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Inverse Theory

Optimized HIV drug treatment using probabilistic inversion

1 Introduction

From its first occurrence in the early beginning of the 1980s until this very day, *Human Immunodeficiency Viruses*, widely known as HIV, have taken 39 million lives. The brutalitiy of the pandemic has motivated scientists all over the world to intensively study the pathogenesis and life cycle of the virus.

Nowadays, it is well-known that HIV directly affacts the patient's adaptive immunity. Under healthy circumstances, this component of the human immune system fights pathogens by a conglomerate of communicating cells with so-called CD4+ or T helper cells as key players. Taking the role of coordinators, they trigger the crucial steps in the immune response which are necesseary to eliminate free virus and already infected cells [2]. In this highly sensitive procedure, HIV attacks the body. Among other target cells, the virus infects CD4+ T lymphocytes and hence paralyses the control center of the adaptive immune system. Consequently, the antibody secretion, originally stimulated by the T helper cells as well as the immunity, that is mediated by cells, break down [4].

The course of an untreated HIV infection differs from patient to patient and so do the observable symptoms, if they appear at all. More reliable metrics to track the extent and stage of the viremia, are the viral load and CD4+ cell count in the patient's blood. After the number of viruses initially exhibits a dramatic increase, causing flu-like symptoms, it stabilizes at some lower level. This, mostly several years lasting stage of clinical latency, is mainly free of symptoms. In spite of this deceptive silence, the virus remains in the body and continously lowers the CD4+ T-cell count. At a certain point, the viral load rises rapidly, reducing the T-cell count to a level at which it cannot provide sufficent protection any more. In this stage, defined as *acquired immunodeficiency syndrome* or shorter AIDS, patients suffer more frequentely and more seriously from opportunistic infections and even cancer. Finally, one of these secondary infections ends fatally [6].

Until the mid-90's, an HIV infected person was most likely doomed to die. Relief from this devastating disease first came with the invention of so-called antiretroviral medication. These drugs interfere with the continously better understood multistep replicative life cycle of HIV in human CD4+ T cells, aiming on halting or at least slowing it down. Patients under *Highly Active Antiretrovial Therapies* (HAARTs) achieve long-lasting viral suppression by combining multiple of such antiretroviral agents. Although these treatment strategies are very efficient in reducing morbidity and mortality of an HIV infection, a full viral eradication remains elusive [7, 13]. A final cure is inhibited by two factors. Firstly, although the stabilized virus counts even fall below the threshold of detecability of most assays, it has been discovered that low levels of free virus remain in the plasma. In addition to this residual viremia, infected memory CD4+ T cells and macrophages as well as dendritic cells that bounded free virus, constitute latent virus reservoirs. These, most of the time silent cells, resume to viral reproduction as soon as the host cell is reactivated. A trigger herefore, could for instance be an interrupted HAART [11, 12].

This observation demonstrates an essential drawback of antiretroviral therapies. Deviations from the strict and complex dosing schedule can not only lead to drug resistance mutations but can also cause a viral rebound. Thus, a full compliance of the patient - meaning the intake of a daily cocktail of pills for the rest of her or his life - is inevitable. In addition hereto, antiretroviral medication also comes along with unpleasant side effects, ranging from low-grade intolerances to life-threatening reactions. All in all, such drug toxicities in combination with a lifelong commitment, adherence issues, the high possibility of drug resistance, high costs and life style issues, make it even harder for the patient to fully commit to the treatment and increase the pressure on science to further improve the HIV therapies [5, 7].

