# Simulating and optimising different HIV drug treatment schemes, with taking the effects of drug resistance development into account

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**Abstract**

We extend existing models of HIV infection and their drug treatment, to incorporate drug resistance developed by the virus. The developed Matlab simulations suggest an optimal treatment plan.

## Contents



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# 1 Introduction

HIV is one of best known sexual transmitted disease. Its effects on the human immune system make patients more susceptible to infectious diseases.

Drug treatments aim to lower the viral load and thus prolong the time till outbreak of the condition known as Aquired Immune Deficiency Syndrome (AIDS).

There are, however, many problems with HIV drug treatments: The virus is very efficient in developing resistance, due to a high mutation rate. In addition all drugs have serious side effects on the immune system itself, so that a minimisation of their administration is desirable. [1]

We extended the combination treatment model provided by [1] and took into account that resistance to the drug increases during treatment, thus decreasing its efficiency over time. We also included the fact that resistance drops over time after administration is terminated; this is because a mutant acquires an increased fitness in the drug environment at the cost of a decreased efficiency in the normal environment. [2] Over time, the perfectly adapted wild-type will benefit from its increased fitness by outcompeting the mutant phenotype that had to compromise its fitness to survive in the drug environment. The model implemented here tries to take advantage of this phenomenon by designing a treatment regime composed of two drugs used in a combinatorial or alternating fashion.

For this purpose, we include functions that enable independent administration of the two drugs at certain time points, to be determined by an optimisation routine. This also enabled us to test the specific treatment regimes that we might be interested in.

In the simulated therapies performed by Atwel et al., taking both drugs at the same time was beneficial to the treatment reducing virus titre by several orders of magnitude. As mentioned above, however, resistance was not taken into account. This might select for resistance against both drugs at the same time, thus altering the long term behaviour of the system. By establishing a treatment plan, which is designed to circumvent the detrimental effects of resistance through using the same drugs in an alternating fashion we can maximise the benefits of the limited range of drugs available. While this model only takes two drugs into account, this could easily be extended to include a greater variety.

# 2 Critique

The report from Atwel et al. we build our work on was clearly structured, explained all the Biology which their models were founded on and included all the information needed to reproduce the results. It was interesting to see how the mathematical model was extended to produce biologically relevant results. Good use of figures and a GUI eased us into the important aspects of the problem. The authors produced a large library of code including Matlab routines and C functions. The code was easy to read mainly due to the sensible choice of names for variables and functions. All files were relatively short, and thus easy to understand. There were several problems with the code though: some files had not been properly merged, and github had introduced some extra lines. More significantly there was a mismatch between the differential equations which had been used in the code and those described in the report. Using our own biological reasoning, we decided to stick with the equations in the report. Before the model is further developed from this stage however, it is necessary to validate our choice. All pieces of code were licenced suitably for open access and licences were clearly visible.

# 3 The Inherited Model

We concentrated our attention on the model for combination thearapy given below:

$$\begin{aligned}
\frac{dT}{dt} &= s - dT - (1 - R_{TT})\beta VT \\
\frac{dI}{dt} &= (1 - R_{TT})\beta VT - \left(\alpha d + k\frac{I}{I+\theta}\right) I \\
\frac{dV}{dt} &= (1 - p_I)pI - cV
\end{aligned}$$

## 3.1 Aim

Using a mathematical model to simulate HIV infection kinetics under the control of antiviral drugs with subsequent drug resistance arising and using this information to develop a hypothetical treatment regime.

## 3.2 Hypothesis

Alternating treatment between two different drugs or set of drugs minimises drug resistance and maximises drug efficiency, as the resistant mutants are outcompeted by the wild-type virus when the drug is withdrawn, extending the time a given drug is effective.

