On a Four Stage Model for Development to AIDS

by
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Abstract: We present a model consisting of four 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.

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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 viruses in the body after which this number comes down and the patient reaches approximately a steady state in the number of healthy CD4+ helper T-cells, productively infected CD4+ cells, latently infected such cells and the number of viruses. In this steady state, which the body reaches in a matter of weeks, the number of viruses is rather small and the patient becomes asymptomatic.

It has been argued in the literature [1] that during this asymptomatic period, the HIV activity in the body is anything but quiet. The life span of a virus producing T-cell is approximately two days and as these cells die, more and more cells are being produced in the body which provide a continuous source of cells for HIV to attack and multiply inside these cells. This activity can be stopped at two stages, one to make the attack on the CD4+T cells less effective and second to reduce the propensity of cells to release viruses. 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.

It has been surmised that as the viruses attack the cells, some of these cells

become productively infected right away while others become so only slowly. These are the latently infected cells and they become "sick", i.e. start breaking up and start producing viruses only sometime in future.

In this paper, we develop a model with four variables which will mimic this behaviour of CD+ T cells and the viruses and outline the effect of protease inhibitors and reverse transcriptase inhibitors in such a model. We take mm^3 as the unit of volume and one day as the unit of time and write [2]

$$x_1'(t) = A_1x_1 - A_2x_1^2 - A_3u_1x_1 \quad \text{.....(1a)}$$

$$x_2'(t) = A_4u_1x_1 - A_5x_2 + A_6y_1 \quad \text{.....(1b)}$$

$$y_1'(t) = A_7u_1x_1 - A_8y_1 \quad \text{.....(1c)}$$

$$u_1'(t) = A_9x_2 - c_1u_1 \quad \text{.....(1d)}$$

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
$y_1(t)$ = number of latently infected CD4+ T cells in the body
$u_1(t)$ = number of viruses in the body at any time t.
Also
A_1 = rate (per unit) 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
$A_3u_1x_1$ = number of infected cells being produced per unit of time
$A_4u_1x_1$ = number of productively infected cells being produced per unit of time
A_5 = rate of clearance of productively infected cells
A_6 = rate at which latently infected cells change into virus producing cells
$A_7u_1x_1$ = number of latently infected cells being produced per unit of time
A_8 = rate of clearance of latently infected cells
A_9 = rate of production of viruses per productively infected cell
c_1 = rate of clearance of viruses.

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 [4]) 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 .00065[3] to .000024 [4] per mm^3 per day. As another example, the values of c_1 in the literature vary from .557[3] to 3.0 per day [5]. 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 viruses 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 viruses 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 estimate of this value is highly unreliable. We shall take this value to be 480 [5]. Now 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 will be taken to be 240.

The parameter A_4 is an indicator of the amount of reverse transcriptase inhibitor in the drug being administered to the patient. When a T-cell is infected by HIV, it becomes either immediately productive or latently productive. If we assume that 20% of the infected cells become latently productive, then $A_7 = .2A_3$. This implies that $A_4 = .8A_3$. So that if the reverse transcriptase inhibitor is 50% effective, then we shall take $A_4 = .4A_3$ and $A_7 = .2A_3$ and so on.

3. Positivity of the solution: We shall prove that if $x_1(0)>0$, $x_2(0)\geq 0$, $y_1(0)\geq 0$, and $u_1(0)> 0$, then these variables stay non-negative 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, y_1, u_1) hits $x_1(t) = 0$, then it cannot move away from it. Since $x_1(0)>0$, this shows that $x_1(t)$ is non-negative in $t \geq 0$. Equations (1c) and (1d) imply that

$$y_1(t) = e^{-A_8 t} y_1(0) + e^{-A_8 t} \int_0^t e^{A_8 t} A_7 x_1(t) u_1(t) dt \quad \text{.....(2a)}$$

and

$$u_1(t) = e^{-c_1 t} u_1(0) + e^{-c_1 t} \int_0^t e^{c_1 t} A_9 x_2(t) dt \quad \text{.....(2b)}$$

Now at $x_2(t) = 0$, we have $x_2'(t) = A_4 u_1(t) x_1(t) + A_6 y_1(t)$. If $x_2(0) > 0$, then 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 $0 \leq t < t_1$. This implies from (2b) that $u_1(t) > 0$ in $0 \leq t \leq t_1$. Also $x_1(t) \geq 0$ in $0 \leq t \leq t_1$. But this implies that $y_1(t) > 0$ 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 $u_1(t) > 0$ in $t > 0$ and then $y_1(t) > 0$ in $t > 0$. This proves the non-negativity of the solution in $t > 0$.

