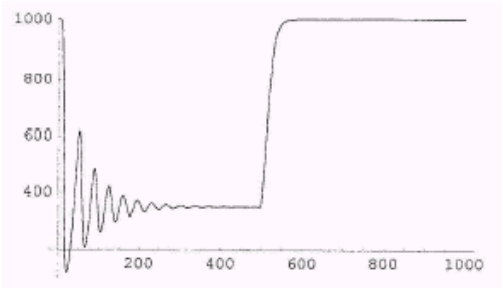

Figure 1. This figure shows the increase in the number of helper T-cells during the first five hundred days after the treatment. In the beginning we have $A_1 = .1$; $A_2 = A_1/1000$; $A_3 = .0000343$; $A_4 = .9A_3$; $A_5 = .5$; $A_6 = .01$; $A_7 = .1A_3$; $A_8 = .5$; $A_9 = 240$; $c_1 = 5$; $A_{11} = .0001$; $c_3 = .1$; $A_{10} = .01$.

On the 500th day, we change A_4 to $.45A_3$, A_6 to .005 and A_9 to 120 keeping all other parameters the same. This implies a protease inhibitor of 50% effectiveness and a reverse transcriptase inhibitor of the same effectiveness. Notice how the number of CD4+ T-cells jumps almost immediately after the treatment.

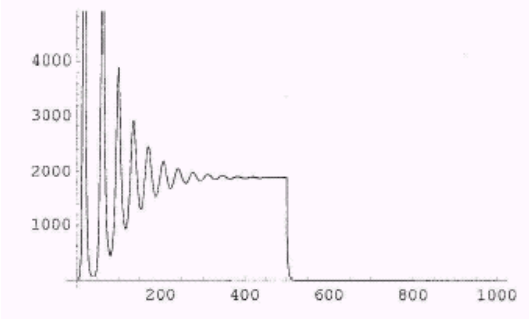

Figure 2. Decay of virions in the same example. Notice also the sharp increase in the number of virions in the beginning. This increase causes the initial symptoms of HIV .

7. Behaviour of Solutions

It is to be noted that if $u_{13} > 0$, then P_2 is unstable. Also, P_1 is always unstable. If P_3 is stable, then since all solutions are bounded,

they must all go to P_3 from everywhere. However, if $u_{13} > 0$, then P_3 may be either stable or unstable. If P_3 is unstable, then all the three points are unstable, and since the solutions are bounded, they may either go to a limit cycle or show chaotic behaviour. For the values of the coefficients that we have assumed below, they seem to go to a limit cycle solution. We show the projection of such a limit cycle on (x_1, x_2, x_3) space for one particular case. Three of the eigenvalues of the characteristic matrix in this case are real negative so that the motion is effectively in a plane.

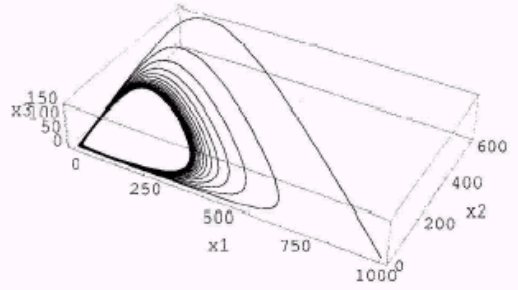

Figure 3. Solution of our equations for $c_1 = 3$; $A_5 = .5$; $A_9 = 240$; $A_2 = A_1/1000$; $A_1 = .6$; $A_4 = .8A_3$; $A_6 = .05$; $A_7 = .2A_3$; $A_8 = .5$; $\alpha = .8$; $\beta = .2$; $A_{10} = .01$; $A_{11} = .0001$; $c_3 = .5$; $N = 480$; $A_3 = .0001$; P_3 is unstable in this case. The initial values are $x_1(0) = 1000$, $x_2(0) = 0$, $x_3(0) = 0$, $u_1(0) = 1$, and $u_2(0) = 0$. In the figure, the solution is running 'inwards' (towards P_3 which is inside the cavity) and counter clockwise for increasing values of time.

8. Viral Blips

These limit cycles could help explain the "viral blips" that are often observed in patients who are being treated with HAART [4]. 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 [4]. However, it is obvious that these limit cycles will also produce these blips. Below, we give 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 instead of going to P_2 because of insufficient medicine. These blips seem to appear once every thirty five days (or less often) in our example and last for a few days. 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 about twenty percent of the time and his viral load is below the detection level, and he/she is probably non-infectious, for 80% of the time. The observed value of virions in these blips are of the order of 50-1000 virus particles/ml, so that it is more convenient for us to take a mililitre as a unit of volume which we have done in the following figure. The high value of the blip in this figure is about 1500/ml which is of the correct order of magnitude. The value of R_0 in this example is 47775.