Remedy can not only be provided by developing novel pharmaceuticals, but also by correctly using the currently available medicine. Due to the diversity of genetic and molecular conditions in different HIV infected patients, an ultimately best therapy does not exist. Wrong combinations of antiretroviral drugs or inappropriate dosing schedules can amplify the side effects and downsides of the current therapeutical standards. Hence, instead of prescribing an off-the-shelf therapy, medical treatment should be tailored to each patient individually, taking her or his anamnesis and personal characteristics into account [5].
This idea however, prompts the justified question of how to find the optimal medication. Testing different treatments by trial and error is cumbersome and painful. Exposing patients to this additional psychological and physical burden is unacceptable.
A promising alternative to this *in vivo* approach is a systematic *in silicon* methodology. Here, the human body is interpreted as a dynamic system and described by mathematical models [10]. The free design parameters of an HIV therapy as well as the characteristics of the considered patient are then encoded by a set of mathematical parameters. Applying tools of inverse theory to estimate the latters from clinical data us to adjust the model to each patient individually. The resulting personalized dynamic system is subsequently used to formulate a control problem. A cost function quantifies not only the success of a therapy but also its burdens which are controlled by parameters such as drug dosages. Minimizing this functional, allows to determine the individually, ideal HIV therapy in a short time.

The following chapter aims at introducing a data-driven workflow that determines an individually optimized HIV treatment. For this, we define an appropriate HIV model and state the control problem, which both provide the foundation of the methodology. Following, the clinical data of a specific patient is simulated by numerically solving the dynamic system. The fourth section demonstrates how we exploit this data to personalize the HIV model by using a Bayesian approach in combination with *Markov Chain Monte Carlo* (MCMC) sampling algorithms. Techniques to solve the arising optimal control problem are mentioned but not explained in detail. Finally, we discuss results, future ideas and potential improvements.

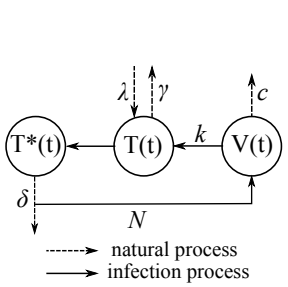
2 The Model for a Personalized HIV Treatment

In this section, we introduce a mathematical model that allows us to simulate the evolution of an HIV infection. After further investigating this model and discussing the impact of antiretroviral drugs, the optimal control problem is formulated.

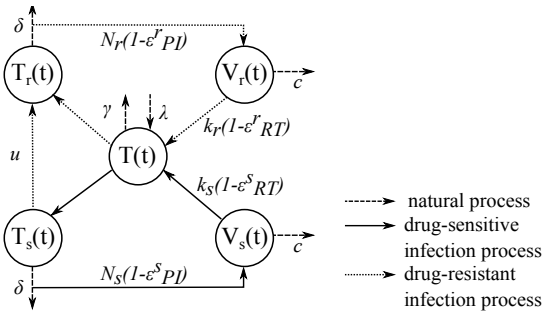
2.1 The Dynamic Model

Since HIV was first simulated in the mid-90s, a wide variety of different models arose. Initially, they attempted to investigate the HIV evolution by a set of linear *ordinary differential equations* (ODEs). These, however, are only applicable for a short period of time, ranging in the orders of days. HIV, treated or untreated, is a disease that lasts for years, and accurate and reliable long-term investigations require non-linear models [1].
In addition hereto, the final model definition is determined by the choice of biological compartments and interactions that one wants to simulate. Some models, for instance, differentiate between potential target cells, usually including CD4+ T cells and macrophages [8]. Once a cell is infected, it can either remain in a latent state or actively reproduce new viral cells, causing different reactions of the patient's immune system [3].

A simple model, for instance, is shown in figure 1a. It describes the evolution of an HIV infection, assuming that no thearpy measures are taken. However, to optimize HAARTs, we have to further evolve this model in order to not only simulate the interaction between viral and immune cells but to also consider the effect of drugs. For this, we first have to review the working principle and impact of HAART. Generally, this therapy is a combination of multiple classes of antiretroviral drugs, each fighting the virus in different ways. Two of these are *reverse transcriptase inhibitors* (RTIs) and *protease inhibitors* (PIs). While the first aims at blocking the initial infection of target cells, the latter causes already infected cells to only produce immature virus. Both these drugs, are solely designed for virus cells with a specific genome. HIV, however, replicates in untreated persons at an exponentional rate, generating up to 10^{10} new free virus cells per day. Essential steps in this duplication are error-prone and hence, the probability of mutations is high. The emerging cells have modified genomes, and the deployed drugs inhibt them less efficiently. Thus, an appropriate model has to distiguish between drug-sensitive and resistant viruses [9]. Such a model is shown in figure 1b.