4. Boundedness of the solution:

Equations (1) give $(x_1+x_2+y_1)' = A_1x_1 - A_2 x_1^2 - (A_3-A_4-A_7)u_1x_1 - A_5x_2 - (A_8-A_6)y_1$. Since x_1, x_2, and y_1 are known to be non-negative, and $A_3 \geq A_4 + A_7$, the right hand side can be seen to be negative for large enough values of $A_1 x_1 + A_5 x_2 + (A_8 - A_6) y_1$ $(>A_1^2/A_2)$. Assuming that $A_8 > A_6$ (which implies sufficiently slow rate of conversion of latently infected cells to productively infected cells), this implies that $x_1 + x_2 + y_1$ is decreasing for large

enough values of $x_1 + x_2 + y_1$. This proves the boundedness of x_1, x_2 and y_1 and then of u_1 as well from equation (2b).

5. The Equilibrium points: There are three equilibrium points of the system, P_1, P_2, and P_3 where $P_1 = \{0, 0, 0, 0\}$, $P_2 = \{A_1/A_2, 0, 0, 0\}$ and $P_3 = \{x_{13}, x_{23}, y_{13}, u_{13}\}$, where

$$x_{13} = A_5A_8c_1/(A_9(A_6A_7+A_4A_8))$$

$$x_{23} = (c_1(A_1A_9(A_6A_7+A_4A_8)-A_2A_5A_8c_1))/(A_3A_9^2(A_6A_7+A_4A_8))$$

$$y_{13} = (A_5A_7c_1(A_1(A_6A_7+A_4A_8)A_9 - A_2A_5A_8c_1))/(A_3(A_6A_7+A_4A_8)^2A_9^2)$$

and

$$u_{13} = (A_1A_9(A_6A_7+A_4A_8)-A_2A_5A_8c_1)/(A_3A_9(A_6A_7+A_4A_8))$$

6. Stability of the equilibrium points: The aim of any treatment is to make P_2 stable. It is to be noticed that x_{23}, y_{13} and u_{13} 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 viruses 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 point and 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 it is equal to $(\lambda+A_1)(a_0 + a_1\lambda + a_2\lambda^2 + a_3\lambda^3)$ where

$$a_0 = -A_1A_9(A_6A_7+A_4A_8) + A_2A_5A_8c_1$$

$$a_1 = A_2A_5A_8 - A_1A_4A_9 + A_2A_5c_1 + A_2A_8c_1$$

$$a_2 = A_2(A_5 + A_8 + c_1)$$

$$a_3 = A_2$$

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

$$A_4A_9 < (A_5A_8+A_5c_1+A_8c_1)A_2/A_1 \quad \text{.....(A)}$$

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 viruses 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

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

As an example, for $c_1 = 3$; $A_5 = .5$; $A_9 = 240$; $A_2=A_1/1000$; $A_1=.6$; $A_3 = .00003$; $A_4=.8A_3$; $A_6 = .05$; $A_7=.2\ A_3$;$A_8=.5$; and $N = 480$; 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. A similar result has been noted by Murray [5]. Also notice that as N increases, the right hand side decreases, which says that as larger and larger number of viruses get released from the productively infected cells, the inhibitors need to be more and more effective for the disease to be eradicated, which makes physical sense. Same remarks apply to A_3.

Now suppose that condition (A) is not satisfied, so that $A_1A_4A_9 = (A_5A_8+A_5c_1+A_8c_1)A_2+\epsilon$ where $\epsilon\geq 0$. This implies that $u_{13}A_3A_9(A_6A_7+A_4A_8)= A_1A_9(A_6A_7+A_4A_8)-A_2A_5A_8c_1 =A_1A_6A_7A_9+A_2A_8(A_5A_8+A_5c_1+A_8c_1)-A_2A_5A_8c_1+\varepsilon = A_1A_6A_7A_9 + A_2A_8(A_5A_8+A_8c_1) +\varepsilon.>0$ 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 $A_6'y_1$ 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. We can now write

$R_0 = (A_1A_9 (A_6A_7 +A_4A_8))/(A_2A_5 A_8c_1)$

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

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 viruses decreases substantially while the number of T-cells goes up significantly because of the treatment. Here is an example in which this happens. In this case u_{13} is positive and therefore P_2 is unstable.

