Development of a Mathematical Model of Viral Kinetics under Immune Control during Primary HIV-1 Infection

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Contents

Abstract

Our report relates to mathematical modelling of early stage HIV infection. Using a paper by Burg et al.[1] as a starting point, we reproduced some of the results the authors observed, and built upon their model. The original paper included 3 ODE models of HIV infection: the target cell limited model, extended model, and simplified extended model. Each model describes the time evolution of three variables: number of healthy cells, number of infected cells and viral titre in the blood.

We found that in the target cell limited model, viral load oscillates unrealistically as it approaches a steady state, and we confirmed that varying the additional parameters in the two extended models suppresses oscillation without altering steady state viral load. We proposed several additions to the model describing treatment strategies. Finally, to facillitate further research we created a set of functions for sensitivity analysis, and a graphical user interface to allow easy plotting of model output for different parameters.

1 Introduction to the Biological Problem (Islom Nazarov)

The human immunodeficiency virus (HIV) is a retrovirus (i.e. built of RNA). It attacks immune cells, such as T lymphocytes and other white blood cells with CD4 receptors on their surfaces. The virus uses the CD4 receptor to bind with and thereby enter the lymphocyte.

The mechanism of host cell infection is as follows: Co-receptors (CCR5 or CXCR4) on immune cells interact with the proteins on the outer surface of virus (extracellular gp120 and transmembrane gp41). Gp120 binds to the CD4 receptor, and this promotes further binding to the co-receptors. Co-receptor binding results in a conformational change, causing gp41 to unfold and insert its hydrophobic domains into the host cell membrane. Gp41 then folds back on itself, drawing the virus towards the cell, and facilitating its fusion with it. The virus nucleocapsid enters the host cell, releasing two RNA strands along with three essential replication enzymes (integrase, protease and reverse transcriptase). Reverse transcriptase begins the reverse transcription of viral RNA forming double stranded DNA using the hosts nucleotides. Integrase cleaves off dinucleotides from each end of the newly synthesised DNA, and transports it into the nucleus via the nuclear pore. It then makes a snip in the host cells DNA and integrates the newly made viral DNA. The host cell genome now contains the genetic information of HIV.

Activation of the cells induces transcription of pro-viral DNA into mRNA. The viral mRNA migrates into the cytoplasm, where the building blocks for a new virus are made. Some of these peptides are cleaved into shorter fragments, and this is an essential step in generating infectious virus particles. The newly synthesised virus RNA is packaged together with new protease, integrase and reverse transcriptase into capsids. The capsid leaves the host cell, acquiring a new set of host and viral proteins. The virus matures and becomes ready to infect more of the hosts immune cells.

Thus, HIV slowly destroys the immune system. Several weeks after initial infection, flu-like symptoms are experienced. The immune system then kicks-in, and the virus retreats into hiding within lymph tissues. The untreated, infected individual usually remains healthy for 5 to 15, years, but the virus continues to replicate in the background, slowly destroying the immune system.

Eventually the body is unable to defend itself and susceptible to opportunistic infections that would normally not affect healthy people. Acquired Immune Deficiency Syndrome (AIDS) is the name given to this final stage of HIV infection, and is characterised by multiple, life-threatening illnesses such as weight loss, chronic diarrhoea, rare cancers, pneumonia, fungal conditions and infections of the brain and eye. At the end of 2009, 32 million people had been infected with HIV (Avert). Barring a medical breakthrough, it could claim the lives of some 60 million people by 2015.

2 The Model (Lucy Hutchinson)

2.1 Target Cell Limited Model

The most basic model used to describe the dynamics of the virus is a system of three coupled ordinary differential equations. The parameters used are listed in the following table:

Parameter Name	Description	Units	Default Value
s	Constant influx rate of target cells	cells/mL/day	100
d	Target Cell Rate Loss Constant	/day	10^{-2}
β	Rate Constant for infection of target cells	mL/RNA/day	1.3×10^{-6}
δ	Infected cells loss constant	/day	0.5
p	Viral production rate	RNA Copies/cell/day	10^3
c	Virus clearance rate	/day	3
α	Viral Cytopathy above normal target death rate	dimensionless	1
k	Activity potential	/day	1
k_0	Depletion Rate	/day	0.2
a_E	Rate of effector cell stimulation	/day (?)	5
θ	Half maximal stimulation threshold	cells/mL	3
d_E	Rate of loss of effector cells	/day	1
R_{TT}	Effectiveness of reverse transcriptase inhibition	%	0.8
t_{st}	Start time for treatment	day	50
p_I	Efficiency protease inhibitor	%	0.8
d_r	Rate of death of cells after treatment	/day	0.1

Note that some of these parameters are used later in the report. These parameters are used to form a set of three ordinary differential equations for

V, the viral load;
T, the concentration of a target cells;
I, the concentration of infected cells.

Equations (1)-(3) form the *Target Cell Limited Model* .

$$\frac{dT}{dt} = s - dT - \beta VT \tag{1}$$

$$\frac{dI}{dt} = \beta VT - \delta I \tag{2}$$

$$\frac{dV}{dt} = pI - cV \tag{3}$$

2.2 Extended Model

The limitations of this target cell limited model are that it only describe the kinetics of the HIV virus in some patients. The model shows several oscillations after the initial peak in viral load. This behaviour is not seen in patients, but by adding infected cell depletion, the models become slightly more realistic. This is shown by the *Extended Model (EM)* with immune control.

$$\frac{dT}{dt} = s - dT - \beta VT \tag{4}$$

$$\frac{dI}{dt} = \beta VT - (\alpha d + k_0 E)I \tag{5}$$

$$\frac{dV}{dt} = pI - cV \tag{6}$$

$$\frac{dE}{dt} = a_E \frac{I}{\theta + I} - d_E E \tag{7}$$

Where E is the concentration of effector cells. This includes a more realistic rate of loss of infected cells, which now depends of the number of effector cells. However, in the paper studied, the authors could not accurately or reliably estimate values for several parameters, so they went on to simplify the extended model, giving the *Simplified Extended Model (EMS)*.

$$\frac{dT}{dt} = s - dT - \beta VT \tag{8}$$

$$\frac{dI}{dt} = \beta VT - (\alpha d + k\frac{I}{I+\theta})I \tag{9}$$

$$\frac{dV}{dt} = pI - cV \tag{10}$$

These equations assume a quasi-steady-state approximation for equation (7) .

