Effect of Antibodies on an HIV Positive Patient

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Abstract: We develop a Mathematical Model to substantiate the hypothesis that AIDS occurs because the immune system of the patient is being degraded by HIV on a daily basis. We shall also show that HIV blips may be generated in a patient either by sleeping infected cells waking up randomly or by the infection coefficient of the virus going up.

I. INTRODUCTION

The HIV virus spreads in the body by entering a CD4+ T-cell and making thousands of copies of itself inside the cell [3,4]. The T-cell dies in the process. These copies (new viruses) are then ready to attack new cells. These CD4+ T cells are an indispensable part of the immune system of the body and the system gets destroyed after a while. If, there is no intervention by antiretroviral drugs, this happens in about ten years. But, every time a virus makes a copy of itself, it is different from its original copy at approximately one location (called a nucleotide). This mistake lends a tremendous advantage to the virus.

This is because when the immune system of the body attacks the virus, its killer cells recognise the virus by some markers on a T-cell's surface that the virus prompts. These markers are called "epitopes". Many of these epitopes are variable and may change as the virus changes at one nucleotide and then at another in response to pressure from the immune system of the body. Sometimes such changes can cause an epitope to become invisible to the immune system, making the virus more difficult for the killer cells of the immune system to detect and destroy it. If therefore, the immune system of the body recognises the virus through its variable epitopes, then the capacity of the immune system to recognise the virus will degrade as more and more of these variable epitopes undergo evolution (the change we have described) and become invisible to the immune system. Thus, after a while, the viruses will grow unchecked.

However, this war between the virus and the immune system is not one-sided. The immune system recovers from its incapacity to recognise new epitopes, so that the "survival advantage" thus conferred on the virus is short lived. After a short time, the immune system attacks the virus with improved antibody fitness and the virus begins to decline. This game of cat and mouse continues till finally the virus gains the upper hand (because the number of undetectable epitopes continues to increase). In the last stage of the game, the patient develops AIDS.

An epitope, therefore, may be considered as the signature of the virus and the virus, in its quest to survive, keeps on changing its signature so that it is more and more difficult for the immune system of the body to recognise the virus. In order to survive inside the body (it cannot survive outside the body for very long), it does three things. One, it constantly changes its 'signature', and thus hides from the immune system of the body. Two, it becomes more and more 'virulent' and attacks and kills more and more immune cells of the body [11] so that such cells become depleted. But since more and more of them are being produced in the body, getting infected, producing more viruses, and dying, the phenomenon results in what are called 'HIV blips' in the HIV literature. And finally, it learns to hide inside some of the 'resting' cells [2,8,9]. These are the cells that do not exhibit the signature of the virus on their surface and the virus may hide inside of them for months, even years and then show up suddenly, so that it is very difficult to eradicate this disease entirely [8]. There are other viruses that have this property and this is why the 'shingles' in your body may appear after they have shown no sign of being there for years. Are the HIV blips the "shingles" in the body of an HIV positive person?

In this paper, we develop a mathematical model to study the phenomenon of decreasing effectiveness of antibodies, and give several examples to indicate that if the parameter in the system that measures the effectiveness of the immune system, decreases with time then the number of healthy cells decreases and the number of virions increases with time. The intermittent increase in antibody effectiveness, which happens when the evolutionary pressure on the virus declines, or which may occur when specific cytokines (IL-2 is an example) are delivered to the system, is modelled by an impulsive differential equation in our model. It has been pointed out in the literature [7] that on activation by IL-2, the killer cells of the body proliferate, even as they become better killers and produce additional cytokines. As with any mathematical model, we can quantify this change to conclude that in a given patient, this antibody effectiveness is going down at this rate. This would, hopefully, lead to individualised and more efficient medical prescriptions for patients.

We also study the phenomenon of HIV blips in an HIV positive patient. After a patient has been treated with antiretrovirals and his viral load has been below the detection level (i.e. less than 50 copies /ml today), his viral load suddenly goes up to above 1000 copies /ml and then comes down. Such movements of the viral load are called HIV blips. We shall show that, in our model, these blips may be generated by the latently infected cells coming to life and producing virions. Since this phenomenon may occur at random, these blips may indeed be random as has been claimed in the HIV literature. However, in our model, these blips may also be generated as the infection coefficient of the disease increases. So that the blips may also be generated signalling a failure of the treatment.