## 3.3 Model development

As a first step we included drug resistance into the model.

$$\begin{aligned}
\frac{dT}{dt} &= s - dT - (1 - R_{TT} + r_{TT})\beta VT && (1)\\
\frac{dI}{dt} &= (1 - R_{TT} + r_{TT})\beta VT - \left(\alpha d + k\frac{I}{I+\theta}\right) I && (2)\\
\frac{dV}{dt} &= (1 - p_I + r_I)pI - cV && (3)\\
\frac{dr_{TT}}{dt} &= -k_{TT}\, r_{TT}\, \ln\left(\frac{r_{TT}}{R_{TT}}\right) && (4)\\
\frac{dr_I}{dt} &= -k_I\, r_I\, \ln\left(\frac{r_I}{p_I}\right) && (5)\\
& && (6)
\end{aligned}$$

Drug resistance $r$ has a sigmoidal shape and takes values between 0 and the maximal drug efficiency $(R_{TT}, p_I)$. It modifies the drug efficiency and although $r$ itself develops when the drug is not administered, it was set to 0 in equations 1 to 3 in those instances, as drug efficiency is also 0. $k$ is a drug specific parameter. Its value has been fitted to represent the timescales observed by [3].

In addition we also wanted to take drug concentration into account:

$$\begin{aligned}
\frac{dT}{dt} &= s - dT - (1 - (R_{TT} + r_{TT})c_{RTT})\beta VT\\
\frac{dI}{dt} &= (1 - (R_{TT} + r_{TT})c_{RTT})\beta VT - \left(\alpha d + k\frac{I}{I+\theta}\right) I\\
\frac{dV}{dt} &= (1 - (p_I + r_I)c_{pI})pI - cV\\
\frac{dr_{TT}}{dt} &= -c_{RTT}\, k_{TT}\, r_{TT}\, \ln\left(\frac{r_{TT}}{R_{TT}}\right)\\
\frac{dr_I}{dt} &= -c_{pI}\, k_I\, r_I\, \ln\left(\frac{r_I}{p_I}\right)
\end{aligned}$$

## 3.4 Finding the best treatment

We used the last of the above models to find the best treatment. In addition to the model described by Atwel et al. it has the following important features:

- drugs can be administrated with different concentrations : it is not an "On/Off" process (continuous variables);

- the virus population reacts to drugs and slowly builds up resistance to it;
- when the concentration of a drug drops below a given threshold, resistance decreases.

This implies that simply giving a drug at a high concentration is not the optimal treatment for a patient since the virus will eventually mutate and the drug will become completely ineffective. Considering that we have two drugs at our disposal, the question we would like to answer is the following:

*What is the best treatment regime?*

What we call a *treatment* is a sequence of instructions that could be given to a patient. For example,

1. Take drug A for 80 days;
2. then take drug A and B for 160 days;
3. then do not take any drugs for 80 days;
4. ...

would be a treatment.

The *best* treatment over a given period of time $\tau$ (expressed in days) is the one that maximises the quantity

$$F(\tau, treatment) = \int_0^\tau T(t).dt,$$

where $T(t)$ is the number of target cells available at time $t$. So that $F$ represents the total number of cells available to the body during the course of the treatment.

We assume throughout that the treatment can not be started immediatly after infection, as we have to account for time till the infection is diagnosed.

Thanks to the model we have at our disposal, we can simulate the effects of many different treatments and compare them using the objective function given above. Thus formalised, the problem becomes an optimisation problem and the rest of this section will focus on our approach to the maximisation of $F$. In the search of a family of "good" treatments we make the reasonable assumption that interesting treatments will be periodic and we look for treatments of the form:

$$f(t) = \sum_{i=0}^{N} a_i^{(1)} cos(it) + b_i^{(1)} sin(it),$$

$$g(t) = \sum_{i=0}^{N} a_i^{(2)} cos(it) + b_i^{(2)} sin(it),$$

where $f(t)$ (resp. $g(t)$) is the concentration of drug A (resp. B) at time $t$. $N$ is chosen to be fairly small, typically between 10 and 20. The $a_i^{(k)}$ and $b_i^{(k)}$ coefficients become the parameters that we will try to vary in order to find the optimal treatment.

A form of stochastic gradient descent is then performed in order to guess the (sub)optimal values of the parameters. Here is an outline of the algorithm :

1. Set the duration $\tau$ of the treatment.
2. Initialise the parameters at random.
3. Solve the system of differential equations in order to get $T$.
4. Compute the value $v$ of $F(\tau, treatment)$.
5. Pick a parameter $p$ at random and set it to $p + \varepsilon$, where $\varepsilon > 0$.
6. Solve the system and get $T$.
7. Compute the new value $v_\varepsilon$ of the objective function

8. Compute $\nabla = (v_\varepsilon - v)/\varepsilon$.
9. Update the parameter using $p_{new} = p_{old} - \nabla.\eta$, where $\eta$ is the learning rate, typically 0.01.
10. Go to step 3.

