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Modelling the Co-infection Dynamics of HIV-1 and M. Tuberculosis

by

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Summary

Modelling of the Co-Infection Dynamics of HIV-1 and M. tuberculosis

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This dissertation focuses on the modelling, identification and the parameter estimation for the co-infection of HIV-1 and M. tuberculosis. Many research papers in this field focus primarily on HIV, but multiple infections are explored here, as it is common in many individuals infected by HIV. Tuberculosis is also responsible for the highest number of casualties per year in the group of HIV-infected individuals.

A model is proposed to indicate the populations of both pathogen as well as key information factors, such as the overall infected cell population and antigen-presenting cells. Simulations are made to indicate the growth and decline in cell-type numbers for a specific individual. Such simulations would provide a means for further, well-founded investigation into appropriate treatment strategies. One previous such model developed by Kirschner is used to obtain a nominal parameter set. Furthermore, the nominal set is then used in conjunction with real-world samples provided by the National Institute for Communicable Diseases in South Africa, to solidify the credibility of the model in the practical case. This is achieved via simulations and employs parameter estimation techniques, namely the Nelder-Mead cost-function method. An identifiability study of the model is also done.

Conclusions drawn from this study include the result that the treatment of M. tuberculosis does not affect the course of HIV-1 progression in a notable way, and that the model can indeed be used in the process of better understanding the disease profile over time of infected individuals.

Keywords

Modelling, HIV and TB parameter estimation, identifiability, dynamic system, bio-engineering, non-linear systems, medical system, simulation of states

Opsomming

Modellering van die Infeksie-Dinamika tussen HIV-1 en M. tuberkulose

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Hierdie verhandeling spreek die probleem van gelyktydige infeksie deur HIV-1 en M. tuberkulose aan vanuit 'n ingenieursoogpunt. Dit behels die modellering, identifikasie en die parameter-afskatting van 'n spesifieke pasiënt se immuunrespons. Verskeie bestaande artikels en navorsingstukke spreek die probleem van 'n enkelinfeksie deur 'n patogeen aan, maar weinig inligting bestaan oor gesamentlike infeksies. Die fokus is dus juis om 'n model daar te stel wat gebruik kan word om 'n spesifieke pasiënt se infeksie op 'n tydsrespons en met die nodige beginkondisies te modelleer en te simuleer.

TB is baie algemeen onder die groep HIV-geïnfekteerde individue, en die grootste aantal sterftes in hierdie groep is ook by verreweg weens die bakterie.

'n Model word voorgestel wat die populasietellings van beide patogene aandui, asook sleutelinligting verskaf oor die totale geïnfekteerde selle populasie en die antogeendraende selle populasie vir 'n spesifieke individu. Simulasies word gedoen om die groei en afname in seltipes voor te stel. Dit verskaf dan ook 'n manier om verdere ondersoeke oor moontlike behandelingstrategieë te doen. 'n Vorige model, ontwikkel deur Kirschner, is gebruik om 'n nominale stel parameters te verkry. Data is by die Nasionale Instituut vir Oordraagbare Siektes (NIOS) in Suid-Afrika verkry. Die data, saam met die nominale parameters, skep 'n goeie basis om die bruikbaarheid van die model te verifieër vir voortgesette studie.

Die algoritme genaamd "Nelder-Mead" is vir optimisering toegepas. Identifiseerbaarheid van die model is ook ondersoek, en afleidings word gemaak oor die aard daarvan. Die wederkerige impak van HIV en TB word ondersoek, en daar word bevind dat die twee patogene se invloed op mekaar minimaal is tydens infeksie.

Sleutelwoorde

Modellering, HIV, tuberkulose, parameter-afskatting, identifiseerbaarheid, patogeen, nie-lineêre stelsels

Abbreviations

APC	Antigen-Presenting Cell
CTL	Cytotoxic T-cell
GUI	Graphical User Interface
HIV	Human Immunodeficiency Virus
Mtb	Mycobacterium tuberculosis

Nomenclature

Model variables

D	Antigen-presenting cells
I	Infected cells : CD4+ and CD8+ T-cells, and APC's
T_4	CD4+ T-cells
T_8	CD8+ T-cells
T_b	Free bacteria
v	Free virions

Notational

$\vec{x_0}$	Initial state vector $[T_{4_0}, T_{8_0}, v_0, T_{b_0}, I_0, D_0]^T$
$\widehat{D}$	Estimated macrophage count vector
$\widehat{I}$	Estimated infected cells vector
$\widehat{T_4}$	Estimated CD4+ T-cells vector
$\widehat{T_8}$	Estimated CD8+ T-cells vector
$\widehat{T_b}$	Estimated bacterial load vector
$\widehat{v}$	Estimated viral load vector
T_{4n}, T_{8n}, v_n	Sample vectors
$\widehat{\dot{X}}$	Estimated states matrix $[\widehat{\dot{T}_4}, \widehat{\dot{T}_8}, \widehat{\dot{v}}, \widehat{\dot{T}_b}, \widehat{\dot{I}}, \widehat{\dot{D}}]$
Φ	A single patient's data matrix
Φ_{nk}	The n-th row and k-th column in a patient's data matrix
$\Phi_{1:}$	The complete 1st data row in the matrix
χ_0	Nominal model parameters vector
$\hat{\chi}$	Estimated parameters vector

Parameters

k_1	Rate resting T_4 cells become infected by free virus
k_2	Rate resting T_4 cells are infected by APC's
k_3	Rate T_8 cells are activated by APC's
k_4	Recruitment rate of macrophages by free virus
k_5	Recruitment rate of macrophages by bacteria
k_6	Death rate : virus by macrophages
k_7	Death rate : virus by T_8 cells
k_8	Death rate : bacteria by T_4 cells
k_9	Death rate : bacteria by macrophages
r_b	Maximal bacterial proliferation rate
D_o	Equilibrium value for macrophages
K	Carry capacity - bacterial population
N_1	Rate free virions are produced by infected cells
N_2	Rate free virions are produced by macrophages
S_4	Source term - Healthy T_4 cells
S_8	Source term - Healthy T_8 cells
μ_v	Natural death rate - virus
μ_I	Natural death rate - infected cells
μ_4	Natural death rate - T_4 cells
μ_8	Natural death rate - T_8 cells
μ_d	Natural death rate - macrophages
μ_b	Natural death rate - bacteria

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I would like to acknowledge the inputs of the following people into making this study possible, and helping me towards keeping faith in its cause:

Firstly, to **Prof. Xiaohua Xia**, my mentor. You have shown tremendous patience during the course of my study. Also, you have given me the best inputs and guidance possible, and you have shown me possibilities with this study that I have never thought possible. I admire your heart for the engineering-approach to biological problems, and I think I am correct in saying that we share a vision and heart for people suffering from these terrible diseases.

To my best friend **Aldi**. By continuously reminding me of the bigger picture, you have restored my faith in the small part of the bigger picture that each study piece paints. You kept my heart in the right place and focused me towards the bigger goal of HIV-related studies: caring.

To **my parents**. Thank you for always believing in me and being available when I need you. You are very close to my heart.

To the **University of Pretoria** and the **NRF** for financial assistance. One can never overlook a gift such as this. Thank you.

Lastly, to **all my friends**: You know exactly what part you played in all this, and it is by no means small. You drive me forward, and I am ever grateful for having you in my life. Thanks!

Dedicated to my best friend:

Aldi

"May we always have the heart to make a difference."

Contents

Part I.

Background and Motivation

1. Introduction

1.1. Problem Definition

IT is no new concept to medical practitioners that there exists the need to alleviate the problem of the HIV and TB co-infection with any practical (and theoretical) means possible. The control-engineering field of study has been involved in recent years in modelling and parameter estimation of biological population systems and immunological response systems. Furthermore, the engineering process used in [1] inherently proposes that a model is constructed, verified and finally made practically useable for designing treatment schedules. The research done and reflected in this dissertation addresses this need. A variety of approaches to modelling HIV and TB separately can be found in references such as [2], [1] and [3]. Elements of these approaches should be used as the basis for building a model for concurrent infections of HIV-1 and M. tuberculosis. The study should entail a thorough attempt at estimation of the model parameters, to fascilitate the movement towards verification. Modelling is the first step in a process of continued research from which possible treatment strategies for this very real problem can be found. The suffering of people, and the prevalence of such a large number of co-infected individuals enhances the urgency for solving this problem.

The modelling should be approached as to point out the features, advantages and disadvantages, and useability of its product and outcome. Furthermore, it should be compared to at least one other similar model from literature to sustain its credibility.

Through employing an optimisation algorithm and mathematical modelling and identification techniques, the model should be simulated and verified against the background of field samples, taken from Southern-African patients with such a co-infection.

The output of this modelling exercise should be a platform from which controllability

(identifiability) should be analysed. Withing the control-engineering realm, this would indicate how one would go ahead to build a control-strategy. Such a strategy would have as output the information on how such a co-infection might be treated optimally per patient. Following from this, it is thus crucial that the whole study be oriented towards practical implementation, rather than mere theoretical simulation with no vision of realisation. Bacterial infections are well-studied ([3–6]), and many pieces of research have been done on the topic of HIV/AIDS modelling ([1, 7–9]). Few studies exist that focus on co-infection ([10] is one example), although co-infection is such a large problem worldwide.

The essence of both modelling approaches should be combined and integrated towards solving the final problem of treatment and monitoring-strategies for co-infected individuals. A guideline for treatment is provided by the CDC workgroup in [11], but this focuses on the practical implication of drug-usage, rather than firstly addressing the fundamental problem of the individuality of patients (ie. their specific cell-type states and parameters). Any practical plan such as this should be based on a firm analysis of monitored patients by means of a model, and only then should a treatment strategy be put in place. It is understandable that one cannot wait for models to be developed before patients are treated, but the problem of understanding each individual should be addressed as soon as possible.

1.2. Humanitarian Motivation

One need only pick up a newspaper in South Africa to find an article dedicated to making people aware of the need for HIV/AIDS and tuberculosis programmes, vaccinations, anti-retroviral treatment and distribution and proper public education with regards to handling the pandemic. It is evident from newspaper articles that a flag is raised that humanity is in dire need of research that drives towards and strives to bring relief and aid for this urgent problem.

About 40 million people worldwide are infected by HIV. Of this number, about 1 third are also infected by M. tuberculosis. This means that roughly 13 million people are co-infected. The casualty rate within the HIV-only group is about 3 million people

a year, and in the TB-only group around 2 million people per year. This indicates that tuberculosis accounts for the most casualties per year in the group of HIV-infected people and promotes the intense need for studies like this, and sets the stage against which this type of research has to make a real contribution.

Tuberculosis is easily spread by bodily fluids, which means that it can become airborne simply by someone sneezing, coughing or spitting. If other people breathe in these droplets, they can get infected by it. It is more common though for a baby to catch it after birth, due to close contact with its mother. Infection probability is not very high: even if a healthy person spends 24 hours of a day for two months with someone with active disease, there's still only a 50% chance that he or she will catch TB. People with a weakened immune system are more at risk.

For many people, TB is the first sign of immune dysfunction associated with HIV infection, and active TB is an AIDS-defining illness. One in 10 people living with HIV will get active TB with a year of being diagnosed with HIV. It can occur early in HIV disease, when CD4+ T-cell counts are relatively high (300 to 400 copies per ml). In early HIV infection, TB usually infects and affects only the lungs. As CD4+ T-cells counts drop, however, TB is more likely to appear in other organs too.

When the immune system responds to TB it can cause HIV levels to increase, and HIV disease may then progress quickly. This, in turn, increases the risk of other opportunistic infections. Practically, however, it has been noted that TB treatment leads to lower HIV levels in people with both infections. This point is simulated and shown to be controversial, as can be seen in Section 12. With the simulation it seems that, if the TB treatment is too sudden or with too high intensity, the HIV levels will increase due to a decrease in the number of macrophages.

The biggest humanitarian problem is identified in the single fact that people do not have access to the necessary drugs and treatment expertise. Even further, when people do have access to this, the treatment is influenced by their returning on the specified dates for follow-up treatment, and it has been seen that this is definitely not always possible. Infrastructure is thus a problem, and treatment schedules have to be changed to fit to irregular visitations.

For a glimpse on the scale at which this co-infection has become a humanitarian

crisis, a case-study from India is quoted from [12]:

> "TB is not only a matter of concern for those infected with HIV but also for HIV- negative people to whom it can spread through droplet infection. It is the only major AIDS-related opportunistic infection to pose this kind of a risk. People who discover they have HIV and who carry the TB germ, are unusually prone to developing active tuberculosis.
>
> The rate of progression to TB disease is 30 - 50 times higher among individuals infected by both TB and HIV as compared to those infected by TB only. This is because of the suppressed immunity in HIV infected and hence the enormously higher risk of reactivation of dormant TB bacilli. In situations of advanced HIV epidemic, HIV is likely to worsen the TB situation. This could also contribute to multi-drug resistance.
>
> About a third of the HIV-positive population worldwide is co-infected with M. tuberculosis. The HIV epidemic has the potential to worsen the TB epidemic as has happened in certain African countries. This is mainly because HIV increases the risk of disease reactivation in people with latent TB and because HIV-infected persons are more susceptible to new TB infection. These patients would add to the incidence of TB thereby leading to increase in new infections and re-infection. HIV is the most powerful risk factor for progression of TB infection to TB disease. A HIV-positive person infected with M. tuberculosis has a 50% - 60% lifetime risk of developing TB disease as compared to an HIV-negative person who has only a 10% risk. This is especially important in India where it is estimated that 40% of the adult population harbors M.tuberculosis. Also, HIV-infected persons who become newly infected with M. tuberculosis rapidly progress to active TB disease. TB disease is the most common opportunistic infection and a major cause of mortality among HIV-positive persons. It is the first manifestation of AIDS in more than 50% of cases in developing countries. HIV by itself does not cause multi-drug resistant TB, but fuels the spread of this dangerous condition by increasing susceptibility to TB infection and also accelerating the progress from infection to disease. In a developing

country like India, the potential extra burden of new TB cases attributable to HIV could overwhelm budgets and support services, as has happened in countries most heavily affected by the HIV epidemic.

Hospital based HIV sero prevalence studies amongst tuberculosis patients from different regions of India have shown a great variation the prevalence rates varying from 0.4% - 28.1% have been reported. In India, there were an estimated 5.1 million people living with HIV at the end of the year 2002. Assuming that about 40% of these persons are co-infected with TB, the estimated TB-HIV co-infection figures will be around 2 million."

The further problem exists of using the classic anti-TB drugs rifampin and rifabutin with anti-HIV drugs. Rifampin interacts with protease inhibitors (PI) and non-nucleoside reverse transcriptease inhibitors (NNRTI) drugs. This forces people on these types of anti-retrovirals to rather use rifabutin for treating TB. The essence of this problem is that drug interactions are a concern with anti-HIV and anti-TB products. Even for people taking both PIs and NNRTIs it may be hard to predict what effect rifabutin will have.

Over the past decade there has been an increase in the appearance of strains of TB that are resistant to two or more anti-TB drugs. These strains are called multi-drug resistant TB, or MDR-TB. In 1997, over 7% of TB strains were resistant to at least isoniazid, and 1.3% were resistant to at least isoniazid and rifampin. People with HIV are six times more likely to have MDR-TB than HIV-negative people. MDR-TB is three times more likely than drug-sensitive TB to cause active disease in HIV-positive people.

A strategy for the control of MDR-TB is laid out in [13], and the model proposed in this study may be adjusted in the future to include the effects of MDR-TB upon treatment.

1.3. Document Layout

The document is laid out and presented in the following way:

Chapters 1 to 3 provide background information on the topic of this dissertation:

Chapter 1 is an introduction to the mathematical problem that is addressed, and gives insight into the humanitarian problem as well.

Chapter 2 provides medical background on the specific immune response of the body to both HIV and TB. The focus is here on how cell-types react and interact and how the lifecycle of virus and bacteria is completed.

Chapter 3 shows how this study contributes to the realm of research, and fits it into the body of knowledge by indicating its scope. Furthermore, the unique stance of the control-engineering approach to problems such as this is briefly explained. An overview is also given of previous research, to give the reader an idea of what has been done before.

Chapters 4 to 9 provide information on how the relevant research and mathematical techniques are implemented:

Chapter 4 steps through the modelling process, and shows how each of the terms in the model has been decided on. It also looks at similaries with other models.

Chapter 5 provides insight into the available data and what can be said about the identifiability of the proposed model. The simpliciation of the model towards achieving identifiability information is discussed, and mathematical equations are given for determining each of the model parameters algebraically. Finally, the number of samples needed for full model identification is discussed.

Chapter 6 discusses the designing of a cost function that will be used in chapter 7 to estimate model parameters for each patient. The cost function is presented as a basic function and then refined at each step to include information known about the dataset and the response, as well as the desired final response. In other words, penalty terms are added, and refinements are made to be able to generate parameters that medically and practically make sense.

Chapter 7 discusses the optimisation routine for estimating parameters. The Nelder-Mead algorithm is discussed and a brief section indicates its main drawback: that of finding a global minimum.
Chapter 8 shows how the simulation architecture is implemented and the thought-process involved in creating it. Problems with simulating and possible solutions are also discussed here.
Chapter 9 provides alternative methods in searching for parameters.

Chapters 10 through 14 provide the results of the study:

Chapter 10 discusses and focuses on the results of 5 specific patients. Each case is discussed at the hand of the available data, the estimated parameters, the initial conditions, the reaching of a steady-state, a medical perspective on the patient and the predicted response.
Chapter 11 sheds light on what happens when treatment is simulated for a specific patient. Both the treatment of HIV and TB is duscussed.
Chapter 12 verifies the validity and usage of the model by means of fitting the model to a published experiment, verifying it by using the field-data and a data-fit benchmark that is devised. Furthermore, randomized data is used to test that the method used to optimise the model's parameters does indeed yield sound results. The performance of the model in such scenarios is also crucial.
Chapter 13 gives the empirical results from the study: Those results that can be termed as "general" or applicable to the whole. Results in this section include the similarities between all patients (again the benchmark is used), shortcomings of the proposed model, improvisations that were made from a general lack of patient data, the choice of nominal parameters, notes on the interaction between HIV and Mtb, medical possibilities using the model and possible treatment strategies.
Chapter 14 concludes the study, and gives a final overview on what has been achieved.

The appendices cover the complete patient simulations results, a description of how the patient benchmarks are devised, statistics about the patient dataset and an overview of the simulation architecture and user-interface tool that was created.

Each chapter ends with a summary and retrospective overview of the chapter. This highlights the main points that are covered in that chapter.

2. Medical Background

THERE are various research publications which focus on modelling the infection of individuals by the Human Immunodeficiency Virus (HIV), for example [14] and [15]. Whilst HIV is classified as a pandemic in the world context and given much-needed attention, both academically and in the media, there is little focus on co-infection states, which are infections that exist alongside HIV within a single body. Such co-infections make out the bulk of problems that individuals living with HIV have to face, as they are more often than not opportunistic, taking advantage of a weakened immune system. In this section a brief medical background from an immunological point of view is given for both HIV and TB.

2.1. HIV-1

If we consider an infection by the Human Immunodeficiency Virus (HIV), a person may contract it via blood-transfusions, needle-pricks, unsafe sexual conduct, or any direct contact with the bodily fluids of an infected person. Some of the latter manners of transfer have a higher risk involved (needle-pricks, unsafe sex), and some a lower risk (contact with bodily fluids). Whichever way a person contracted the virus, it immediately starts acting in an invasive manner by infecting and killing the CD4+ T-cells, which form part of the immune response and white blood cells. Indeed, the measure of a person's HIV infection can and is most notably done by taking his or her current CD4+ T-cell count. A decline in this number is thus a very good indicator that a person may be infected with HIV. At this point it is important to note that normal CD4+ T-cell counts range in the order of 1000 to 2000 copies per ml of blood plasma. Simultaneously, whilst killing off CD4+ T-cell counts, the virus also reproduces by

means of these helper T-cells. This differs significantly from tuberculosis, as the TB bacteria can reproduce on its own account without the need for other celltypes. In the process of infecting CD4+ T-cells, the T-cells also continue their own reproductive process. The problem here is that once a T-cell is infected, and that cell reproduces, the viral RNA is reproduced along with it, which means that infected cells produce new infected cells.

When one considers the cytotoxic T-cells (or CD8+ T-cells), they are seen as the cells that primarily kill the virus off. Typical values for CD8+ T-cells range from 300 to 1000 copies per ml, which means that the ratio of CD4+ T-cells to CD8+ T-cells in the body is between 1.2 and 2.2. The creation of new virions activate CD8+ T-cells, thus the more free virus in the body, the more CD8+ T-cells will be activated. It is estimated that as many as ten billion HIV-1 virions are produced and destroyed in an infected individual each day [16] Thus, when one CD8+ T-cell meets an individual HIV-1 copy, this encounter will trigger a mechanism that increases the production of CD8 cells. This means that the growth rate of the fighters of the HIV-1 (the predominant HIV straint in the west) will increase. The number of those encounters will be proportional to the product of the populations of CD8 and HIV-1.

The main interactions between HIV-1 and the immune response cells can thus be summarised as :

- HIV-1 uses CD4 cells to replicate, with inversely-proportional growth-rates.
- CD8+ T-cell counts increase in response to increased HIV-1 load.
- CD8+ T-cells attack and kill the virus.
- The growth rate of HIV-1 increases with and increase in HIV-1 and CD4+ T-cell populations.
- The growth rate of HIV-1 decreases with a decrease in growth of the HIV-1 and CD4 populations.

2.2. M. Tuberculosis

If we consider an infection by Mycobacterium tuberculosis, this pathogen progresses differently to HIV in the immune system. The immune response is not immediate, but develops over the course of 2 to 15 days. After 1 day, though, a notable increase in the CD4+ T-cells can be seen, as well as cells called Antigen-Presenting Cells. These cells (APCs or otherwise known as macrophages) form the primary response against TB. The initial site of Mtb infection is the alveoli of the lung, where it comes into contact with lung macrophages and dendritic cells. Macrophages respond to bacterial infections by the process of phagocytosis: the engulfment of bacteria [4]. These macrophages are both uninfected and unactivated, meaning that they do not contain bacteria (uninfected) and are less efficient at phagocytosis than activated macrophages. Activated macrophages become efficient at phagocytosis and bacterial killing due to the presence of T cells. Phagocytosis can be divided into two main operations: engulfment and killing. The macrophage first uses its receptors to bind to the bacteria, surrounding it by a membrane and then internalizing it into a compartment called a phagosome. Within the macrophage, lysosomes, which contain enzymes, peptides and proteins, can then fuse with the phagosome to generate a phagolysosome. The lysosomal contents are then released, killing the bacteria. Mtb, however, interferes with phagosome-lysosome fusion and thus survives in the phagosome and grows in the host macrophage. During Mycobacterium tuberculosis (Mtb) infection, epithelial cells, resident macrophages, T cells and bacteria each release chemokines that promote migration of immune system cells to the infection site. Similar processes also occur in tumors, wound healing and arthritis. It is speculated that if macrophages phagocytose and kill bacteria quickly, infection can conceivably be cleared. However, Mtb has evolved to resist killing by unactivated macrophages. In fact, it prefers to reproduce within macrophages. The intracellular bacteria population of its host macrophage can become so large that the macrophage bursts and dies.

The immune response to a TB infection by means of the CD4+ T-cells happens by damaging of the cellular material in the outer extremities of the bacteria. This causes the bacteria to disintegrate and die as a result. Another way that bacteria is killed

off happens by means of macrophages. The macrophages form a sort of an envelope around the bacteria and digests it. This envelope may become a solid mass in some individuals with active TB disease, and cause the "granuloma", a hardened clump of macrophages (similar to a tumour), that characterises tb by their occurence in the lungs. Five percent of people living with tb in their bodies would progress to such an active state in their lifetime, whilst 90 percent would never have active TB [17]. The problem with tuberculosis in the immune system is that it can become resistant to killing by macrophages. A person that this happens to would most likely develop active TB.

Previous mathematical models have been developed to consider macrophage dynamics [5], for example: partial differential equation (PDE) models in tumor biology; ordinary differential equation (ODE) models in Mtb infection, phagocytosis, HIV infection and in the immune response to an unspecified disease or infection. Wigginton and Kirschner developed a model of the adaptive, cell-mediated immune response to Mtb infection [6].

During the course of TB, severe tissue damage may occur as a consequence of the immune response. This response may be mediated primarily by T cells and activated macrophages. Thus, although it is clear that the Th1-type response plays an important role in immunity to M. tuberculosis, it must also be carefully regulated to ensure that severe tissue damage does not occur.

It should be noted that, in this study, macrophages as a cell-type is modelled as being in a rested state. If terms from other parts of the model include the macrophages, these antigen-presenting cells are classed as being activated.

2.3. Chapter Summary

This chapter gave background information to the medical problems that people face with infections by HIV and tuberculosis. A summary of the immune response to both pathogen was given, and some statistics on infection-rates and the effect of increases and decreases of certain cell-types on another were also given.

3. Contribution to Research

3.1. Scope and Control-Theoretic Engineering Approach

THE mind-map shown in figure 3.1 outlines the scope of this study. This research strived to conform to the path of modelling a system, identifying the parameters for it per dataset and simulating the responses and treatment. The control-theoretic approach to the modelling and control of biomedical systems is something that can be seen from [18], and the same continued-research route is planned for this research. This means that the model will be used as the basis for defining treatment-schedules by controller-design (not included in the scope of this dissertation though). This approach leans itself towards practical implementation of optimal-control on people.

A parameter estimation routine has been created and the cost-function refined that is used to estimate all parameters of the proposed co-infected model. An identifiability study shows which parameters can be algebraically determined from the measured outputs and which not. The estimation procedure is used to fit the model successfully to data received from the National Institute of Communicable Diseases in Johannesburg, South Africa.

A benchmark is created to compare patients included in the study to another. The benchmark indicates which patients' parameters are more accurately found than others. Furthermore, an analysis of the method of optimisation is done to indicate and prove that it actually works well with this model. The results from this study include an indication of what to expect during treatment of either HIV or TB, and the effect either has on the other. This document outlines co-infection of HIV-1 and TB in the sense

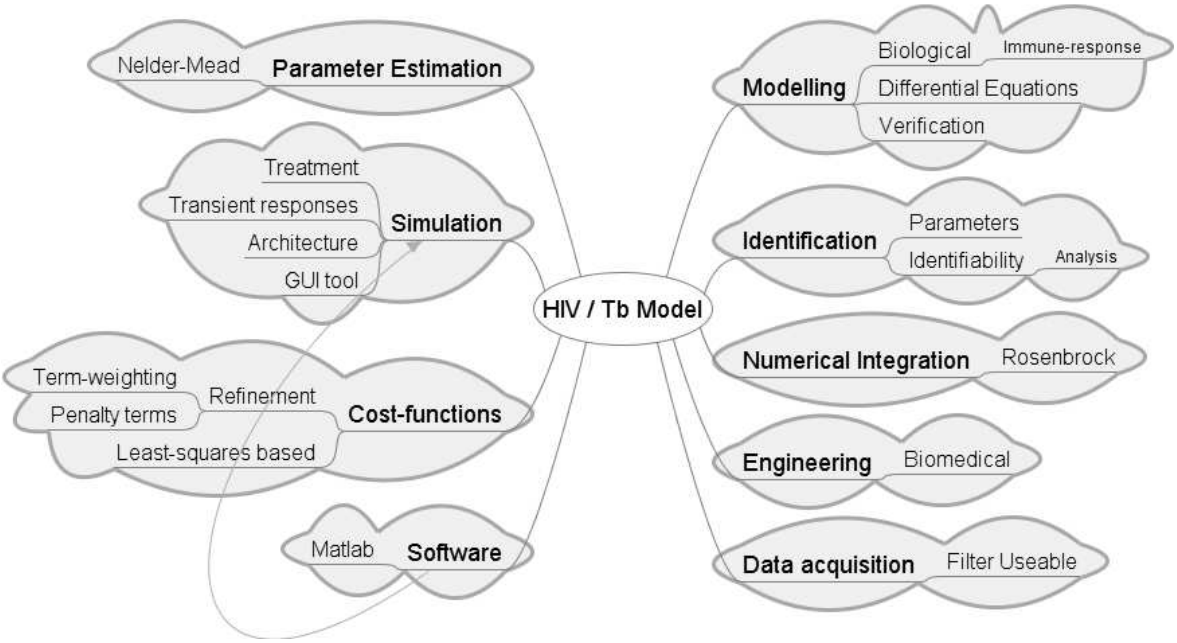

Figure 3.1.: Scope of this research.

of producing a viable deliverable: a means of forecasting, per individual, what would happen to the progression of virus and bacteria in their bodies. This leads to a basis from which strategies for treatments can be researched and put in place. Ultimately, any such modelling is truly a bold undertaking, as can be seen from [19] and the technology and theory available to do this makes it a very rewarding and exciting field. It changes people's lives.