II. THE MODEL

As our model, we write [5,6]

$$x_1'[t] = A_1x_1 - A_2 x_1^2 - A_3u_1x_1 \ldots\ldots\ldots\ldots\ldots\ldots (1a)$$

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Manuscript Received July 22, 2011, Revised Aug 19, 2011.

$x_2'[t] = A_4u_1x_1 - A_5x_2 + A_6x_3 - A_{14}\,u_2\,x_2$.....(1b)
$x_3'[t] = A_7u_1x_1 - A_8x_3 - A_6\,x_3$..... .....(1c)
$x_4'[t] = A_{11}u_1x_1 - A_{10}x_4$..... .....(1d)
$u_1'[t] = A_9\,x_2 - c_1\,u_1$ .....(1e)
$u_2'[t] = A_{13}u_1 + A_{12}x_2 - c_3\,u_2$.....(1f)

In this model, the quantities x_1, x_2, x_3, x_4, u_1, and u_2 denote the number of susceptible cells, the productively infected cells, the latently infected cells, cells that carry defective provirus, virions and antibodies respectively. The role of parameters A's and c's is clear from the context.

Role of Antibodies : It should be noted that if we decrease A_{14} in eq.(1b) above (which is the same as decreasing the effectiveness of antibodies), then x_2 tends to go up. In turn u_1 tends to go up, and then in turn x_1 tends to go down, and so on (of course, as x_1 goes down, there is a secondary cascade of events which we ignore at this moment). It follows that the *expected* effect of antibodies (u_2's) not recognising productively infected cells (x_2's) in our model is for the number of healthy cells (x_1's) to go down and for the virions (u_1's) to go up. This is what happens in a patient in later stages of the disease. We shall now study the behaviour of our system.

Positivity of the Solution: It is important in order for our model to be relevant, that the solutions of our equations, starting in the "positive space", ($x = \{x_1,x_2,x_3,x_4,u_1,u_2\} \geq \{0,0,0,0,0,0\}$) stay in this space and stay "bounded" in it. Negative or unbounded values of any of the variables are clearly non admissible. We shall therefore prove that: If $x_1(0)>0$, $x_2(0)\geq 0$, $x_3(0)\geq 0$, $x_4(0)\geq 0$, $u_1(0)>0$, and $u_2(0)\geq 0$, then these variables stay non-negative (and bounded) in $t > 0$. We shall say that $x \geq 0$ iff all the components of x are non negative.

Proof of positivity: Note that we can write our equations as $x' = F(x) - G(x)$ where $F(x) = \{A_1x_1, A_4u_1x_1+A_6x_3, A_7u_1x_1, A_{11}u_1x_1, A_9x_2, A_{13}u_1 + A_{12}x_2\}$ and the remaining terms are in G(x). Now notice that in $x \geq 0$, $F(x) \geq 0$ and for each x_i, $G_i(x) = 0$ if $x_i = 0$. This says that if the moving point $\{x_1,x_2,x_3,x_4,x_5,x_6\}$ is in the non negative space, then no component of F(x) is negative and if the point is on any "plane" $x_i = 0$, then that component cannot become negative (because $x_i = F_i(x)-G_i(x) \geq 0$). Considering that the right hand sides are polynomials, this proves the invariance of the positive space for our system.

Boundedness: Notice that $[x_1+x_2+x_3+x_4]' = A_1x_1 - A_2x_1^2 - A_3u_1x_1 + A_4u_1x_1 - A_5x_2 + A_6x_3 - A_{14}u_2x_2 + A_7u_1x_1 - A_8x_3 - A_6x_3 + A_{11}u_1x_1 - A_{10}x_4$. Since $A_3 \geq (A_4+A_7+A_{11})$, the right hand side is seen to be negative for large enough values of $A_1x_1+A_5x_2+A_8x_3+A_{10}x_4$ ($> A_1^2/A_2$). Combined with positivity of x_1, x_2, x_3, and x_4, this shows the bounded ness of these variables and then those of u_1 and u_2 follows from equations (1e) and (1f).