This is a very naive approach and it can be improved in many ways (*e.g.* adaptive learning rate, good choice of initial values, etc...). However, in most cases, it converges fairly fast and gives good results in comparison to less evolved algorithms at it takes advantage of our ability to use the model in order to "predict" the outcome.

The authors acknowledge the fact that the algorithm described above relies on somewhat weak mathematical and biological foundations and that not much justifications were given as to why such an approach was chosen. Indeed, while not proven, the assumption that good treatments should be periodic seems very sensible from a biological point of view. Using a stochastic gradient descent to guess the Fourier coefficients is a simple, but sound, approach that was chosen because of the limited amount of time at our disposal.

# 4 Treatments

All treatments last for 800 days. No treatment is administered for the first 80 days; this takes into account a lag time for the patient to discover the infection. Drugs are then administered/ or not administered for 80 days at a time as described in the following table.

Table 1: Treatment plans used (1 = on, 0 = off) starting at the indicated time period (in days).

| | **Time** | **0** | **80** | **160** | **240** | **320** | **400** | **480** | **560** | **640** | **720** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No** | **drug1** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Treatment** | **drug2** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Continuous** | **drug1** | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Treatment** | **drug2** | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Alternating** | **drug1** | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 |
| **Treatment** | **drug2** | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 |
| **Optimal** | **drug1** | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 0 |
| **Treatment** | **drug2** | 0 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 0 |

# 5 Results

Viral kinetics without drug treatment resembles qualitatively the kinetics observed in the inherited model (Fig. 1). However, some differences between the results reported here and the previous groups were observed. this is can be explained by discrepancies between equations in the report and the code and by the fact that extensions were to account for drug concentrations and drug resistance. Nevertheless the results were sufficiently similar for the no treatment condition to confidently continue with implementing different treatment regimes. During continuous combination therapy target cells recover to a satisfactory level, however, after resistance for both drugs has reached its maximum efficiency (0.8 after 250 days) the concentration of CD4 cells drops and stabilises at around 6000 cells/ml (Fig. 2). Alternating treatment improves the cell count quickly and after 300 days results in the full recovery of healthy CD4 cells. Resistance increases and decreases as administration of drugs is alternated but remains low for both drugs over the whole treatment period (Fig. 3). Infected cells and virus titre oscillate but are also controlled sufficiently. The optimised treatment recovers CD4 cells as quickly as continuous treatment and prolongs the efficiency in the same way as the alternating treatment (Fig. 4). Comparing all treatments by overlaying the healthy CD4 cell count shows the increased recovery and the prolonged drug efficiency of the optimised treatment plan (Fig. 5).

# 6 Limitations of model

Accuracy of parameters controlling rise and fall of resistance:

- The threshold of 5% drug concentration, which decides whether resistance develops;
- The time it takes for resistance to develop;
- The time it takes for resistance to diminish;
- The maximum efficiency of drug resistance;
- Values accurately describing the decreased fitness a given mutation causes compared to the wild-type.

The model is very general and in an ideal scenario should be personalised by e.g., using biomarkers to inform the model and adjust the crucial parameters. Only takes into account two drugs. Should be extended to include more drugs and sets of drugs.

# 7 Conclusion

We successfully implemented a mathematical model that takes into account drug resistance and calculates the best possible treatment regime for two different drugs or set of drugs over a given time. The criterion for best treatment is the total count of CD4 cells after the treatment is terminated, and although the algorithm comprises a degree of stochasticity, it has proven to be able to provide treatment plans that perform better than intuitively effective treatment plans.

# References


[1] K Atwell, A Berrington, R Woloszczuk, L Hutchinson, I Nazarov, "Development of a Mathematical Model of Viral Kinetics under Immune Control during Primary HIV-1 Infection," *DTC-office*, 2013.