3.2. Overview of Previous Research

Previous research related to the topic of this dissertation include:

- Modelling the immune response to HIV [3, 20–22], estimating parameters for an HIV-only model [23] and simulating treatment strategies for HIV [18, 24–26]
- Controller-design for an HIV-only model [27–31].
- Co-infection modelling of tuberculosis and HIV without model-verification by field data [10].
- Determining the identifiability properties of an HIV model [32].
- Control-theoretic approach to determining when to initiate HIV therapy [18].
- Modelling of combined-drug therapy strategies for HIV [33].

- Modelling the immune-reponse to tuberculosis [4, 6, 17]
- Establishing the role macrophages play in during the immune-response [34, 35].
- Establishing criteria for the control of drug-resistant tuberculosis [13].

3.3. Contribution

This study contributes towards establishing a model for the co-infection of HIV and TB, and also verifying this model with data from physical patients. This type of verification is crucial for any mathematical model before it can be used in further study. The study goes one step further by contributing knowledge of how HIV and TB affect one another, and comments on how well the model fits the relevant patient-data. Lastly, the study contributes towards research in the biomedical modelling field by laying a foundation from which controllers and control-strategies for the diseases can be determined.

3.4. Chapter Summary

A brief overview of the scope of this research was given in this chapter, and a list of previous research done in this field was given. The contribution this study makes to the body of academic knowledge was pointed out.

Part II.

Implementation

4. Modelling

WHEN the immune-response to foreign antigen in the body is considered in context of HIV and TB, the result can primarily be seen as a cellular-mediated response, as opposed to a response involving anti-bodies (also known as a humoral response). The former response involves APCs (Antigen Presenting Cells), which form a sort of an envelope around the foreign material and "present" it to the CD4+ T cells (CD4+ T cells can generally be described as T cells that express the surface protein CD4, and has the role of helping the immune system function. The relevance here is that HIV infects cells that are CD4-positive).

Different types of APCs exist, for example macrophages and dendritic cells, but dendritic cells have been identified as the most efficient APCs during the course of specifically HIV-1 disease progression [36], and will thus be the APC of choice for the proposed model. From here on, the CD4+ T cells enable and command the other major players in the immune-response, namely helper CD4+ T cells, APC's and CTL's (which are cytotoxic or activated CD8+ T cells). APCs embrace the foreign material as dictated by the CD4+ T cells and kill them, while CTLs are able to kill infected cells directly. The latter is known as a primary immune response. To model the immune-response behavior of both HIV and TB, it is necessary to understand that the two infections are similar with regards to their pathogenesis (both are foreign microbes that evade the immune-system's cellular responses), but are very different in their cellular biology, hence the challenge of providing medication to infected patients of the two pathogen, and the core motivation for this study.

4.1. Immune Response Interpretation

In the light of the discussions on the immune reponse to the individual pathogen, shown in sections 2.1 and 2.2 (HIV-1 and Mtb respectively), the thorough modelling process is undertaken here. The immune response is considered where both diseases exist in a single compartment, which means that only one of either the blood plasma, lymph nodes, skin tissue etc. is used to show the interactions of cell-types. The compartment in which the infection is modelled is the blood plasma. Two-compartmental models for the HIV-only case already exist which shows interaction between cells in, for example, the blood and the lymph tissue [37]. The blood compartment is chosen as it corresponds to physical measurement strategies (Measurements are usually taken from patients' blood plasma).

In figure 4.1, the model and all the parameters are represented graphically.

To start off, one can consider the CD4+ and CD8+ T-cells in an uninfected individual. Both CD4+ and CD8+ cells have a natural growth, or source term, which is the rate at which these cells are produced in a healthy person. The source terms may either be modelled as functions of time [10] or as constant terms, which is the chosen option for this study.

Thus, we say that the change in CD4+ and CD8+ T-cells is firstly influenced by the natural growth:

$$\frac{dT_{4(1)}}{dt} = S_4 \tag{4.1}$$

$$\frac{dT_{8(1)}}{dt} = S_8 \tag{4.2}$$

Similarly, these cell types both also die a natural death (they have a finite lifetime), at a specific rate for each individual. This death rate is signified throughout this text with μ. Thus, together, and in the uninfected case, the equations become:

$$\frac{dT_{4(2)}}{dt} = S_4 - \mu_4 T_4 \tag{4.3}$$

$$\frac{dT_{8(2)}}{dt} = S_8 - \mu_8 T_8 \tag{4.4}$$

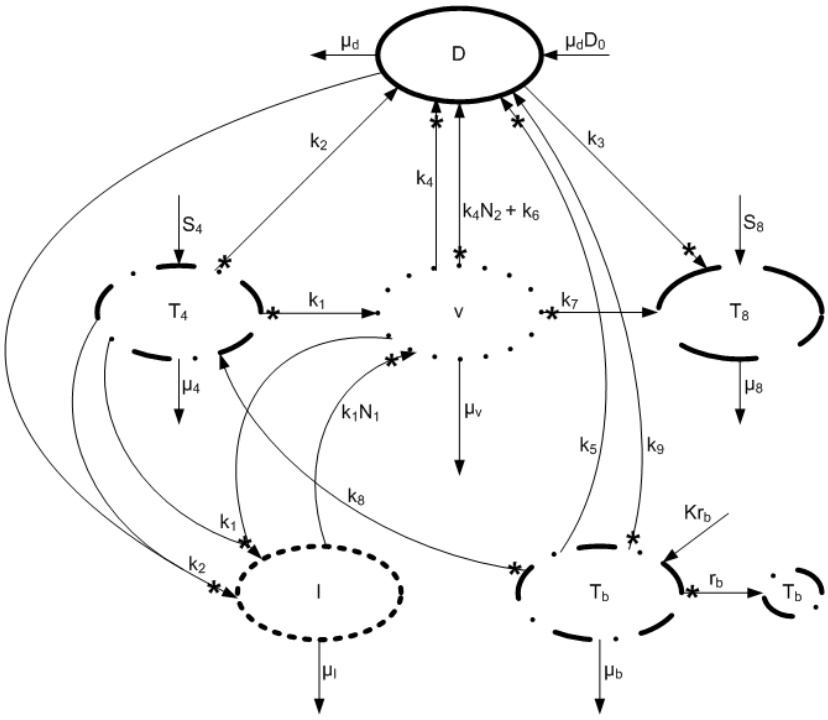

Figure 4.1.: Graphical representation of the modelled relationship between the various cell-populations. An arrow that leaves a population indicates a decrease and an arrow that enters a population indicates an increase. To prevent ambiguity, the asterisk (*) indicates on which population on either side of the relationship the increase or decrease is applicable.

Following this, one can continue to the infected case, where both the viral load, the bacterial load and the antigen-presenting cells (APC's) start to play a role and have an influence as the primary immune response to the foreign pathogen. Also, a distinction is made at this point between infected cells and uninfected cells, to better monitor the progression, growth and decline in healthy cell populations. The healthy CD4+ cell growth is influenced by the presence of bacteria and virus, hence terms are added to indicate this. We add a term for the decline in healthy CD4+ T-cells due to their infection by virus. The rate at which this happens is k_1:

$$\frac{dT_{4(3)}}{dt} = S_4 - \mu_4 T_4 - k_1 v T_4 \tag{4.5}$$

Following the decline in healthy CD4+ T-cells by viral infection, a similar decline is experienced by means of macrophages, or dendritic T-cells. This decline indicates

the nature of what antigen-presenting cells do during the immune-response, which is to envelop foreign material. Thus, the reason for modelling activated or, as is the case with some macrophages in their activated state, infected macrophages, is to see the contribution they make in their role as primary immune response to specifically tuberculosis. In the light of this, a term is added to (4.5), in which CD4+ T-cells die at the hand of infected macrophages at a rate k_2:

$$\frac{dT_{4(4)}}{dt} = S_4 - \mu_4 T_4 - k_1 v T_4 - k_2 D T_4 \tag{4.6}$$

Next, we move forward to the CD8+ T-cells, and add a term to (4.4) to signify their activation by infected macrophages. At a daily rate of k_3, the macrophages thus increase the cytotoxic T-cells (CTL's, or CD8+ T-cells):

$$\frac{dT_{8(2)}}{dt} = S_8 - \mu_8 T_8 + k_3 D T_8 \tag{4.7}$$

This modelling concludes the response of CD4+ T-cells and CD8+ T-cells. The next cell-type taken is that of the macrophages. Macrophages also die natural deaths, but are modelled different to CD4+ T-cells and CD8+T-cells in this regard. They are characterised as having an equilibrium value, which means that with no current immune-response, there will still be activated macrophages. It means that any newly-activated macrophages will be offset by this equilibrium value, as modelled here (where D_o is the equilibrium macrophage population):

$$\frac{dD_{(1)}}{dt} = \mu_d (D_o - D) \tag{4.8}$$

To continue, the macrophages are activated by free virus at a rate k_4:

$$\frac{dD_{(2)}}{dt} = \mu_d (D_o - D) + k_4 D v \tag{4.9}$$

and are also activated by the tuberculosis bacteria at a rate k_5:

$$\frac{dD_{(3)}}{dt} = \mu_d (D_o - D) + k_4 D v + k_5 D T_b \tag{4.10}$$

This concludes the modelling of the role of the macrophages in this study. The remaining items to model are the infected cells, the HI-virus and the tb bacteria.

Starting with the infected cells (To qualify the meaning of "infected cells", it has to be said that it means "infected CD4+ T-cells"), we model a natural death term for them, with rate μ_I, in:

$$\frac{dI_{(1)}}{dt} = -\mu_I I \tag{4.11}$$

The number of infected cells would increase by means of CD4+ T-cells that are infected by virus at the same rate k_1 that was presented in (4.5):

$$\frac{dI_{(2)}}{dt} = k_1 v T_4 - \mu_I I \tag{4.12}$$

Furthermore, the infected cells would also increase by infected macrophages at a rate k_2. This gives:

$$\frac{dI_{(3)}}{dt} = k_1 v T_4 + k_2 D T_4 - \mu_I I \tag{4.13}$$

which is the complete differential equation for the infected cells.

The viral load is modelled firstly with a natural death term, at rate μ_v:

$$\frac{dv_{(1)}}{dt} = -\mu_v v \tag{4.14}$$

New virions are produced by infected CD4+ T-cells at a rate $k_1 N_1$, where k_1 is from (4.12), and signifies the rate at which CD4+ T-cells become infected and N_1 is the number of virions produced by each infected cell. All this is shown in the next equation:

$$\frac{dv_{(2)}}{dt} = k_1 N_1 I - \mu_v v \tag{4.15}$$

Next, three terms are added to signify a decline in virus. The first of these is a decline due to the envelopment by macrophages at a rate k_4. This rate is the same rate from (4.10) that macrophages are activated by free virus. Furthermore, the number of virions that are enveloped follows from the number of free virions produced by the infected macrophages, which is N_2.

To summarize the addition of the latter term, one can say that the number of virions produced per macrophage (which is N_2 times D, and then times the infection v), is killed at rate k_4 and is shown as:

$$\frac{dv_{(3)}}{dt} = k_1 N_1 I - k_4 N_2 D v - \mu_v v \tag{4.16}$$

The second decline in virus is also by macrophages, but this addition is modelled so that a degree of freedom is added for macrophages that produce a single virion each in the same time-frame that other produce several. In essence the complete decline in macrophages in (4.16) can be modelled as :

$$\frac{dv_{(4)}}{dt} = k_1 N_1 I - k_4 N_2 D v - k_6 D v - \mu_v v \tag{4.17}$$

which is thus:

$$\frac{dv_{(5)}}{dt} = k_1 N_1 I - (k_4 N_2 + k_6) D v - \mu_v v \tag{4.18}$$

Finally, for the viral load, the decline in virions due to them being killed by cytotoxic T-cells (CD8+ T-cells) is given at a rate k_7 in:

$$\frac{dv_{(6)}}{dt} = k_1 N_1 I - (k_4 N_2 + k_6) D v - k_7 v T_8 - \mu_v v \tag{4.19}$$

The last cell-type that we consider in this modelling exercise is the response of M. tuberculosis in the immune response cycle.

A logistic bacterial growth term was taken from [10] to indicate the source dynamics of such an infection. This means that a bacteria is produced at a constant equilibrium value of K, with quadratic growth typical to a bacterial infection [3] and proliferates at a maximum rate of r_b, shown here:

$$\frac{dT_{b(1)}}{dt} = r_b T_b (K - T_b) \tag{4.20}$$

A decrease in the number of bacteria is firstly an onset of natural bacterial death at a rate μ_b:

$$\frac{dT_{b(2)}}{dt} = r_b T_b (K - T_b) - \mu_b \tag{4.21}$$

Furthermore, the death of bacteria by means of CD4+ T cells at rate k_8:

$$\frac{dT_{b(3)}}{dt} = r_b T_b(K - T_b) - k_8 T_b T_4 - \mu_b \tag{4.22}$$

and the death of bacteria by macrophages at rate k_9 is shown here :

$$\frac{dT_{b(4)}}{dt} = r_b T_b(K - T_b) - k_8 T_b T_4 - k_9 T_b D - \mu_b \tag{4.23}$$

This completes the modelling of the immune response for both virus and bacteria depicted in this study. Furthermore, the inclusion of the major players in the immune response, namely the macrophages, CD4+ and CD8+ T-cells enhance the credibility of the modelling exercise, and provides valuable insights into the actual reponse for a patient.

4.2. The Complete Model

The complete model from the modelling in the previous section is:

$$\begin{aligned}
\frac{dT_4}{dt} &= S_4 - \mu_4 T_4 - k_1 v T_4 - k_2 D T_4 \\
\frac{dT_8}{dt} &= S_8 - \mu_8 T_8 + k_3 D T_8 \\
\frac{dI}{dt} &= k_1 v T_4 + k_2 D T_4 - \mu_I I \\
\frac{dD}{dt} &= \mu_d (D_o - D) + k_4 D v + k_5 D T_b \\
\frac{dv}{dt} &= k_1 N_1 I - k_4 N_2 D v - k_6 D v - k_7 v T_8 - \mu_v v \\
\frac{dT_b}{dt} &= r_b T_b (K - T_b) - \mu_b T_b - k_8 T_b T_4 - k_9 T_b D
\end{aligned} \tag{4.24}$$

4.2.1. Model Attributes

The completed model contains 6 state variables or populations, where, once again, T_4 is denoted as healthy T_4 cells, I is the infected cell population, T_8 is activated T_8 cells or CTLs, D is Antigen Presenting Cells, v is the viral load and T_b the bacterial load. It contains 22 parameters that need be estimated for fitting to individual patients.

4.2.2. Link with Problem Definition

To link the model with the problem definition in section 1.1, it can be said that it satisfies the criteria of being a model for concurrent infections of HIV and TB. It is also a model that can be analysed for its ability to be identified and used in the practical case. The advantages and disadvantages have been considered under the previous heading, and the similarity to another model has been shown. It can consequently be

said that the model proposed in (4.24) through (4.24) addresses the problem outlined in the problem definition at the start of this dissertation, and lies the foundation from which analysis and practical usecases can be considered.

4.3. Similar Models

4.3.1. 4-Dimensional Model

The first model that this one is compared to, is the one described in [37]. It describes the action taken by the CTLs (CD8+ T-cells) during the immune response to an HIV-1 infection. Different infection-patterns are simulated by them, and specifically the movement between two infection-compartments, namely the blood plasma and the lymphatic tissues, is considered.

Similarities:

- The infected CD4+ T-cells is modelled in both [37] and (4.25).
- Viral count, activated CD4+ T-cells and CD8+ T-cells and macrophages are modelled in both systems.
- Both models employ natural birth and death terms.

Differences:

- The model in [37] is a two-compartmental model, while (4.25) is modelled as being only in 1 compartment, the blood plasma.
- The model in [37] shows both active and inactive cell populations for each cellular infection type, while (4.25) shows only activated cells.
- [37] has 13 differential equations, (4.25) has 6.
- (4.25) models the effect of concurrent viral and bacterial infections, [37] doesn't.

4.3.2. 2-Compartmental 13-Equation Model

The second model that is considered is the one described in [10]. It is a co-infection model for HIV-1 and M.tuberculosis with 4 state variables.

Similarities:

- Macrophages, viral load and bacterial load are modelled in both [10] and (4.25)
- Both models employ natural source and death terms.
- Logistic growth of a quadratic nature is used to model an increase in bacteria.

Differences:

- [10] has 4 states, while (4.25) has 6 states.
- The 4-dimensional model described in [10] does not contain a separate modelling of infected CD4+ T-cells cells.
- The model in [10] is not verified using field data. It is done and described in this study.
- Modelling of the T-cell population in [10] is a single equation, whereas the model described in (4.25) distinguishes between $CD8+$ T-cells and $CD4+$ T-cells.
- [10] considers the growth of CD4+ T-cells with a saturation constant. This means that it is limited in its growth. (4.25) does not take this into account.

4.4. Chapter Summary

This chapter showed how a co-infection model was constructed from medical knowledge of the immune response. The model was compared to other, similar models, and the differences and similarities pointed out.

5. Identifiability

WITH determining the identifiability properties of a system, it has been shown by [38] to be one of the most useful mathematical conclusions available to non-linear modelling theorists. It provides valuable insights also for a control-theoretic approach of the co-infection problem. One of the first examples of the use of identifiability in context of a biological immune-response model (in this case an HIV model) can be seen in [7].

As explained in thorough detail (from a practical control-engineering perspective) in [32], identifiability of a system indicates to the modeller whether or not all the parameters of a system can be uniquely determined from the measured outputs. It further provides information on how many such measurements are needed at each output.

The identifiability analysis provided in this section is shown to be incomplete in the sense that it highlights only the confidence that lies in determining certain parameters, but does not indicate a complete identifiability of all parameters of the co-infection model.

5.1. Identifiability Calculations

In this section follows a logical progression of the calculations for simplifying the proposed co-infection model, with the purpose of indicating its algebraic identifiability. The procedure followed here is similar to that seen in [32].

We start out with the model:

$$\begin{aligned}
\dot{T}_b &= r_b T_b(K - T_b) - \mu_b T_b - k_8 T_b T_4 - k_9 T_b D && (5.1)\\
\dot{v} &= k_1 N_1 I - k_4 N_2 D v - k_6 D v - k_7 v T_8 - \mu_v v && (5.2)\\
\dot{T}_4 &= S_4 - \mu_4 T_4 - k_1 v T_4 - k_2 D T_4 && (5.3)\\
\dot{I} &= k_1 v T_4 + k_2 D T_4 - \mu_I I && (5.4)\\
\dot{T}_8 &= S_8 - \mu_8 T_8 + k_3 D T_8 && (5.5)\\
\dot{D} &= \mu_d(D_o - D) + k_4 D v + k_5 D T_b && (5.6)
\end{aligned}$$

Next, the measured outputs are defined. They are:

$$\begin{aligned}
y_1 &= T_4\\
y_2 &= T_8\\
y_3 &= v
\end{aligned} \qquad (5.7)$$

We substitute (5.7) into the model to formulate it in terms of the measured outputs, which then yields:

$$\begin{aligned}
\dot{T}_b &= r_b T_b(K - T_b) - \mu_b T_b - k_8 T_b y_1 - k_9 T_b D && (5.8)\\
\dot{y}_3 &= k_1 N_1 I - k_4 N_2 D y_3 - k_6 D y_3 - k_7 y_3 y_2 - \mu_v y_3 && (5.9)\\
\dot{y}_1 &= S_4 - \mu_4 y_1 - k_1 y_3 y_1 - k_2 D y_1 && (5.10)\\
\dot{I} &= k_1 y_3 y_1 + k_2 D y_1 - \mu_I I && (5.11)\\
\dot{y}_2 &= S_8 - \mu_8 y_2 + k_3 D y_2 && (5.12)\\
\dot{D} &= \mu_d(D_o - D) + k_4 D y_3 + k_5 D T_b && (5.13)
\end{aligned}$$

From (5.12), we see that:

$$D = \frac{\dot{y}_2 - S_8 + \mu_8 y_2}{k_3 y_2} \qquad (5.14)$$

Substituting (5.14) into (5.10) yields:

$$\begin{aligned}\dot{y}_1 &= S_4 - \mu_4 y_1 - k_1 y_3 y_1 - k_2\left[\frac{\dot{y}_2 - S_8 + \mu_8 y_2}{k_2 y_2}\right] y_1 \\ &= S_4 - \mu_4 y_1 - k_1 y_3 y_1 - \frac{k_2}{k_3}\frac{\dot{y}_2 y_1}{y_2} + \frac{S_8 k_2}{k_3}\frac{y_1}{y_2} - \frac{k_2 \mu_8}{k_3} y_1 \\ &= \theta_1 - \theta_2 y_1 - \theta_3 y_3 y_1 - \theta_4 \frac{\dot{y}_2 y_1}{y_2} + \theta_5 \frac{y_1}{y_2} \end{aligned} \tag{5.15}$$

where

$$\begin{aligned}\theta_1 &= S_4 \\ \theta_2 &= -\left(\frac{k_2 \mu_8}{k_3} + \mu_4\right) = \theta_4\left(\mu_8 + \frac{1}{\theta_4}\mu_4\right) \\ \theta_3 &= -k_1 \\ \theta_4 &= -\frac{k_2}{k_3} \\ \theta_5 &= \left(\frac{S_8 k_2}{k_3}\right) = -\theta_4 S_8\end{aligned}$$

Higher-order derivatives of y_1 will read as

$$y_1^{(i)} = \theta_2 (x_1)^{(i-1)} + \theta_3 (x_2)^{(i-1)} + \theta_4 (x_3)^{(i-1)} + \theta_5 (x_4)^{(i-1)} \tag{5.16}$$

where

$$\begin{aligned}x_1 &= y_3 y_1 \\ x_2 &= \frac{\dot{y}_2 y_1}{y_2} \\ x_3 &= \frac{y_1}{y_2}\end{aligned}$$

Consequently, S_4, k_1, $\frac{k_2}{k_3}$, $\left(\mu_8 \frac{k_2}{k_3} + \mu_4\right)$ and S_8 can be computed from any persistently exciting trajectory[1] $y(t)$ such that rank $\delta(\dot{y}_1, \ddot{y}_1, {y_1}^{(3)}, {y_1}^{(4)}, {y_1}^{(5)})/\delta(\theta_1, \theta_2, \theta_3, \theta_4, \theta_5) = 5$, that is if

[1] This concept is defined on pages 268 and 269 of [32].

$$rank\begin{bmatrix} 1 & -y_1 & -x_1 & -x_2 & -x_3 \\ 0 & -\dot{y}_1 & -\dot{x}_1 & -\dot{x}_2 & -\dot{x}_3 \\ 0 & -\ddot{y}_1 & -\ddot{x}_1 & -\ddot{x}_2 & -\ddot{x}_3 \\ 0 & -{y_1}^{(3)} & -{x_1}^{(3)} & -{x_2}^{(3)} & -{x_3}^{(3)} \\ 0 & -{y_1}^{(4)} & -{x_1}^{(4)} & -{x_2}^{(4)} & -{x_3}^{(4)} \end{bmatrix} = 5$$

For determining output y_2, we first rewrite (5.10) to yield

$$D = \frac{\dot{y}_1 - S_4 + \mu_4 y_1 + k_1 y_3 y_1}{-k_2 y_1} \tag{5.17}$$

Substituting (5.17) into (5.12) then gives

$$\begin{aligned} \dot{y}_2 &= S_8 - \mu_8 y_2 + k_3 \left[\frac{\dot{y}_1 - S_4 + \mu_4 y_1 + k_1 y_3 y_1}{-k_2 y_1}\right] y_2 \\ &= S_8 - \mu_8 y_2 - \frac{k_3 \mu_4}{k_2} y_2 - \frac{k_3}{k_2}\frac{\dot{y}_1 y_2}{y_1} + \frac{k_3 S_4}{k_2}\frac{y_2}{y_1} - \frac{k_3 k_1}{k_2} y_3 y_2 \\ &= S_8 + y_2\left[-\mu_8 - \frac{k_3 \mu 4}{k_2}\right] + \frac{\dot{y}_1 y_2}{y_1}\left[-\frac{k_3}{k_2}\right] + \frac{y_2}{y_1}\left[\frac{k_3 S_4}{k_2}\right] + y_3 y_2\left[-\frac{k_3 k_1}{k_2}\right] \\ &= \theta_6 + \theta_7 y_2 + \theta_8 \frac{\dot{y}_1 y_2}{y_1} + \theta_9 \frac{y_2}{y_1} + \theta_{10} y_3 y_2 \end{aligned} \tag{5.18}$$

where

$$\begin{aligned} \theta_6 &= S_8 \\ \theta_7 &= \left(-\mu_8 - \frac{k_3 \mu_4}{k_2}\right) = -\frac{\theta_2}{\theta_4} \\ \theta_8 &= \left(-\frac{k_3}{k_2}\right) = \frac{1}{\theta_4} \\ \theta_9 &= \left(\frac{k_3 S_4}{k_2}\right) = -\frac{\theta_1}{\theta_4} \\ \theta_{10} &= \left(-\frac{k_3 k_1}{k_2}\right) = -\frac{\theta_3}{\theta_4} \end{aligned}$$

It can thus be seen that the parameters θ_6 through θ_{10} are dependent on θ_1 through θ_5, and no new parameter information can be gained from analysing the higher-order derivatives of y_2.