2.3 Implementation of the model

We have reproduced the results from the paper using Matlab. We created three functions to solve the three sets of equations (derivativesTCL.m, derivativesEM.m and derivativesEMS.m, as well as a function to plot the results in a figure (SolveAndPlot.m). We found that using the parameters given in the paper, the results for viral load, target cell concentration and infected cell concentration were all easily reproducable. The parameter values are stored in a struct called params.m.

3 Stability Analysis (Adam Berrington)

The steady state behaviour of the models has been analysed according to Burg et al. Section 2.1 and Appendices A, B.

Analysing the steady state behaviour of the various models described above yields information about the predictability of the model i.e. whether an infective or non-infective states exist at all and the dynamics of the solutions. The authors of the paper claim, and it has been verified in this work, that the virus titer in the Targeted-Cell-Model is prone to oscillations, a phenomenon which is not observed in patient data.

Eigenvalues of the TCL and EMS model are calculated in this report in an aim to reproduce work carried out by Burg et al. A negative real part of eigenvalues calculated for a given system suggests the point is stable. The stability of the models can therefore be analysed for various user defined parameter values.

3.1 TCS Model – EigenvaluesTCL.m

We can perform an approximation to the TCL system to reduce it to a 2D system of equations. Assuming that virus dynamics are rapid such that $\frac{dV}{dt} \approx 0$, we obtain the expression ($V \approx pI/c$). This approximation is justified in the work done on the parameter sweeps.

The steady state equations or nullclines are now easily obtained analytically by setting equations (1)-(3) equal to zero. Performing a substitution where $\beta' = \beta p/c$, the TCL model results in

$$\frac{dT}{dt} = 0 \Rightarrow T = \frac{s}{d + \beta' I} \tag{11}$$

$$\frac{dI}{dt} = 0 \Rightarrow I = 0 \quad \text{or} \quad T = \frac{\delta}{\beta'}. \tag{12}$$

Thus there are two steady states defined by $(T_1 = s/d, I_1 = 0)$ and $(T_2 = \delta/\beta', I_2 = s/\delta - d/\beta')$. Clearly the first defines a non-infective steady state and the second is the infective steady state provided $R_0 > 1$, where $R_0 = \beta' s/\delta d$.

To examine whether a given state is stable or unstable, we can look at the eigenvalues of the system at that particular point. The eigenvalues are found from the Jacobian matrix, J, which for the TCS model looks as follows:

$$J = \begin{bmatrix} -d - \beta' I & \beta' T \\ \beta' I & \beta' T - \delta \end{bmatrix} \tag{13}$$

Thus for the infective steady state, $(T = T_2, I = I_2)$ the Jacobian reduces to

$$J(T_2, I_2) = \begin{bmatrix} -\beta' s/d & -\delta \\ -\beta' s/\delta - d & 0 \end{bmatrix} \tag{14}$$

Matlab can now be used to directly compute the eigenvalues from this matrix, and this can be calculated for each set of parameter values.

The file Eigenvalues.m performs these calculations and when called in the GUIPlotter.m script it outputs the eigenvalues and stability parameter R_0 to screen for the input defined by the user.

3.2 EMS Model – EigenvaluesEMS.m

A similar analysis was performed for the EMS model in the script EigenvaluesEMS.m, yet here the analytic solution becomes more complicated. Performing the same approximation as before ($V \approx PI/c$) and setting the resulting 2D ODE system to zero we find again two steady states. One is the non-infective state as in the TCS model ($T_1 = s/d, I_1 = 0$). The infective steady state equation is then found from solving a quadratic equation of the form $AI_2^2 + BI_2 + C = 0$, where

$$\begin{aligned} A &= \beta'(k + \alpha d) \\ B &= ad^2 - \beta' s + \alpha d\beta'\theta + kd \\ C &= \theta(\alpha d^2 - \beta' s) \end{aligned} \tag{15}$$

Hence, for an infective steady state to exist in this model ($I_2 > 0$), we require $B^2 - 4AC > 0$ which leads to the condition $\sigma > 1$, where $\sigma = \beta' s/(\alpha d)^2$. Much like R_0 in the case above, σ is the stability parameter for this model.

As before we are required to set up the Jacobian for the infective steady state, which leads to

$$J(T_2, I_2) = \begin{bmatrix} -d - \beta' I_2 & \beta' T_2 \\ \beta' I_2 & -k\theta \frac{I_2}{(I_2+\theta)^2} \end{bmatrix} \tag{16}$$

We are now in a position to use *Matlab* to computer the eigenvalues for any desired input parameters.

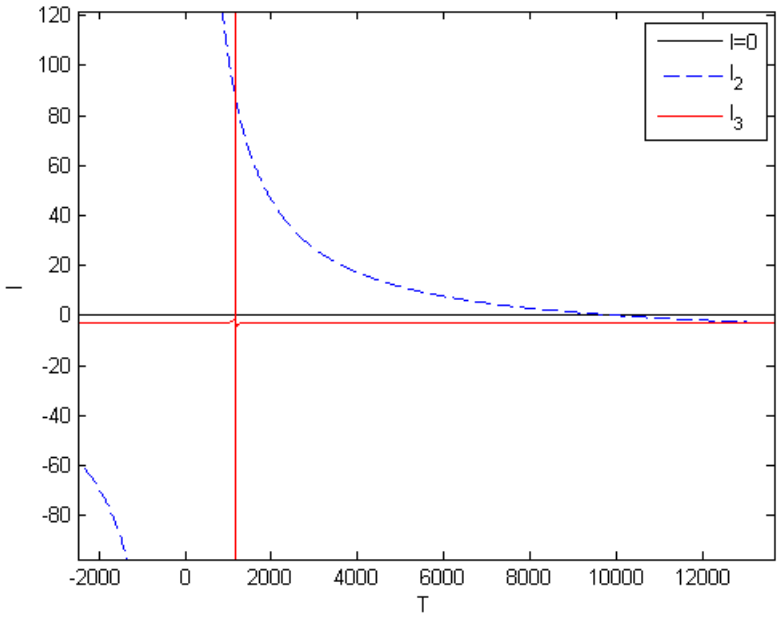

Figure 1: Nullclines for the EMS model. $I = 0$, $I_1 = (s - dT)/\beta' T$, $I_2 = \theta(\beta' T - k)/(k + \alpha d - \beta' T)$ The crossing points of the model indicate the stable points and hence two points of stability are found for the infective steady state (I $\neq$ 0) as described by Burg et al. The default parameter values ($\alpha = 1, s = 100, d = 0.01, \beta = 1.3 \times 10^{-6}, k = 1$, p = 2000, c = 3 and $\theta = 3$) are plotted.