(a) Dynamics of untreated HIV infection



(b) Dynamic of HIV infection under HAART

Figure 1: The above diagrams visualise two scenarios of an HIV infection. Model (a) describes the evolution of an untreated infection by distiguishing between uninfected target cells $T(t)$, infected ones $T^*(t)$ and viral cells $V(t)$. A healthy body strives to maintain a constantly high number of CD4+ T cells. While these cells die at the end of their life span with frequency γ, the human immune system continuously produces new ones at a birth rate λ. However, under the impact of HIV, the number of immune cells $T(t)$ is not only reduced by natural death but also due to the virus. First, CD4+ T cells are infected at rate k and the viral genetic material is included in their cellular DNA. During the remaining life time, the infected cell replicates the viral genes until it finally bursts, described by the bursting rate δ, and releases N new viral cells. Some of these, again, start infecting healthy CD4+ T cells while the rest die before they find a host cell which they can exploit to multiply their viral genes. Parameter c describes the death rate of viral cells. Opposed to that, model (b) explains the dynamics of a treated HIV infection, taking arising drug-resistant virus mutations into account. Although, the principle of the infection cycle remains the same, the extended model now differentiates between two cocirculating populations of cells: the ones which are susceptible to drugs, i.e. $V_s(t)$ and $T_s(t)$ as well as those that aren't, described by $V_r(t)$ and $T_r(t)$. Drug-resistant virus cells lead to infected cells which solely reproduce further resistant viruses. In contrast hereto, in a CD4+ T cell which is infected by a drug-sensitive virus, the HIV genome might mutates during replication and becomes resistant. Additionally, the diagram illustartes the effect of HAARTs. Tabel 1 summarises the meaning of the used parameters.

According Rong et al. [9], the dynamics in figure 1b, can be described by the following set of differential equations:

$$
\begin{aligned}
\dot{T}(t) &= \lambda - \gamma T(t) - k_s(1-\varepsilon^s_{RT})V_s(t)T(t) - k_r(1-\varepsilon^r_{RT})V_r(t)T(t),\\
\dot{T}_s(t) &= (1-u)k_s(1-\varepsilon^s_{RT})V_s(t)T(t) - \delta T_s(t),\\
\dot{V}_s(t) &= N_s\delta(1-\varepsilon^s_{PI})T_s(t) - cV_s(t),\\
\dot{T}_r(t) &= uk_s(1-\varepsilon^s_{RT})V_s(t)T(t) + k_r(1-\varepsilon^r_{RT})V_r(t)T(t) - \delta T_r(t),\\
\dot{V}_r(t) &= N_r(1-\varepsilon^r_{PI})\delta T_r(t) - cV_r(t).
\end{aligned}
\tag{1}
$$