The last measured output, y_3, is determined by first solving for the infected cells I:

From (5.9) we have

$$I = \frac{\dot{y}_3 - D(-k_4N_2 - k_6)y_3 + k_7y_3y_2 + \mu_v y_3}{k_1N_1} \tag{5.19}$$

Substituting (5.14) for D into (5.19) gives

$$\begin{aligned} I &= \dot{y}_3\left[\frac{1}{k_1N_1}\right] + y_3\left[-\frac{(-k_4N_2 - k_6)\mu_8}{k_3k_1N_1} + \frac{\mu_v}{k_1N_1}\right] + y_3y_2\left[\frac{k_7}{k_1N_1}\right] \\ &+ \frac{\dot{y}_2y_3}{y_2}\left[-\frac{(-k_4N_2 - k_6)}{k_3k_1N_1}\right] + \frac{y_3}{y_2}\left[\frac{(-k_4N_2 - k_6)S_8}{k_3k_1N_1}\right] \end{aligned} \tag{5.20}$$

with first derivative

$$\begin{aligned} \dot{I} &= \ddot{y}_3\left[\frac{1}{k_1N_1}\right] + \dot{y}_3\left[-\frac{(-k_4N_2 - k_6)\mu_8}{k_3k_1N_1} + \frac{\mu_v}{k_1N_1}\right] + (y_3y_2)^{(1)}\left[\frac{k_7}{k_1N_1}\right] \\ &+ \left(\frac{\dot{y}_2y_3}{y_2}\right)^{(1)}\left[-\frac{(-k_4N_2 - k_6)}{k_3k_1N_1}\right] + \left(\frac{y_3}{y_2}\right)^{(1)}\left[\frac{(-k_4N_2 - k_6)S_8}{k_3k_1N_1}\right] \end{aligned} \tag{5.21}$$

From (5.5) we also have an equation for I as follows:

$$I = -\frac{1}{\mu_I}\dot{I} + \frac{k_1}{\mu_I}y_3y_1 + \frac{k_2}{\mu_I}\left[\frac{\dot{y}_2 - S_8 + \mu_8y_2}{k_3y_2}\right]y_1 \tag{5.22}$$

Now we substitute (5.21) for $\dot{I}$ into (5.22) to get

$$\begin{aligned} I &= \ddot{y}_3\left[-\frac{1}{k_1N_1\mu_I}\right] + \dot{y}_3\left[\frac{(-k_4N_2-k_6)\mu_8}{k_3k_1N_1\mu_I} - \frac{\mu_v}{k_1N_1\mu_I}\right] \\ &+ (y_3y_2)^{(1)}\left[-\frac{k_7}{k_1N_1\mu_I}\right] + \left(\frac{\dot{y}_2y_3}{y_2}\right)^{(1)}\left[\frac{(-k_4N_2-k_6)}{k_3k_1N_1\mu_I}\right] \qquad (5.23) \\ &+ \left(\frac{y_3}{y_2}\right)^{(1)}\left[\frac{-(-k_4N_2-k_6)S_8}{k_3k_1N_1\mu_I}\right] + y_3y_1\frac{k1}{\mu_I} \qquad (5.24) \\ &+ \frac{y_1\dot{y}_2}{y_2}\left(\frac{k_2}{\mu_Ik_3}\right) + \frac{y_1}{y_2}\left(\frac{-k_2S_8}{\mu_Ik_3}\right) + y_1\left(\frac{k_2\mu_8}{\mu_Ik_3}\right) \qquad (5.25) \\ & \qquad (5.26) \end{aligned}$$

Now, we can substitute for I into equation (5.9) to get $\dot{y}_3$:

$$\begin{aligned} \dot{y}_3 &= \ddot{y}_3\left[-\frac{1}{\mu_I}\right] + \dot{y}_3\left[\frac{(-k_4N_2-k_6)\mu_8}{k_3\mu_I} - \frac{\mu_v}{\mu_I}\right] \\ &+ (y_3y_2)^{(1)}\left[\frac{-k_7}{\mu_I}\right] + \left(\frac{\dot{y}_2y_3}{y_2}\right)^{(1)}\left[\frac{(-k_4N_2-k_6)}{k_3\mu_I}\right] \\ &+ \left(\frac{y_3}{y_2}\right)^{(1)}\left[\frac{-(-k_4N_2-k_6)S_8}{k_3\mu_I}\right] + y_3y_1\left[\frac{{k_1}^2N_1}{\mu_I}\right] \\ &+ \frac{y_1\dot{y}_2}{y_2}\left[\frac{k_2k_1N_1}{\mu_Ik_3}\right] + \frac{y_1}{y_2}\left[\frac{-k_2S_8k_1N_1}{\mu_Ik_3}\right] \\ &+ y_1\left[\frac{k_2\mu_8k_1N_1}{\mu_Ik_3}\right] + \frac{y_3\dot{y}_2}{y_2}\left[\frac{(-k_4N_2-k_6)}{k_3}\right] \\ &+ \frac{y_3}{y_2}\left[\frac{(k_4N_2+k_6)S_8}{k_3}\right] + y_3\left[\frac{(-k_4N_2-k_6)\mu_8}{k_3}\right] \\ &+ y_3y_2(-k_7) + y_3(-\mu_v) \qquad (5.27) \end{aligned}$$

We can thus determine the following parameters from higher-order derivatives of y_3:

$$
\begin{aligned}
\theta_{11} &= -\frac{1}{\mu_I} \\
\theta_{12} &= \left[\frac{(-k_4N_2 - k_6)\mu_8}{k_3\mu_I} - \frac{\mu_v}{\mu_I}\right] = -\theta_{11}\left[\theta_{20} + \theta_{24}\right] \\
\theta_{13} &= \frac{-k_7}{\mu_I} = -\theta_{11}\theta_{23} \\
\theta_{14} &= \frac{(-k_4N_2 - k_6)}{k_3\mu_I} = -\theta_{11}\theta_{20} \\
\theta_{15} &= \frac{-(-k_4N_2 - k_6)S_8}{k_3\mu_I} = \theta_{11}\theta_{20}\theta_6 \\
\theta_{16} &= \frac{{k_1}^2N_1}{\mu_I}, \rightarrow N_1 = -\frac{\theta_{16}}{\theta_{11}\theta_3} \\
\theta_{17} &= \frac{k_2k_1N_1}{\mu_Ik_3} = \theta_4\theta_{16} \\
\theta_{18} &= \frac{-k_2S_8k_1N_1}{\mu_Ik_3} = \theta_5\theta_{16} \\
\theta_{19} &= \frac{k_2\mu_8k_1N_1}{\mu_Ik_3} \rightarrow \mu_8 = \frac{\theta_{19}}{\theta_4\theta_{16}} \\
\theta_{20} &= \frac{(-k_4N_2 - k_6)}{k_3} \\
\theta_{21} &= \frac{(k_4N_2 + k_6)S_8}{k_3} = \frac{\theta_5\theta_{20}}{\theta_4} \\
\theta_{22} &= \frac{(-k_4N_2 - k_6)\mu_8}{k_3} = \frac{\theta_{20}\theta_{19}}{\theta_4\theta_{16}} \\
\theta_{23} &= -k_7 \\
\theta_{24} &= -\mu_v
\end{aligned}
$$

5.2. Identifiability Properties of the System

At this point, we tabulate all the parameters that have been determined, and the number of samples needed to do so. This can be seen in table 5.1. If a parameter was determined in, for instance, the equation for y_1, it was assumed that the value of the determined parameter would be used in all cases where it is situated in other equations as well. Thus, parameters that have been determined in previous equations are taken as constant for any further calculations.

Table 5.1.: Samples needed to determine parameters of each equation

Eqn.	Parameters	Samp. y_1	Samp. y_2	Samp. y_3	Par. Total
$\dot{y}_1$	θ_1 through θ_5	6	7	6	5
$\dot{y}_2$	θ_5 through θ_{10}	0	0	0	5
$\dot{y}_3$	θ_{11} through θ_{24}	6	7	8	14
Total					24

From the above table it can thus be seen that the total number of samples needed to determine θ_1 through θ_{24} from measurements of y_1, y_2 and y_3 respectively is 6, 7 and 8.

The model as shown in (4.25) is not algebraically identifiable. Table 5.2 maps the individual parameters in (4.25) to the clumped parameters that were determined in the identifiability calculations from the previous section (θ_1 through θ_{24}), and indicates the confidence which we have in determining their value in the optimisation routine by indicating if they are algebraically identifiable or not.

Table 5.2.: Algebraic identifiability properties of the parameters

Parameter	Clumped Representation	Algebraically Identifiable
S_4	(θ_1)	Yes
S_8	$\left(-\frac{\theta_5}{\theta_4}\right)$	Yes
k_1	$(-\theta_3)$	Yes
k_2	N/A	No
k_3	N/A	No
k_4	N/A	No
k_5	N/A	No
k_6	N/A	No
k_7	$\left(\frac{\theta_{13}}{\theta_{11}}\right)$	Yes
k_8	N/A	No
k_9	N/A	No
N_1	$\left(-\frac{\theta_{16}}{\theta_{11}\theta_3}\right)$	Yes
N_2	N/A	No
μ_v	$(-\theta_{24})$	Yes
μ_I	$\left(-\frac{1}{\theta_{11}}\right)$	Yes
μ_4	$\left(\theta_2 - \frac{\theta_{19}}{\theta_{16}}\right)$	Yes
μ_8	$\left(\frac{\theta_{19}}{\theta_4\theta_{16}}\right)$	Yes
μ_d	N/A	No
μ_b	N/A	No
D_o	N/A	No
K	N/A	No
r_b	N/A	No

5.3. Data

Following the study of the identifiability properties of the system, the next step would be the attempt at identification of the parameters by means of field data. It should investigated whether there is actually data available in the field to identify the parameters marked out with the partial identifiability analysis presented in this section. If

this was not the case, the identifiability study is purely theoretic, with no practical implication. For the proposed co-infection state, a set of data was consequently obtained from Dr. Clive Gray at the National Institute for Communicable Diseases in Johannesburg, South-Africa. Table 5.3 provides a summary of the characteristics of the received data, and some statistics on its usability and selection of prime candidates for verification of the proposed model.

The proposed model has six states, and three measured outputs. The selection of the measured outputs is not arbitrary, but is dictated by medical procedure, which, from a practical and feasible point-of-view, tests for HIV antibodies in the blood, and measures CD4+ and CD8+ T-Cell counts. The measured outputs are consequently defined as the viral load, the CD4+ T-cell count and CD8+ T-cell count.

It should be noted that, for the statistics of the patients, *all patients are infected by M. tuberculosis.*

The criteria for selection of a patient towards being included or excluded from the study was not arbitrary. Patient 1, for instance, was not included into the study due to its first sample being incomplete.

A list of the criteria used for selection is shown here:

- If the first sample, and hence the initial conditions for a patient, was incomplete, the patient was not used.
- If the last sample date was not at 78 weeks for a patient, the patient was not used.
- If a patient was not HIV positive, the patient was not used.
- If a patient died during, or even at the end of the sample period, his data was not used in this study.

From the list of criteria and the layout of patients in table C.1, it can consequently be seen which patients have been included into the simulations in this study. If a patient was ticked as “useable”, then it was included. Some deductions and interesting observations can be made about the information in both tables 5.3 and C.1.

For instance:

- With the specified selection criteria only 28 % of the total patient group was useable for this study. It means that the criteria was very stringent, but it also means that quality-of-results is retained. The results can thus safely be seen as

being taken from the best available subset of the dataset.

- Roughly half of the HIV-positive subset of the dataset was useable (39 out of 89).
- 43 % of patients were monitored or had samples for a timespan of 0-78 weeks.
- Roughly a third of all patients' data obtained was HIV negative.

Table 5.3.: Properties of the data-set : Totals

Attribute	Total
Patients	137
HIV positive	89
HIV negative	48
0 weeks sample intact	136
78 weeks sample intact	60
First and last sample intact	59
Seven samples complete - any cell-type	47
Useable patients	38
Unuseable patients	99
Percentage useable	27.7 %

5.4. Chapter Summary

This chapter looked at the implementation of an identifiability study for the model proposed in (4.25). The study found that only a few of the original model parameters could be algebraically identified, and then only if the required amount of samples are available. The available data was discussed along with statistics about the complete dataset and the number of useable patients. A sub-set of patients was selected as candidates for this study from the sub-set of useable data-sets, based on a simple list of criteria. The criteria was chosen to ensure quality-of-data, and to fit to the requirements (number of samples) of the identifiability analysis. Lastly, the model was linked with the data in an effort to show how many patients and which patients conform to the requirements.

6. Cost

6.1. Basic Cost Function : J_w

ESTIMATION of parameters employ a scalar cost-function and the Nelder-Mead algorithm, similar to that which is described in [23]. The basic cost for each of the measured variables is calculated based on the least-squares distance between the measured samples and the model response.

In light of this, the cost-function is given as:

$$J_w = \sum_{n=1}^{N} \frac{(\widehat{T}_4(t_n) - T_{4n})^2}{mean(T_{4n})N} + \sum_{n=1}^{K} \frac{(\widehat{v}(t_n) - v_n)^2}{mean(v_n)K} + \sum_{n=1}^{L} \frac{(\widehat{T}_8(t_n) - T_{8n})^2}{mean(T_{8n})L} \quad (6.1)$$

This cost-function divides the squared-difference of the sample- and the model reponse-vectors by the mean of the samples times the number of samples. This is done to accommodate sample errors and lessen the effect on the cost of samples that have a large variance relative to other samples in the set. For instance, if 6 of 7 samples had values of order 10^3 and one sample was of order 10^4, without the mean-division that single sample would have the greatest influence on the basic cost, which is undesirable.

6.2. Refinements and Penalty Terms

It is notable to mention that by using a minimization method on (6.1), of the nature of Nelder-Mead (described in [39]), the least-squares distance is not the only limitation one can put on calculating the cost. Knowledge of the measurements and their characteristics can also be built into the cost-function by means of extra penalty terms. These terms would encapsulate information such as the reaching of steady-states, the

rates of production and death of cells in relation to one another, and also the specific value at steady state. This means that one drives the model in a certain response "direction" or towards a specific "goal" by adding these terms.

6.2.1. Log-Based Viral Load

To continue with the cost-function from the previous section, one should note that tests for viral load are based on the log-scale (from [40]), hence (6.1) now becomes

$$J_w = \sum_{n=1}^{N} \frac{(\widehat{T_4}(t_n) - T_{4n})^2}{mean(T_{4n})N} + \sum_{n=1}^{K} \frac{(log\widehat{v}(t_n) - v_n)^2}{mean(logv_n))K} + \sum_{n=1}^{L} \frac{(\widehat{T_8}(t_n) - T_{8n})^2}{mean(T_{8n})L} \quad (6.2)$$

This incorporates the nature of the viral load measurement-strategy, to further avoid errors in calculation. Viral load counts can vary over a significantly larger range in relation to that of CD4+ T-cells or CD8+ T-cells. A typical viral load measurement can be anywhere from 50 copies per ml to several hundreds-of-thousands of copies per ml. This high range of variability led to the log-based measuring of viral load counts. To incorporate a log-based term into the cost-function, however, requires adjustment of that term to have an equal effect on the cost relative to the other terms. This weight-adjustment is shown in section 6.2.6.

6.2.2. Parameter Constraints

For each of the parameters in the proposed model, constraints can be imposed based on known practical limits for each specific parameter, as well as intuitive knowledge of the limits. To explain:

- Certain parameters occur throughout the bibliographical realm of biological modelling of the immune response. These parameters usually have tried-and-tested and accepted values. For instance, in different studies, namely both [1] and [10], it can be seen that the natural death rate of the viral load has a value around 2.5 per day. This parameter can either be kept at 2.5 or limited between 0 and 2.5. The choice thus can depend on the trade-off between how realistic the parameter value is for the practical case, or the freedom with which the optimisation routine can modify parameters to fit the model response to the field-data.

- Parameters can intuitively only vary between zero and a pre-determined value. The higher the range over which a parameter can vary, the easier it is for the optimisation routine to find a set of parameters that minimizes the given cost function. However, if the range is too large, the parameter might have an unrealistic value. For this reason, literature was consulted to determine a feasible range for well-known parameters, and more leeway was given with parameters that are not so well known in literature
- It is important to constrain parameters to have a positive value, as the sign of a term should only be governed by that which is added to the term upon modelling. If the parameters in a term change sign, the validity and reasoning behind the term is lost.

With the points discussed in this section in mind, the lower and upper limits were defined for each of the model parameters in table 6.1.

Table 6.1.: Parameter constraints for (4.25)

Parameter	Lower Limit	Upper Limit	Units
S_4	10e-4	5000	/day
S_8	0.1	5000	/day
k_1	10e-13	500	/day-vir.
k_2	10e-12	500	/day-cell
k_3	10e-13	500	/day-cell
k_4	10e-9	50	/day
k_5	10e-8	1000	/day
k_6	10e-6	1000	$\mathrm{mm^3 d^{-1}}$
k_7	10e-5	1000	$\mathrm{mm^3 d^{-1}}$
k_8	10e-5	1000	$\mathrm{mm^3 d^{-1}}$
k_9	10e-5	1000	$\mathrm{mm^3 d^{-1}}$
N_1	0.001	10000	none
N_2	1	10000	none
μ_v	0.001	3	/day
μ_I	0.001	5000	/day
μ_4	3e-11	1000	/day
μ_8	5e-9	1000	/day
μ_d	5e-9	1000	/day
μ_b	0.0005	1000	/day
D_o	1	10000	$\mathrm{mm^{-3}}$
K	0.001	15500	$\mathrm{mm^{-3}}$
r_b	0.001	1600	/day

6.2.3. Known Parameters

Some parameters, as have been said in the previous section, are known from literature. These parameters can be fixed in the optimisation routine before the simulation is run and the cost calculated, but after the optimisation was done. From the identifiability calculations in section 5.1, it was also seen that to determine the identifiable parameters, at least 8 measurements of the viral load is needed. The maximum available number of viral load samples is 7, thus we need to lessen the number of higher-order equations for the viral load. This is done by fixing certain parameters (It can be shown that by just fixing μ_v, one less equation is needed, and thus 1 less sample for the viral load). Consequently a correction is made to the optimised parameter values to force certain parameters into having a specific value. The following is a list of parameters taken from literature [1, 4, 10, 23, 41], that are well-known and established through practical experience and measurements:

Table 6.2.: Fixed parameters from literature

Parameter	Value	Units
μ_v	2.5	/day
μ_4	0.007	/day
μ_b	0.5	/day
μ_d	0.003	/day

To qualify each of the choices in table 6.2:

- From [42] a study of viral turnover rates indicate that HIV has a minimal half-life of approximately 6 hours. This means that in 1 day, the approximate death rate of $\mu_v = 2.4$ per day is well-founded.
- From [43], the natural lifespan of CD4+ T-cells was chosen as 143 days. This value was also used in [33], and although the natural lifespan of CD4+ T-cells is not well-known, the experimental value of $\mu_4 = 0.007$ per day is feasible.
- The natural growth and death of M. tuberculosis are well-studied and the value of $\mu_b = 0.5$ per day was taken from both [41] and [44].

- The natural death rate $\mu_d = 0.003$ per day, of dendritic T-cells, or macrophages, was taken from [35]

6.2.4. Maximum Derivative Reduction

If we consider the acquired dataset, it can be seen by inspection that many patients reach a steady state on the viral load. Furthermore, from similar model simulations such as those done in [10], it can be seen that the co-infection state (in other words, both the viral and the bacterial load) also settle into a steady-state. Using this information, as well as the information from the vaccine-readiness study (for HIV) done in [45] it is safe to assume that the proposed model (4.25) should also have a point where it reaches steady-state. From a medical perspective this intuitively makes sense, as a doctor would find it the easiest point at which to start giving the patient medication. With conditions that don't vary, the projected effect of medication can more easily be determined, whereas giving a patient medication during a fluctuating transient (before steady-state), would be both irresponsible and difficult to predict the outcome.

To explain the concept of maximum derivative reduction, one should consequently imagine that any curve of a linear nature has a certain point where its derivative has a larger scalar value than anywhere else on the curve. If this scalar is reduced, and the whole curve searched continuously for the point of the highest derivative, one can continue to reduce it and "force" the line into becoming a straight line with a zero-derivative. In other words we can drive the curve or response to a steady state.

This refinement is added for the viral load and the bacterial load to (6.2), to become:

$$J_r \quad = J_w + max\left(\frac{dv}{dt}\right) + max\left(\frac{dT_b}{dt}\right) \tag{6.3}$$

At each iteration of the optimisation routine, the maximum derivative of the viral load and bacterial load response is taken, and, because the optimisation minimizes the cost function, the maximum derivative is minimized, leaving a constant, linear response after optimisation.

6.2.5. Steady-State Value

Altough the response for the viral load is driven towards fitting it to the dataset, and although we are also driving the viral load and the bacterial load towards steady-states, the difference between the model response and the specific value at steady-state is also added to the cost. This is done to ensure that we can add extra weight to reaching the specific value that a patient's viral load settles at. If the difference between response and data is added as a pure difference, this would result in a possible negative value for the term, which would render the cost-function unusable (the possibility that the whole cost function has a negative value exists). To solve this problem, the difference is squared, and the positive square-root taken.

The cost function is now:

$$J_r = J_w + max\left(\frac{dv}{dt}\right) + max\left(\frac{dT_b}{dt}\right) + \sqrt[+]{(\widehat{v}_K - v_K)^2} \tag{6.4}$$

In (6.4), the value v_K is thus the last viral-load sample from a patient taken at 78 weeks. This value is taken as the steady-state value of the response.

6.2.6. Term-Weighting

All the terms in (6.4) can be weighted according to how important each optimisation goal is relative to others. The list of goals is, from what has been said in previous sections:

- Fit the response to the field data
- Reach a steady-state on all measured variables' outputs
- Reach a specific value at steady-state

With experimenting with a cost function, one can see the order of each term of the cost-function relative to another. Using this information, the initial qualifying or selection of weights would be based on which refinements are more important than others, and the terms weighted to have equal or different effects based on the importance of each item in the list of goals given above. In the case of the proposed model, the fitting of the model to the field data would be the most important, as this condition

is known from, and inherent in, the data. The next most important goal would be to reach a steady state value, and lastly to reach the actual steady-state value. The latter prioritisation is done so that a trade-off between reaching sample values and reaching the steady-state value is met. The last two prioritisations can also be made to be of equal weighting.

Weighting was done according to the scheme in the following table 6.3. It is important to note the order of each of the terms, and the respective weight added to the term to produce a new order for it. The weighs were chosen after experimental results from several patients indicated them to fit the prioritisation that was just discussed.

Table 6.3.: Cost function terms weighting

Term	Order Before Weighting	Weight	New Order
$\log \widehat{v}$ and data	10^0	100	10^2
$\widehat{T}_4$ and data	10^2	1	10^2
$\widehat{T}_8$ and data	10^2	1	10^2
Max. derivative : Viral load	10^3	0.02	10^1
Max. derivative : TB	10^3	0.02	10^1
Viral load final value	10^4	$5\text{x}10^{-4}$	10^0

It can be seen from table 6.3 that the priorities have been set up according to the requirements that were just discussed. The biggest influence will come from the sample fitting, then the maximum derivative, and then the final viral load value (Orders 10^2, 10^1 and 10^0 respectively).

6.3. Complete Cost Function

The final cost function after refinements have been added, is given as :

$$\begin{aligned} J_T &= \sum_{n=1}^{N} \frac{(\widehat{T}_4(t_n) - T_{4n})^2}{mean(T_{4n})N} + \sum_{n=1}^{K} \frac{(log\widehat{v}(t_n) - v_n)^2}{mean(logv_n))K} + \sum_{n=1}^{L} \frac{(\widehat{T}_8(t_n) - T_{8n})^2}{mean(T_{8n})L} \\ &+ max\left(\frac{dv}{dt}\right) + max\left(\frac{dT_b}{dt}\right) + \sqrt[+]{(\widehat{v}_K - v_K)^2} \end{aligned} \tag{6.5}$$

6.4. Chapter Summary

This chapter discussed and designed a cost-function for use in a parameter optimisation routine. The basic cost function was proposed and numerous refinements were discussed and added to the basic cost function. The result from this chapter is a complete cost-function that would drive the optimisation routine towards the goals of achieving a steady-state for each response, reaching the correct steady-state value and fitting the field data. The weighting of the cost-function terms relative to another was also discussed, to make sure that equal chances are given towards reaching all of the required goals.

7. Parameter Estimation

7.1. Estimation Steps

INIn this section, the steps for estimating the parameters for a patient is laid out. The optimisation algorithm developed by Nelder and Mead, postulated and verified in [46], was employed to minimize the final cost-function as developed in chapter 6 and shown in (6.5). Detailed information on how the Nelder-Mead algorithm minimizes a function of multiple variables, can be found in [46].

The Nelder-Mead Simplex search method (as it is formally known) does not rely on a smooth cost function to ensure proper minimization. This means that it is robust and can handle irregularities and divergent cost function behaviour. It should be said, though, that the Nelder-Mead algorithm can only ensure reaching a local minimum, and that other optimisation strategies will have to be followed if the global minimum is a desired outcome.

The next few sub-sections discuss each of the steps in the parameter estimation routine:

i. Determine the initial state vector $\vec{x_0}$ by using the first sample of the CD4+ T-cells, CD8+ T-cells and viral load, as well as selecting an arbitrary value for the initial bacterial load, macrophages and infected cell count.

ii. Select a nominal parameter set, χ_0, to start the optimisation routine with. This parameter set was obtained from fitting the proposed model to the published results of the 4-dimensional model, and the procedure can be seen in section 10.1.

iii. The timespan over which optimisation takes place t_s, the initial state vector $\vec{x_0}$, the nominal parameter set χ_0, the data sample vectors T_{4n}, T_{8n}, v_n and the

estimated parameter set (initially empty), $\hat{\chi}$, is passed to the optimisation function. The optimisation function returns a value, calculated through evaluating the cost function, to the optimisation algorithm (Nelder-Mead). The Matlab-routine, $fminsearch$, was employed for implementation of the Nelder-Mead algorithm

iv. Within the optimisation function, before the state-vector $\vec{x}$ is numerically integrated, parameter constraints are enforced. The constraints ensure that parameters may not have negative values, and also that they may not have unrealistically, impractical values.

v. Some parameters may be fixed from literature. These are implemented at this point.

vi. Numerically integrate the state vector $\vec{x}$. The result from this is the estimated states matrix $\widehat{\mathbf{X}}$.

vii. Determine, at this point, the estimated states' values that correspond, in time, to the samples that were obtained. Each estimated state vector will have the same length as that of the sample vectors. The result from this step is that we have 6 vectors: the 3 estimated state vectors ($\widehat{v}$, $\widehat{T}_4$ and $\widehat{T}_8$) and the 3 sample vectors (T_{4n}, T_{8n} and v_n).

viii. At this point, the estimated state vectors and the sample vectors are passed to the cost function J_T seen in (6.5).

ix. Calculation of the cost follows the reasoning discussed in chapter 6. With the use of the least-squares distances between the sample vectors and the estimated state vectors, and the relevant refinements, the calculated cost is returned to the optimisation function.

x. The optimisation algorithm adjusts the parameters (or the vertices of the simplex, as seen in [39]), and the optimisation steps are repeated. For the optimisation routine to stop, certain conditions are specified. The first condition is that of a tolerance on a change in the calculated cost. This is set very low, at 0.01. If consecutive cost calculations fall within 0.01 of another, the optimisation routine is finished. Furthermore, two exit conditions are set : The number of optimisation function evaluations is set at 5000, and the number of iterations of the routine is set at 1000. These values were adjusted from practical experience with the

simulation architecture discussed in appendix A.

xi. If it was found that, during estimation, the parameter-constraints were breached, a basic cost of high value is returned. This, in itself, will drive the optimisation routine away from selecting parameters that might breach the constraints.

7.1.1. Initial Conditions Selection

The selection of the model initial conditions was made based on both an intuitive selection (in other words a well-informed guess), and by taking the values of the first samples in the dataset for a specific patient. To illustrate this, we consider the initial state vector:

$$\vec{x_0} = \begin{bmatrix} T_{40} \\ T_{80} \\ V_0 \\ I_0 \\ D_0 \\ T_{b0} \end{bmatrix}$$

If the vector of patient-data at time $t = 0$ days, was $\Phi_{1:} = [\ 0\ 4.628154\ 42477.01599\ 640\ 1862\ ]$, then the initial state vector would firstly be constructed like this:

$$\vec{x_0} = \begin{bmatrix} 640 \\ 1862 \\ 42477.01599 \\ I_0 \\ D_0 \\ T_{b0} \end{bmatrix}$$

There is no information that can be used to directly determine the values for I_0, D_0 and T_{b0}. However, an intelligent guess can be made as a starting point.

Two methods were used to guess the values, of which the first is described in the following steps:

i. To guess T_{b0}:

A study was done in [47] to determine the CD4+ T-cells counts for a large group of patients during their first few months of submission. The patients were co-infected with HIV-1 and TB, and they were from Africa. These results, taken from [47], is shown in table 7.1. By using these values, let's make the rough assumption that the maximum value in the range grows linearly over each month, with a starting-value of 475. Furthermore, the average difference between the maximum value in the range per month is roughly 45. If we assume a medium-sized TB infection as a starting point, with value 700 copies per ml (Seen from results in [10]), then the assumed linear relationship between the CD4+ T-cell growth and the TB growth is shown in figure 7.1. The figure can now visually be used to guess an initial value for the TB count, cased on the initial value of that patient's CD4+ T-cell count. For instance, for the example we are using, the initial CD4+ T-cell count is 640, hence by inspection of figure 7.1, the initial TB count is chosen as 800.

ii. To guess D_0:

According to [48], the approximate number of white blood cells in a healthy human is 6000 copies per ml. Of these, the percentage macrophages is between 1 and 6% ([34]), and around 10% are CD4+ T-cells ([49]). This information is, although for a healthy human, the best relationship to use when guessing initial values of the macrophages population for a patient. If we thus take the CD4+ T-cell count as 640, and with the same relationship say that the ratio of CD4+ T-cells to the total white blood cell population of 6000 is then 10.6%. If we then take 4% less than that, we reach 6.6%, which amounts to 396 copies per ml. The initial value for the macrophage population of this specific patient is thus guessed as 396 copies per ml.

iii. To guess I_0:

The total number of infected cells are assumed to be double that of the uninfected CD4+ T-cells, thus, in this case the infected cells would be 1280.