3.3 Reproducibility

3.3.1 Nullclines

The nullclines, calculated from Equation 15, are plotted and shown in Figure 1. They reproduce the graph presented by the authors in Figure 3, yet a quantitive comparison can not be obtained since no scaling or parameter values are given. However, we can be fairly certain that our model is reproducing the behaviours claimed and therefore have confidence in the further work we have implemented.

3.3.2 Stability Parameters

Interestingly, our implementation reveals that the eigenvalues for the EMS model are always negative provided $\sigma > 1$, therefore it is locally stable everywhere as suggested in Appendix B. The authors of the original paper describe how the oscillations experienced in the TCS model are reduced in the EMS mode by increasing θ and this is confirmed in the stability paramater values and resulting plots we have generated.

4 Effect of Parameter Variation (Kathryn Atwell)

When investigating the properties of an ODE model, it is a good idea to try varying each parameter around its normal value, to see the effect this has on the model's output. For a good model, the influence each parameter has over the output should be proportional to its importance in the actual biological system. So, if we're confident that the model is good, varying parameters helps identify the most important aspects of the biological system. More usually, it is carried out to improve the model, by finding parameters with an unacceptably high or low influence. Low influence parameters are candidates to remove from the model to simplify it, while high influence parameters whose value we can't estimate well are a potential source of error (because the model is sensitive to small inaccuracies).

In our case, we chose to investigate the effect of parameter variation on two model outputs:
- *Final virus titre*
- *Final number of target cells*

These were chosen for their medical relevance. According to the paper by Burg *et al*., a high steady state virus titre corresponds to a more severe progression of HIV/AIDS. The number of target cells remaining is an indicator of the remaining strength of the immune system.

For each of the three models in the paper (target cell limited, extended, and simplified extended), parameters were varied one at a time by 10% either side of their normal value. Normal parameter values were taken to be the ones used in the paper's figures (see our parameter initialising script params.m for a full list). Plots were produced showing model outputs as a function of each parameter. For a more quantitative comparison, a sensitivity coefficient was also computed for each parameter, that is normalised to take account of its usual size. For a parameter with normal value p:

$$\text{Sensitivity coefficient} = \frac{\text{Output}(1.1p) - \text{Output}(0.9p)}{0.2p\text{Output}(p)}$$

Results

Example graph

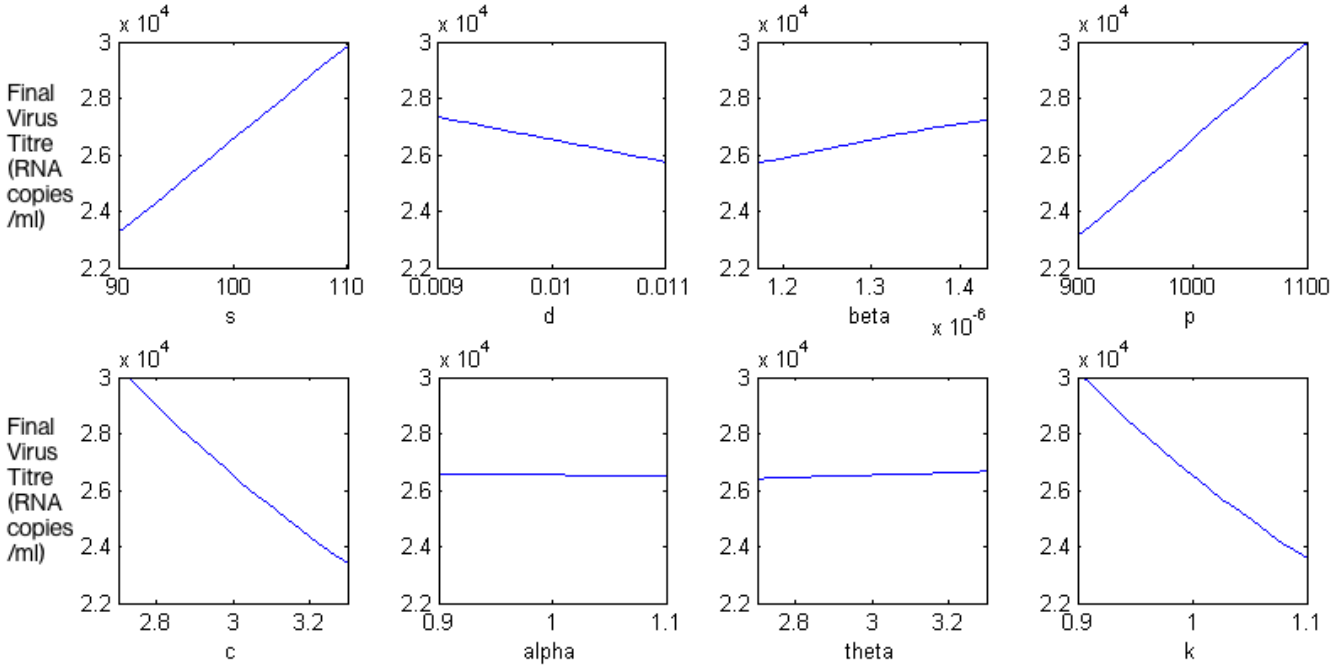

Figure 2: Plot of final virus titre as a function of each parameter in the Extended Simplified model of HIV infection.