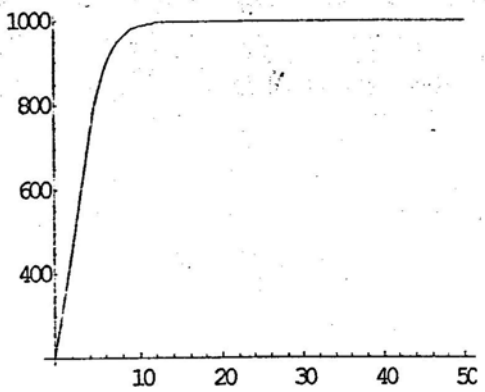

Fig 1: This figure shows the increase in the number of helper T-cells during the first fifty days after the treatment. The values of the parameters are c_1=3; A_5 = .5; A_9=120; A_2=A_1/1000; A_1=.6; A_3=.00003; A_4=.398A_3; A_6=.05; A_7 =.2A_3; A_8=.5. Assuming N = 480, this implies a 50% efficient protease inhibitor and a slightly better than 50% efficient reverse transcriptase inhibitor. The initial value of these cells is 200. The effect on the patient is seen in less than two weeks.

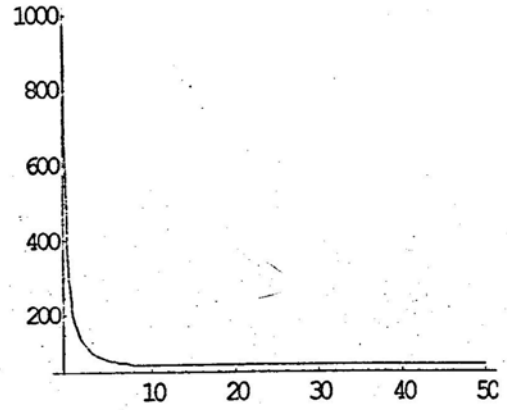

Fig 2: Decay of viruses in the same example as Fig.1. The initial value of the viruses is 1000.

7. Influence of A_9: In Fig.3, we give the lower limits to the values of A_9 which cause P_3 to become unstable. These values were found to change rather imperceptibly as A_1 changed from .01 to .6 and we have not shown this extremely small change in the diagram. It follows from this figure that, given the values of other parameters as we have assumed, A_3 cannot be much less than .00002 (otherwise A_9 would have to be greater than about 850 for P_3 to be unstable), and that larger values of A_3 will require smaller values of A_9 for P_3 to become unstable, which may give rise to "hiv blips" [6].

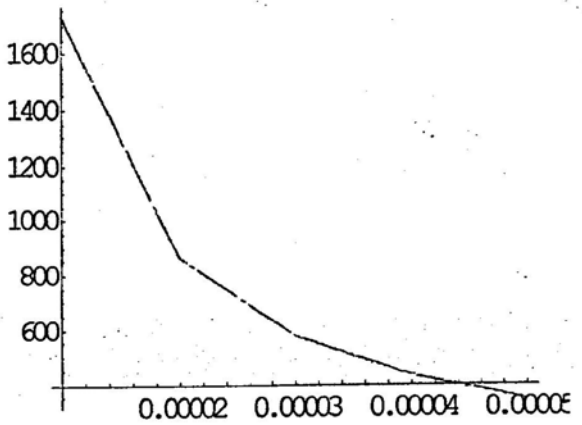

Fig.3: Values of A_9 plotted along y-axis against values of A_3 (x-axis). The point P_3 becomes unstable for values of A_9 above these values. These values were found to be indistinguishable (on the graph) as A_1 changed from .01 to .6. This graph is a superposition of a number of graphs for various values of A_1 . The values of other parameters are A_2 = A_1 /1000; A_4 = .8A_3; A_5= .5; A_6= .05; A_7= .2A_3; A_8 = .5; c_1= 3.;

8. 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, y_1) space for one particular case.