Points of Equilibrium: There are three points of equilibrium in the "non-negative" space. These are $P_1 = \{0,0,0,0,0,0\}$, $P_2 = \{A_1/A_2,0,0,0,0,0\}$, and $P_3 = \{x_{13},x_{23},x_{33},x_{43},u_{13},u_{23},\}$, where

$x_{13} = ((A_6+A_8)\,c_1\,(A_1\,A_{14}\,(A_9\,A_{13}+A_{12}\,c_1)+A_3\,A_5\,A_9\,c_3))/(A_2\,(A_6+A_8)\,A_{14}\,c_1\,(A_9\,A_{13}+A_{12}\,c_1)+A_3\,(A_6\,A_7+A_4\,(A_6+A_8))\,A_9^2\,c_3)$
$x_{23} = (c_1\,(A_1\,(A_6\,A_7+A_4\,(A_6+A_8))\,A_9 - A_2\,A_5\,(A_6+A_8)\,c_1)\,c_3)/(A_{14}\,A_2\,(A_6+A_8)\,c_1\,(A_{13}\,A_9+A_{12}\,c_1)+A_3\,(A_6\,A_7+A_4\,(A_6+A_8))\,A_9^2\,c_3)$
$u_{13} = A_9\,x_{23}/c_1$; $x_{33} = A_7\,u_{13}\,x_{13}/(A_8 + A_6)$;
$x_{43} = (A_{11}\,u_1\,x_1)/A_{10}$; and $u_{23} = (A_{13}\,u_1 + A_{12}\,x_2)/c_3$;

Basic Reproduction Number: It is obvious from the above that the disease is endemic if and only if

$R_0 = (A_1\,(A_6\,A_7+A_4\,(A_6+A_8))\,A_9)/(A_2\,A_5\,(A_6+A_8)\,c_1) \geq 1$.

It follows that R_0 is the Basic Reproduction Number of this dynamic[12].

Effect of A_{14}: It is easy to see that for $R_0 > 1$, i.e. if the disease is present, then as A_{14} decreses, x_{13} decreases and u_{13} increases (differentiate these expressions w.r.t. A_{14}). This is the phenomenon observed in an HIV positive patient on a daily basis, i.e. in $x_1(t)$ and $u_1(t)$. Assuming P_3 to be an attractor, the expressions for $x_{13}(t)$ and $u_{13}(t)$ will approach their limiting values, so that we expect the values of $x_1(t)$ to decrease and $u_1(t)$ to increase for increasing values of t, though not monotonically. We proceed to give some examples to show how they do so in these examples. In our first example, this decrease is stepwise. The value of A_{14} = .000009 for $t \leq 100$, and is decreased by .000001 every 300 days till t = 1900 and then to .000001 at t = 1900 and then to zero at t = 2200. Here are the values of x_1,

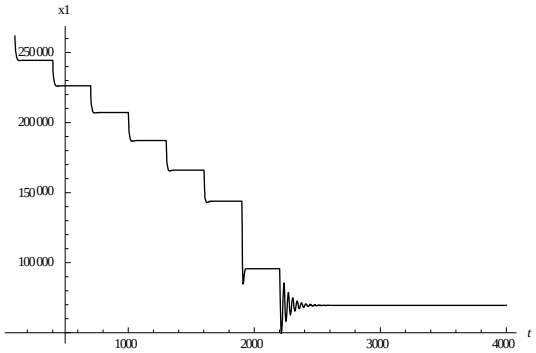

Fig. 1 : Values of x1[t] when the effect of antibodies (the value of A_{14} in our model) changes stepwise.

and those of u_1.