Here, $T(t)$ denotes the concentration of uninfected target T cells. Generally, by index s we denote the drug-sensitive strain whereas index r marks the drug-resistant one. Thus, $T_s(t)$ is the concentration of cells that are infected by drug-sensitive viral cells $V_s(t)$, whereas $T_r(t)$ is the concentration of cells that are infected by drug-resistant viral cells $V_r(t)$. All concentrations are given in $1/ml$. Note, that the five compartments in model 1 are not directly observable in clinical data. Instead, blood measurements only give insight into the total viral load, i.e. $V_{tot}(t) = V_r(t) + V_s(t)$ and the overall number of immune cells, given as $T_{tot}(t) = T(t) + T_r(t) + T_s(t)$. Further, λ represents the birth rate of uninfected T cells per day, γ is their per capita daily death rate. The constant rates k_s and k_r describe how fast uninfected cells are infected by drug-sensitive and resistant virus, respectively. At the same time, these rates are reduced by the use of RITs. The efficacy of the drug is given by the dimensionless parameters ε^s_{RT} and ε^r_{RT}, both ranging between 0 and 1. Since sensitive viruses are more susceptible to drugs, $\varepsilon^s_{RT} > \varepsilon^r_{RT}$.
We assume that both kinds of infected cells, $T_s(t)$ and $T_r(t)$, burst and consequently die at the same daily rate δ. For sensitive virus cells, the number of released virus cells is denoted by N_s while N_r describes the same quantitiy in the drug-resistant case. However, under the deployment of PIs, not all of the newly generated free virus cells are themselves capable of infecting healthy immune cells. This is encoded in the efficacy parameters ε^s_{PI} and ε^r_{PI}. Again, $0 \leq \varepsilon^s_{PI} \leq 1$, $0 \leq \varepsilon^r_{PI} \leq 1$ and $\varepsilon^s_{PI} > \varepsilon^r_{PI}$. Virus cell populations are only reduced by their

Parameter	Value	Description
λ	$10^4\,\mathrm{ml}^{-1}\mathrm{day}^{-1}$ (estimated)	Birth rate of uninfected cells
γ	$0.01\,\mathrm{day}^{-1}$ (estimated)	Natural death rate of uninfected cells
k_s	$2.4 \times 10^{-8}\,\mathrm{ml\,day}^{-1}$ (estimated)	Infection rate of target cells by drug-sensitive virus
k_r	$2.0 \times 10^{-8}\,\mathrm{ml\,day}^{-1}$ (estimated)	Infection rate of target cells by drug-resistant virus
u	3×10^{-5} (given)	Mutation rate from sensitive to resistant strain
δ	$1\,\mathrm{day}^{-1}$ (estimated)	Death rate of infected cells
N_s	3000 (estimated)	Burst size of drug-sensitive strain
N_r	2000 (estimated)	Burst size of drug-resistant strain
c	$23\,\mathrm{day}^{-1}$ (estimated)	Clearance rate of free virus
ε^s_{RT}	varies (given)	Efficacy of RTIs for sensitive strain
ε^r_{RT}	varies (given)	Efficacy of RTIs for resistant strain
ε^s_{PI}	varies (given)	Efficacy of PIs for sensitive strain
ε^r_{PI}	varies (given)	Efficacy of PIs for resistant strain
ε_s	varies (given)	Overall drug efficacy for sensitive strain
ε_r	varies (given)	Overall drug efficacy for resistant strain
α	varies (given)	Resistance level of mutant strain

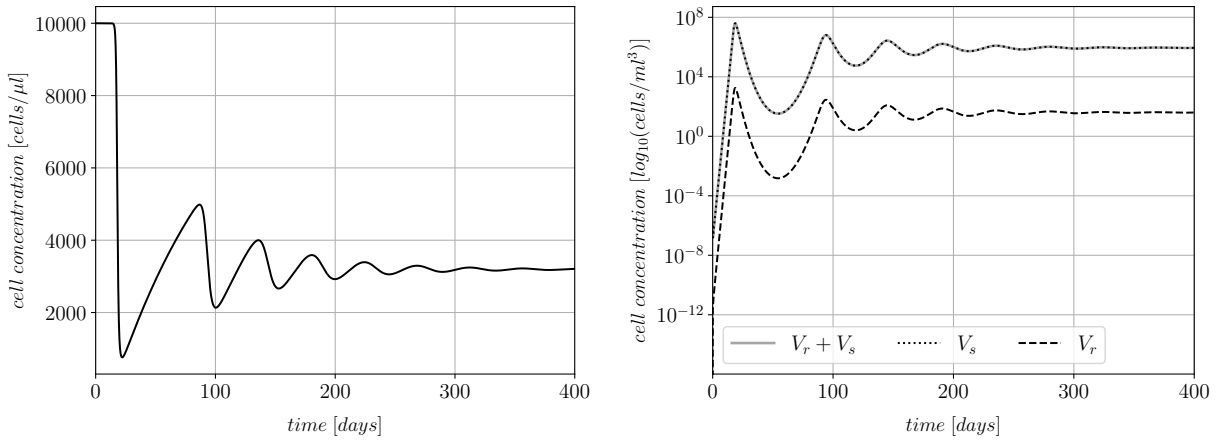
Table 1: The tabel gives an overview about the model parameters, their definitions and physical units. The listed values, which are used for the numerical simulations to investigate the model, are based on a paper by Rong et al. [9].