The second method that was used is much simpler. Any arbitrary values were selected for the initial conditions of bacteria, macrophages and infected cells. The

simulations were run, and the initial conditions were modified using the GUI-tool described in appendix B. With the tool, the responses can be visually inspected while the initial conditions are changed, to see if they can be manipulated to fit the data better. Once the user of the GUI is satisfied with the results, the values can be used to re-simulate the specific patient and obtain better results.

Finally, for this specific patient, the initial conditions vector is thus:

$$\vec{x_0} = \begin{bmatrix} 640 \\ 1862 \\ 42477.01599 \\ 1280 \\ 396 \\ 800 \end{bmatrix}$$

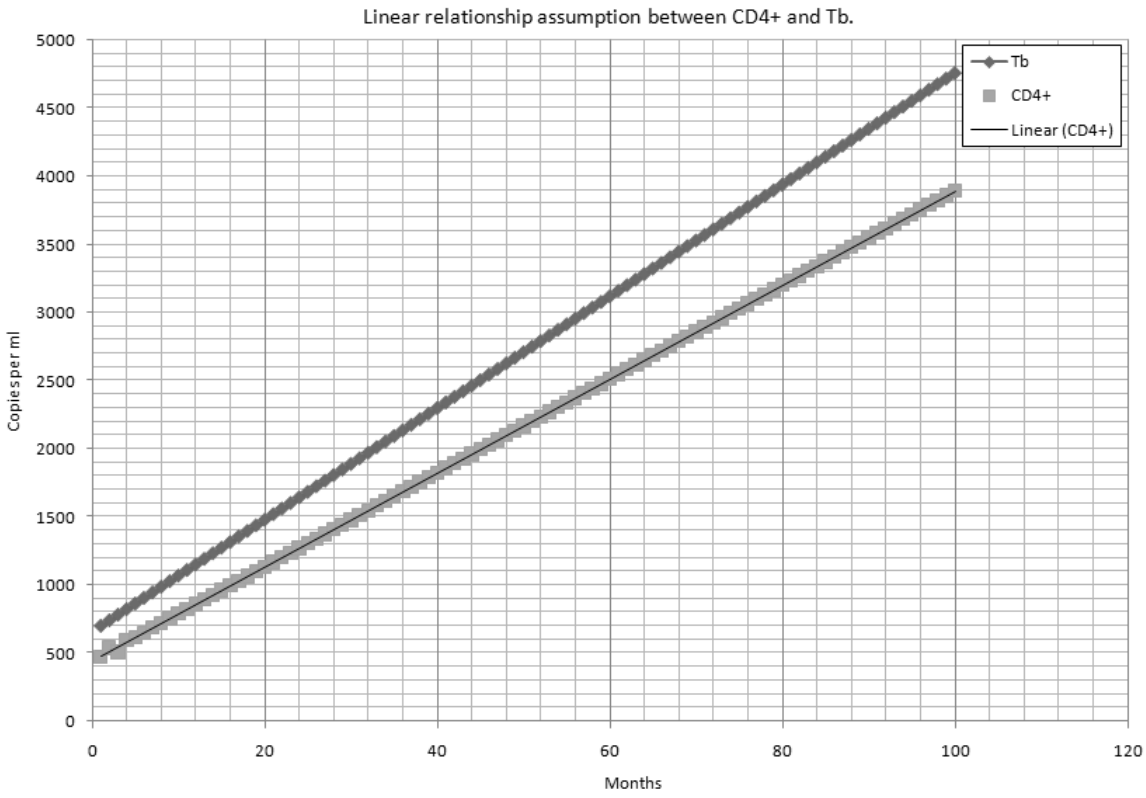

Figure 7.1.: Assumed linear relationship between the maximum range for CD4+ T-cells over time and TB growth.

Table 7.1.: CD4+ T-cells counts for co-infected patients during their first few months of submission. ([47])

	CD4 count on submission	Month 1	Month 2	Month 3
Sample size	104	73	56	45
Median	230	270	260	380
Range	90-475	90-540	120-510	200-600

7.1.2. Nominal Parameter Set

An initial default set of parameters for the model was chosen from [10] and [37]. This set is seen in table 7.2. By inspection of the initial simulations, it was found that the set does not produce very good results, as the minimization does not converge to a feasible local minimum with a well-formed model response (to qualify "well-formed", the optimisation goals listed in section 6.2.6 should be considered. To continue, a new set of nominal parameters were found by generating data from the 4-dimensional model in [10], and using this data as a "patient", thereby estimating a set of parameters for the proposed model in (4.25) to fit to the 4-dimensional model. This set is seen in table E.1. A further, last refinement, was done: This entailed simulating and optimising the parameters for all patients using the parameters in table E.1, and then taking the patient with the best benchmark (from table D.1), and using their parameters as the refined nominal parameter set. This set is seen in table E.2, and was used as the basis from which the complete patient simulation-results in appendix E was obtained.

7.1.3. Optimisation Function

The optimisation function is a function that is passed to the optimisation algorithm. In practice, this function is implemented as an algorithm that enforces parameter constraints, sets model initial conditions, numerically integrates the state vector, and returns the calculated value through the cost-function. It thus takes as inputs the timespan t_s, the initial state vector $\vec{x_0}$, the nominal parameter set χ_0, the data sample vectors T_{4n}, T_{8n}, v_n and the estimated parameter set $\hat{\chi}$. Its output is a calculated scalar value, which is the cost from (6.5). It can thus be written as:

Table 7.2.: Nominal parameter set purely from literature

Parm.	Description	Value	Units
S_4	Source - Healthy T_4 cells	10	/day
S_8	Src - T_8 cells	10	/day
μ_4	Dth rate - T_4 cells	$2.2\text{x}10^{-1}$	/day
μ_8	Dth rate - T_8 cells	$7.5\text{x}10^{-5}$	/day
μ_b	Dth rate - tb	$5\text{x}10^{-7}$	/day
μ_d	Dth rate - Dendr. cells	$5\text{x}10^{-2}$	/day
μ_v	Dth rate - HIV	$1\text{x}10^{-11}$	/day
μ_I	Nat. death : inf. cells	$3\text{x}10^{-3}$	/day
k_1	Rate - T_4 cells	$2.0\text{x}10^{-5}$	/day-vir.
k_2	Rate - T_4 cells by APC's	$2.0\text{x}10^{-7}$	/day-cell
k_3	Rate - T_8 cells by APC's	$1.0\text{x}10^{-7}$	/day-cell
k_4	Recr. - APC's by HIV	$3.3\text{x}10^{-7}$	/day
k_5	Recr. - APC's by Mtb	$2.5\text{x}10^{-7}$	/day
k_6	Dth rate : virus by APC's	$7.4\text{x}10^{-5}$	mm^3d^{-1}
k_7	Dth rate : virus by T_8	$9.8\text{x}10^{-11}$	mm^3d^{-1}
k_8	Dth rate : tb by T_4	$5\text{x}10^{-10}$	mm^3d^{-1}
k_9	Dth rate : tb by APCs	$5\text{x}10^{-10}$	mm^3d^{-1}
D_o	APCs equilib. value	140	mm^{-3}
K	Carry. cap.: tb pop.	550	mm^{-3}
r_b	Max. tb prolif. rate	$1\text{x}10^{-4}$	/day
N_1	Free vir. by inf. cells	500	none
N_2	Free vir. by APCs	500	none

$$f(t_s, \vec{x_0}, \chi_0, \hat{\chi}, T_{4n}, T_{8n}, v_n) = J_T \tag{7.1}$$

The steps followed by the optimisation function is shown here, in pseudo-code form:

Begin

Set the model initial conditions $\rightarrow \vec{x_0}$

if (first iteration) **then**

Enforce parameter constraints $\rightarrow \chi_0$

Set model parameters $\rightarrow \chi_0$

else

Enforce parameter constraints $\rightarrow \hat{\chi}$

Set model parameters $\rightarrow \hat{\chi}$

endif

Set fixed parameters in model

Integrate (numerical) $\rightarrow \int \dot{\widehat{X}}$ to get $\widehat{X}$

Construct $\widehat{v}$, $\widehat{T}_4$ and $\widehat{T}_8$ from $\widehat{X}$

Calculate and return value of cost : J_T

End

7.1.4. Enforce Constraints

When parameter constraints are enforced, we make sure that parameters fall within acceptable values from literature, as well as making logical sense. In this light, negative parameters can never be used, as the sign of a term is part of the intuitive modelling process. All constraints are therefore enforced to let parameters have non-zero values that are bounded on the smaller end by the minimum allowable value for that parameter and at the top end by acceptable values from literature. All parameter constraints used in this study can be seen in table 6.1.

7.1.5. Numerical Integration

The implementation of the numerical integration part of the optimisation routine was done in Matlab's *Simulink* environment. A typical screenshot of how a part of the model was constructed is shown in figure 7.2.

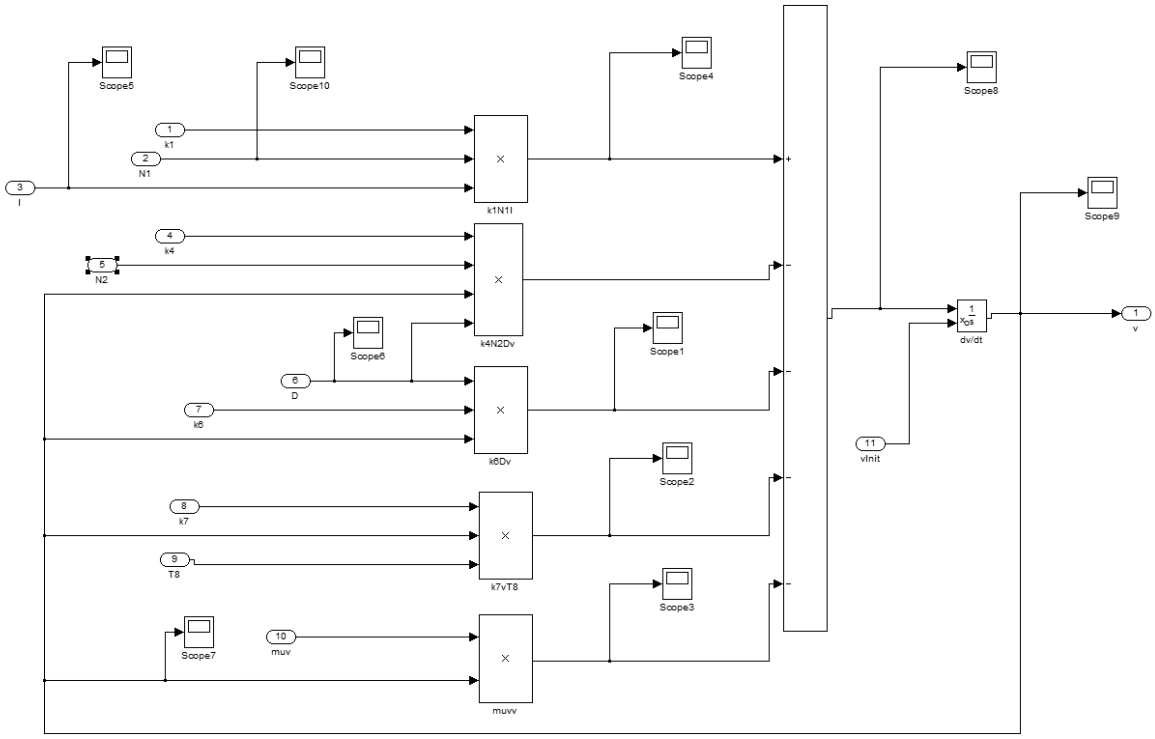

Figure 7.2.: Viral-load sub-block in Simulink for the co-infection model.

With integrating in the Simulink environment, one can select integration routines of different orders, each with a more accurate result the higher the order. The trade-off is the time it takes to integrate, together with the time-steps involved if the model is highly non-linear. For this study, the variable-step ODE23s (stiff./Mod. Rosenbrock) solver was used. It proved to provide relatively quick integration results, while being able to handle the small time-steps involved with this model. The step-size was variable, with the minimum step size set at 10^{-15}.

To explain the previous paragraph, the Matlab help section provides some information with regards to this solver:

> " ode23s is based on a modified Rosenbrock formula of order 2. Because it is a one-step solver, it can be more efficient than ode15s at crude tolerances.

It can solve some kinds of stiff problems for which ode15s is not effective.

For a stiff problem, solutions can change on a time scale that is very short compared to the interval of integration, but the solution of interest changes on a much longer time scale. Methods not designed for stiff problems are ineffective on intervals where the solution changes slowly because they use time steps small enough to resolve the fastest possible change. Jacobian matrices are generated numerically for ode15s and ode23s."

The proposed model in (4.25) can be described as a "stiff" problem, and because of its high non-linearity its values can change very quickly in relation to the interval of integration. The specific solver used was thus theoretically and, as is shown in the simulation results, practically a good choice.

7.1.6. Estimated State Vectors

The construction of the estimated state vectors $\widehat{v}$, $\widehat{T}_4$ and $\widehat{T}_8$ is a fairly simple process, shown in the following pseudo-code representation (Note that t_n represents the data sample times and $\mathrm{t}(\widehat{X})_i$ the time in row i of the estimated outputs matrix):

Begin
  n = 1
  for i=1 to (number of rows in $\widehat{X}$) **do**
    if $t_n == \mathrm{t}(\widehat{X})_i$ **then**
      $\widehat{v}_n = \widehat{X}_{i2}$ (the 2nd column contains the viral load response)
      $\widehat{T}_{4n} = \widehat{X}_{i5}$ (the 5th column containts the T_4 cells reponse)
      $\widehat{T}_{8n} = \widehat{X}_{i6}$ (the 6th column containts the T_8 cells reponse)
      n = n + 1
    endif
  endfor
End

7.2. Chapter Summary

In this chapter, the implementation of the parameter optimisation routine was discussed. Each step of the routine was looked at and, where applicable, short section of pseudo-code was given to indicate the logical reasoning for that step. The notion of intelligent "guesswork" was discussed with regards to the selection of the initial conditions for the macrophages, infected cell count and the bacterial load. Furthermore, a method was defined to reach a proper nominal parameter set for this study. Lastly, issues such as the selection of parameter constraints, exit conditions for the optimisation routine, fixed parameters and the construction of estimated state vectors for use with the cost function were discussed.

8. Simulation

IMPLEMENTATION of the simulation architecture was done with ease-of-use and flexibility in mind. In this chapter, the process of implementation is laid out, from planning what functionality the software should have to the construction thereof with the available development tools. Certain problems and solutions in the simulation process is discussed here and recommendations are made on how to use the simulation architecture effectively. A detailed description of the simulation architecture code functionality can be found in appendix A.

8.1. Planning

The diagram which was used in the planning process of the functional modules for the simulation architecture is shown in figure 8.1. To describe the diagram, we first look at the inputs. The I/O-handling function takes the nominal parameter set, the patient data, physical output folders that are defined, simulation options (discussed in section 8.3) and the initial state values, parses the inputs if needed and converts the input to matrices and vectors. In this format Matlab can perform calculations on it and deliver the necessary results. The I/O-handling function interfaces with the parameter search algorithm, the optimisation function used by the algorithm and also stores the patient data into vectors for use by the other function blocks. Two function blocks handle the setting of constraints to the parameters and the fixing of parameters to values known from literature. The model is simulated (numerically integrated) by the integration function, and results from the model are also plotted through the plotting function. Estimated state vectors are constructed from the integrated states, and this result is fed to the cost function, from where the cost is calculated and a benchmark for the patient

set. The cost function output value is further used to start the iterative process again, thus it is monitored by the parameter search algorithm for it to make adjustments and improve the optimisation output. The outputs from the architecture are the plotted dependent variables (after integration), optimised parameter sets in latex format for document-automisation, a file containing all the patient benchmarks and files for each patient's optimal parameter set in plain-text.

The next tool that was designed is a GUI-tool that allows the user to instantaneously change parameters within the proposed model and see the results plotted in real-time. The goal of this tool is mainly to be able to change the initial conditions to see what the effect would be, and to use any improvement seen as a new starting-point for the optimisation routine on the specific patient involved. To explain the planning diagrom in figure 8.2, the first things we look at are the inputs. The inputs are optimised parameter sets that were generated by the simulation architecture for each patient, a setting of the initial conditions for the states and the selection of a patient (and a patient's data). With these inputs, the user is able to simulate and integrate the states by setting parameter-sliders to a desired value, while the graphs in the GUI update in real-time. The focus with this tool should be to use the initial conditions sliders the most, to ensure that the model response is lined up with the data, especially because only 3 of the 6 initial conditions are known.

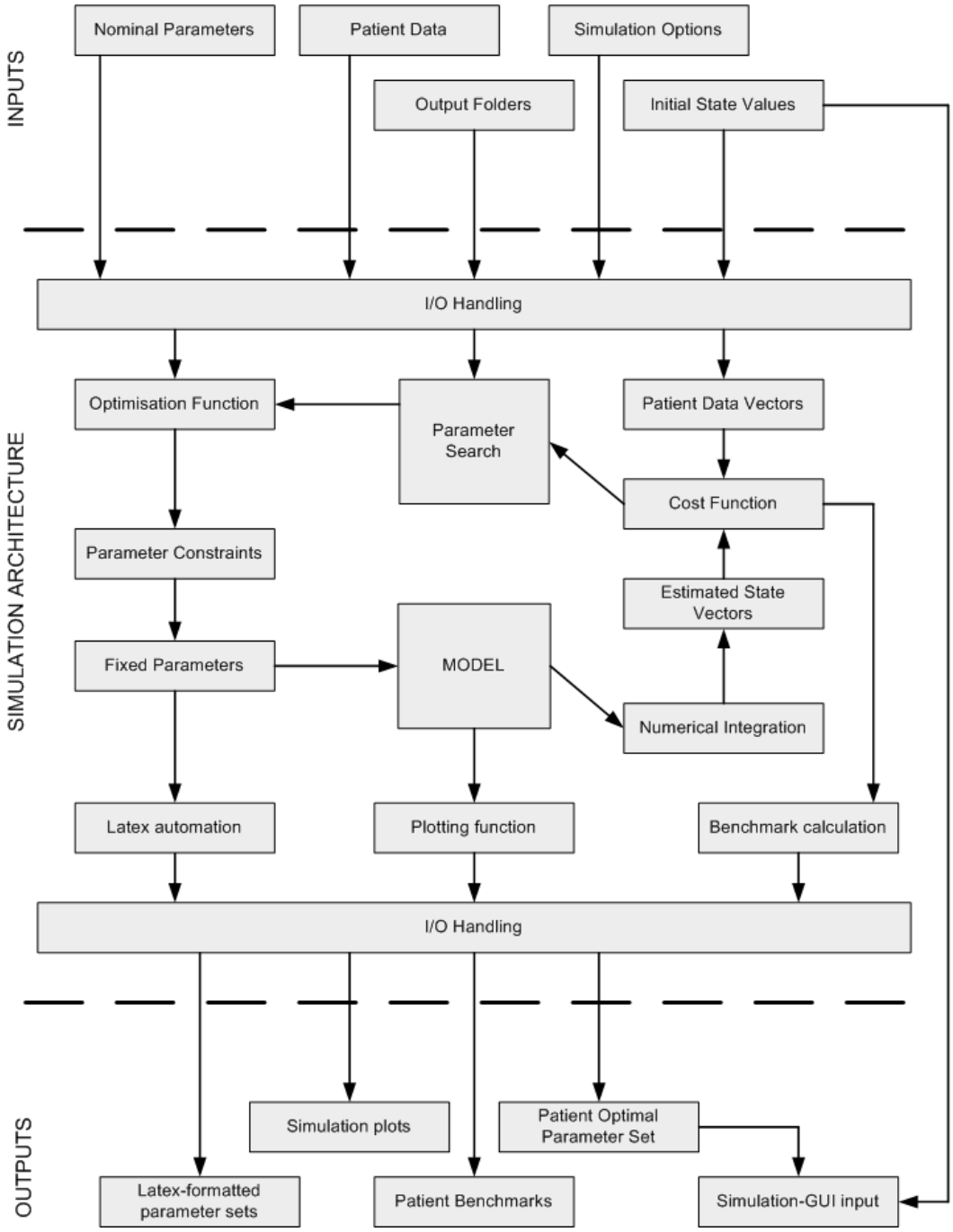

Figure 8.1.: High-level planning diagram for construction the simulation architecture.

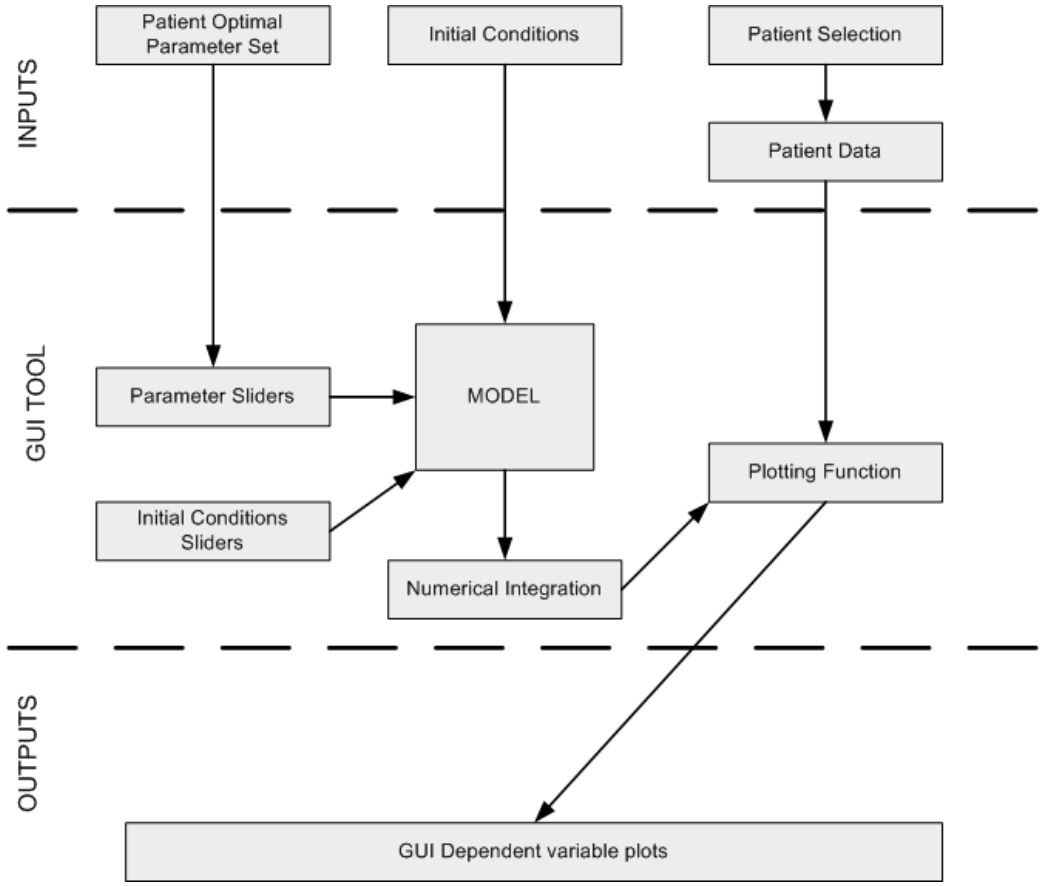

Figure 8.2.: High-level planning diagram for the GUI-tool.

8.2. Construct

The construction of the simulation architecture was done with the following goals in mind:

- Modularity
- Flexibility
- Ease-of-use
- Input/Output transparency and structuring
- Different simulation options
- Robust data-handling

Modularity:

The functional blocks shown in figure 8.1 were grouped together into Matlab m-files. This mapping of function-to-file was done to group functions of a similar nature into the same file, and is shown in table 8.1.

Flexibility:

The construction emerging from the modularity criteria leads to a compact selection of m-files, each with a grouped selection of functionality. This functionality can easily be extended because of the modular nature of the coded sections. To illustrate the flexibility, one can add new fixed parameters for the model to fixed_parameters.m, and they will reflect throughout all the files where fixed parameters are implemented.

Ease-of-use:

It is arbitrary to see that this architecture is not complex to use. The small selection of options available to the user in table 8.3 adds to this. With only these few options, the user can simulate treatment, simulate the whole selection of patients or just a single patient, set parameters for controlling the generation of data or normal plots and indicate which parameter sets should be used.

Input/Output transparency and structuring:

If the inputs and outputs are transparent to the user it means that they needn't be changed or manipulated when the simulation starts. They just need to be put into the correct input folder and the data parser and I/O functionality will handle them. Furthermore, transparency and structure means that inputs are provided in input-folders and output are written to output folders. These folders are created automatically, which makes it easy for the user of the architecture to find the relevant output information. The folder-structure for the simulation architecture is shown in figure 8.3.

Different Simulation Options:

The different simulation options can be seen in section 8.3. This criteria is adhered to to give the user a diverse selection of options with a single architecture. It makes the simulation architecture into an encompassing tool for simulating the co-infection model.

Robust data-handling:

Handling of data can sometimes be a problem if the data is not parsed correctly and presented to the software in a state that is dissimilar to that which it had in the data files. With this architecture, data is parsed into matrices and samples are removed if they are incomplete (Refer to section 13.3.1 for an illustration on how this done). This makes the data-handling robust and ensures that data filtered before it is fed to the architecture with high integrity and usability.

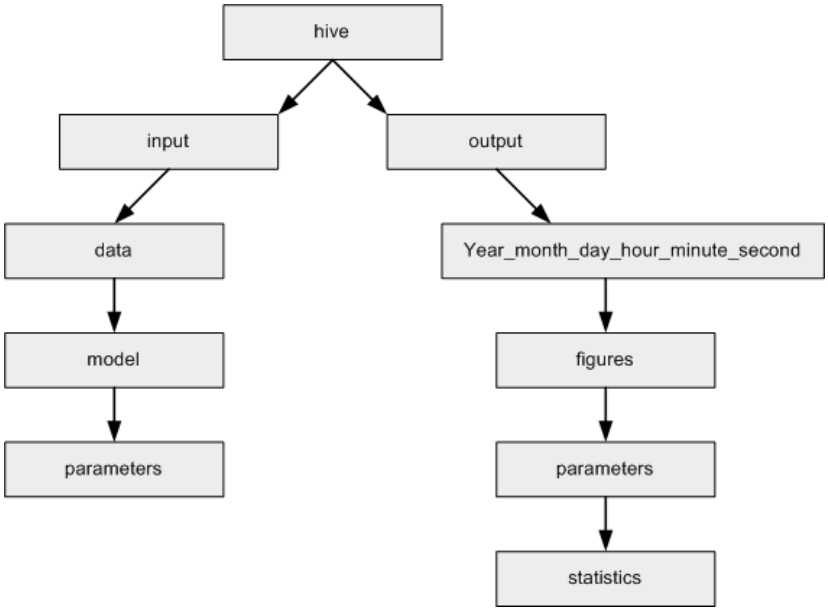

Figure 8.3.: Folder structure for the simulation architecture.

It is arbitrary to see that this architecture is not complex to use. The small selection of options available to the user in table 8.3 adds to this. With only these few options, the user can simulate treatment, simulate the whole selection of patients or just a single patient, set parameters for controlling the generation of data or normal plots and indicate which parameter sets should be used.

Table 8.1.: Mapping of planned architecture functional blocks to M-files

Functional Block.	M-file
Nominal Parameters	start.m
Output Folders	start.m
Simulation Options	start.m
Initial State Values	start.m
Benchmark Calculation	start.m
Parameter Search	main.m (using fminsearch.m)
Plotting function	main.m
Patient Data	data_parser.m
I/O Handling	All files.
Optimisation Function	optimise.m
Patient Data Vectors	optimise.m
Estimated State Vectors	optimise.m
Model	model.mdl used in main.m and optimise.m
Parameter Constraints	parameter_constraints.m
Fixed Parameters	fixed_parameters.m
Latex Automation	latexoutput.m
Cost Function	cost.m
Numerical Integration	Simulink environment

8.3. Options

The following table lists and describes all the options that can be set for the simulation architecture:

Table 8.2.: Simulation architecture user options.