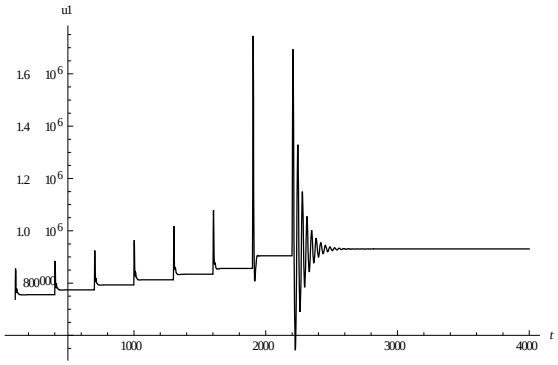

Fig. 2 : Values of u1[t] when the effect of antibodies (the value of A_{14} in our model) changes stepwise. The values of other parameters are A1 = .1; A2 = A1/1000000; A3=.0000001; A4 = .5 A3; A5 = .5; A6 = .05; A7 = .15 A3;

ISBN: 978-988-19251-7-6
ISSN: 2078-0958 (Print); ISSN: 2078-0966 (Online)

A8 = .05; A9 = 500; A10 = .05; A11 = .35 A3; A12=.5; A13 = .1; c1=4; c3 = .5;

Here is another example.

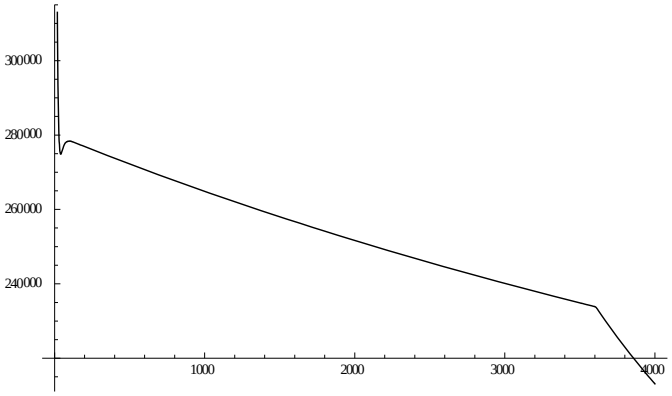

Fig. 3 : Values of x_1 for A_3=.0000001 and for decreasing values of A_{14}. The values of A_{14} are given by the which function in *Mathematica* and are A_{14}[t_] := Which[t < 100, .00001, t < 3600, .00001/(1 + .0001 (t - 100)), t < 10000, .00001/(1 + .0001 (t - 100) + .0005 (t - 3600)), True, 0]. Notice that values of x_1 go to about 200/μl in about ten years. This is what happens in actual patients.

Antibody Boosting: AIDS generally occurs when the number of CD4+ cells in a patient, x_1's in our model, falls below 200/μl. It would follow from above that the onset of AIDS can be delayed if we can influence the term $A_{14}\, x_2\, u_2$ in eq. (1b) in our model. We model this change as a change in the parameter A_{14}, which change may appear by administering an appropriate drug periodically (injections of IL-2 and IL-7 have shown promise) by the following equation

$dA_{14}/dt = -k_1\, A_{14}$, for $t \neq t_k$ with
$\Delta A_{14} = A_{14}(t_k^+) - A_{14}(t_k^-)$.....(1g)

In the above equation (1g), the quantity A_{14} is boosted by an amount ΔA_{14} at times $t = t_k$, presumably through an injection of a drug, and the effectiveness of the drug deteriorates exponentially according to Exp[$-k_1 t$]. This leads to

$A_{14}(t_k^+)=(\Delta A_{14})(1-\text{Exp}[-kk_1\tau])/(1-\text{Exp}[-k_1\tau])$

where τ is the interval at which the drug is being administered and k is the number of times it has been administered. Notice that this quantity approaches $(\Delta A_{14})/(1-\text{Exp}[-k_1\tau])$ as k goes to infinity. If we call this quantity Q, then we have an impulsive periodic orbit going from $Q\text{Exp}[-k_1\tau]$ to Q.

We show the results when A_{14} is boosted every thirty days for 600 days when half life of the drug is 60 days, with A_3 = .0000001. Here are the values of A14.