daily clearance rate c.
With the parameters ε_{RT} and ε_{PI}, we describe the efficacy of the single antiretroviral drugs. Summarizing these to the overall drug efficacy $\varepsilon = 1 - (1 - \varepsilon_{RT})(1 - \varepsilon_{PI})$ allows us to assess the efficacy of the combination therapy. Hence,

$$\begin{aligned} \varepsilon_s &= 1 - (1 - \varepsilon^s_{RT})(1 - \varepsilon^s_{PI})\,, \\ \varepsilon_r &= 1 - (1 - \varepsilon^r_{RT})(1 - \varepsilon^r_{PI})\,. \end{aligned} \tag{2}$$

Drug efficacy ε_s only depends on the current therapy can directly be derived from drug dosages and intake durations. At the same time, we assume that the resistance level of the HIV mutants can be quantified by the parameter α ($0 < \alpha < 1$), which represents the reduction in drug effectiveness by $\varepsilon^s_{RT} = \alpha\varepsilon^r_{RT}$ and $\varepsilon^s_{PI} = \alpha\varepsilon^r_{PI}$. Additionally, the rate at which $T_s(t)$ cells become drug-resistant during the process of replication is given by the parameter u ($0 \leq u < 1$). In this chapter, we assume mild mutations, i.e. they appear rather seldomly and if they do, their susceptibility is only little reduced. Mathematically, this behaviour is achieved by setting $u = 3 \times 10^{-5}$ and $\alpha = 0.2$. With that, the efficacy parameters in relation 2 are known and constant.
Opposed to that, the remaining parameters, summarized in $\vec{\theta} = \{\lambda, \gamma, k_s, k_r, N_s, N_r, \delta, c\}$, strongly depend on the patient. With the given information about the therapy, they can be estimated from blood measurements. Descriptions and units of all parameters are summarized in table 1.

Before tailoring the above model 1 to a specific patient, its dynamic and steady state behaviour is validated by comparing numerical results to clinical observations and findings from research. In addition hereto, such simulations give deeper insight into the impact of antiretroviral drugs. If not stated differently, parameters are taken from table 1.
Firstly, we consider a pretreatment situtaion. A patient, who has been healthy until the very day of infection, has a CD4+ T cell count of $T(0) = 10^6\,\mathrm{ml}^{-1}$. If she or he is infected by a viral load of $V_s(0) = 10^{-6}\,\mathrm{ml}^{-1}$, the untreated virus (i.e. $\varepsilon_s = \varepsilon_r = 0$) evolves within the first weeks as depicted in figure 2. Note, that although the transmitted pathogens could have already been mutated, it is assumed that $V_r(0) = 0\,\mathrm{ml}^{-1}$. The further inital values are set to 0 [8].
From figure 2 it can be seen, that the dynamic characteristics of the model coincide with the previously described stages of an untreated HIV infection. While in the first few weeks, the viral load increases strongly, the number