Option	Description
OPTIMISE	The selection of this option enables the parameter optimisation routine. If this option is not selected, the model is integrated and plotted with the provided nominal parameter set.
OPTIMISED_AS_NOMINAL	Use the currently-available optimised parameter set as the nominal set for the patient(s)
USE_GENERATED_DATA	Use a specified, generated data set rather than one one of the acquired patients' sets.
GENERATE_DATA	Generate data samples from the numerical integration of the patient states.
REDUCED_SAMPLES	If GENERATE_DATA is selected, this option will generate a reduced number of data samples from the model simulation
T4_VARIANCE T8_VARIANCE V_VARIANCE	If GENERATE_DATA is selected, each of these options enable the user to select the variance of the data that is generated for the T4 cells, T8 cells and viral load.
TREATMENT	If this option is "true", then treatment for the patients is simulated
TREATMENT_START_TIME	This option indicates at what time during the simulation treatment should start.
P P_I	P is the vector of patient numbers. P_I is the matrix of patient initial conditions. It should be changed at indexes corresponding to the patient numbers vector.
MANUAL Y	If the MANUAL option is "true", then a single patient can be selected for simulation, using the option Y to specify the patient's index in the patient number vector P.

8.4. Tools Used

The tools that were used during the construction of the simulation architecture and the GUI-tool are:

- Matlab's Simulink environment was used to visually contruct the model itself, as seen in part in figure 7.2
- *guide*, the Matlab "GUI design editor" was used to construct and build the GUI-tool.
- Software tools Microsoft Visio and Freemind were used to plan how the simulation architecture should work and function.

8.5. Usage Procedure : GUI and Architecture

The simulation architecture and the GUI-tool can be used by themselves, but the best effect and optimisation can be done when they are used in conjunction with one another. The summarised procedure for using them together for finding a set of patient parameters and initial conditions is:

i. Set the options in the architecture to be MANUAL and select the patient in index Y. Alternatively all patients can be simulated by setting the MANUAL option to "false".
ii. Run the m-file called start.m to start and finish the simulation.
iii. The optimised parameters for the patient(s) are written into the specific timestamped output folder with a subfolder called "parameters". Furthermore, they are also written to a general parameters folder where the simulation GUI may use them.
iv. After looking at the plots in the "figures" folder, the user might decide that the initial conditions need to be adjusted to formulate a better response and steady-state.
v. The GUI-tool should be loaded at this point and the relevant patient selected.
vi. Adjust the GUI sliders, specifically the initial conditions for macrophages, infected cells and the bacterial load.

vii. If the user is satisfied by the response generated by the GUI, the initial conditions should be noted and changed in the P_I matrix in the simulation architecture. This sets the specific patient's initial conditions up for the next simulation.

viii. Set the USE_OPTIMISED_PARAMETERS option to "true". Now, the optimisation routine will start at the response that was seen in the GUI, and a better optimisation will be found for that patient.

8.6. Problems and Solutions

Certain problems were encountered during the construction of the simulation architecture software. These problems are briefly listed here, and the way in which they were solved is also lined out.

8.6.1. Incomplete and Inaccurate Datasets

Incomplete and inaccurate datasets were a problem due to the inaccuracies in the nature of medical sampling process, as well as the logistics of retrieving complete datasets from patients. If there were no entries at a specific sampling time for, say the viral load, but at the same time there were values for the CD4+ T-cells and CD8+ T-cells, the whole sampling day was removed. The cost-function relies on complete data being available at any specific sampling time, otherwise the cost is calculated wrongly, which results in the optimisation routine steering away from parameters that would otherwise have been proper and feasible.

8.6.2. Negative Estimation and Negative Log

The problems of having to deal with data and simulation results that do not make logical sense were handled almost simultaneously. If one numerically integrates any of the states and the resulting values prove to be of negative sign, this information becomes unusable (negative populations do not exist) and had to be handled by ensuring that the optimisation routine steers away from selecting parameters that force the model into producing negative results. Consequently, if a negative estimation was detected,

the value was squared to remove the sign and the positive square-root taken to leave a positive value. This corrects the negative value by removing its sign, and in effect it leaves a value that is twice the numerical distance away from the original value. The result is that the estimation would be completely wrong and result in a higher cost at the cost-function which, in turn, would steer the optimisation routine away from the parameters that caused this inaccurate value.

8.7. Chapter Summary

In this chapter we looked at how the simulation architecture for this study was constructed and implemented. We considered the architecture and the GUI-tool, and laid out procedures for using each of these tools. The construct of the simulation architecture was also discussed with certain goals in mind. These goals range from being flexible and modular to having different available options and robust data-handling. The chapter finished off with some problems encountered during the construction of the software, and how these problems were overcome.

Part III.

Results and Conclusions

9. Simulation of 5 Patients : Case-Studies

FOR this section, a selection of 5 patients were made from appendix E. The 5 patients were chosen in the following way:

- One patient was chosen from the top 10 valued benchmarks in appendix D.
- 2 patients from the middle valued section of the benchmarks in appendix D.
- 2 patients from the 10 lowest-valued benchmarks in appendix D.

The reason for this selection is to be able to reflect on a patient that has a complet set of data available, patients that have fewer samples available, and patients that have virtually no available samples, and then comparing all these patients to one another. Furthermore, the resilience of the model is shown across the spectrum of patients and their available datasets. This ensures that, after looking at these 5 patients, one can see that the model is capable of simulating a response for a patient even in a "drought" of data so-to-speak.

Each patient's results is discussed and considered in this section, and a section on the correlations between patients' results finalises the chapter. The results were obtained using the simulation archicture described and listed in appendix A. The complete set of simulation results is given in appendix E.

9.1. Case 1 : Patient 28

Data samples: The dataset for patient 28 is taken from table E.11 and shown below. It should be noted that this patient scored in the top 10 of the benchmark table[1]. From the data, one can see that the patient starts at a high HIV infection[2] of around 77000 counts per ml. One can see that both the CD4+ T-cells and the CD8+ T-cells stay relatively constant over the total sampling period, while the viral load stays very high at over 60000 counts per ml over the sampling period. There are samples missing for this patient's viral load at weeks 52 and 78, so it might be said that it shouldn't have been included into the study. Notwithstanding this fact, it can be seen that even if the inclusion-criteria is not followed, a patient's response may still be simulated and refined with very good results.

Table 9.1.: Patient 28 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.885887	76893.03446	106	1616	T_4	106
2	5.015975	103746.8693	106	1189	T_8	1616
4	4.836153	68572.97634	113	1224	v	76893.03446
8	5.129406	134711.9119	88	1005	T_b	2033
26	4.986351	96906.07419	80	983	I	300000
52			111	977	D	8983
78			62	1774		

Benchmarks: The benchmarks for patient 28 were calculated as $BM_1 = 29.3$, $BM_2 = 41.03$, $BM_f = 96.37$. The initial benchmark (BM_1) indicates an evaluation of the basic cost function. This value is low in comparison with most of the patients in the benchmark table, which indicates that the data fits well to the model. The interim benchmark value changed because of the two missing samples at weeks 52 and 78, but it is still enables this patient to be ranked as the 6th best patient in the simulation.

[1] Refer to the benchmark table D.1 or the discussion in section D on how the benchmark was constructed to know how it works and what exactly it means that one patient has a better benchmark than another.

[2] A low infection would be around 50 copies per ml, and a high infection above 10000 copies per ml

Simulated response:

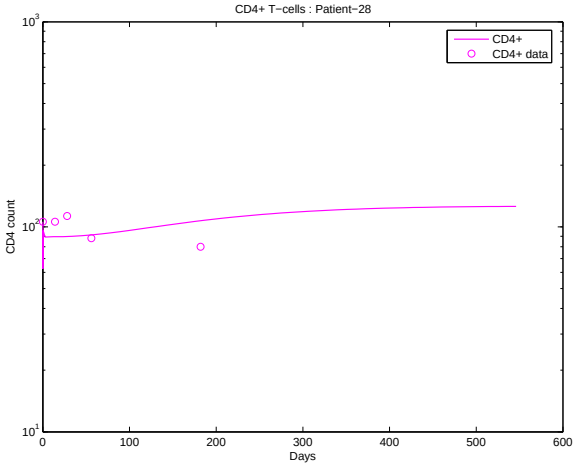

Figure 9.1.: CD4+ T-Cells

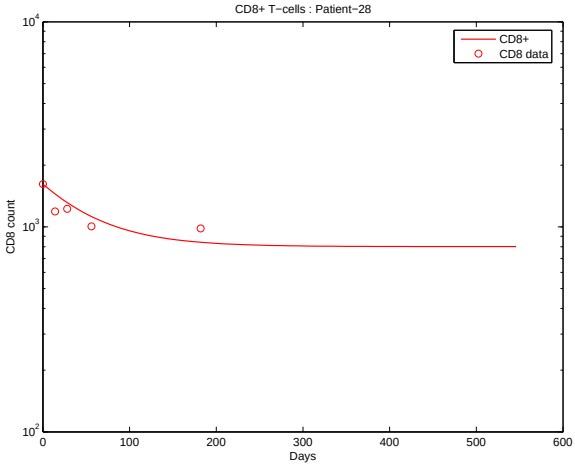

Figure 9.2.: CD8+ T-Cells

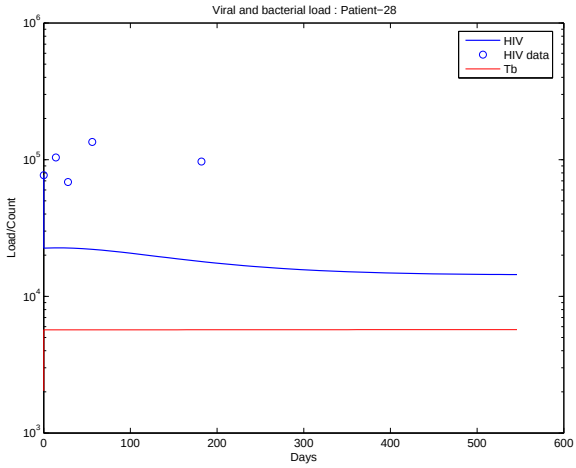

Figure 9.3.: Viral and bacterial load

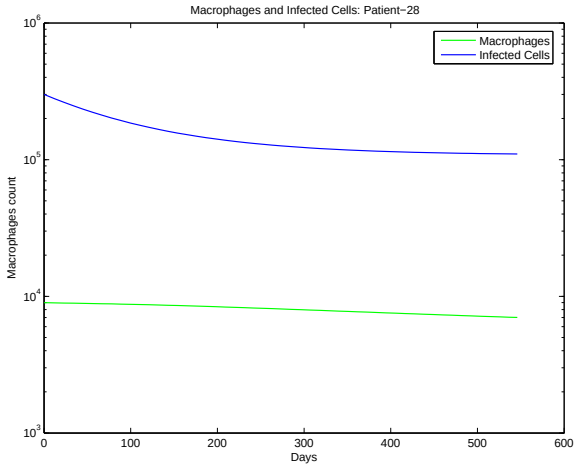

Figure 9.4.: Macrophages and infected cells

Steady state: The viral load response reaches a steady state which is lower than the initial value of 77000, but also lower than that of the last viral load sample, which makes the response for the viral load inaccurate (This is handled in the next section which considers the refinement of the response). The bacterial load reaches a steady state value of around 5800 copies per ml. The CD4+ T-cell count seems to be increasing slightly at a scale of 10^2. The CD8+ T-cell count settles at a steady-state value of

around 900 copies per ml.

Initial conditions: As with all the patients, the initial conditions for the viral load, CD4+ T-Cells and CD8+ T-cells were taken as the first available data sample of the patient. This means that at least 3 of the 6 model-equations have initial conditions that are taken from the data. For the macrophages, infected cells and bacterial count, intelligent "guesswork" had to be done using the second of the two methods described in section 7.1.1. This method uses the simulation GUI tool described in appendix B. For a first simulation, initial, arbitrary values were chosen for the unknown conditions. The initial conditions before refinement were chosen as $\vec{x_0} = [106\ 1616\ 76893.03\ 2033\ 30000\ 8983]$. The tool was employed by means of simulating patient 28's model response as well as plotting the data (in the GUI-tool). The sliders for the initial conditions of the macrophages, infected cells and bacterial counts were changed until the model aligned as close as possible with the data. No change was made to $\hat{\chi}$, the parameters that came from the optimisation routine, and the model was re-simulated using the updated initial conditions and the optimised parameter set shown above. The updated initial conditions vector became $\vec{x_0} = [168\ 614\ 3531\ 2800\ 120\ 700]$ as a result of this exercise.

Optimised parameters:

Table 9.2.: Optimised parameter set : Patient28

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	4087.3602	/day
S_8	Src - T_8 cells	21.3856	/day
k_1	Rate - T_4 cells	0.00072155	/day-vir.
k_2	Rate - T_4 cells by APCs	7.4965e-007	/day-cell
k_3	Rate - T_8 cells by APCs	4.4467e-009	/day-cell
k_4	Recr. - APCs by HIV	1.0204e-008	/day
k_5	Recr. - APCs by Mtb	1.0003e-007	/day
k_6	Dth rate : virus by APCs	0.00020057	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.0073997	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.17152	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.35929	mm^3d^{-1}
N_1	Free vir. by inf. cells	6441.2969	none
N_2	Free vir. by APCs	8267.0906	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.022309	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.023727	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1009.7222	mm^{-3}
K	Carry. cap.: tb pop.	5691.6519	mm^{-3}
r_b	Max. tb prolif. rate	44.1253	/day

Refined response:

The refined reponse from using the GUI tool is now:

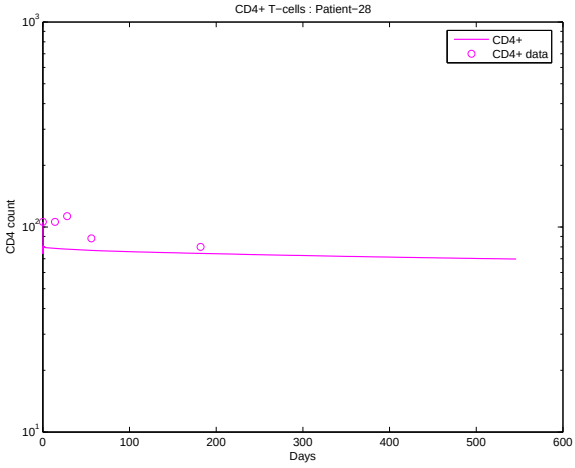

Figure 9.5.: CD4+ T-Cells

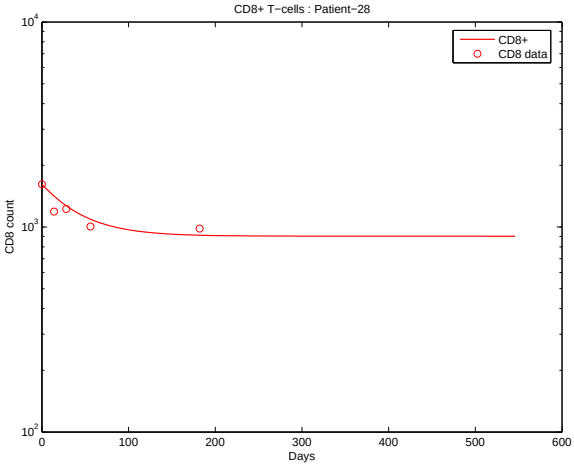

Figure 9.6.: CD8+ T-Cells

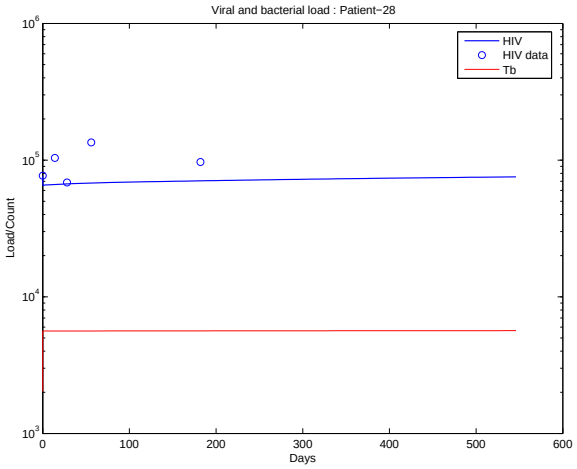

Figure 9.7.: Viral and bacterial load

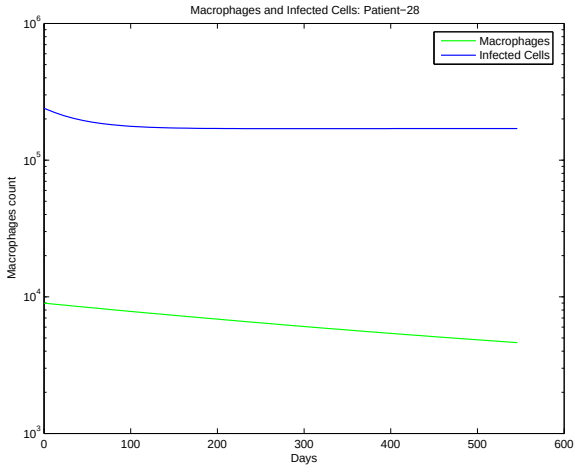

Figure 9.8.: Macrophages and infected cells

Summary and interpretation: It can be seen from the refined model results that the viral load settles at a value closer to the sample data values. After refinement, however, it can be seen that the CD4+ T-cell count and the macrophages are slowly decreasing while the viral load is slowly increasing. This patient's immune system seems to slowly lose its ability to keep the high viral load infection in combination with the TB load, in place.

9.2. Case 2 : Patient 30

Data samples: Patient 30 has a benchmark in the middle-section of the benchmark table. Although this is the case, the reason for it is the high variance of the viral load samples over the simulation period. The patient start with an initially high viral infection, as well as a high bacterial infection. Both these infections settle into a steady state after roughly a year (350 days) of the infection. The viral load settles between 2000 and 3000 copies per ml and the bacterial load between 200 and 300 copies per ml.

From the data, one can see that both teh CD4+ T-cells and the CD8+ T-cells stay relatively constant over the simulation period, but the viral falls almost to undetectable levels at 26 weeks. The model optimisation, however, does not follow the high variability in viral load, but rather settles on the final sample value. All data samples for this patient are available, which, from an identification point-of-view, means that all the identifiable parameters could be determined.

Table 9.3.: Patient 30 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	2.582063	381.9996808	726	1125	T_4	726
2	4.278044	18968.98093	834	1903	T_8	1125
4	2.91803	827.9993579	747	1803	v	381.9996808
8	3.04454	1108.000611	1095	1382	T_b	1710
26	1.869232	74.00004776	1029	1388	I	4010
52	2.897077	788.9999942	921	1209	D	5290
78	3.371806	2353.997515	922	1349		

Benchmarks: The benchmarks for patient 30 were calculated as $BM_1 = 141.5$, $BM_2 = 141.5$, $BM_f = 87.48$. The initial benchmark (BM_1) has the same value as the interim benchmark (BM_1). This indicates the availability of all the data samples. However, this patient's benchmark is very high in relation to the better-optimised patients (such as patient 64 and 44). This is a result of the high variability of the viral load samples, and doesn't mean that the patient's parameters were badly-searched. In comparison with the best-optimised patient, number 64, the only difference is that the viral load for patient 64 doesn't vary over such a large range as patient 30. Otherwise,

the responses are both acceptable and usable to predict the respective patients' cell population growths.

Simulated response:

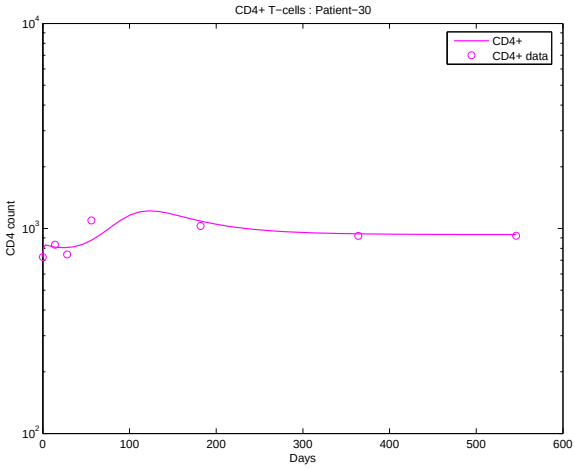

Figure 9.9.: CD4+ T-Cells

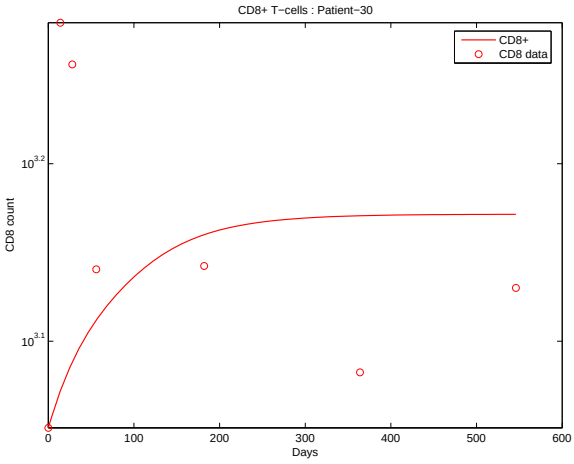

Figure 9.10.: CD8+ T-Cells

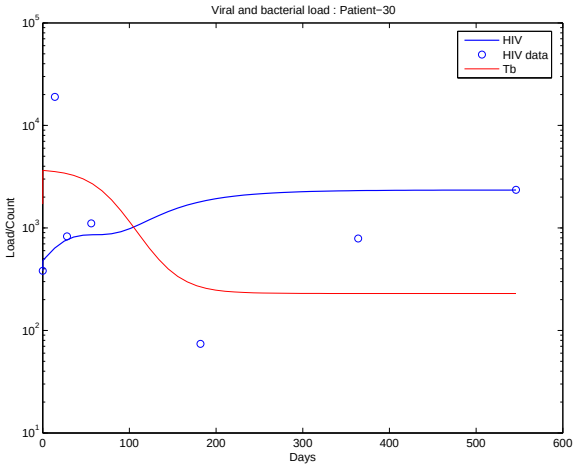

Figure 9.11.: Viral and bacterial load

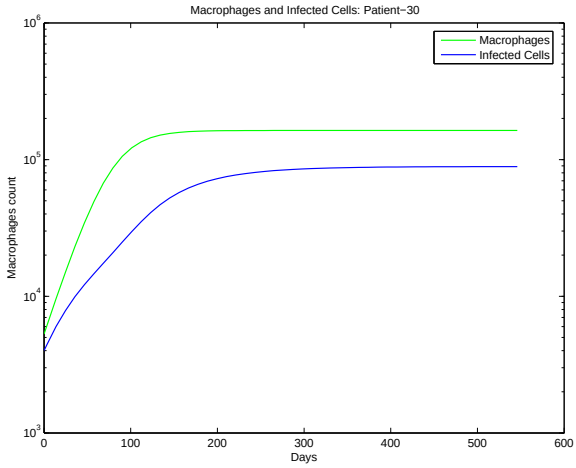

Figure 9.12.: Macrophages and infected cells

Steady state: The viral load response reaches a steady state which is exactly on the value of the last patient data sample. Although it seems that the CD8+ T-cells data points varies significantly, the data range falls between 10^3 and $10^{3.3}$. Thus, the CD8+ T-cell count settles at an acceptable value only slightly higher than the last sample point. The CD4+ T-cell count almost fits the data samples exactly, which makes this

patient's overall response very acceptable.

Initial conditions: The initial conditions vector before refinement is $\vec{x_0} = [726\ \ 1125\ \ 381.9\ \ 1710\ \ 4010\ \ 5290]$. The optimised parameters, $\hat{\chi}$, weren't changed, and the model was re-simulated using initial conditions as refined in the GUI simulation tool. The refined initial conditions are $\vec{x_0} = [726\ \ 1125\ \ 381.9\ \ 1670\ \ 3200\ \ 1310]$.

Optimised parameters:

Table 9.4.: Optimised parameter set : Patient30

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	1382.6544	/day
S_8	Src - T_8 cells	14.4762	/day
k_1	Rate - T_4 cells	0.00051918	/day-vir.
k_2	Rate - T_4 cells by APCs	3.571e-006	/day-cell
k_3	Rate - T_8 cells by APCs	3.3441e-009	/day-cell
k_4	Recr. - APCs by HIV	7.0711e-008	/day
k_5	Recr. - APCs by Mtb	8.7176e-006	/day
k_6	Dth rate : virus by APCs	8.2112e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.012341	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.50759	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.96108	mm^3d^{-1}
N_1	Free vir. by inf. cells	3664.3445	none
N_2	Free vir. by APCs	8646.6517	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.015356	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.010751	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1825.6973	mm^{-3}
K	Carry. cap.: tb pop.	3573.674	mm^{-3}
r_b	Max. tb prolif. rate	31.9077	/day

Refined response:

The refined reponse from using the GUI tool is now:

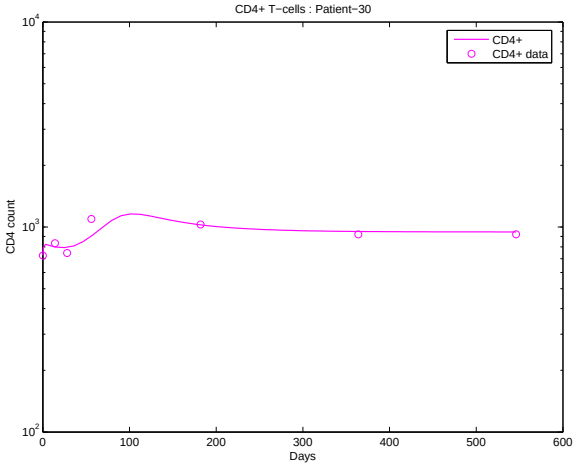

Figure 9.13.: CD4+ T-Cells

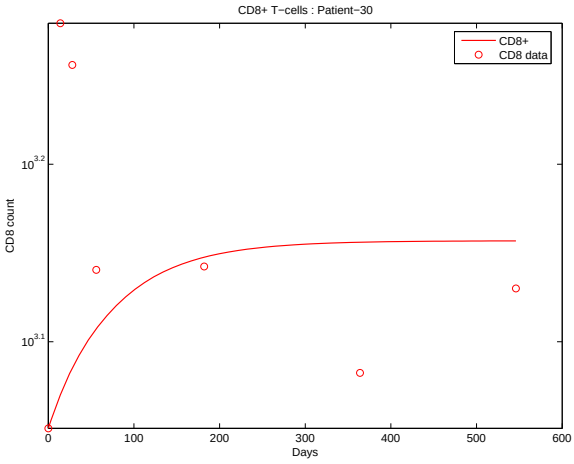

Figure 9.14.: CD8+ T-Cells

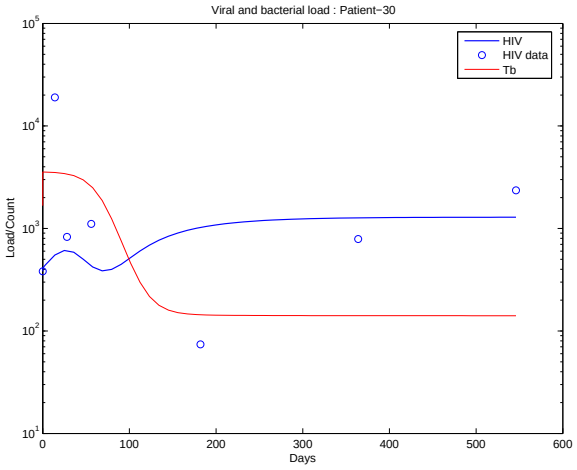

Figure 9.15.: Viral and bacterial load

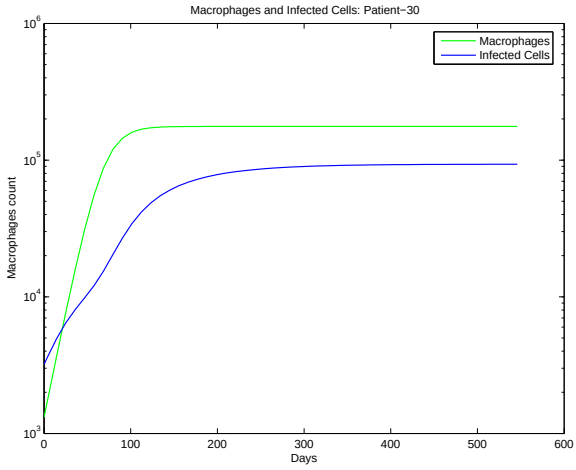

Figure 9.16.: Macrophages and infected cells

Summary and interpretation: It can be seen that the refined results do not look much better than the first simulation results. The patient already had a very good response to begin with. With the refined results, the viral load now settles below the final sample value, but between the second-to-last and final value. The CD4+ T-cell count response fits the data slightly better, and the CD8+ T-cell count remains unchanged. In effect, this refinement resulted in a smaller cost, but a loss of the viral-load steady-state value criteria. This, in itself, is not a problem in terms of the patient

itself, as the responses still resemble the data very well. For the patient itself, the viral load settles above 1000 copies per ml, which is a medium-sized infection. After a year, this patient's immune response seems to keep the viral and bacterial loads in a steady, treatable state.