Sensitivity coefficients

Final virus titre				Final target cell count			
	TCL	Extended	Simplified		TCL	Extended	Simplified
s	225	249	249	s	0.320	8.98	9.00
d	-0.00260	-0.00597	-0.00596	d	-0.000009	-0.000008	-0.000009
beta	0	0.000001	0.000001	beta	-0.000003	-0.000003	-0.000003
delta	-1.14			delta	0.999		
p	2250	2570	2570	p	-2020	-2000	-2000
c	-6.84	-7.82	-7.82	c	5.99	5.94	5.94
alpha		-0.0257	-0.0257	alpha		0.0196	0.0196
theta		0.280	0.276	theta		-0.0213	-0.212
k			-2.49	k			1.89
k0		-0.499		k0		0.378	
a_E		-12.5		a_E		9.45	
d_E		2.47		d_E		-1.91	

5 Developing the Model (Ronja Woloszczuk and Islom Nazarov)

Having reproduced the results for stability of viral load and concentrations of Target and Infected cells, our group decided it would be interesting and biologically relevant to extend the given models to include treatment for HIV. This involved adding new terms to the TCL, EM and EMS models which represent the loss of infected and target cells.

5.1 HIV Therapy

At present there is no cure for AIDS, but a range of drugs are available to slow its progress. The majority of anti-HIV drugs aim to inhibit viral replication. Nucleoside analogues such as zidovudine (AZT), and also non-nucleoside reverse transcriptase inhibitors (NNRTIs) inhibit the activity of the viral enzyme reverse transcriptase. In doing so, they prevent the formation of functional viral DNA, which would otherwise be integrated into the host DNA of infected cells.

Inhibition of viral protease, an enzyme essential for generating functional virus particles, is another very effective form of therapy. Clinically, protease inhibitors have been the most effective of the three types of drugs. However, AIDS drugs are often administered in combination cocktails of three or more kinds simultaneously, as this helps slow the rate at which HIV develops resistance to drugs. The resistance is developed partly due to inefficient viral reverse transcriptase action, which rapidly results in the generation of mutated HIV viruses. This will help virus to evolve rapidly and can eventually outpace the drugs.

Fusion inhibitors are a newer class of drug that works by preventing HIV from fusing with T-cell membranes by stopping HIV from binding with CD4 receptors that it uses to enter cells. Enfuvirtide binds to gp41 and prevents it from creating an entry pore for the capsid of the virus, thereby keeping it out of the cell.

A vaccine is an alternative approach that is still being developed, but is still many years away from completion. However, unlike the way most vaccines work, the HIV-1 vaccine may not only have to prime antibodies to attack the virus, but its second action may also need to increase T-cell production. Most recent results from vaccine trials undertaken in South Africa, Kenya, the US and Thailand have not yield promising results.

5.2 Model Development

At present there is no cure for AIDS, but a range of drugs are available to slow its progress. The majority of anti-HIV drugs aim to inhibit viral replication. Nucleoside analogues such as zidovudine (AZT), and also non-nucleoside reverse transcriptase inhibitors (NNRTIs) inhibit the activity of the viral enzyme reverse transcriptase. In doing so, they prevent the formation of functional viral DNA, which would otherwise be integrated into the host DNA of infected cells. This means that the virus is, in spite of being able to enter its target cell, unable to replicate inside it and produce new virus particles. Therefore, inhibition of the reverse transciptase (RT) effectively results in a reduced viral infection rate.

5.3 Reverse Transcriptase Treatment

In the simple model, reverse transciptase inhibition can be incorporated by reducing the target cell infection rate, as proposed by

$$\frac{dT}{dt} = s - dT - (1 - R_T T)\beta VT \tag{17}$$

$$\frac{dI}{dt} = (1 - R_T T)\beta VT - \delta I \tag{18}$$

$$\frac{dV}{dt} = pI - cV \tag{19}$$

whereby $R_T T$ represents the effectiveness of the reverse transciptase inhibition. The equations took the last available value for T(t), I(t) and V(t)before treatment as initial values for the ODE system. Treatment starts after the initial infection at a time $t_s t$, e.g. 75 days after the initial infection, generally when virus numbers have reached steady state levels. The initial infection proceeds as described above.

In an ideal case, all productive infection is eliminated during the treatment phase, i.e. the effectiveness of the treatment is 100

Similar outcomes are observed when the extended model (equations (20)-(13)) and the simplified extended model (equations(24) (26)) are modified to incorporate reverse transciptase treatment, although virus clearance from the boll occurs at a lower rate.

$$\frac{dT}{dt} = s - dT - (1 - R_{TT})\beta VT \tag{20}$$

$$\frac{dI}{dt} = (1 - R_{TT})\beta VT - (\alpha d + k_0 E)I \tag{21}$$

$$\frac{dV}{dt} = pI - cV \tag{22}$$

$$\frac{dE}{dt} = a_E \frac{I}{\theta + I} - d_E E \tag{23}$$

The Simplified Extended Model becomes

$$\frac{dT}{dt} = s - dT - (1 - R_{TT})\beta VT \tag{24}$$

$$\frac{dI}{dt} = (1 - R_{TT})\beta VT - (\alpha d + k\frac{I}{I + \theta})I \tag{25}$$