(a) Uninfected CD4+ T cells

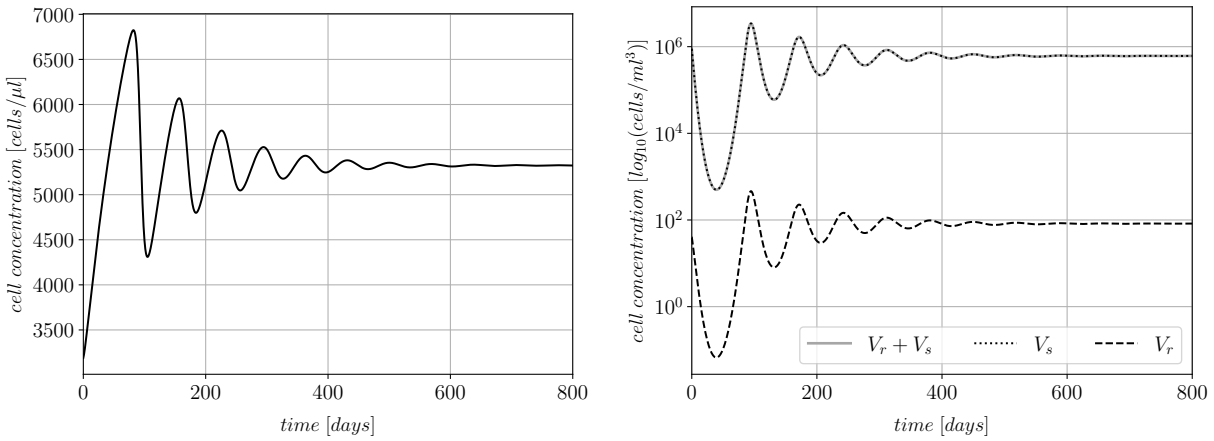
(b) Viral load

Figure 2: Simulation of the pretreatment evolution of an initial HIV infection. For the inital state, the following values are assumed: $T(0) = 10^6\,\mathrm{ml}^{-1}$, $T_s(0) = 0\,\mathrm{ml}^{-1}$, $T_r(0) = 0\,\mathrm{ml}^{-1}$, $V_s(0) = 10^{-6}\,\mathrm{ml}^{-1}$ and $V_r(0) = 0\,\mathrm{ml}^{-1}$ [8]. Diagram (a) describes evolution of the uninfected CD4+ T cells during the first year. After an inital break-in of $T(t)$, which is followed by oscillations, the immune cell concentration finally settles at a low level. At the same time, the total number of viral cells, i.e. $V_r(t) + V_s(t)$ increases. This behaviour is shown in figure (b), where the concentrations of the total viral load as well as its two strains $V_r(t)$ and $V_s(t)$, is plotted in a semi-logarithmic scale. Similar to the immune cells, the concentrations of the virus exhibits oscillations, before it remains roughly constant.

of uninfected T cells collapses, resulting in often observed flu-like symptomes. Following this, the model shows how the state of clinical latency sets in. Here, the viral loads as well as T settle in a steady state. Figure 2b demonstrates that without medication, the drug-sensitive strain dominates the infection throughout the considered time interval.

We assume that at this point of the disease, the infection is recognized and HAART is prescribed. With a presumed low resistance level of $\alpha = 0.2$, the therapy is quantified by $\varepsilon^s_{RT} = 0.4$ and $\varepsilon^s_{PI} = \varepsilon^r_{PI} = 0$. As initial values, the steady states of the pretreatment simualtion are chosen.
The numerical results, given in figure 3, show that indeed the therapy lowers the viral load and allows the number of uninfected immune cells to rise again.