9.3. Case 3 : Patient 58

Data samples: With patient 58, the viral-load sample is missing at week 8. This patient also has a very high viral infection, with the highest viral load count reaching 500000 at 26 weeks. With this said, the variance on the CD4+ T-cells is not very high: It starts at around 300 copies per ml and ends on the same value. The maximum CD4+ T-cells count reached is 580 copies per ml.

Table 9.5.: Patient 58 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	5.459334	287961.2168	327	1146	T_4	327
2	5.69897	499999.995	429	1939	T_8	1146
4	5.362121	230208.3118	327	1349	v	287961.2168
8			357	1596	T_b	2900
26	5.69897	499999.995	164	791	I	1020
52	3.595386	3939.000174	582	2328	D	5000
78	4.430623	26953.9861	302	1037		

Benchmarks: Patient 58 has an initial benchmark of $BM_1 = 512.73$ and an interim benchmark of $BM_2 = 598.19$. The latter value is the second-highest of all the patients in the simulated set. Although this is the case due to high variance of the viral load, all the dependent variables reach a steady state. The viral load settles below the last viral load sample value.

Simulated response:

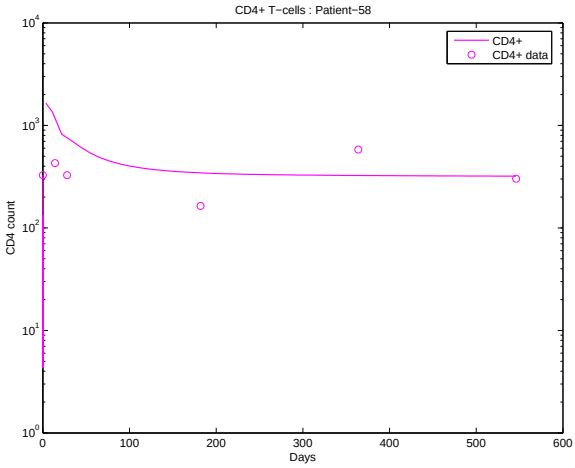

Figure 9.17.: CD4+ T-Cells

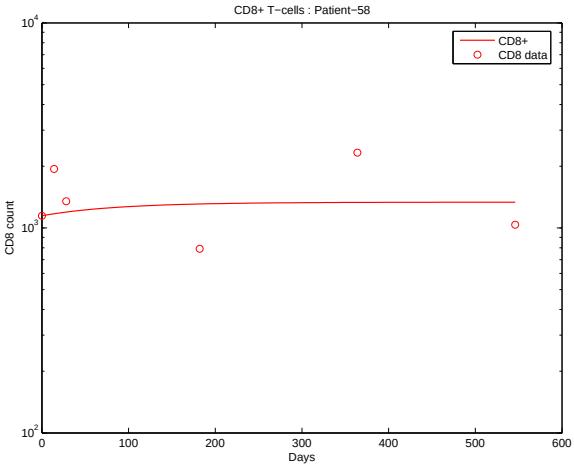

Figure 9.18.: CD8+ T-Cells

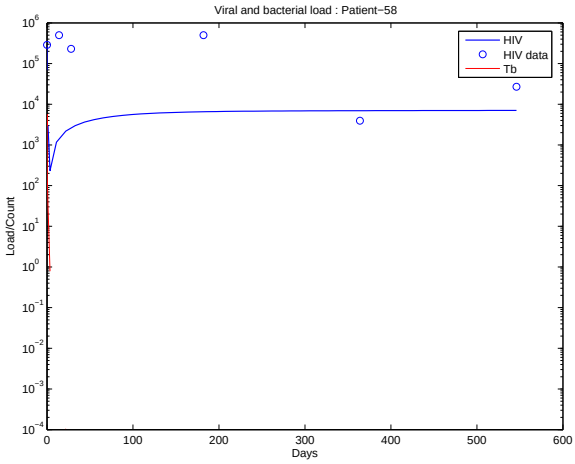

Figure 9.19.: Viral and bacterial load

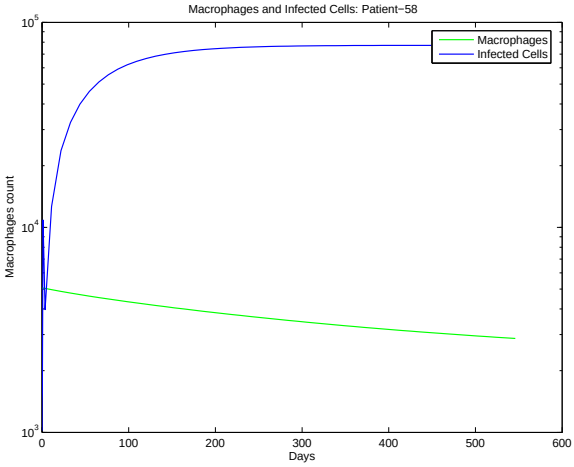

Figure 9.20.: Macrophages and infected cells

Steady state: The viral load response reaches a steady state which is just below 10000. This value should be lifted in the refinement process to about 26000, which is the final sample value for this patient. The CD8+ T-cell count settles a bit higher than its last sample. It is supposed to settle just above 1000. The CD4+ T-cell count settles on the correct value.

Initial conditions: The initial conditions vector before refinement is $\vec{x_0} = [327\ \ 1146\ \ 287961.2168\ \ 2900\ \ 1020\ \ 5000]$. The optimised parameters, $\hat{\chi}$, weren't changed, and the model was re-simulated using initial conditions as refined in the GUI simulation tool.

The refined initial conditions are $\vec{x_0} = [327\ \ 1146\ \ 287961.2168\ \ 60\ \ 100000\ \ 5000]$.

Optimised parameters:

Table 9.6.: Optimised parameter set : Patient58

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	1266.137	/day
S_8	Src - T_8 cells	14.256	/day
k_1	Rate - T_4 cells	0.00055716	/day-vir.
k_2	Rate - T_4 cells by APCs	3.144e-006	/day-cell
k_3	Rate - T_8 cells by APCs	3.2516e-009	/day-cell
k_4	Recr. - APCs by HIV	7.4716e-008	/day
k_5	Recr. - APCs by Mtb	8.015e-006	/day
k_6	Dth rate : virus by APCs	8.255e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.011857	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.51857	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.83158	mm^3d^{-1}
N_1	Free vir. by inf. cells	3355.499	none
N_2	Free vir. by APCs	9217.7805	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.016369	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.01065	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1788.7933	mm^{-3}
K	Carry. cap.: tb pop.	6220.508	mm^{-3}
r_b	Max. tb prolif. rate	33.2554	/day

Refined response:

The refined reponse from using the GUI tool is now:

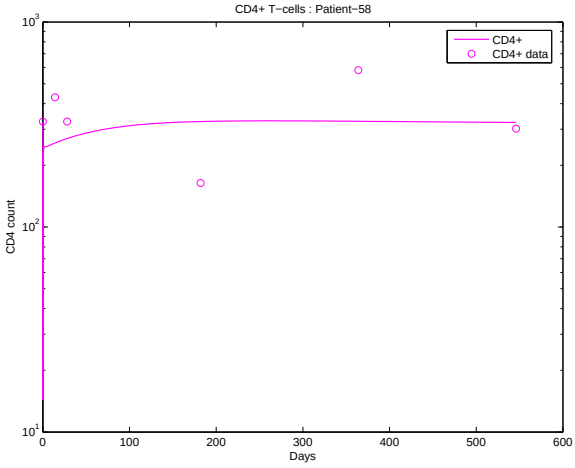

Figure 9.21.: CD4+ T-Cells

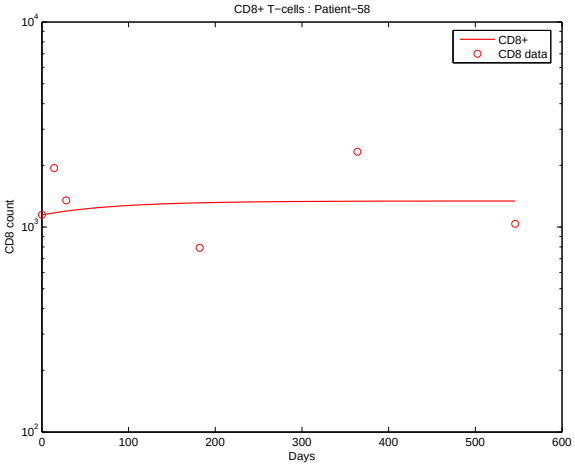

Figure 9.22.: CD8+ T-Cells

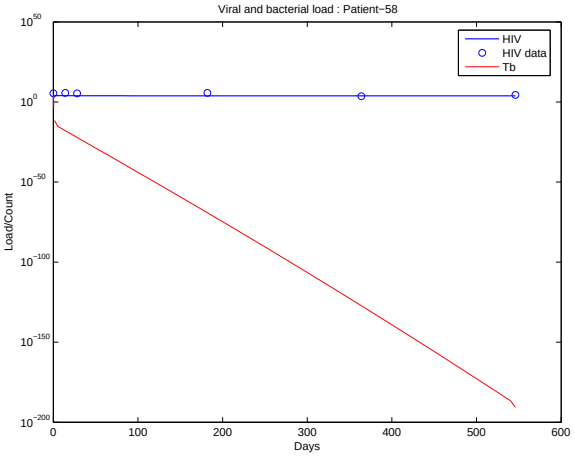

Figure 9.23.: Viral and bacterial load

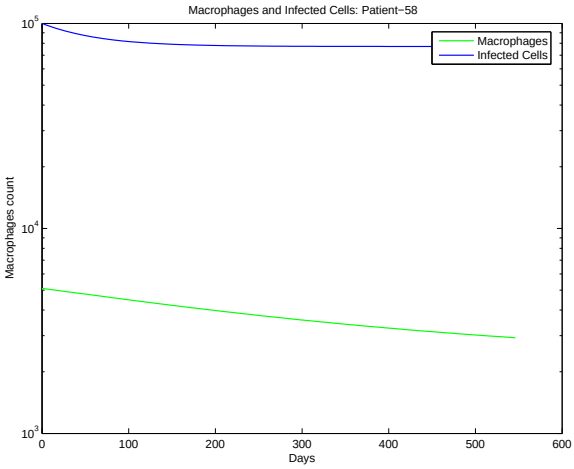

Figure 9.24.: Macrophages and infected cells

Summary and interpretation: With the refined response, the viral load now settles on the correct value, but the bacterial load seems to decrease very quickly. It could be that the refinement process fell into a local minimum that is not usable or the bacterial load for this patient is actually very low to begin with. If the bacterial load does not proliferate it would mean that the patient might have been on medication during the sampling period.

9.4. Case 4 : Patient 13

Data samples: The data samples for patient 13 are not complete. There are samples of the viral load missing at week 4 and samples of the CD4+ and CD8+ T-cells missing at week 78. The viral load infection in this patient start from a high infection of 26000 copies per ml virions to a lower (but still a high infection) one of 7400 copies per ml. Although the CD4+ T-cells simulation response indicate that the values vary, on a larger scale (and by inspection of the data) they don't vary that much at all. The count stays roughly within 450 to 650.

Table 9.7.: Patient 13 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.420137	26310.97852	516	899	T_4	516
2	4.683605	48261.96496	657	1072	T_8	899
4			648	1189	v	26310.97852
8	4.193236	15604.0021	529	919	T_b	2900
26	3.816175	6549.000144	599	1175	I	1020
52	4.044853	11087.99445	470	817	D	5000
78	3.873611	7474.996609				

Benchmarks: The benchmarks for patient 13 were calculated as $BM_1 = 50.77$, $BM_2 = 71.08$, $BM_f = 93.71$. This places patient 13 in the middle group of patients in the benchmark table, which means that it was neither one of the best-optimised nor one of the worst-optimised. With the necessary refinements in this section, one can see the difference the initial conditions make to the model response. This patient would feature at a higher position in the benchmarks table if the table was devised from refined results.

Simulated response:

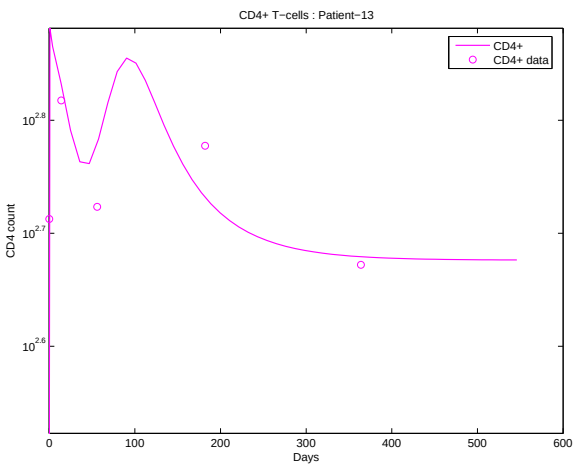

Figure 9.25.: CD4+ T-Cells

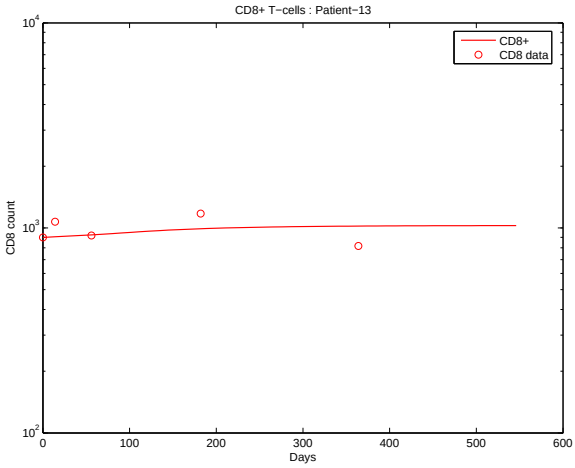

Figure 9.26.: CD8+ T-Cells

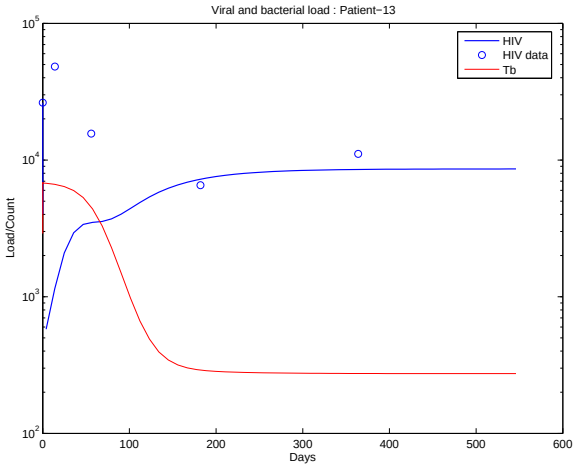

Figure 9.27.: Viral and bacterial load

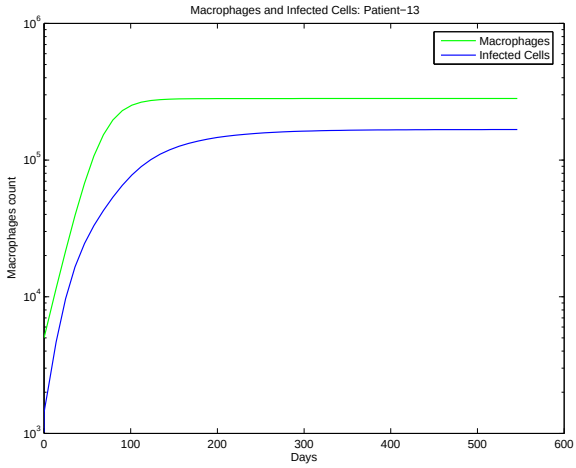

Figure 9.28.: Macrophages and infected cells

Steady state: All the responses for patient 13 reach a steady state value. The CD4+ T-cell count takes the longest to settle on a value at 550 days. The viral load response reaches a steady state which is just below 10000. This value should be slightly higher at 10000 copies per ml because the last data sample is removed for the sake of integrity. The infected cells and macrophages both reach values over 10^5.

Initial conditions:

The initial conditions vector before refinement is $\vec{x_0} = [516\ \ 899\ \ 26310.978\ \ 2900\ \ 1020\ \ 5000]$. The optimised parameters, $\hat{\chi}$, weren't changed, and the model was re-simulated using initial conditions as refined in the GUI simulation tool. The refined initial conditions are $\vec{x_0} = [516\ \ 899\ \ 26310.978\ \ 1885\ \ 15000\ \ 1937]$.

Optimised parameters:

Table 9.8.: Optimised parameter set : Patient13

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	1735.8644	/day
S_8	Src - T_8 cells	12.3872	/day
k_1	Rate - T_4 cells	0.00029341	/day-vir.
k_2	Rate - T_4 cells by APCs	6.5126e-006	/day-cell
k_3	Rate - T_8 cells by APCs	2.977e-009	/day-cell
k_4	Recr. - APCs by HIV	6.7928e-008	/day
k_5	Recr. - APCs by Mtb	4.8011e-006	/day
k_6	Dth rate : virus by APCs	6.393e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.012017	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.28517	mm^3d^{-1}
k_9	Dth rate : tb by APCs	1.2022	mm^3d^{-1}
N_1	Free vir. by inf. cells	7746.8966	none
N_2	Free vir. by APCs	1057.3111	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.015878	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.012472	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	2187.8813	mm^{-3}
K	Carry. cap.: tb pop.	6268.5353	mm^{-3}
r_b	Max. tb prolif. rate	13.4855	/day

Refined response:

The refined reponse from using the GUI tool is now:

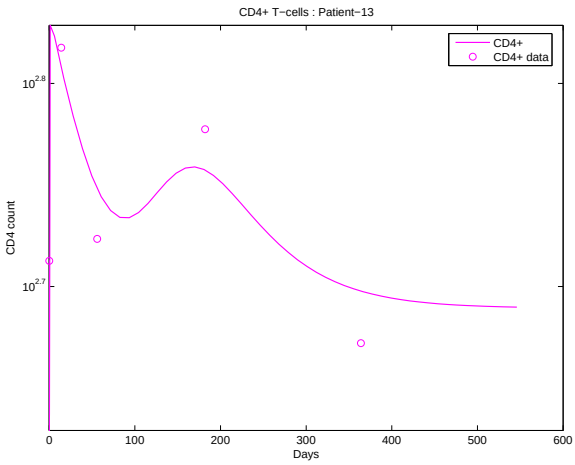

Figure 9.29.: CD4+ T-Cells

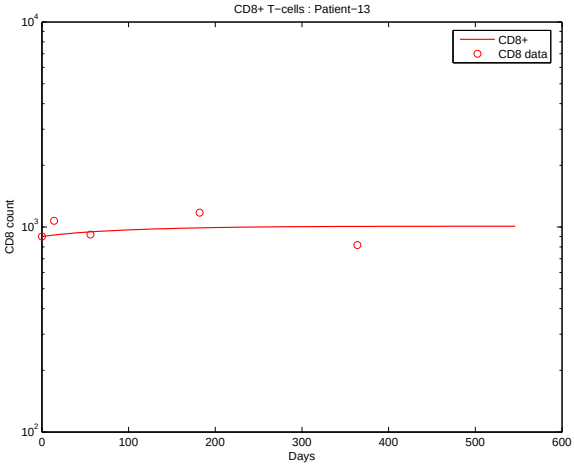

Figure 9.30.: CD8+ T-Cells

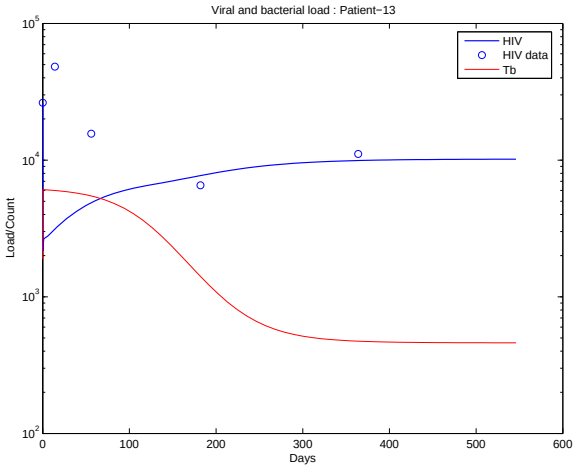

Figure 9.31.: Viral and bacterial load

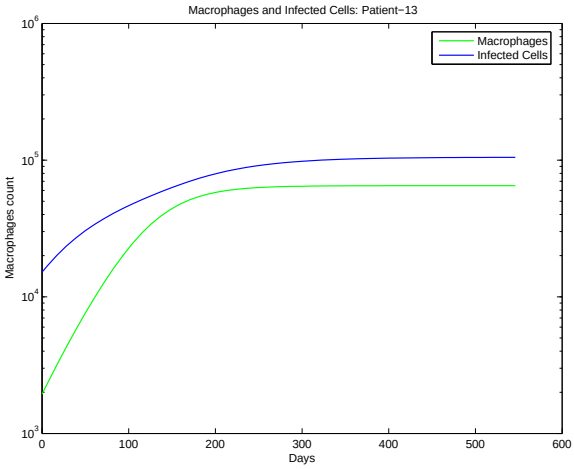

Figure 9.32.: Macrophages and infected cells

Summary and interpretation: For patient 13, the difference between the original response and the refined response is not significant. The attempt at parameter estimation for 5 samples and the effect of this reduced number on the final parameter estimation is also not very problematic. All responses reach steady-states, and the only value that settles higher than anticipated in this case is that of the CD4+ T-cells.

9.5. Case 5 : Patient 11

Data samples: Patient 11's dataset is shown in table 9.9. The dataset has 7 complete samples for each measured cell-type. The initial values for the viral load is 42477 copies per ml, which makes this infection a reasonable high one. The CD4+ T-cells are initially 640 counts per ml and the CD8+ T-cells 1862 copies per ml.

Table 9.9.: Patient 11 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.628154	42477.01599	640	1862	T_4	640
2	4.489902	30895.98176	839	1437	T_8	1862
4	5.11807	131241.1418	461	1117	v	42477.0159
8	4.570192	37169.95198	643	1372	T_b	2800
26	5.575584	376343.1364	424	624	I	28000
52	5.341431	219498.2186	294	222	D	700
78	4.908828	81063.99447	333	718		

Simulated response:

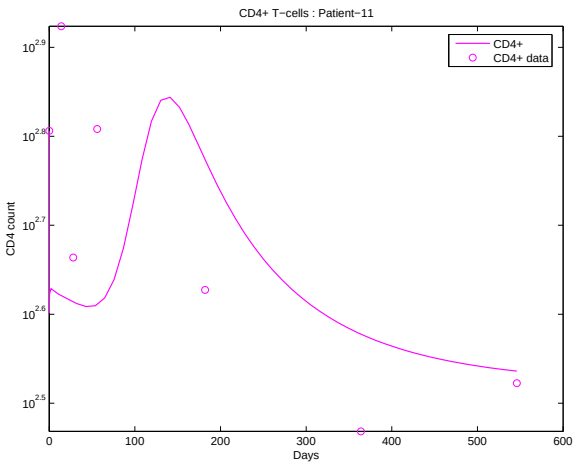

Figure 9.33.: CD4+ T-Cells

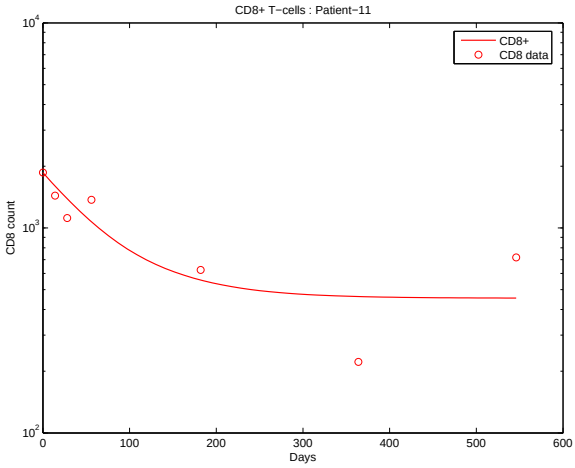

Figure 9.34.: CD8+ T-Cells

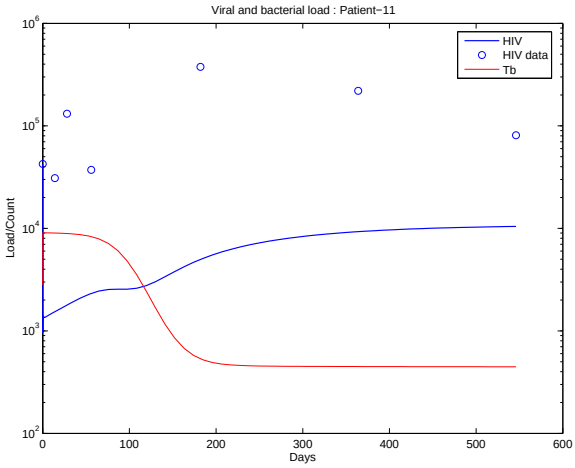

Figure 9.35.: Viral and bacterial load

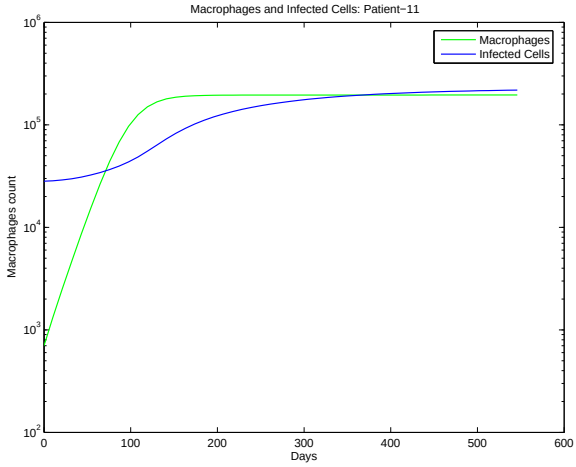

Figure 9.36.: Macrophages and infected cells

Benchmarks: The benchmarks for patient 11 were calculated as $BM_1 = 201.38$, $BM_2 = 201.38$, $BM_f = 82.18$. These values place patient 11 in the highest calculated benchmarks at the bottom of table D.1. This is an indication that this patient's parameter optimisation did not fare so well against the best patient in the set, and that one can expect responses that do not fit so well to the supplied field data.

Steady state: From the steady-state response of the viral load one can see that the model doesn't fit well to the data at all. The responses for CD4+ T-cells and CD8+ T-cells fit well enough though to say that they are acceptable for use. The refinement seen for this patient in figure 9.5 addresses the problem of fitting the viral load response to its data. The macrophages and infected cells reach a similar steady-state value at about $2x10^5$ copies per ml.