$$\frac{dV}{dt} = pI - cV \tag{26}$$

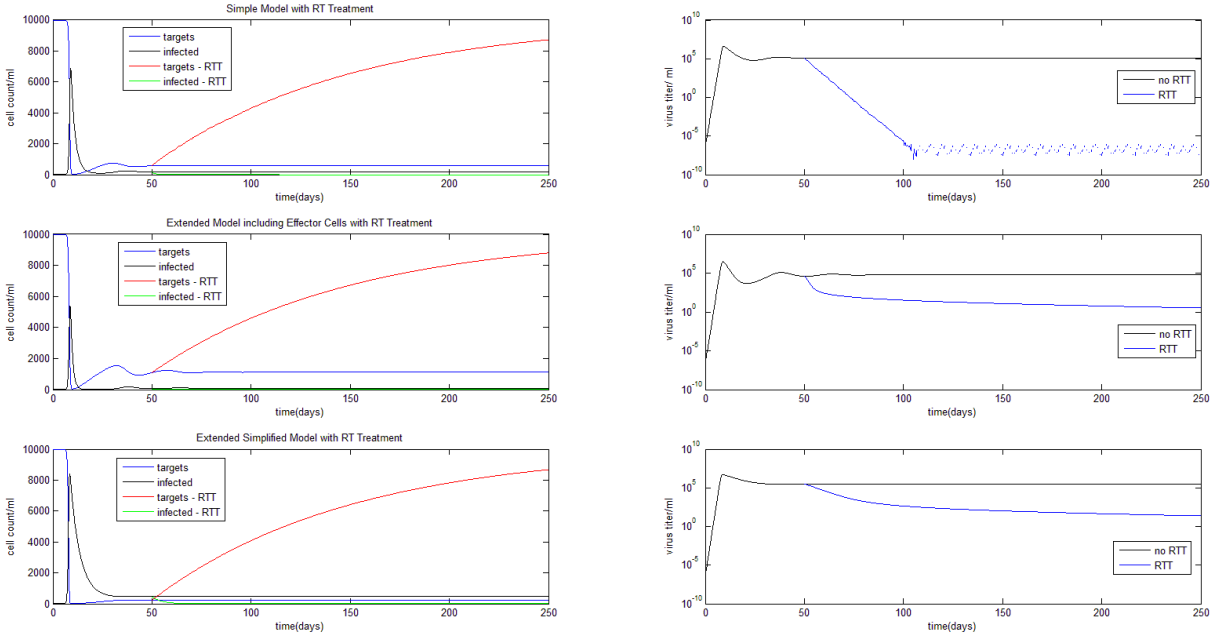

Figure 3: Effect of adding reverse transcriptase treatment on all models

In a more realistic setting (Figure 3), where reverse transciptase treatment is not fully able to stop target cell infection, not all infected cells are eliminated and, hence, target cell continue to be infected. Instead of recovering to pre-treatment levels, target cells continue to be turned into infected cells. Interestingly, only treatments with an effectiveness of more than 50% results in a reduction of infected cells and the steady state virus titre, suggesting that treatment in this system must be very effective indeed to disrupt steady state dynamics of the virus production. This feature is especially pronounced in the simplified extended model. Moreover, treatment is often only effective in the first phase of the treatment, in the sense that even if the number of infected cells and the virus titre drop initially, both recover at later stages of the treatment. Positive effects could still be achieved, as the ratio of target to infected cells is improved.

5.4 Protease Inhibitors

Inhibition of viral protease, an enzyme essential for generating functional virus particles, is another very effective form of therapy. Clinically, protease inhibitors have been the most effective type of drugs. Administration of protease inhibitors, results in the release of a mixture of infectious (V_I) and non-infectious virus particles into the blood (V_{NI}), whereby the rate generation of infectious and non-infectious particles depends on the number of infected calls and the effectiveness of the protease inhibitor (P_I). In the ideal case of a 100% effectiveness of the drug, only non-infectious particles would be produced.

V_I and V_{NI} can be incorporated into the models in the following way :

Simple Model:

$$\frac{dT}{dt} = s - dT - \beta VT \tag{27}$$

$$\frac{dI}{dt} = \beta VT - \delta I \tag{28}$$

$$\frac{dV_I}{dt} = (1 - p_I)pI - cV \tag{29}$$

$$\frac{dV_{NI}}{dt} = p_I pI - cV \tag{30}$$

Extended Model:

$$\frac{dT}{dt} = s - dT - \beta VT \tag{31}$$

$$\frac{dI}{dt} = \beta VT - (\alpha d + k_0 E)I \tag{32}$$

$$\frac{dV_I}{dt} = (1 - p_I)pI - cV \tag{33}$$

$$\frac{dV_{NI}}{dt} = p_I pI - cV \tag{34}$$

$$\frac{dE}{dt} = a_E \frac{I}{\theta + I} - d_E E \tag{35}$$

Simplified extended model:

$$\frac{dT}{dt} = s - dT - \beta VT \tag{36}$$

$$\frac{dI}{dt} = \beta VT - (\alpha d + k\frac{I}{I + \theta})I \tag{37}$$

$$\frac{dV_I}{dt} = (1 - p_I)pI - cV \tag{38}$$

$$\frac{dV_{NI}}{dt} = p_I pI - cV \tag{39}$$

All the ODE systems were solved with matlab ode45 solver, using the last values before treatment as the initial values T0, I0 and VI0. We assumed that there were no non-infectious particles present before the start of the treatment.

Treatment with protease inhibitors results, as for the reverse transciptase inhibitor treatment, in an increase in the number of target cells and a reduced number of infected cells. The number of infectious virus particles decreases in all models, while the number of non-infectious particles increases rapidly and, for effective treatment, even exceeds the number of infectious particles present (Figure 4). Overall, the simple model is, as for the reverse trascriptase, the most responsive to treatment and the least responsive is the simplified extended model. Interestingly, this model also shows altered dynamics for the target cell recovery, which is much less efficient than in the other two models.