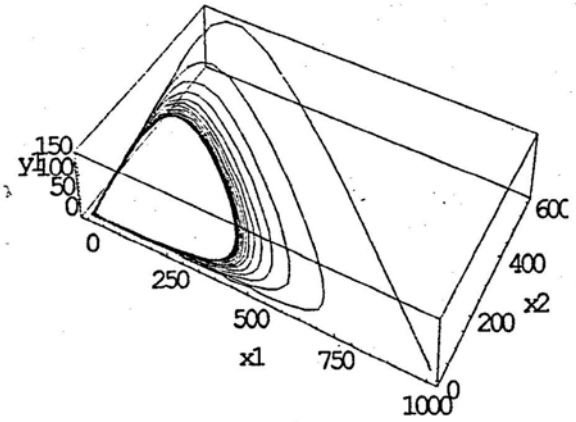

Fig 4: Solution of our equations for c_1=3; A_5=.5; A_9=240; A_2=A_1/1000;A_1=.6;A_3=.0001; A_4 =.8 A_3; A_6=.05; A_7 =.2 A_3; A_8 =.5. P_3 is unstable in this case. The initial values are x_1 (0)=1000, x_2 (0)=10, y_1(0)=5, and u_1(0)=10. In the figure, the solution is running 'inwards' (towards P_3) and counter clockwise for increasing values of time.

In Fig.5 we show the same limit cycle coming from "the other side", i.e. with the solution starting from close to P_3. This figure tends to confirm that the solution indeed has a **stable** limit cycle.

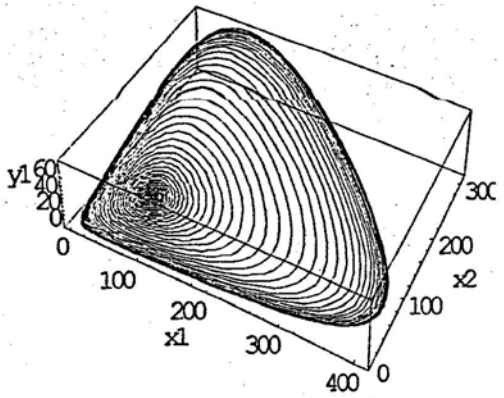

Fig 5: Solution of our equations for the same values of parameters as in Fig. 4. P_3 is unstable as in Fig. 4. The initial values are x_1(0)=76, x_2(0)=69, y_1(0)=16, and u_1(0)=5542. In the figure, the solution is running 'outwards' (away from P3) and counter clockwise for increasing values of time.

We also tried the case of A_4 =.9A_3 and A_7=.1 A_3 and the case of A_4 =.99A_3 and A_7=.01 A_3, implying a 10% and a 1% production of latent cells, keeping the values of all other constants the same as before and found a similar limit cycle in each case. These results will not be shown here.

9. Viral Blips: These limit cycles could help explain the "viral blips" that are often observed in patients who are being treated with HAART [6]. HAART may reduce the viral load of a patient below the detection level (approximately 50 copies /ml) 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. However, it is obvious that

these limit cycles will also produce these blips. Below, we give several examples of such blips in our model. Because the values of the parameters in our model are uncertain, these blips may not represent any actual situation, however the idea that hiv blips may occur because of insufficient dose, as is the case in our model, is worthy of further investigation. It is obvious from Fig.6 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 $\mathbf{P_3}$ instead of going to $\mathbf{P_2}$ because of insufficient medicine. These blips seem to appear once every six months (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 ten per cent of the time and his viral load is below the detection level, and he/she is non-infectious, for 90% of the time (the value of u_1 in the middle of the two blips was of the order of 10^{-8}). This is a huge break on the transmission potential of the disease. If we increase the value of A_9 (implying a lower value of protease inhibitor), these blips would be higher.