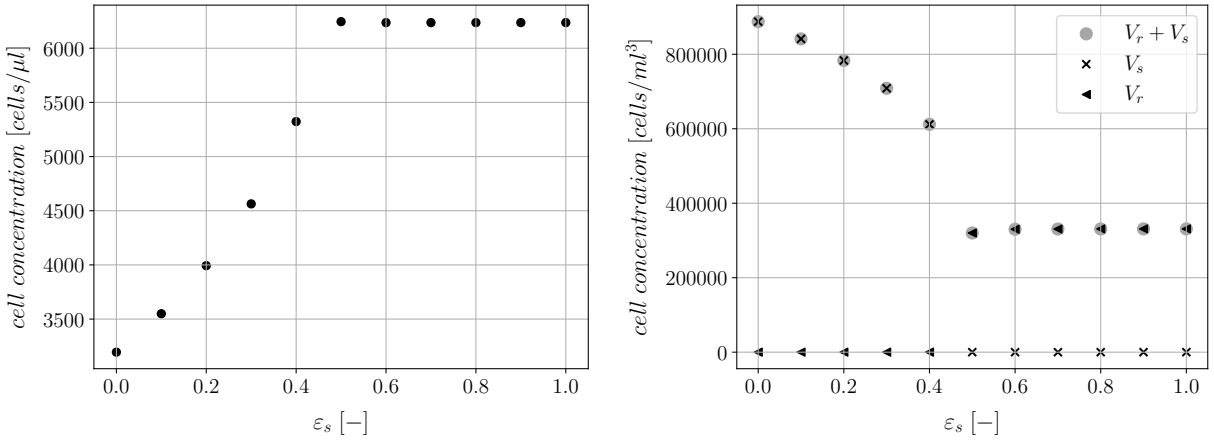
An essential feature of the model is the development of the steady states as a function of medication efficacy of the drug-sensitive strain. This is demonstrated in figure 4, where the CD4+ T cell and viral count are plotted over ε_s. From diagram 4a, it can be seen that for low values of ε_s, HAART achieve an increase in the number of uninfected target cells. However, above a certain point, this growth saturates and the concentration remains on a constantly high level. We denote this point of maximal efficacy by $\varepsilon_{s,max}$. For the given set of model parameters, its value is $\varepsilon_{s,max} \approx 0.5$. A similar behaviour can be observed on the virus side, shown in figure 4b. In the lower ε_s regime, the total virus count behaves inversely proportional to drug efficacy. For $\varepsilon_{s,max} \leq \varepsilon_s$ this reduction halts after a large drop and the number of free virus settles in a steady state.
An explanation for this behaviour can be found by investigating the evolution of the viral load more closely. While the inital success of the therapy is based on pushing the number of V_s beneath the threshold of detectability, the point of saturation sets in when the concentration of the drug-resistant strain erraticly increases. The following consistency of the infection arises from two factors. Firstly, due to the low level of V_s no new mutations emerge. Secondly, RTIs inhibit novel infections of the target cells and hence, the number of drug-resistant virus remains on a stable level. Note, that antiretroviral medications are not in- but only less efficient in attacking drug-resistant viruses. This is included into the model by defining $\varepsilon^r_{RT} = \alpha\varepsilon^s_{RT}$ (as long as $\alpha > 0$).
The quintessence hereof is, that above a certain value $\varepsilon_{s,max}$, simply increasing dose or potency of antiretroviral drugs does not automatically result in an improvement of the therapy but only in an enhancement of their side effects. At the same time, this turning point depends on the model parameters, i.e. on each patient individually. This finding emphasises the necessity to personalize the model.