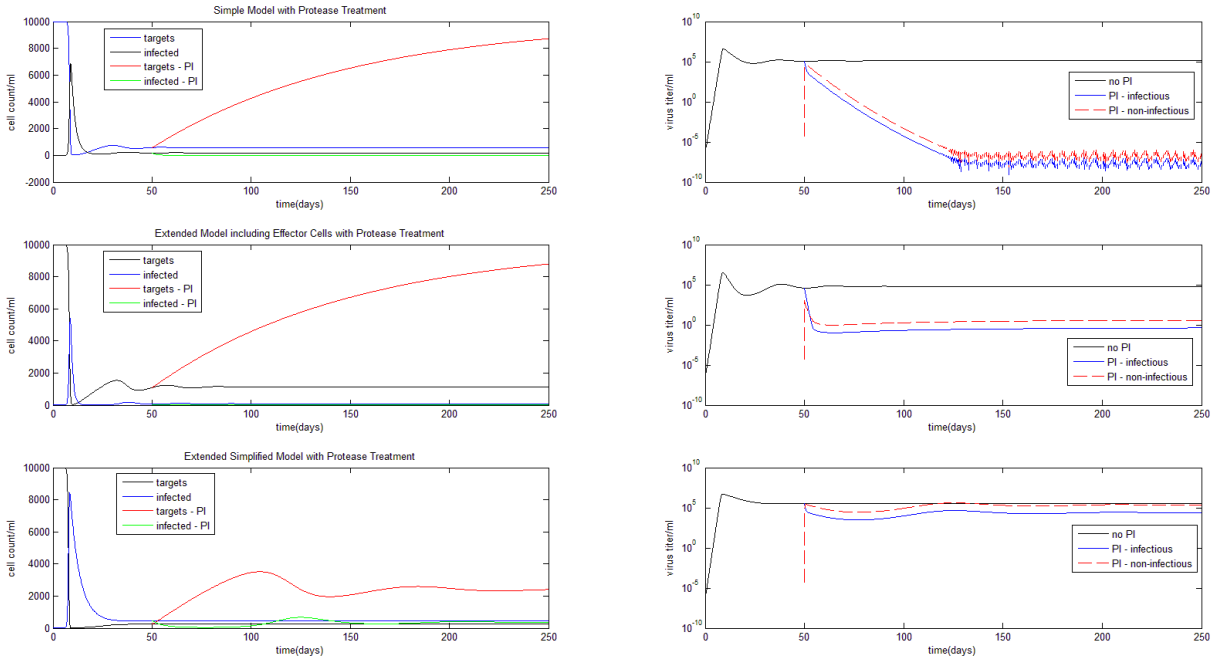

Figure 4: Effect of adding Protease Inhibitor treatment on all models

5.5 Combination Therapy

Frequently, HIV drugs do not prove effective on their own in the long term. Resistance is developed partly due to the inefficient action of viral reverse transcriptase, which causes the generation of mutated viruses. This helps the virus to evolve rapidly and can eventually outpace the drugs.

Therefore, HIV drugs are often administered in combination cocktails of several drugs to help slow the rate at which HIV develops resistance to drugs.

Although combination therapy generally involves more than two drugs, we chose to look at the dynamics of the three models when subjected to two drug treatments.

Simple Model:

$$\frac{dT}{dt} = s - dT - (1 - R_{TT})\beta VT \tag{40}$$

$$\frac{dI}{dt} = (1 - R_{TT})\beta VT - \delta I \tag{41}$$

$$\frac{dV_I}{dt} = (1 - p_I)pI - cV \tag{42}$$

$$\frac{dV_{NI}}{dt} = p_I pI - cV \tag{43}$$

Extended Model:

$$\frac{dT}{dt} = s - dT - (1 - R_{TT})\beta VT \tag{44}$$

$$\frac{dI}{dt} = (1 - R_{TT})\beta VT - (\alpha d + k_0 E)I \tag{45}$$

$$\frac{dV_I}{dt} = (1 - p_I)pI - cV \tag{46}$$

$$\frac{dV_{NI}}{dt} = p_I pI - cV \tag{47}$$

$$\frac{dE}{dt} = a_E \frac{I}{\theta + I} - d_E E \tag{48}$$

Simplified extended model:

$$\frac{dT}{dt} = s - dT - (1 - R_{TT})\beta VT \tag{49}$$

$$\frac{dI}{dt} = (1 - R_{TT})\beta VT - (\alpha d + k\frac{I}{I + \theta})I \tag{50}$$

$$\frac{dV_I}{dt} = (1 - p_I)pI - cV \tag{51}$$

$$\frac{dV_{NI}}{dt} = p_I pI - cV \tag{52}$$

In this case, the treatment seems to be very successful with infected cell numbers and virus titres rapidly declining to zero and target cell counts rapidly recovering. The virus titre is removed more efficiently than in either single therapy. (Figure 5)