[2] Hance, A.J., Lemiale, V. et al., "Changes in human immunodeficiency virus type 1 populations after treatment interruption in patients failing antiretroviral therapy," *Journal of Virology*, vol. 75, pp. 6410–6417, 2001.

[3] Douglas D. Richman, "HIV drug resistance," *Annu. Rev. Pharmacol. Toxicol.*, vol. 32, pp. 149–64, 1993.

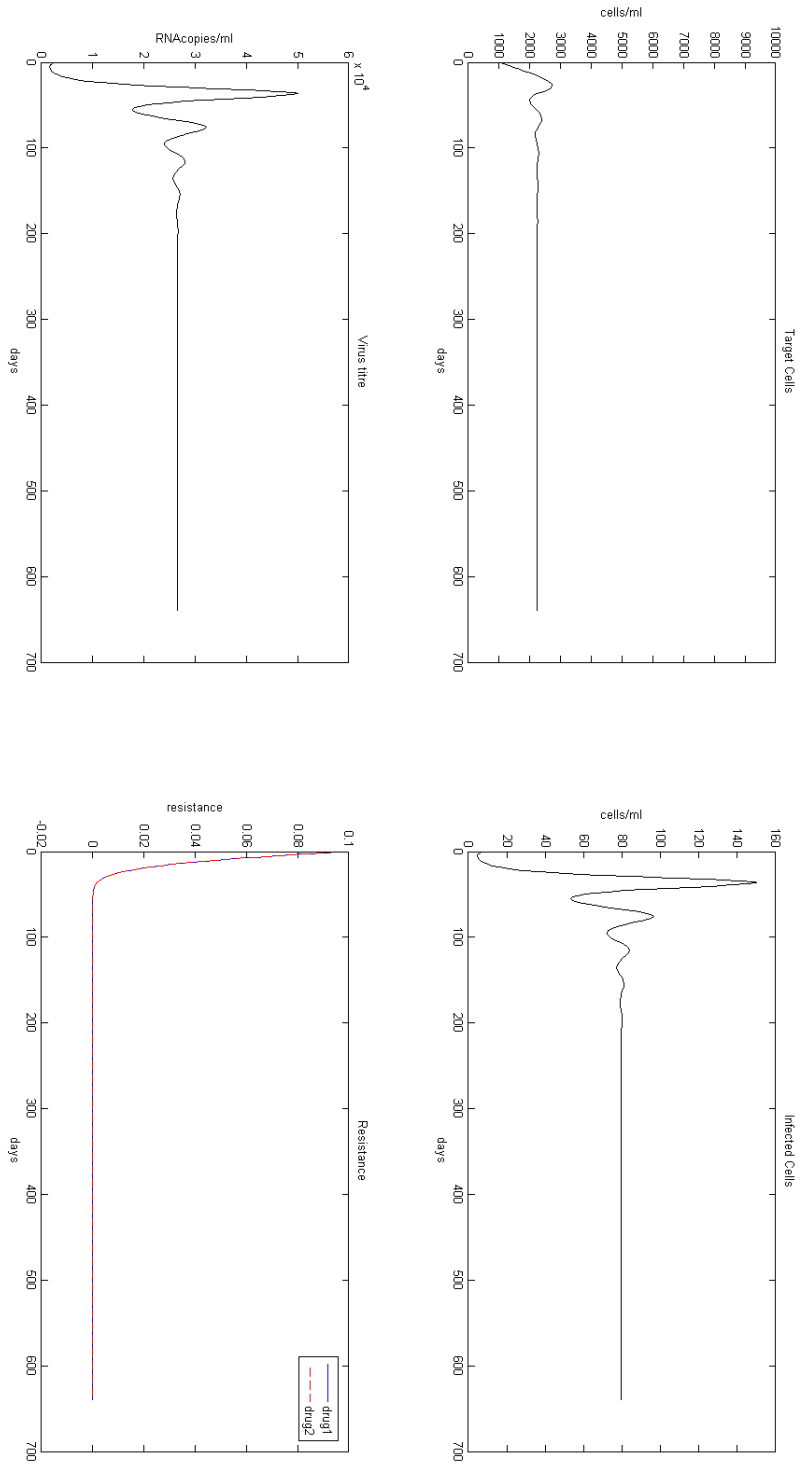


Figure 1: No treatment. Viral kinetics without drug treatment resembles qualitatively the kinetics observed in the inherited model. Quantitatively, however, there are some differences between our results and the previous group's; this is due, in part, to the discrepancies found in some equations, which are not exactly the same in the code and in the report, and also due to extensions that we implemented e.g., increase and decrease of drug resistance. Regardless of this, we observe the expected behavior for the variables modeled; in particular, an elevated virus titre and a correlated increase in infected cell concentration can be observed. The resistance remains low as no drug is administered that can select for mutations.