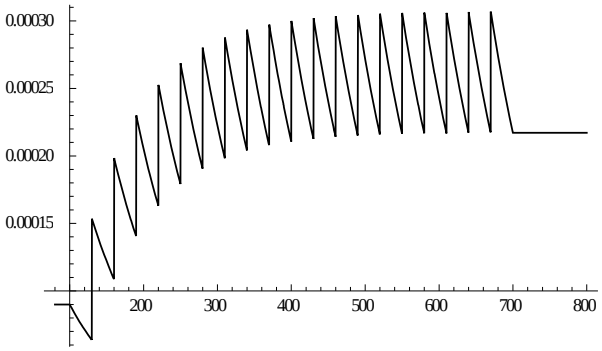

Fig. 4: Values of A14 when the antibodies are boosted by an appropriate injection every 30 days. The drug deteriorates with a half life of 60 days. The values of other parameters are A1=.1, A2=A1/1000000, A3=.0000001, A4 = .5A3, A5=.5, A6=0, A7=.15A3, A8=.05, A9=500, A10=.05, A11=.35A3, A12=.5, A13=.1, c1=4, c3=.5.

Here are the corresponding values of x_1 and u_1 . Notice that x1 goes from about 850 to about 900/μl which are very good values for x1.

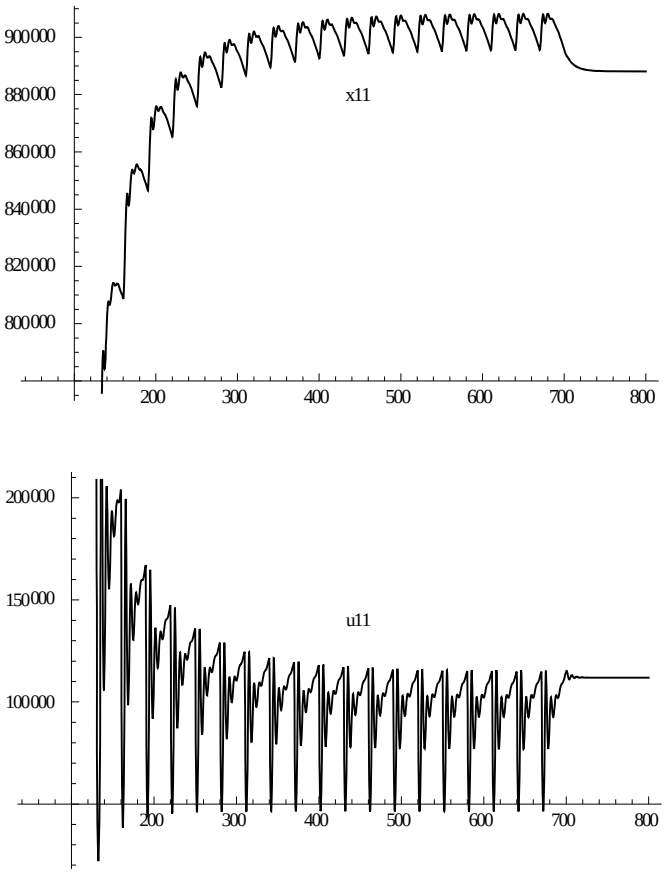

Fig. 5 : Values of x_1 and u_1 for A_3=.0000001. The parameter A_{14} is held constant at .00009 for 100 days and then allowed to decay for 30 days. Starting at 130 days, it is boosted by .00009 every thirty days and allowed to decay exponentially with a half life of 60 days, for 400 days.

Here is the solution when two doses are missed. Notice that it takes more than 10 doses to come back to the same state of health showing that adherence to doctors' orders is very important.

ISBN: 978-988-19251-7-6
ISSN: 2078-0958 (Print); ISSN: 2078-0966 (Online)