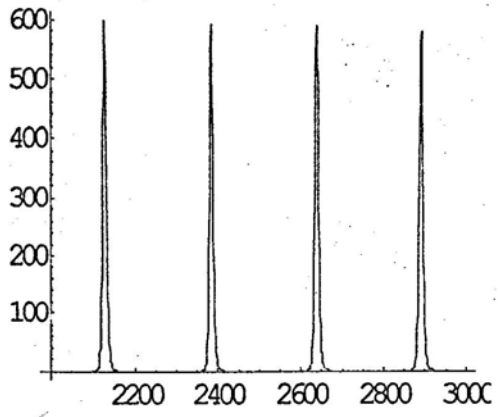

Fig.6: Viral Blips in our model plotted against time. The values of the parameters are $\mathbf{A_1}$ = .01; $\mathbf{A_2}$ = $\mathbf{A_1}$/1000; $\mathbf{A_3}$ = .000343; $\mathbf{A_4}$ = .3$\mathbf{A_3}$; $\mathbf{A_5}$ = .5; $\mathbf{A_6}$= .05; $\mathbf{A_7}$= .4$\mathbf{A_3}$; $\mathbf{A_8}$ = .5; $\mathbf{A_9}$= 80; $\mathbf{c_1}$ = 2.30399;

This example also shows that these blips should disappear if we increase the dose sufficiently. It is because of insufficient amount of reverse transcriptase inhibitor and protease inhibitor that the point $\mathbf{P_2}$ is unstable and too high a value of $\mathbf{A_9}$ is producing these limit cycles and the consequent blips. As an example, the value of $\mathbf{A_9}$ in the above figure is 80. The results in this figure are based upon application of 50% efficient reverse transcriptase inhibitor and 66.6 % efficient protease inhibitor (assuming N = 480). If we drive this value of $\mathbf{A_9}$ to a sufficiently low level, (by increasing the protease inhibitor), then $\mathbf{P_2}$ is stable and these blips will disappear.

As pointed out above, these blips are higher if we increase the value of A_9 implying a lower value of protease inhibitor. In the next figure, we give an example of lower intensity blips by increasing the value of protease inhibitor.

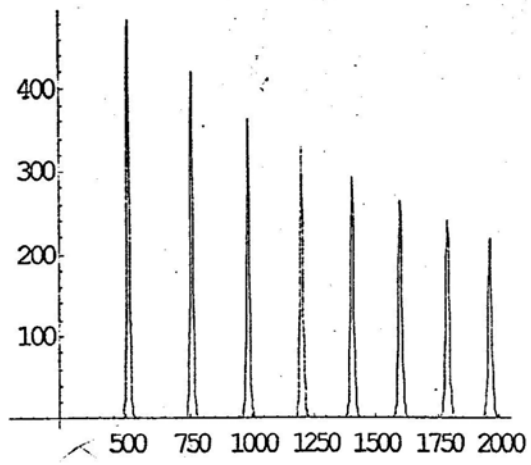

Fig 7: Blips for A_9= 50. The values of the other parameters are the same as in Fig. 6. In this case P_3 is stable and the solution is going to this point. However, the approach to this point is oscillatory and it takes more than 16 years (t = 6000) for the solution to come close to this point. In practical terms, it never reaches (for a patient). However, the size of the blips is decreasing with time.

10. Effect of ARV's: In order to illustrate a point, we shall now give another example of what happens after a patient is administered protease inhibitor and reverse transcriptase inhibitor.

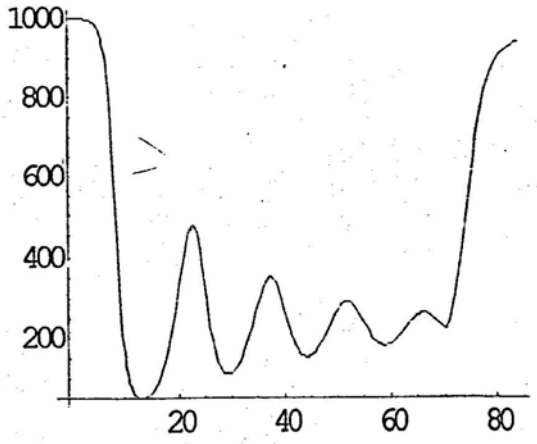

Fig.8: Number of CD4+ T-cells in the body after administration of both protease inhibitor and reverse transcriptase inhibitor on day 70. In the beginning we have A_1 =.6, A_2=A_1/1000, A_3=.0000345, A_4=.8A_3, A_5=.5, A_6 =.05, A_7=.2A_3, A_8=.5, A_9 =240, and c_1=3 implying no treatment. If unchecked, the number of CD4+ T-cells will go down to 220, which is about right. However, on day 70, we change A_4 to .32A_3 and A_9 to 120 implying a 50% effective protease inhibitor and a 60% effective reverse transcriptase inhibitor. It is obvious from this figure that the number of CD4+ T cells goes up sharply in the beginning and then slowly. This is in accordance with the behaviour found by Perelson et al in a medical study [8];