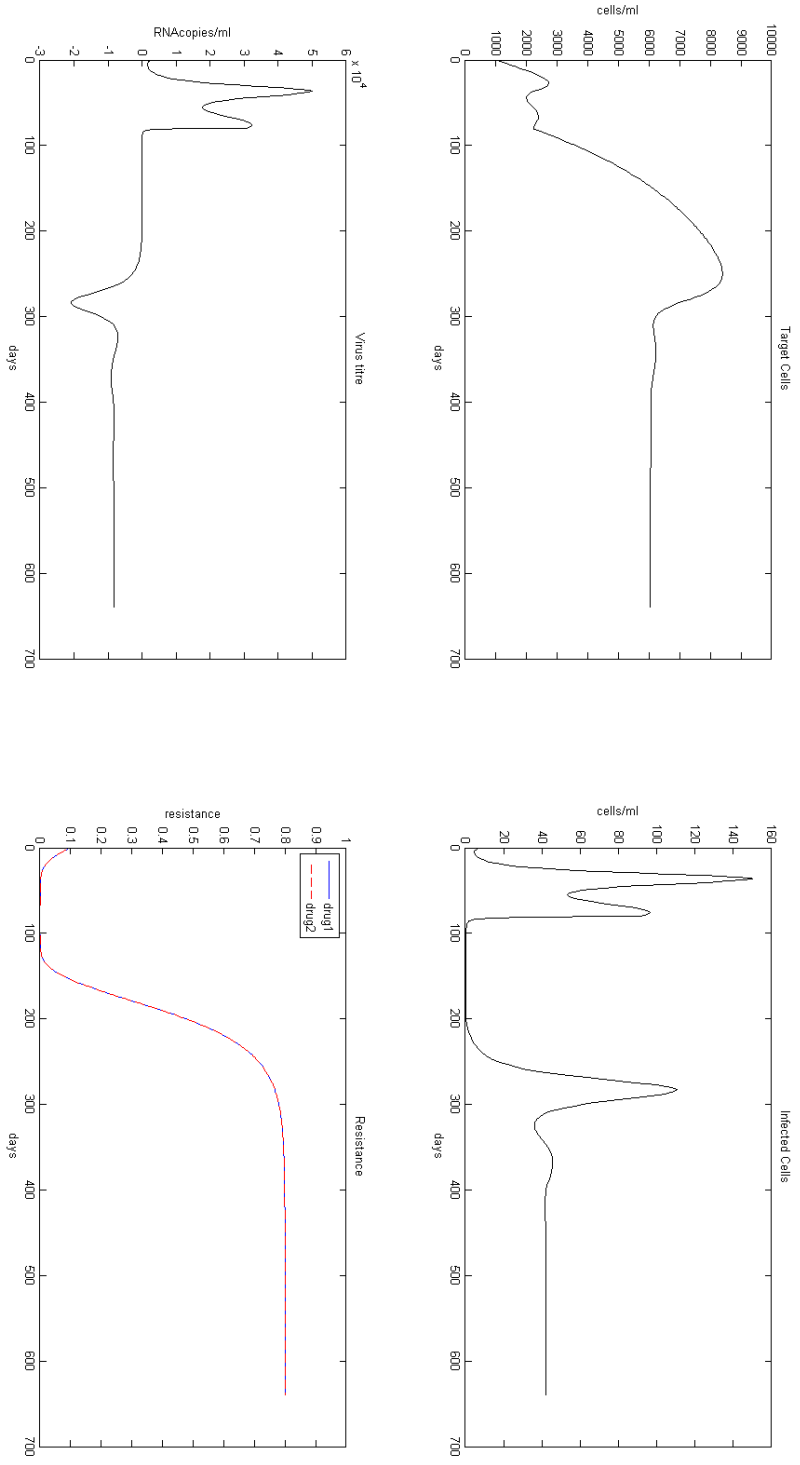


Figure 2: Continuous combination therapy. After both drugs are initially administered the target cells recover to a satisfactory level, however, after resistance has reached its maximum efficiency (0.8) the concentration of CD4 cells drops and stabilises at around 6000 cells/ml. This development correlates with a preceding rise in infected cells and a subsequent drop in virus titre (negative virus titre is a flaw in the model and cannot be explained at the current moment).