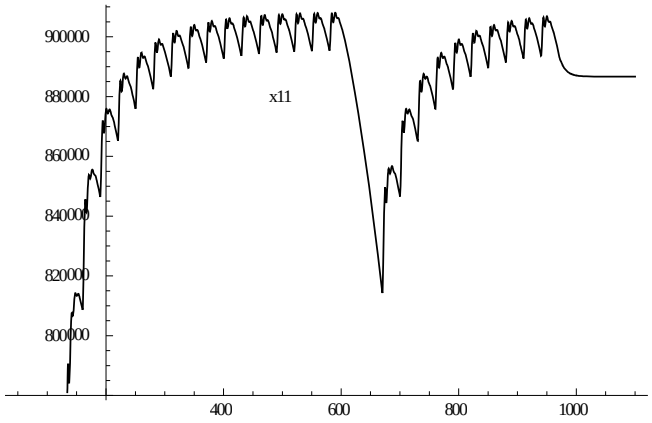

Fig .6 Values of x_1 when two doses are missed

HIV Blips: We also looked at the phenomenon of HIV Blips [1] in this model. After a patient has been on antiretrovirals and his viral load has been undetectable (i.e.< 50/ml) for a long time, the load suddenly comes back up temporarily to more than 1000/ml and then goes down again [10]. This phenomenon is called HIV blips. HIV Blips are sometimes dismissed as statistical anomalies. They are known to occur in approximately 25% of patients on HAART. They occur in our model for large values of A_3. Here is a sample. Notice that the values of u_1 go from about 20/ml (below the detection level) to about 1200/ml (above the detection level). This is what happens in patients. In our model, about 80% of the time is spent when HIV is below the detection level. The blips occur about every 35 days.

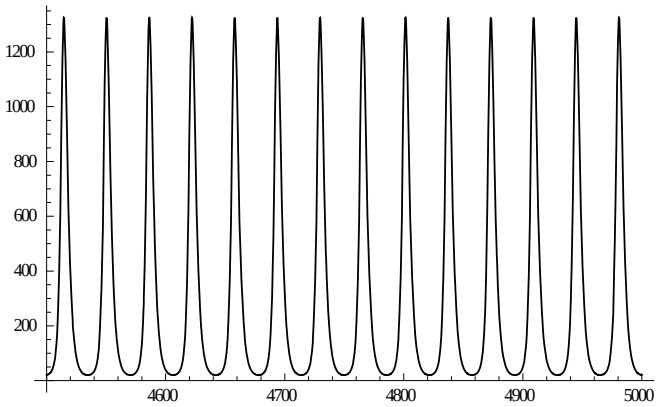

Fig. 7 : HIV Blips in our model. The values of parameters are A1 = .15; A2 = A1/1000000; A4 = .24 A3; A5 = .4; A6 = .005; A7 = .01 A3; A8 = .005; A9 = 300; A10 = .05; A11 = .75 A3; A12 = .0001; A13 = .001; A14 = .0001;c1=2; c3 = .05; A3 = .0005;

Blips may also be created by sudden and unpredictable activation of latently infected cells. Here is an example where blips are created at t = 500 and then at t = 600.

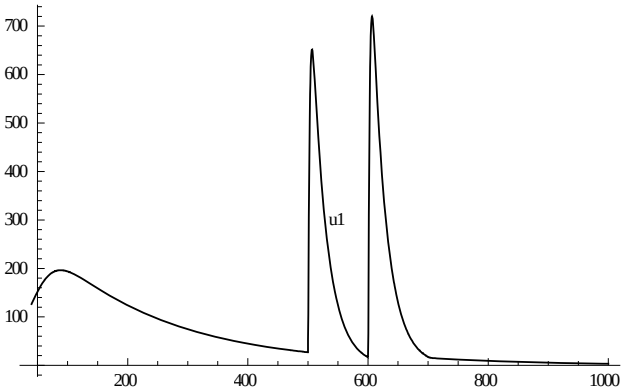

Fig .8 : Blips appear in response to changes in the latently infected cells.

The medical opinion is that if the blips are of short duration and low intensity, then they may simply be ignored. However, if they are persistent, then they may indicate failure of treatment. Our results support both of these situations. If they are persistent, then perhaps A_3 is large and the virus has become extremely virulent, which implies failure of treatment. If they are not repetitive, then they might have originated in some sleeping cells coming to life and do not imply failure of treatment.

ACKNOWLEDGMENT

I am indebted to Prof. K. E. Sanderson of the University of Calgary for helpful suggestions. Thanks are also due to Rita Aggarwala for spending long hours looking over the manuscript.

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