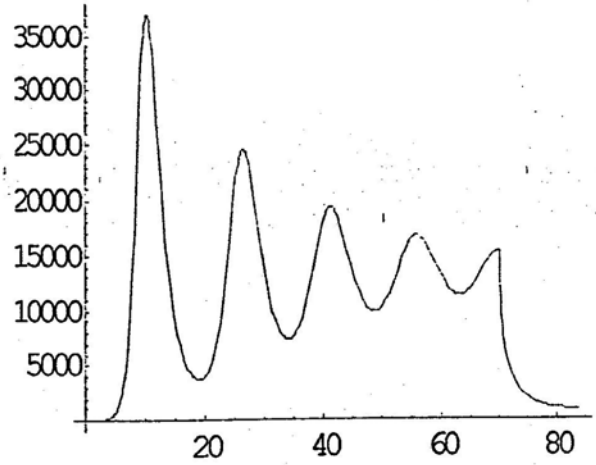

Fig 9: Number of viruses for the same case as in Fig.1. Notice how the viruses drop dramatically after the administration of drugs.

The drop is very sharp in the beginning, and then slow. This is in accordance with the behaviour found by Perelson et al in a medical study [8]. It should also be kept in mind that, depending upon the values of other parameters, if the values of A_4 and A_9 are not low enough, then this drop in the number of viruses may be temporary, and if we wait long enough, viral blips will appear.

11. A curious comparison: The decay in Fig. 9 has been termed "biphasic" by Perelson et. al. in the medical study cited above [8]. However, this decay must be multi phasic because the characteristic matrix of our system at P2 or P3 has four eigenvalues. We give below a diagram which shows that, except near the origin, one decay can be very well approximated by another such decay but with appropriate coefficients

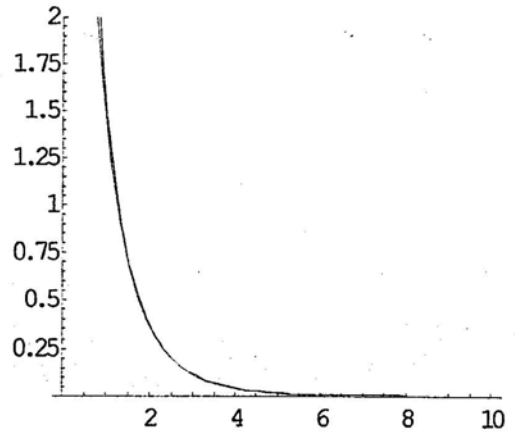

Fig 10: In this figure the two curves $y = 5e^{-2x} + 2e^{-x}$ and $y = 5e^{-2x} + 2e^{-x} + e^{-3x} + e^{-4x}$ are superposed on each other to show that a biphasic decay and a multiphasic decay are indistinguishable from each other in such a figure.

12. The stability of P_3: In this case, the determinant of the characteristic matrix turns out to be $a_0 + a_1\lambda + a_2\lambda^2 + a_3\lambda^3 + a_4\lambda^4$, where

$a_0 = A_3A_5A_8c_1u_1$,

$a_1 = (1/(A_9(A_6A_7+A_4A_8)^2))(A_5A_8c_1(A_2(A_8c_1(A_6A_7+A_4A_8)+A_5(A_4A_8^2+A_6A_7(A_8+c_1)))+A_3A_4A_9u_{13}(A_6A_7+A_4A_8)))$

$a_2 = (1/(A_9(A_6A_7+A_4A_8)))(A_2A_5^2A_8c_1+A_8A_9c_1(A_6A_7+A_4A_8)+A_5(A_6A_7A_9(A_8+c_1)+A_8(A_4A_8A_9+A_2c_1(A_8+c_1))))$