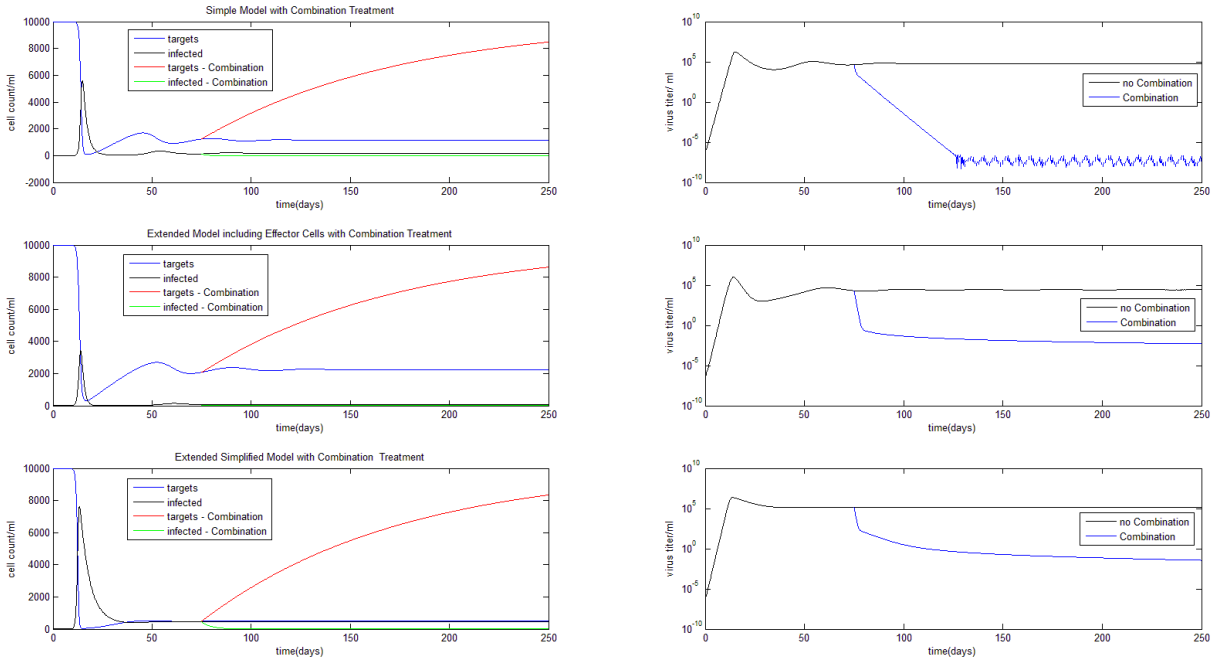

Figure 5: Effect of adding combined treatment on all models

5.6 Immunosurpression caused by anti-HIV Drugs

While AZT and other drugs used in combination therapy with protease inhibitors do not cause low CD4 counts in the short term, it is probable that administration for long periods will lower CD4 counts significantly. However, the original study of AZT's toxicity to CD4 lymphocytes claimed that only very high concentrations, much higher than concentrations used in clinical practice, were capable of affecting CD4+ lymphocytes. Five later studies, which failed to be mentioned in the Physicians Desk Reference, found that AZT was toxic to CD4 lymphocytes at about the same dosage that is given to people diagnosed HIV-positive [2]. Thus, AZT can attack a person's own immune system, thereby defeating the therapeutic purpose of the drug.

In the 1999 Physician's Desk Reference that describes AZT, Glaxo Wellcome put the following warning at the start of the section:

"RETROVIR (ZIDOVUDINE) MAY BE ASSOCIATED WITH SEVERE HEMATOLOGIC TOXICITY INCLUDING GRANULOCYTOPENIA AND SEVERE ANEMIA PARTICULARLY IN PATIENTS WITH ADVANCED HIV DISEASE (SEE WARNINGS). PROLONGED USE OF RETROVIR HAS ALSO BEEN ASSOCIATED WITH SYMPTOMATIC MYOPATHY SIMILAR TO THAT PRODUCED BY HUMAN IMMUNODEFICIENCY VIRUS." (PDR 1999).

An example of a study that documented the toxic effects of AZT on immune system of healthy subjects was published in the Annals of Hematology in 1994[3]. Out of the 14 people enrolled, only 11 could continue to take the drug for more than four weeks. The three people who could not make it to four weeks dropped out due to "severe subjective symptoms". Neutropenia developed in 36% (4 of 11) of the people who completed 4 weeks of AZT treatment. Remarkably, these side effects developed within only 4 weeks, while patients diagnosed HIV-positive often stay on AZT and other similar drugs for years. It appears, therefore, that these drugs are causing a variety of AIDS-like symptoms, which are being blamed on HIV itself.

5.7 The inclusion of immunosurpressant effects on our model

We, chose to incorporate a parameter, which could mimic the increased CD4 death rate, into our models. This parameter (d_r) introduces treatment-induced factor that leads to the death of both healthy and infected HIV cells, as can be seen in equations (53) and (54) for the simple model.

Simple Model:

$$\frac{dT}{dt} = s - (d + d_r)T - (1 - R_{TT})\beta VT \tag{53}$$

$$\frac{dI}{dt} = (1 - R_{TT})\beta VT - (\delta + d_r)I \tag{54}$$

$$\frac{dV_I}{dt} = (1 - p_I)pI - cV \tag{55}$$

$$\frac{dV_{NI}}{dt} = p_I pI - cV \tag{56}$$

Extended Model:

$$\frac{dT}{dt} = s - (d + d_r)T - (1 - R_{TT})\beta VT \tag{57}$$

$$\frac{dI}{dt} = (1 - R_{TT})\beta VT - (\alpha d + d_r + k_0 E)I \tag{58}$$

$$\frac{dV_I}{dt} = (1 - p_I)pI - cV \tag{59}$$

$$\frac{dV_{NI}}{dt} = p_I pI - cV \tag{60}$$

$$\frac{dE}{dt} = a_E \frac{I}{\theta + I} - d_E E \tag{61}$$

Simplified extended model:

$$\frac{dT}{dt} = s - (d + d_r)T - (1 - R_{TT})\beta VT \tag{62}$$

$$\frac{dI}{dt} = (1 - R_T T)\beta VT - (\alpha d + d_r + k\frac{I}{I + \theta})I \tag{63}$$

$$\frac{dV_I}{dt} = (1 - p_I)pI - cV \tag{64}$$

$$\frac{dV_{NI}}{dt} = p_I pI - cV \tag{65}$$

Both the extended model and the simplified extended model were modified to incorporate d_r.

The introduction of this parameter makes clear that even at a relatively low death rate induced through the treatment can prevent recovery of the target cells (Figure 6). Hence, while the number of infected cells decline rapidly as HIV is combatted in the body, the patient will still suffer from immune-deficiency symptoms.