Optimised parameters:

Table 9.10.: Optimised parameter set : Patient11

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	2693.2148	/day
S_8	Src - T_8 cells	6.1628	/day
k_1	Rate - T_4 cells	0.00029021	/day-vir.
k_2	Rate - T_4 cells by APCs	2.0228e-008	/day-cell
k_3	Rate - T_8 cells by APCs	3.453e-009	/day-cell
k_4	Recr. - APCs by HIV	1.2308e-008	/day
k_5	Recr. - APCs by Mtb	9.7248e-006	/day
k_6	Dth rate : virus by APCs	0.00011307	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.0073092	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.48524	mm^3d^{-1}
k_9	Dth rate : tb by APCs	1.2114	mm^3d^{-1}
N_1	Free vir. by inf. cells	7958.2288	none
N_2	Free vir. by APCs	4780.0053	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.0010004	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.013038	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1903.4418	mm^{-3}
K	Carry. cap.: tb pop.	8163.3506	mm^{-3}
r_b	Max. tb prolif. rate	22.9096	/day

Initial conditions: The initial conditions chosen for this patient before refinement was $\vec{x_0}$ = [640 1862 42477.0159 2800 28000 700]. The updated initial conditions, after refinement became $\vec{x_0}$ = [640 1862 42477.0159 2800 11000 700] as a result of this exercise.

Refined response:

The refined reponse from using the GUI tool is now:

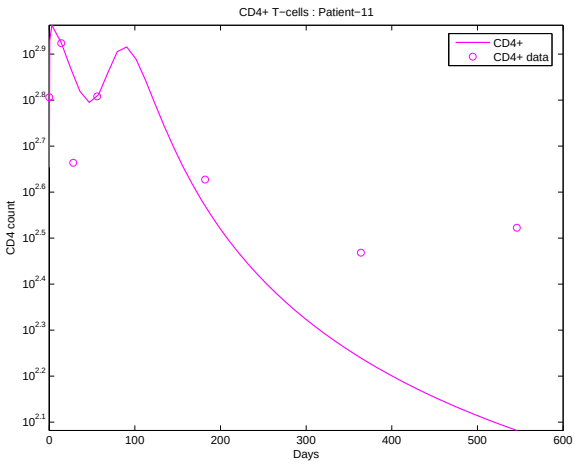

Figure 9.37.: CD4+ T-Cells

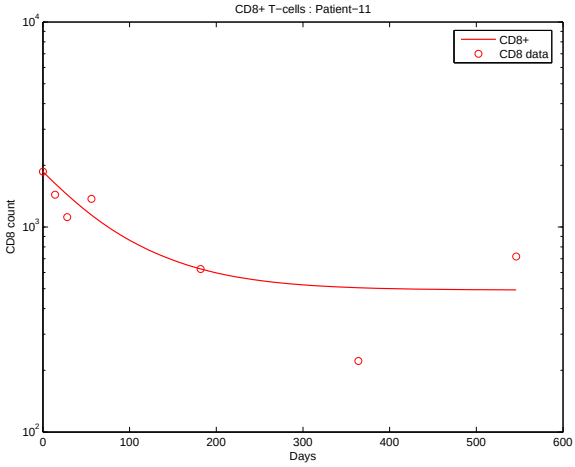

Figure 9.38.: CD8+ T-Cells

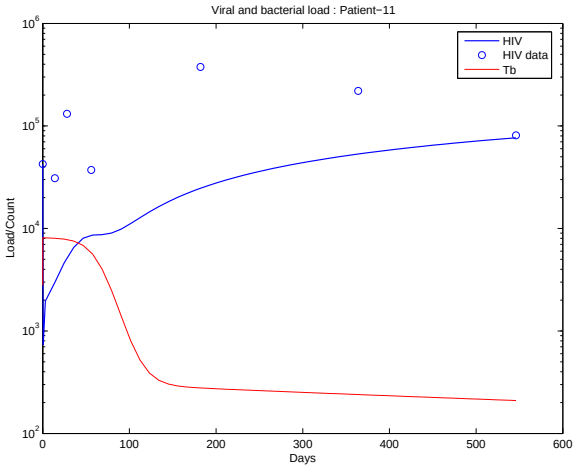

Figure 9.39.: Viral and bacterial load

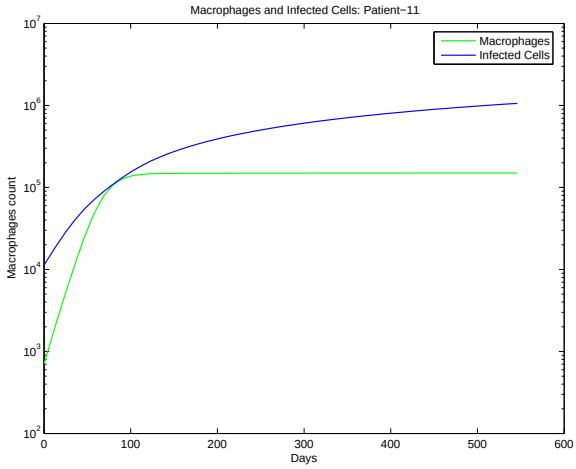

Figure 9.40.: Macrophages and infected cells

Summary and interpretation: For patient 11, the initial response of the viral load did not fit very well to the supplied field data. After refinement, as was seen, the response is much better. Now, the updated initial conditions allow for a better data-fit, and the steady-state values are accurate.

9.6. Chapter Summary

In this chapter, 5 patients were selected and put under scrutiny as a case-study per patient. The responses for all the patients were improved using a refinement methodology involving the simulation GUI tool for selection of better initial conditions. With the better initial conditions, and starting with an optimised parameter set of each individual patient, the refinements were obtained. Comments were made on the steady-state values, the fitting of model response to samples, and the changing of initial conditions for each patient.

10. Model Verification

10.1. Reproducing Published Results

THE 4-dimensional co-infection model given in [10] was used to verify the proposed model in this research. This was done by reproducing the model response from [10], and then using the 4-dimensional model as input-data to (4.25). Using the same simulation architecture as described in appendix E, with a model built from the equations for the 4-dimensional model and using its initial conditions, the reproduced response was generated as:

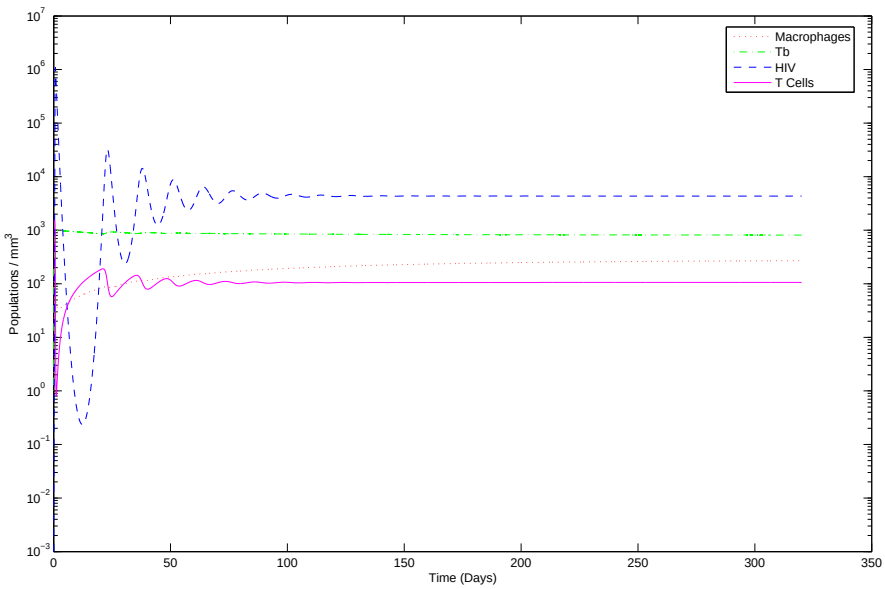

Figure 10.1.: Reproduced result from a published experiment ([10], Figure 5.)

This response is similar to Figure 5 from [10].

To continue the process of verification of the proposed model, the response in figure 10.1 was sampled at 1 sample per week for 45 weeks (315 days), and used as a virtual "patient". The reasoning behind this is that one would search for an optimal set of parameters for the HIV/TB model using the generated data as a patient. Once the HIV/TB model has been optimised to fit to the 4-dimensional model, the confidence in the HIV/TB model would be higher than before, as the proposed model then fits a published experiment. Furthermore, a nominal set of parameters is then available for use with the parameter optimisation to fit actual patient datasets.

The optimised curves from the model in (4.25) and the data generated from the 4-dimensional model is shown here:

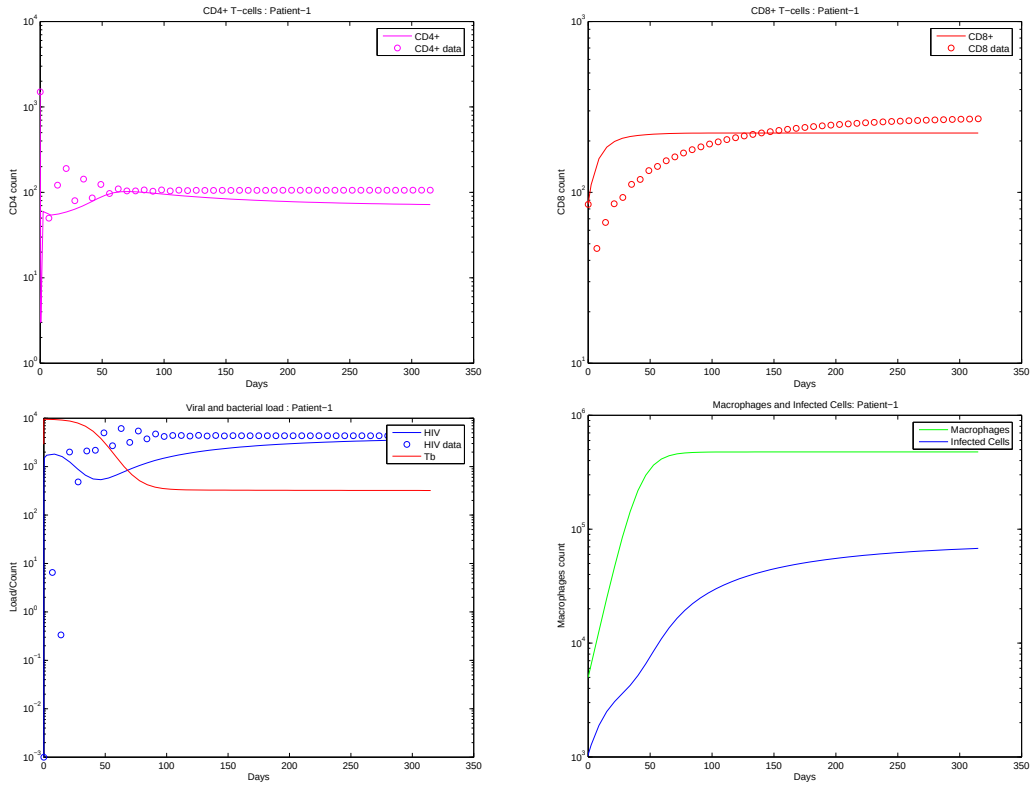

Figure 10.2.: Parameter optimisation fitting to the 4-dimensional model from [10]

From the results above one can see that the fitting of the proposed model to another model is very successful. The confidence in the proposed co-infection model is enhanced, and a suitable new nominal parameter set was found. This set can be seen in table E.1. Although data was generated for the macrophages from the 4-dimensional

model, this data wasn't used, as the proposed model and consequently the simulation program does not allow for measurements other than the viral load, CD4+ T-cells and the CD8+ T-cells. Nonetheless, the retrieved generated data is suitable to create a starting point for further refinement and simulation.

In the light of verification of the model, one can say that by visual inspection the proposed model, with the parameters from table E.1 fits to the model created in [10]. This verifies that, with respect to previous research, this model is sound and fits into the body of knowledge on the subject of co-infection dynamics.

10.2. Verification by Field Data Fit

The most important method for verification of the model, and one that is seldom found in similar studies, is the use of actual field data. This means that the optimisation routine changes parameters to fit the model to the data and predict actual patients' cell-counts over a period of time. In this section, two considerations for model verification by field data is made. The one consideration is the use of a patient with a complete set of available data. This is not a stringent verification, as a complete dataset is the best available condition under which the model can be verified. The second method, which is more stringent, is the use of a patient with a very limited set of data (only 2 or 3 available samples). If the model response would make sense for both patients, this would be an indication that the proposed model is acceptable for use, and able to provide sensible, valid results for a wide selection of different patients. In other words, we are testing the two extremities : very good data and very bad data.

10.2.1. Complete Patient Dataset

The patient selected in this section has 7 available data samples, the most for this study. Although several patients have got full sets of samples available, patient 30 was chosen because of its well-formed response. The next figure is considered in detail to determine if the response makes sense from a medical point of view, and that the model indeed fits the data well.

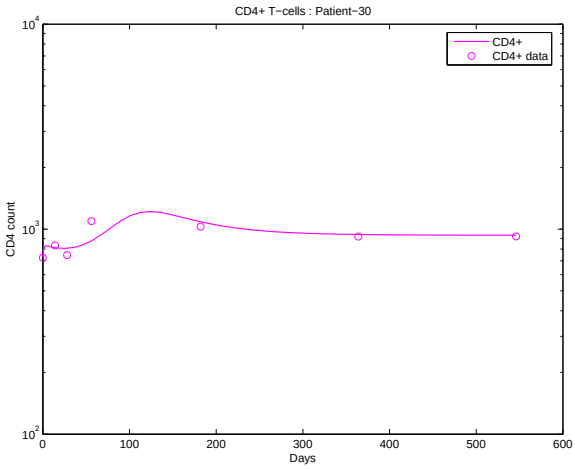

Figure 10.3.: CD4+ T-Cells

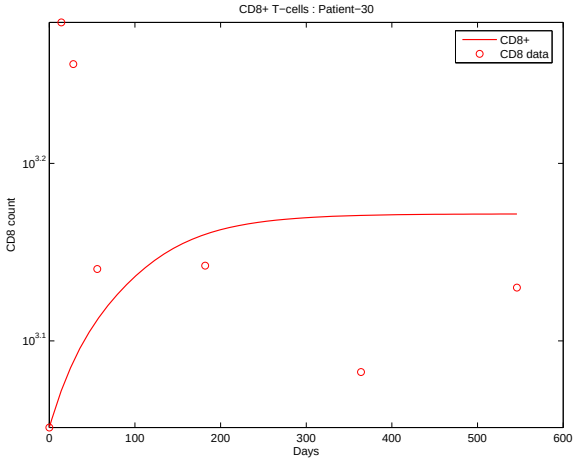

Figure 10.4.: CD8+ T-Cells

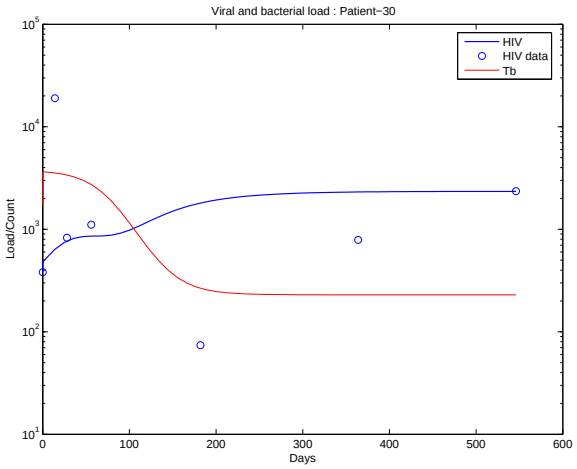

Figure 10.5.: Viral and bacterial load

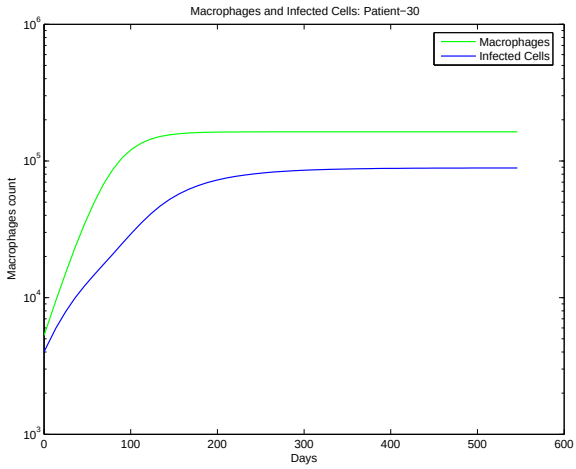

Figure 10.6.: Macrophages and infected cells

Viral load:

The optimisation goals of reaching the correct steady-state value was adhered to with the viral load response. The response both reaches a steady-state and settles on the final sample value. Although the response doesn't go through all the samples, this is seen as a trade-off inherent in the model. Because the Nelder-Mead algorithm searches for a local minimum, it might be that the global minimum (a response that travels through all the data samples simultaneously) could still be found. Whether this is possible or not is unknown, but for the practical case this response fits to the data in such a way that it is usable to simulate treatment and visualize the viral load count

progression over time.

CD4+ T-cells and CD8+ T-cells:

The CD4+ T-cell count almost fits to all the data samples simultaneously. This verifies the response with all available samples for the CD4+ T-cell count. The CD8+ T-cells do not vary as much as is depicted in figure 10.2.1. It can be said that the response is very good, fitting the data almost exactly in the range of 10^3 through $10^{3.3}$, and reaching a proper steady-state.

Bacterial load:

Because the bacterial load is not measured, there exists a chance that the response would not be properly formed and might not reach a steady-state. This is not the case with this patient. The response settles just above 300 bacteria per ml, which makes this a well-formed and verified response.

Macrophages and infected cells:

Both the macrophages and the infected cells reach steady-states. The infected cells number around $8x10^4$ during the end of the simulation period and the macrophages around $1.8x10^5$. With these responses being formed without direct fitting to field data, it can be said that they contribute towards verifying that this model indeed conforms and satisfies the criteria for parameter estimation and qualifies as well-formed responses.

Verification:

Considering the above points, the model is verified using the field data from a patient will all 7 samples available. The estimation criteria is satisfied and the responses are adequate, well-formed and practically useable.

10.2.2. Reduced Patient Dataset

The patient selected in this section has 3 available data samples, less than half of a complete set. Patient 83 was chosen, and in the next few paragraphs the response is

duscussed and linked with the idea of verifying the model using a reduced-set patient.

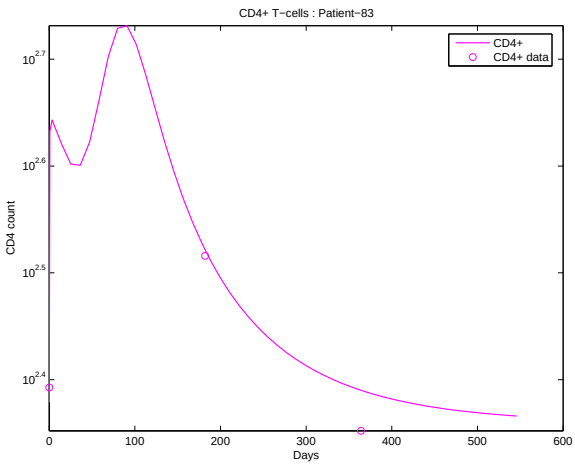

Figure 10.7.: CD4+ T-Cells

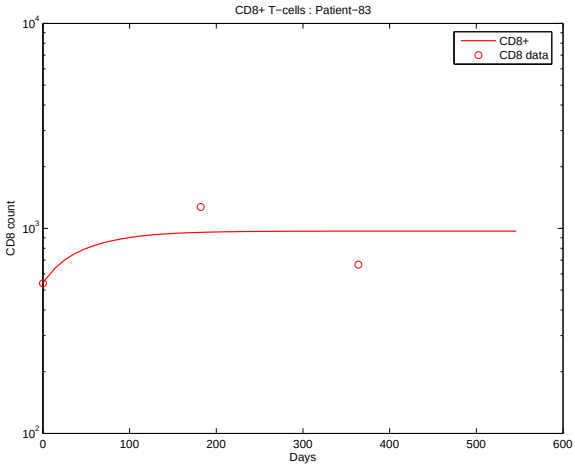

Figure 10.8.: CD8+ T-Cells

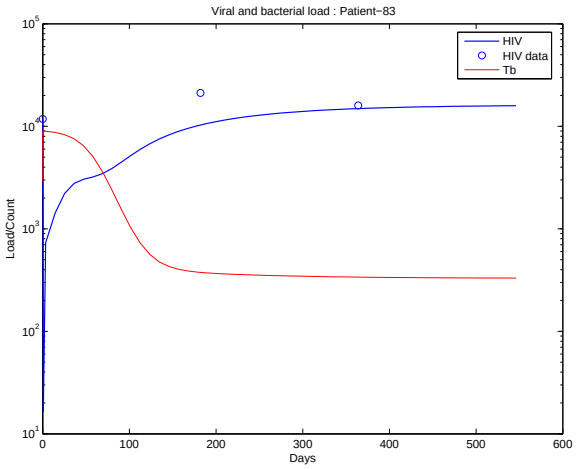

Figure 10.9.: Viral and bacterial load

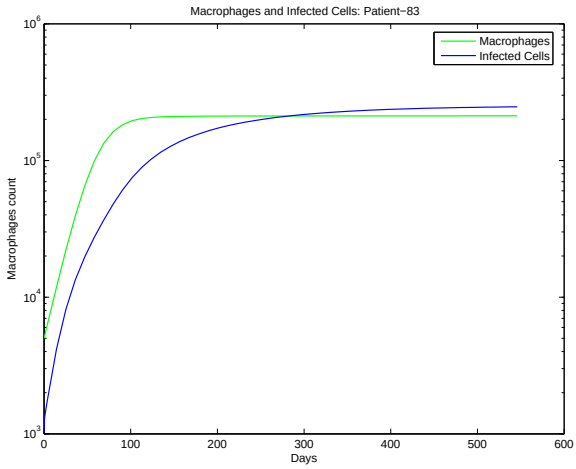

Figure 10.10.: Macrophages and infected cells

Viral load:

The viral load for this patient with a reduced number of samples (3 samples as opposed to 7) settles on the proper steady-state value corresponding to the last available sample. The response does is not close to the first sample though, but closer to the second sample at roughly 180 days.

CD4+ T-cells and CD8+ T-cells:

The CD4+ T-cells response fit to at least 2 of the 3 samples very well. The response almost settles into a steady state after 550 days.

Bacterial load:

The bacterial response is well-formed, and settles at a value of just above 300 bacteria per ml.

Macrophages and infected cells:

The macrophages and infected cells both reach a steady-state at around 400 days into the simulation. Their values are similar, at $2x10^5$ and $2.3x10^5$ respectively.

Verification:

Even with a reduced number of samples, the model response is still well-formed. All the cell-types reach a steady state and fit the data samples well enough to be deemed acceptable. This verifies that, even with a reduction in the number of samples, the model and optimisation routine is robust enough to deliver a response that conforms to the optimisation and cost-function goals that were set in section 6.2.6.

10.3. Chapter Summary

In this chapter, the model was verified in two ways. Firstly, a published experiment was reproduced, and data generated from its response. This data was used as input to the proposed co-infection model, after which it was seen that the model can fit easily to the generated data. The second verification was done by fitting the model to the actual field data from a patient with a full set of available samples and a patient with a limited set of available samples.

11. Method Verification

TO verify that the parameter optimisation method is feasible and useable, random data was generated in different frequencies of samples and with different variances. Without a random component in the data (as is seen for example in the 4-dimensional model generated data in figure 10.2, the model fits the data almost exactly. A known patient's model response was used to generate random data with a "high" variance of 10^5 for the viral load. For the CD4+ T-cells, a variance of 3500 and for the CD8+ T-cells a variance of 5000 was used. The lower variances were chosen as of 10^4 for the viral load, 500 for the CD4+ T-cells and 900 for the CD8+ T-cells.

11.1. Many Random Samples : Small Variance

With a high frequency of samples with small variances, the responses can be seen in figure 11.1. The response fits the data almost perfectly. This is not a very stringent test for the optimisation routine, as the data closely resembles the model response from which it was generated. With this in mind, the model still fits as well to many samples with small variances as if there were no variance or any random component at all. The only difference between the model response fitting to the generated data and the original response with the viral load is between 0 and 200 days, where the model response has a lower value than the original response. The macrophages response settles at a lower value than before and the infected cells also have a higher steady-state value. The CD4+ T-cells and CD8+ T-cells are virtually identical to their original responses.

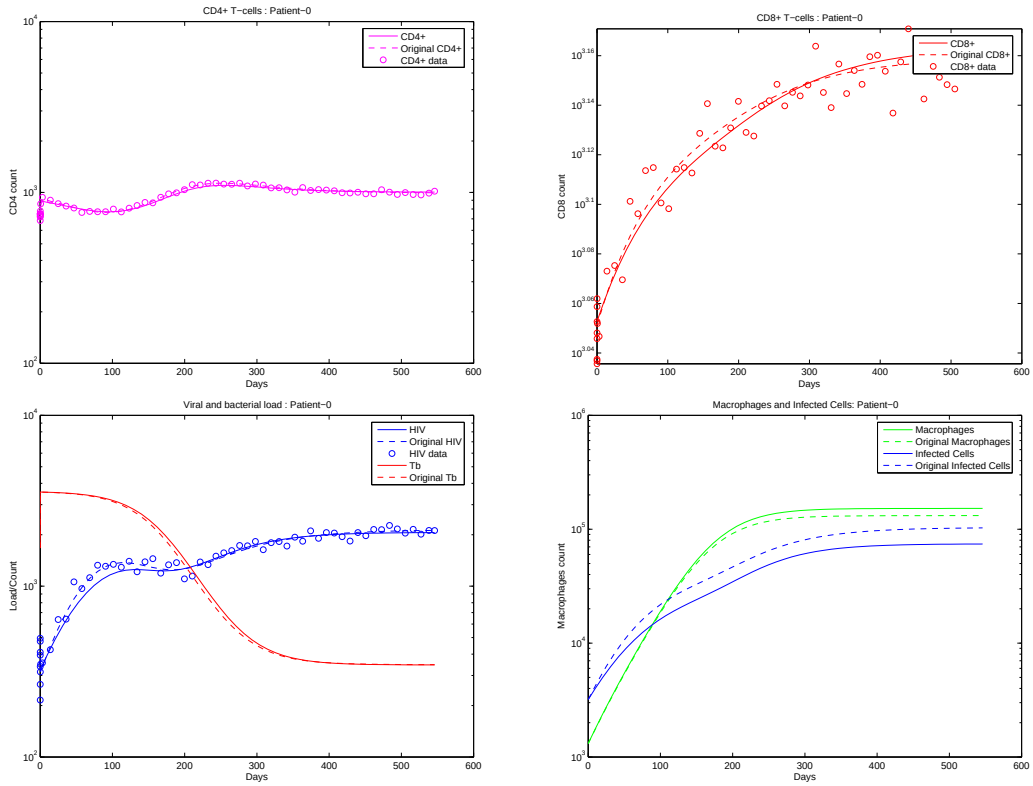

Figure 11.1.: Model response optimised to fit many samples with a small variance

11.2. Fewer Random Samples : Small Variance

If fewer sample values with a small variance of $\sigma^2 = [10^4 \ 500 \ 900]$ for the viral load, CD4+ T-cells and CD8+ T-cells respectively are generated, the model response now worse for the viral load and CD8+ T-cells but still virtually the same for the CD4+ T-cells and the bacterial load. The viral load and the CD8+ T-cells now settle at a lower values than before, with the macrophages and the infected cell counts also differing slightly in their final values. With fewer samples, the criteria for fitting to the data is more stringent. In this case, the variance is not high, thus the responses do not differ that much. With higher variances, as can be seen in the next sections, the responses differ more from the original graphs. Although the latter is true, the general shape and the criteria that formed the graphs still hold, which will be summarised in the conclusion section.