$a_3 = A_2x_{13}+A_5+A_8+c_1$,

and $a_4 = 1$

Since $x_1>0$ and we need $u_{13}>0$ for P_3 to be reachable, all these coefficients are clearly positive if P_3 is reachable. However, the two more requirements for stability in this case, namely $(a_1a_2 - a_0a_3) > 0$ and $a_3(a_1a_2 - a_0a_3) - a_1^2a_4 > 0$ may or may not be satisfied. Depending upon the values of the coefficients, one of these numbers may be positive and the other negative, or both negative or both positive. 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 $c_1 = 3$, $A_1 = .6$, $A_2 = A_1/1000$, $A_4 = .8A_3$, $A_5 = .5$, $A_6 = .05$, $A_7 = .2A_3$, $A_8 = .5$, and $A_9 = 240$, these two quantities are positive, and therefore P_3 is stable for all positive values of A_3 less than .0000719944. The value of this

parameter has been estimated at .0000343 by some writers [5].

13: A_3 changing with time: It is to be noticed that in the above examples, the steady state is reached too soon, about six months after the patient contracts the disease. In actual cases, the number of CD4+ T cells keeps on going down for years, till this number goes down to about two hundred in approximately ten years, when some other phenomena like opportunistic infections take over. While the value of A_3 has been approximated as $(3.43*10^{-5})$ by some writers [5], this value was found as the mean of a number of observations in only one experiment at one time and it is by no means clear that this value does not change with time as the HIV virus "evolves" in a patients' body. As a matter of fact, some writers have studied such a change in the value of A_3 [1]. If we assume such change, and assume that the viral activity, as measured by the parameter A_3, increases with time, then the phenomenon of decreasing CD4+ T cells with time can be emulated in our model. We give an example.

We assume that $A_3(t) = 2.0*10^{-5} + (5.0*10^{-9})t$ and keep other constants the same as above (A_1=.6, A_2=A_1/1000, A_5=.5, A_6=.05, A_8=.5, A_9=240, c_1=3) except A_4 and A_7 which are again assumed to be equal to .8 $A_3(t)$ and .2 $A_3(t)$ as before. Notice the extremely small change in the value of A_3 with time. Now the number of CD4+ T-cells goes down steadily as shown in Fig 11. In this case, this number goes down steadily (after the initial oscillations) to 199 cells in ten years (t = 3650).

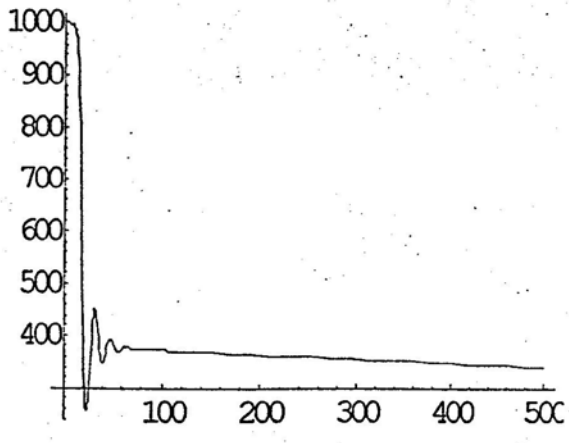

Fig 11: Number of CD4+ T cells going down steadily for the first 500 days for the values of the constants as given in the text. In ten years (t=3650), this number will go down to 199 cells.

14. References:

1. N Stilianakis and D. Schenzle: On the Intra-host Dynamics of HIV-1 Infections, Mathematical Biosciences, Vol.199 (2006) pp.1-25.

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Notes:
1. Sec.6, page 4, top right hand corner. The sentence should read:
We look at the characteristic matrix of the system (1) at P_2 and find that A_2 times its determinant is equal to ……
2. Sec. 6, page 5, bottom left. The Sentence should read
Now suppose that condition (A) is not satisfied, so that $A_1A_4A_9 = (A_5A_8+A_5c_1+A_8c_1)A_2+\varepsilon/A_8$ where $\varepsilon \geq 0$.
3. Sec 12, page 10, bottom left.
the quantity u_1 in the expression for a_0 should be u_{13}.
4. Sec 12, page 10, right half.
Sentence should read
Since $x_{13}>0$ and we need…….