(a) Uninfected CD4+ T cells

(b) Viral load

Figure 3: Simulation of the evolution of an HIV infection under HAART. It is $\varepsilon^s_{RT} = 0.4$, $\varepsilon^r_{RT} = \alpha\varepsilon^s_{RT}$ with $\alpha = 0.2$ and $\varepsilon^s_{PI} = \varepsilon^r_{PI} = 0$. The steady states of the preceding pretreatment simulation are used as initial values, i.e. $T(0) = 3.19 \times 10^5\,\mathrm{ml}^{-1}$, $T_s(0) = 6.81 \times 10^3\,\mathrm{ml}^{-1}$, $T_r(0) = 0.46\,\mathrm{ml}^{-1}$, $V_s(0) = 8.88 \times 10^5\,\mathrm{ml}^{-1}$ and $V_r(0) = 39.95\,\mathrm{ml}^{-1}$ [8]. Diagram (a) shows the evolution of the CD4+ T cell count during the first two years of therapy. Similar can be seen in diagram (b), where the concentration of the viral load is depicted on a semi-logarithmic scale. Immune and viral cells are in a constant competition. Initially, therapy surpresses the reproduction of viral cells and hence, their concentration rapidly sinks. Consequently, more uninfected T cells are produces and $T(t)$ peaks in that first therapy phase. At the same time, this increased number of potential host cells for the virus again fuels its replication, resulting in a growth of $V_r(t)$ and $V_s(t)$ increase again. Figure (a) and (b) exhibit this interplay in form of oscillations. With time, this interaction settels at a constant level and the concentration of immune and viral cells remain roughly constant. Further, figure (b) gives insight into the behaviour of the two viral strains. Since we are assuming mild mutations which occure seldomly, the concentration of the drug resistant virus is remarkably smaller than $V_s(t)$.



(a) Uninfected CD4+ T cells

(b) Viral load

Figure 4: The above diagrams show the dependency of the HIV infection on the drug efficacy parameter ε_s. In the considered case, it is $\varepsilon^s_{PI} = 0$, $\varepsilon^s_{RT} = 0.4$ and $\alpha = 0.2$. Hence, the simulations basically demonstrate the impact of RTIs. Diagram (a) depicts the evolution of the immune cells over increasing ε_s. Diagram (b) shows the same for the concentration of the viral strains. Although, initially enhancing the medication leads to a sinking viral cell count and hence, to a growing CD4+ T concentration, this behaviour changes for a sufficiently high ε_s. Above a certain threshold, the viremia is dominated by drug-resistant HIV cells. The patient does not longer respond to the therapy and her or his count of uninfcted immune cells remain constant under increasing ε_s.

2.2 The Optimal Control Problem

An optimal therapy is one, that maximizes the level of CD4+ T cells while deploying as few medication as possible. Here, we assume that more and stronger drugs, i.e. higher ε_s and ε_r, are associated with heavier side effects. Further, as shown in the preceding subsection 2.1, above a certain threshold efficacy $\varepsilon_{s,max}$, the effects of HAART saturate.
From mathematical point of view, finding an ideal therapy can be formulated as an optimal control problem. For this, we quantifiy the cost of HAART in the time interval $[t_0, t_1]$, by the functional

$$J(\varepsilon) = \int_{t_0}^{t_1} \left(T^2(t) - A_1\varepsilon_s^2 - A_2\varepsilon_r^2\right) dt. \tag{3}$$

The above relation has the following interpretation. The positive effect of the therapy, represented by the number of uninfected CD4+ T cells, is reduced by the negative side-effects of the drugs. This medication burden is quantified by the product of the control parameters $\varepsilon = (\varepsilon_s, \varepsilon_r)^T \in [0, 1]^2$ and their weight constants A_1 and A_2 [1, 14]. Ideally, $T(t)$ is maximised while $A_1\varepsilon_s^2 + A_2\varepsilon_r^2$ is minimized. Hence, we seek an optimal control ε_{opt}, such that

$$\varepsilon_{opt} = \underset{\varepsilon\in[0,1]^2}{\arg\max} \left(J(\varepsilon_{opt})\right). \tag{4}$$

3 The Data

1. Numerical simulation of data: predefine a set of true parameters; simulate viral load over time (represent multiple blood tests)
2. Introducing statsistical errors: each measurement of viral load is taken in distinct intervals, i.e. assuming independent measurements

4 The Methods

5 The Results

6 Discussion

7 Conclusion and Outlook

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