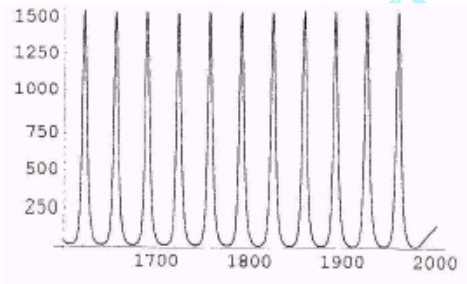

Figure 4. Viral blips in our model plotted against time. The values of the parameters are $c_1 = 2$; $A_5 = .4$; $A_9 = 240$; $A_2 = A_1/1000000$; $A_1 = .2$; $A_4 = .24A_3$; $A_6 = .005$; $A_7 = .01A_3$; $A_8 = .01$; $\alpha = .8$; $\beta = .2$; $A_{10} = .0001$; $A_{11} = .0001$; $c_3 = .05$; $N = 480$; $A_3 = .00065$;

The blips in the above figure are also produced by the solution going into a limit cycle. We show the projection of this limit cycle on the $\{x_2, u_2\}$ plane in the following figure. Three of the eigenvalues in this case are real negative so that the motion is effectively in a plane, though not necessarily in the $\{x_2, u_2\}$ plane.

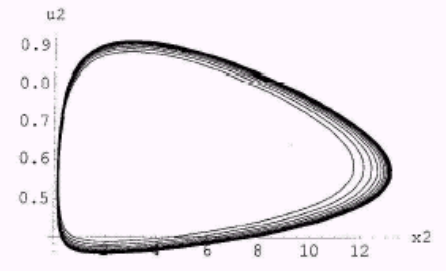

Figure 5. An example of a limit cycle in our model. The values of the parameters are the same as in Fig 4.

9. The Stability of P_3

In this case, the determinant of the characteristic matrix turns out to be $a_0 + a_1\lambda + a_2\lambda^2 + a_3\lambda^3 + a_4\lambda^4 + a_5\lambda^5 = 0$, where the a_i's are appropriate constants. The expression of these a_i's in terms of the parameters in our equations (the A_i's and the c_i's) are just too long to be reproduced in this paper, however it can be seen after considerable simplification that all the a_i's are of the same sign (positive or negative) provided $u_{13} > 0$.

Since $x_{13} > 0$ and we need $u_{13} > 0$ for P_3 to be reachable, all these coefficients can be seen to be positive if P_3 is reachable. However, the three more requirements for stability in this case, namely

$$a_1a_2 - a_0a_3 > 0,\ a_3a_4 - a_2a_5 > 0,$$

and

$$(a_1a_2 - a_0a_3)(a_3a_4 - a_2a_5) - (a_1a_4 - a_0a_5)^2 > 0$$

may or may not be satisfied. Depending upon the values of the coefficients, some of these numbers may be positive and the others negative. If all the five roots are real and negative, then the approach to P_3 is non-oscillatory and HIV blips will not appear. If three roots are negative and the other two are complex with negative real parts, then P_3 is stable, approach to P_3 is oscillatory and HIV blips of decreasing magnitude will appear while if the other two roots are complex with

positive real parts, then 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 $c_1 = 2$; $A_5 = .4$; $A_9 = 240$; $A_2 = A_1/1000000$; $A_1 = .2$; $A_4 = .24A_3$; $A_6 = .005$; $A_7 = .01A_3$; $A_8 = .01$; $\alpha = .8$; $\beta = .2$; $A_{10} = .0001$; $A_{11} = .0001$; $c_3 = .05$; $N = 480$, these three quantities are positive, and therefore P_3 is stable for all positive values of A_3 in the interval $1.28249 \times 10^{-8} < A_3 < 1.85719 \times 10^{-7}$. For higher values of A_3 and consequently higher values of R_0, we should get limit cycles and persistent HIV blips in our model.

10. A_3 Changing with Time

It should be pointed out that the value of A_3 observed in the patients is of the order of $3.43 * 10^{-8}$/day if we take one mililitre as the unit of volume [6], so that our value of .00065 in the above example is way out of line. At $A_3 = 3.43 * 10^{-8}$, and the values of other parameters as assumed above, the point P_3 is stable and persistent blips should not appear. We strongly suspect that due to "evolution" of the HIV virus, this value is changing rapidly with time, which produces these blips as the value of A_3 increases. We observe that our blips are of the correct order of magnitude and they appear at approximately the same interval as observed in the patients. According to one study [4], "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." [4].

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