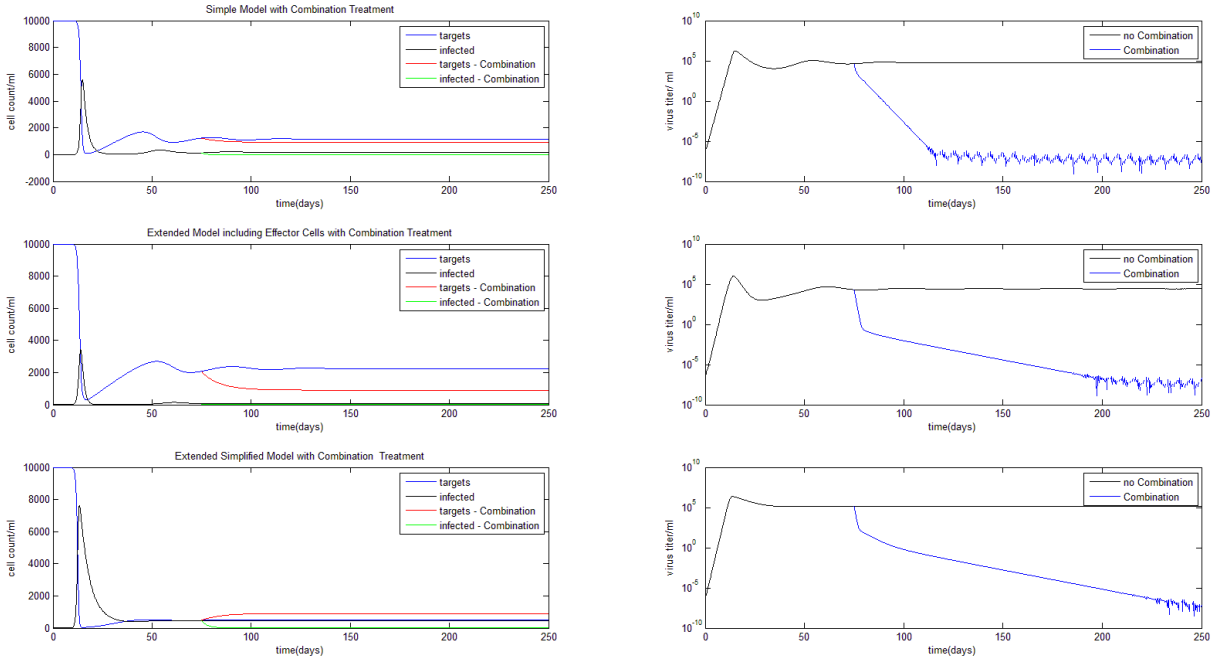

Figure 6: The effect of inclusion of the death of CD4 cells

6 The GUI (Lucy Hutchinson)

It is interesting to explore how the variation of certain values can affect the results for viral load, target cells and infected cells. We have created a user-friendly interface with sliders to vary several parameters, for each of the three models. The interface also allows the user to quickly see the stability of the chosen model for the input parameters used. Default values which appear when a model is selected in the GUI are those which are listed in the paper itself and there is a push button to reset the default values for all parameters. The GUI also incorporates a push button which switches to solving the extended model (including treatment). The user can choose to change the start date for treatment and the efficiency of the treatment.

The GUI can be used to demonstrate the reproducability of the data in Burg. et al, and also to further explore the effects of parameters and the effects of including treatment in the models.

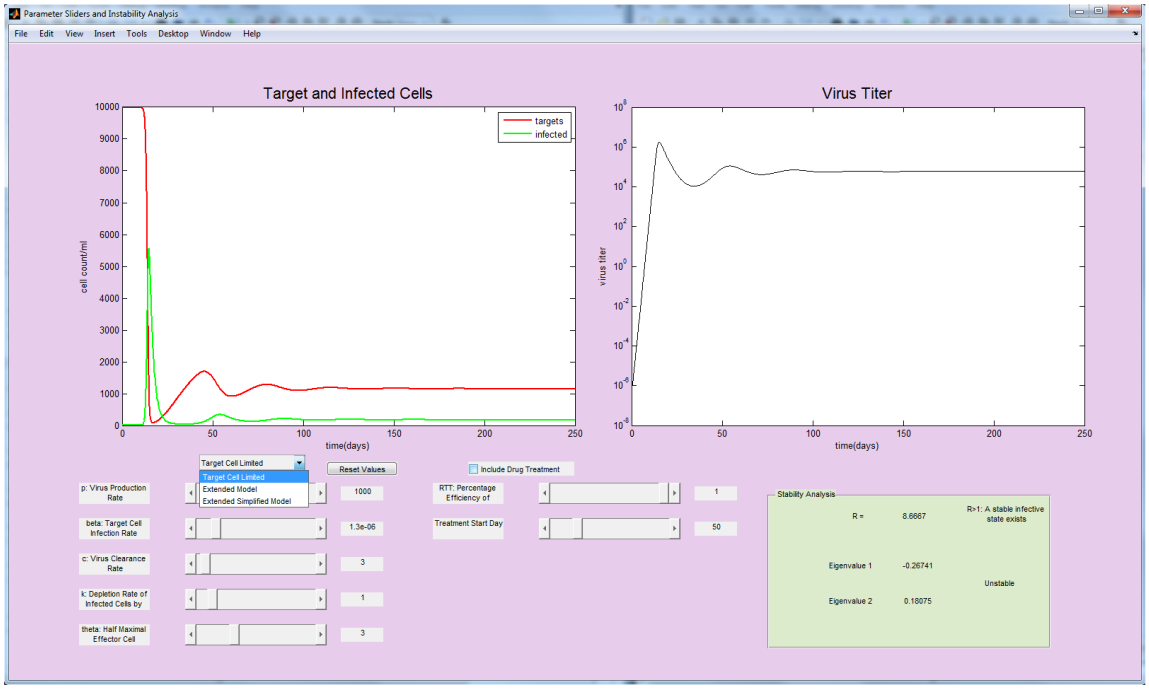

Figure 7: Screenshot showing the GUI built to vary parameters and visualise results

7 Future Work (Islom Nazarov)

Fusion inhibitors are a newer class of drug that works by preventing HIV from fusing with T-cell membranes by stopping HIV from binding with CD4 receptors that it uses to enter cells. Enfuvirtide binds to gp41 and prevents it from creating an entry pore for the capsid of the virus, thereby keeping it out of the cell.

In addition, two further new classes of drugs are being developed are: BMS- 663068, by Bristol-Myers Squibb, binds to a protein gp120 on the surface of HIV. Ibalizumab, from TaiMed Biologics, binds to a protein on the surface of CD4 cells. Both drugs prevent HIV from attaching to and CD4 cells and prevent it from creating an entry pore for its capsid.

A vaccine is an alternative approach that is still being developed, but is still many years away from completion. However, unlike the way most vaccines work, the HIV-1 vaccine may not only have to prime antibodies to attack the virus, but its second action may also need to increase T-cell production. Most recent results from vaccine trials undertaken in South Africa, Kenya, the US and Thailand have not yield promising results.

With the current treatment regimes HIV-1 plasma viral load rebounds from viral reservoirs such as resting CD4 T lymphocytes, monocytes and macrophages, remaining a major obstacle in attempting HIV eradication. Thus, more recently the researchers investigating application of immunotherapy in people with HIV. For example the potential use of a protein IL-7 (protein that helps immune cells develop and survive) to increase immune function are being investigated. Thus if time permitted it would have been appealing to include and model the effect of IL-7s immunotherapy and work out the how effective would IL-7 be in maintaining the healthy target cells (CD4) count.

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