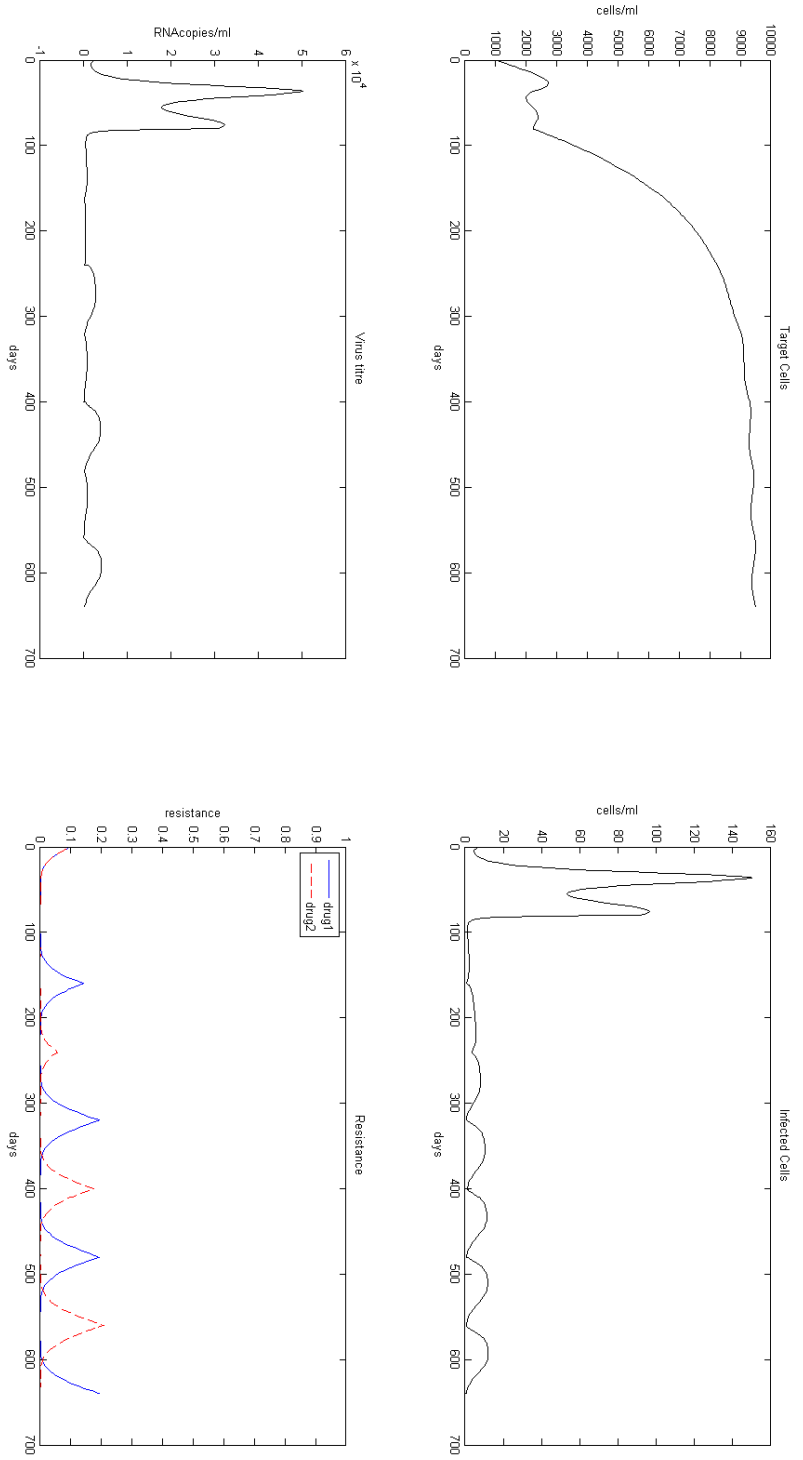


Figure 3: Alternating treatment. Target cells recover quickly and reach a plateau after 300 days. Infected cells and viral titre remain low for the time after the first drug is administered (first 80 days). Resistance increases and decreases as administration of drugs is alternated but remains low for both drugs over the whole treatment period. Infected cells and virus titre oscillate but are also controlled sufficiently.

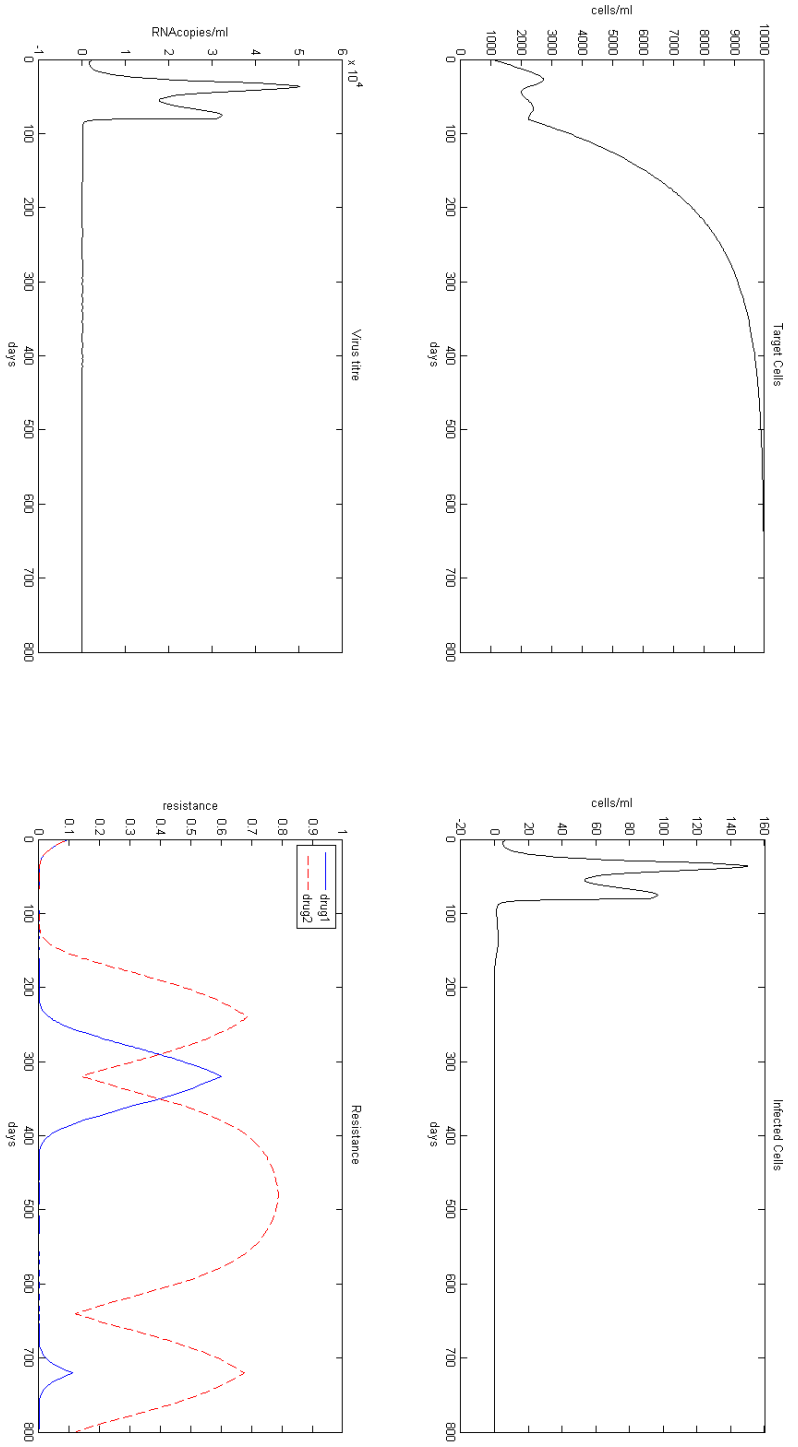


Figure 4: Optimised treatment. The optimised treatment presented here is the result of the Fourier Optimisation algorithm. The total number of target cells is maximised over the period of treatment (800 days in this case). The optimal treatment plan contains sections of no drugs, both drugs and one drug only. Interestingly there is a period of 160 days without any treatment where target cells continue to recover. This is likely to be an artefact of the model and may not reflect a realistic outcome.

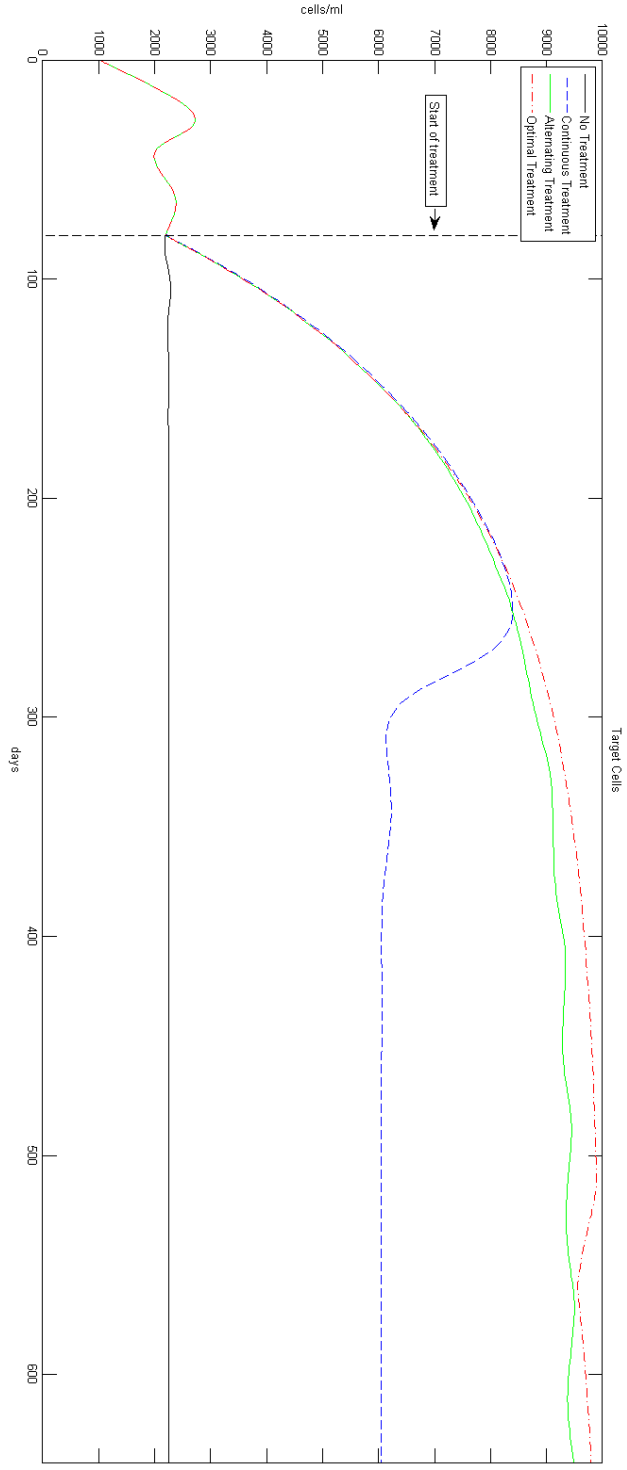


Figure 5: Overlay of target cell graph. A figure showing the CD4 cell count (target cells) for the three treatments and the untreated patient. Initially all three treatments increase the target cell count, however the continuous treatment results in early drug resistance and a subsequent loss of CD4 cells. Alternating treatment prolongs drug efficiency at the cost of slower target cell recovery. The optimal treatment, however, recovers CD4 cells as quickly as continuous treatment and prolongs the efficiency in the same way as the alternating treatment.