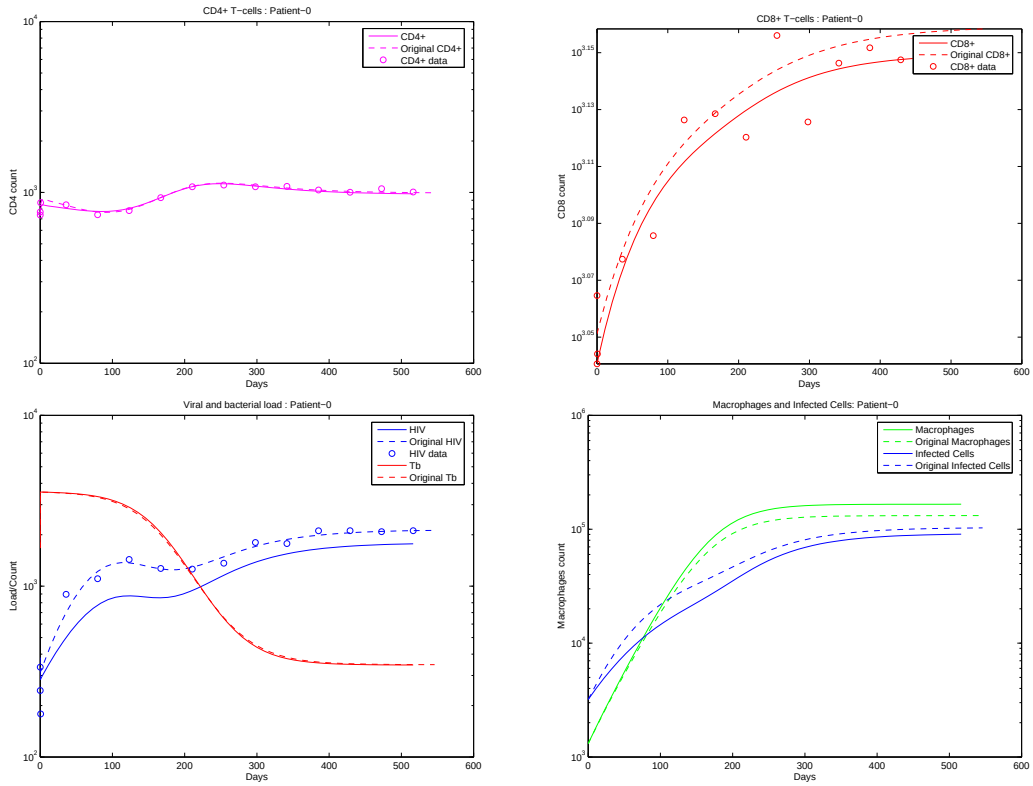

Figure 11.2.: Model response optimised to fit fewer samples with a small variance

11.3. Many Random Samples : Large Variance

With using many random sample values with a large randomized variance of $\sigma^2 = [10^5 \ \ 3500 \ \ 5000]$ for the viral load, CD4+ T-cells and CD8+ T-cells respectively, it can be seen that the responses are starting to differ more significantly from the original graphs. The shape of the graphs, with the transient part and the steady-state, stay the same though. The CD8+ T-cells still fit well to the original response, as well as the macrophages. The transient part of the CD4+ T-cells differ in value but not in shape, and the same steady-state value is reached. The viral load response reaches a lower value than before, while the bacterial load also reaches approximately the same value as before.

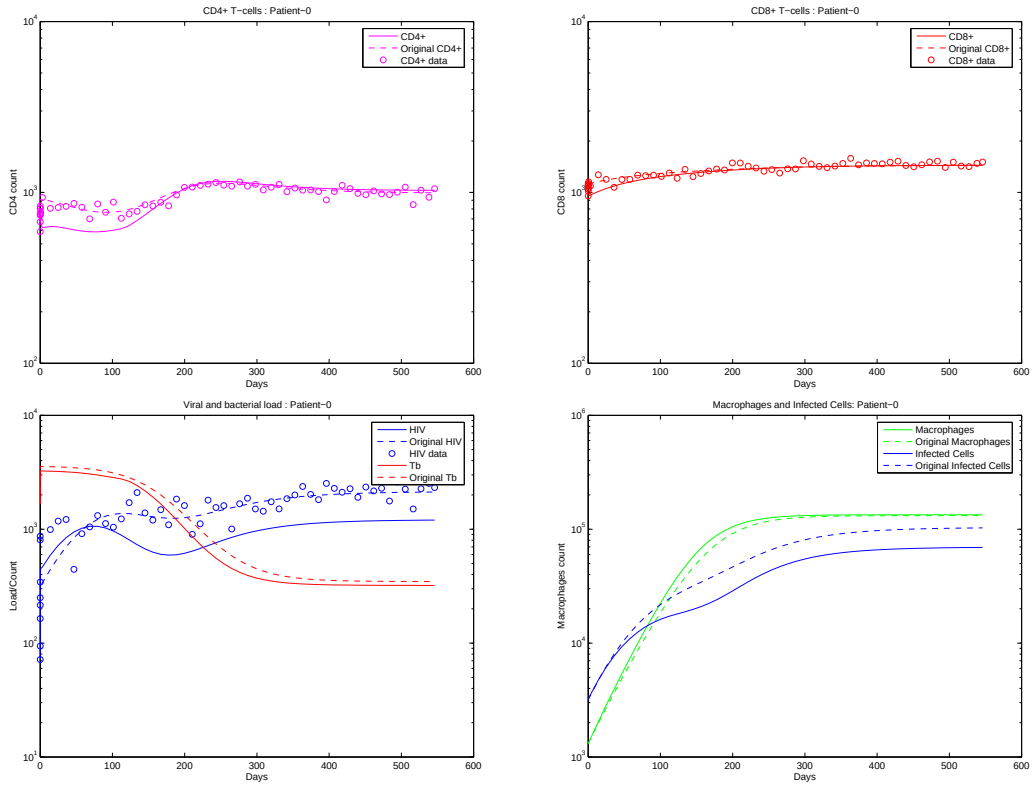

Figure 11.3.: Model response optimised to fit many samples with a large variance

11.4. Fewer Random Samples : Large Variance

The most stringent test for the optimisation routine would be a reduced number of samples as used in this section, with a large variance of $\sigma^2 = [10^5 \ 3500 \ 5000]$ for the viral load, CD4+ T-cells and CD8+ T-cells respectively. The graphs for the CD4+ T-cell count and the bacterial count still reach the correct steady-state values though, and the shapes of all the responses are similar to the original responses. The viral load once again reaches a lower steady-state value than before, which is also the case for the infected cells, macrophages and the CD8+ T-cells. This test indicates that, although a limited number of samples with high random variance is used, the model response after parameter optimisation is still feasible and useable, which furthers the case for the chosen optimisation method very well.

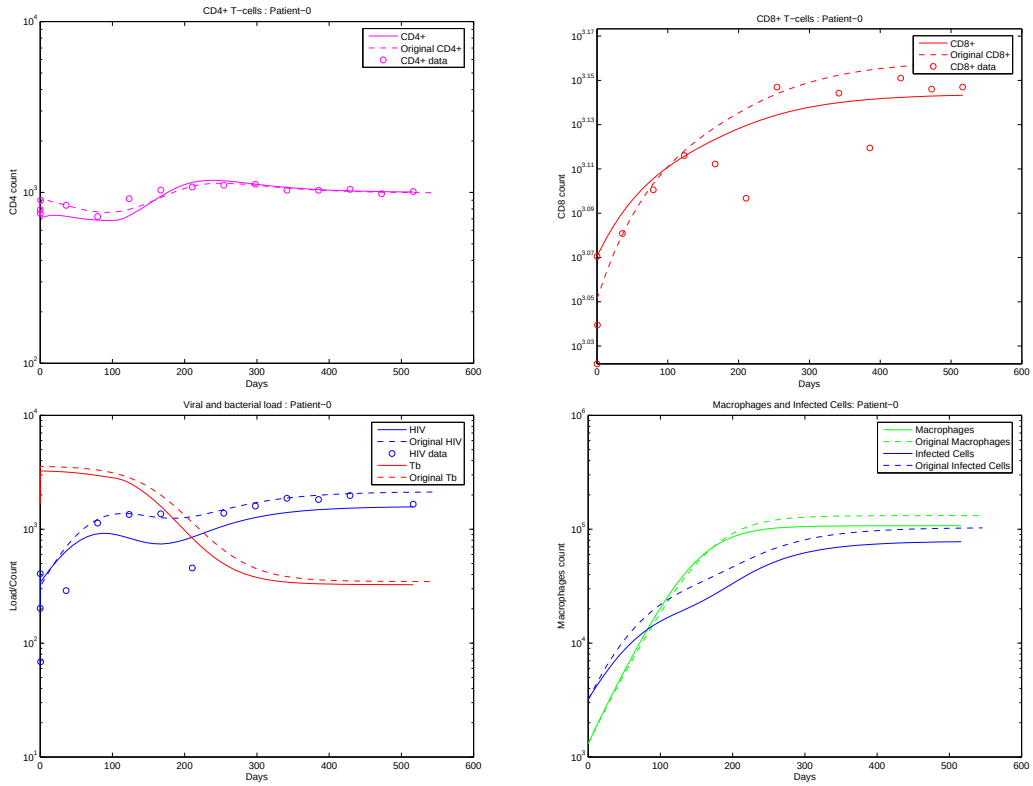

Figure 11.4.: Model response optimised to fit fewer samples with a large variance

11.5. Chapter Summary

In this chapter, the method of optimisation, namely a cost-function based Nelder-Mead algorithm implementation, was tested for its ability to optimise parameters for randomized patient data-samples. The tests were done from the least stringent, low-variance data with many samples, to the most stringent, high-variance random data with only a few samples. In all cases the optimisation could be done successfully, with the shape and expected model response kept intact. This confirms and verifies that the method of optimisation used is effective.

12. Response to Treatment

12.1. Treating TB at Steady-State

RESPONSES for treating tuberculosis at steady-state (in this case the treatment start time is 1000 days) is shown in figure 12.1. The treatment was "administered" by ramping the value of μ_b by 100 copies per ml per day from day 1000 onwards. The interesting effect here is that the number of macrophages also decline significantly during this period, which in turn causes the number of virions to increase. The effect of treating tuberculosis on HIV should thus be considered seriously before high dosages of tuberculosis treatment is given to a patient. The renewed increase in the viral load can easily be seen from the following two terms from (12.1) for the viral load from the proposed model.

$$\frac{dv}{dt} = ... + k_4 N_2 D v - k_6 D v - ... - ... \tag{12.1}$$

The above two terms are evaluated for values of D in the following table (Parameter values are taken from patient 30). D declines due to a decline in the bacterial load, which in turn causes the viral load to increase. The values for the first term $k_4 N_2 D v$ cause the viral load to increase and lose its steady-state at low values of macrophages.

The CD4+ T-cells increase slightly, but start to decline after 2500 days. The CD8+ T-cells also start to decline at 1000 days.

Table 12.1.: Viral load terms influence indirectly by a change in bacteria and consequently macrophages.

Macrophages (D)	$k_5 N_2 D v$	$k_6 D v$
1000	6.11459555	0.82112
750	4.585946663	0.61584
500	3.057297775	0.41056
250	1 .528648888	0.20528
100	0.611459555	0.082112
50	0.305729778	0.041056
25	0.152864889	0.020528
10	0.061145956	0.0082112
5	0.030572978	0.0041056

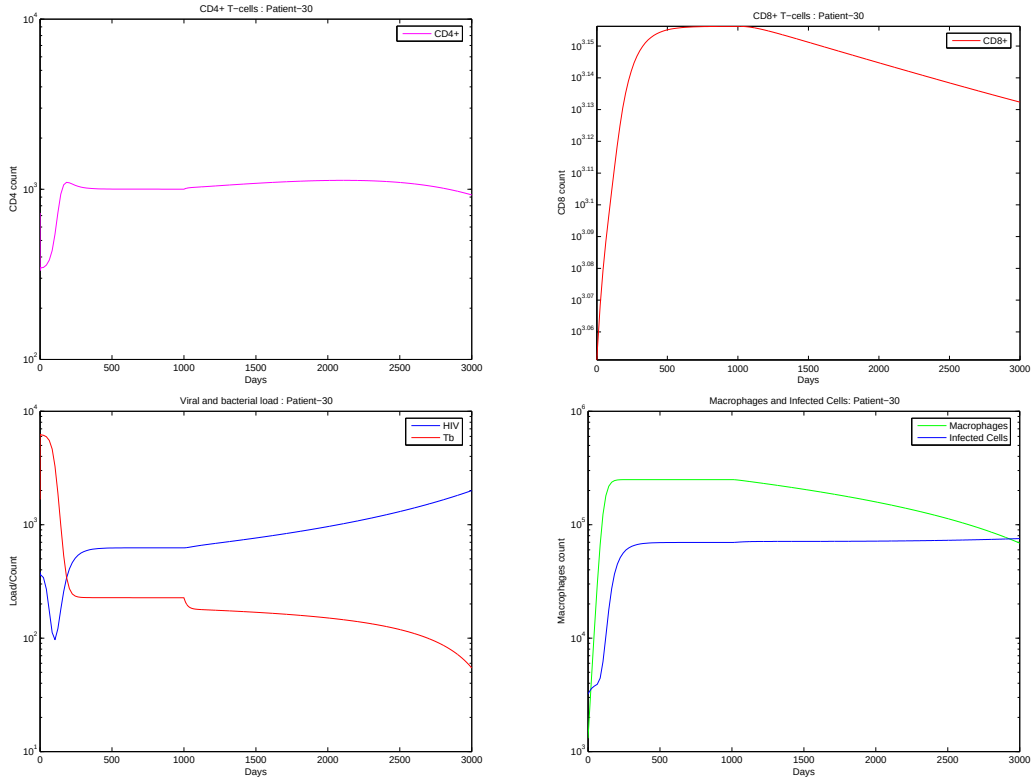

Figure 12.1.: Treatment of TB at steady-state, starting at 1000 days.

12.2. Treating HIV at Steady-State

With the treatment of HIV at 1000 days, a ramp function was employed and added to the value of μ_v with a slope of 3 counts per ml per day. It can be seen that the effect of HIV on tuberculosis is virtually non-existent (which is different to the effect a change in TB has on HIV). If the viral load decreases, the CD4+ T-cell count increases and settles at a new, higher value. The result seen in figure 12.2 indicates that the treatment of HIV has little effect on the immune response in general. Over the time period simulated, neither the CD8+ T-cell count nor the macrophages and infected cell show any change. This further suggests that viral levels could be controlled to acceptable levels over a long period before TB treatment is started, but the effect of long periods on TB proliferation is unknown in this simulation. The opposite case, administering TB treatment before HIV is treated, can also be considered, but as is seen in the previous section the dosages should be kept low to prevent the virus from escalating in value.

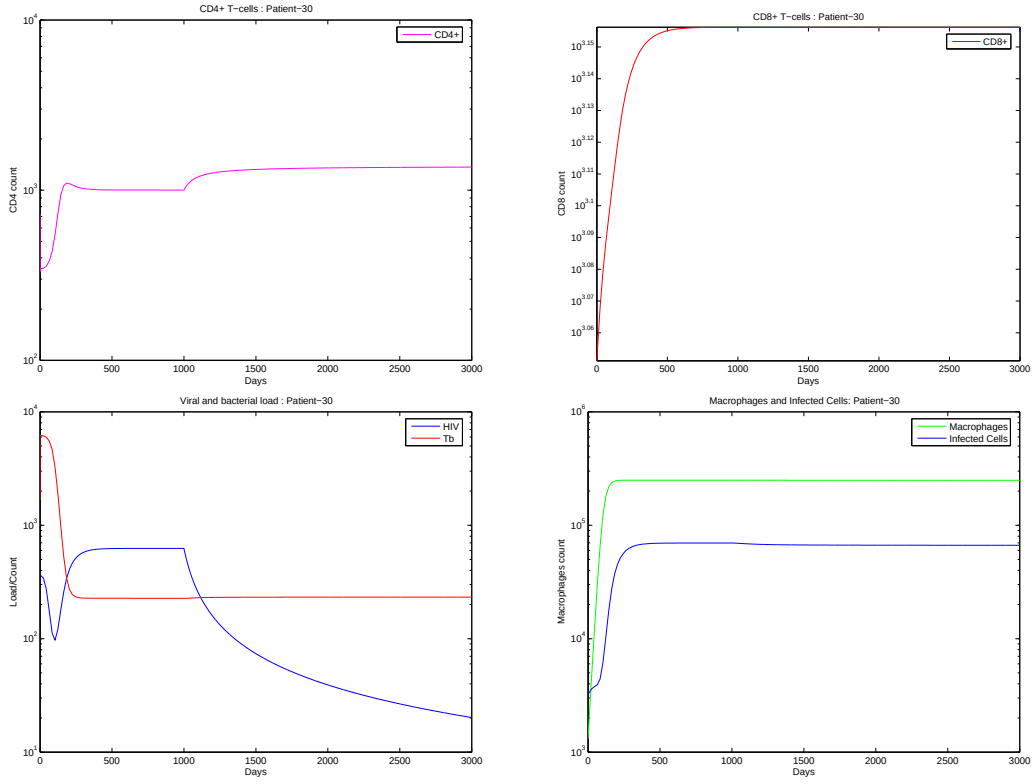

Figure 12.2.: Treatment of HIV at steady-state, starting at 1000 days.

12.3. Chapter Summary

In this chapter, the effect of treatment was briefly considered for both HIV and TB. The effect of a change in HIV on the bacterial response and of tuberculosis on HIV was monitored, and it was found that HIV-changes do not affect the immune response that much. The controversial effect of a change in TB was noticed as having an increasing effect on HIV if the TB death-rate is increased. The conclusion was made that treatment of TB should be well-planned and be considered in lighter dosages, to prevent the decline in macrophages from causing HIV to increase in value.

13. Empirical Results

THE general results from all experiments on patients, in correlation with one another, are looked at in this chapter. In the true sense of the word, "empirical" means that it is applicable to the complete "empire" or scope, which in this case comprises of all the patients' results, simulations, datasets and optimised parameters. Certain correlations can be drawn from the latter and indeed are done here. Simulation-results from generated-data fittings are considered as well as the treatment-results from section 12. The effect of HIV on TB and of TB on HIV is also considered.

13.1. Comparing Patient Benchmarks

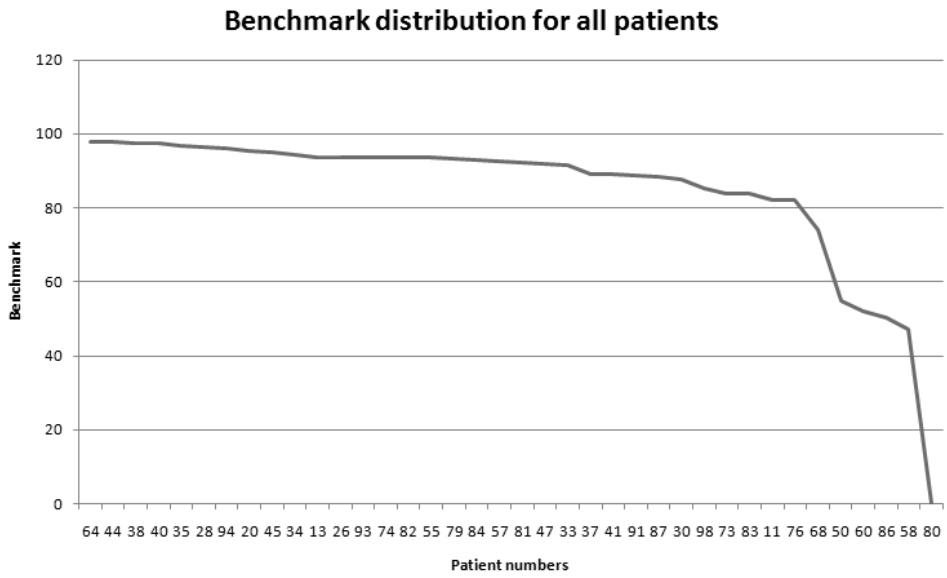

Figure 13.1.: Final benchmark distribution for all patients

The complete list of benchmarks for all patients calculated by using the method shown in section D, is given in table D.1

The above figure shows the distribution of patient benchmarks with patient having the best benchmarks grouped to the left of the graph and patients with the worst benchmarks grouped to the right of the graph. A few very interesting deductions can be made from the figure:

- At least 30 of the 38 patients have benchmarks above 80%. This indicates that these 30 patients' responses are not very different in how well they fit to their respective datasets and that they compare very well with the best patient in the set.
- 6 patients have benchmarks of 60% and lower. These patients compare poorly to the best patient in the set. Their responses might be improved by using the process describe in refinement parts of section 9.
- The benchmarks give one an idea of the consistency of the optimisation routine. The routine was consistent in its results for the patients that had benchmarks above 80%. As these patients comprise about 78% of the total number of patients, the optimisation routine was consistent for patients with and without complete datasets available in at least 78% of the cases.

13.2. HIV/TB Interworking

This section comments on the interworking between HIV and TB as seen from results and simulations. The importance of deductions made here can be pulled through to the practical case of identifying patients' infections and scheduling treatment for them. The interworking described here is by no means refined, but follows from the proposed model that was verified in section 10, and optimised with a method verified in section 11.

13.2.1. HIV's Influence on TB

The direct influence of HIV on TB cannot be seen by purely looking at the model equations in 4.25. The effect can be seen by inspection of results of treatment in section 12. The effect that a change in the viral load has on the bacterial load seems minimal, if any at all. The viral load from figure 12.2 was changed to decline quickly,

but no change in TB can seen. As a result, the conclusion can be made here that the effect of treating HIV (changing the model response) has little or no effect on the TB response.

13.2.2. TB's Influence on HIV

The effect of TB on HIV is different to the effect the HIV has on TB. If the bacterial load is changed, as can be seen in figure 12.1, the viral load starts to increase. This is inherent in the model equation for the viral load, which responds and relies heavily on the macrophage count. The macrophage count is influenced by a decline in bacteria, hence the viral load is also affected heavily. If a doctor or medical practitioner considers the treatment of people with the co-infection, information such as this should be considered. Because TB treatment is scheduled on a 6 or 9 month cycle, the simulations shown in figure 12.1 would not be of much help, other than to say that the viral load will increase if TB is treated. On the other hand, anti-retrovirals may be given to a patient before TB is treated, which wouldn't affect the immune-response very much (from figure 12.2), but then it should be noted that the TB could kill the patient before anti-retroviral treatment is finished. For this reason, the profile of patients should be taken and treatment properly simulated, to see the effect of different types of treatments administered in different combinations in relation to another.

13.3. Techniques and Improvisations

In this section, a layout is made of all the useful techniques and methods that were improvised and constructed as a result of this study. The techniques are presented on a cause-and-effect basis, with the effect being the creation of the relevant technique, and the cause the reason for its creation.

13.3.1. Lack of Data Samples

Where the data from a patient was laced with incomplete measurements (ie. no measurements at all for one or all of the cell-types), the effect on the cost function would have been both unknown and unpredictable. Due to the fact that the cost function takes the least-squares error from all the samples of a relevant cell-type, what value would one use for an incomplete measurement? Surely one cannot use the first obvious choice, namely zero. This would be both untrue from a medical perspective and would create sudden irregularities in the cost function. More unrealistic to handle would be the log-based value of the viral load. How would one take the log of zero?

The next probable choice would be to interpolate data between samples. The problem with this is that the immune-reponse is non-linear by nature, hence this approach would be an approximation. Furthermore, it would mean that we are manufacturing data, which, in the scope of this study, would mean that we are deviating from the goal of fitting a model to pure measurements. This would thus greatly distract from providing credibility and confidence in the model.

Neither of the choices above would result in the model gaining credibility from the point of view of being stable in the literary academic environment, hence a third choice was employed : simply removing bad data.

Wherever the data samples for a specific day was not complete, all the samples from that day were removed. This is illustrated with the following example:

Let A be the matrix of samples from a specific patient, shown in (13.1)

$$A = \begin{bmatrix} \overbrace{\text{week}}^{} & \overbrace{\log(\text{viral load})}^{} & \overbrace{\text{viral load}}^{} & \overbrace{\text{CD4+}}^{} & \overbrace{\text{CD8+}}^{} & \overbrace{\text{Completeness}}^{} \\ 0 & 2.582063 & 381.9996808 & 726 & 1125 & \text{Complete} \\ 2 & 4.278044 & 18968.98093 & 834 & 1903 & \text{Complete} \\ 4 & 2.91803 & 827.9993579 & 747 & 1803 & \text{Complete} \\ 8 & 3.04454 & 1108.000611 & & 1382 & \text{Incomplete row} \\ 26 & 1.869232 & 74.00004776 & & 1388 & \text{Incomplete row} \\ 52 & 2.897077 & & 921 & 1209 & \text{Incomplete row} \\ 78 & 3.371806 & & 922 & 1349 & \text{Incomplete row} \end{bmatrix} \tag{13.1}$$

Following the removal of incomplete rows from (13.1), the new patient data matrix A^* is now

$$A^* = \begin{bmatrix} \overbrace{\text{week}}^{} & \overbrace{\log(\text{viral load})}^{} & \overbrace{\text{viral load}}^{} & \overbrace{\text{CD4+}}^{} & \overbrace{\text{CD8+}}^{} & \overbrace{\text{Completeness}}^{} \\ 0 & 2.582063 & 381.9996808 & 726 & 1125 & \text{Complete} \\ 2 & 4.278044 & 18968.98093 & 834 & 1903 & \text{Complete} \\ 4 & 2.91803 & 827.9993579 & 747 & 1803 & \text{Complete} \end{bmatrix} \tag{13.2}$$

It can be seen that 4 of the 7 sample-points for the patient was removed. The results for a patient with many of its sample-points removed in this way is shown in figure E.29.

13.3.2. Refinement : Nominal Parameter Sets and Initial Conditions

A technique that flowed from incomplete knowledge of the initial conditions for half of the dependent variables in model (4.25) was the creation of two methods to "guess" initial conditions intelligently, and one procedure to refine a patient's response by retrieving a better nominal parameter set. The procedures worked very well, as can be seen in the refinement parts of the case studies done in section 9. A brief summary of the three techniques is given here:

i. The first method to guess initial conditions involves having knowledge of the number of healthy CD4+ T-cells in a patient. This information is then assumed to have a linear ratio in relation to the number of CD4+ T-cells in the body. In this way the graph seen in figure 7.1 can be used to 'read off' an approximated initial bacterial count. The viral load, CD4+ T-cells and CD8+ T-cells are initial conditions are taken as being the first sample point for a patient. The macrophages is guessed by using the known ratio of macrophages to the total CD4+ T-cells, and the infected cells are guessed at being double that of the uninfected cells.

ii. The second method for guessing initial conditions is to use the simulation GUI devised and discussed in appendix B. By visual inspection one can change the initial conditions and monitor the response changes until they are acceptable to

the user. This method was employed for most of the simulations in this study.

iii. A refinement procedure for obtaining a better nominal parameter set was created. A nominal set from literature is used as a starting point. Using this set, generated data from the 4-dimensional model created in [10] was used in the optimisation routine. A new set of parameters were thus found, and this set was used to simulate all patients with. The optimised parameter set for each individual patient that came from the latter simulations was consequently taken as the final nominal parameter set used to obtain refined results per patient. Thus, using the previous two methods, and the optimised parameter set from a specific patient, that patient could be re-simulated and a refined result obtained.

13.3.3. Devising the Patient Benchmarks

When starting out with a new patient dataset and optimising parameters per patient, it is difficult to get an overview of how well the different patients fare in relation to another, and if the optimisation routine is actually working well for most of the patients. With this said, a patient benchmark was created and defined in appendix D. These benchmarks give the user of the optimisation algorithm a birds-eye view of all the patients and a base from which to compare each of them with another. A benchmark does not make sense outside of the purpose for which is was designed. The final benchmarks, given as a percentage, indicate how similar patients' optimisation was in relation to the best patient in the set. This devising of this technique is seen as a result of this study in itself, and provided information on which patients should be selected for case studies, as well as giving valuable insights into how well optimisation worked for patients with a limited number of available samples.

13.4. Chapter Summary

In this chapter some results that apply to all patients are considered. Benchmarks were compared and discussed, and the results of tools and methods devised as a result of this research were considered.

14. Conclusion

14.1. Outcomes and Interpretations

THIS study proposed a model for showing the co-infection dynamics of HIV-1 and M. tuberculosis. The following broad list indicates what has been achieved with this research, and the next section discusses possible future research possibilities.

- A co-infection model was proposed, based on a medical explanation of cell-population growth and decay with regards to the immune response to foreign pathogen.
- The co-infection model was compared to similar co-infection models, and the differences and similarities pointed out.
- An identifiability study was done on the proposed model in (4.25). This study indicated that only 8 of the 22 model parameters can be identified algebraically. The available data samples were not enough to determine all the identifiable parameters. On average, only 7 samples per measured output was available, hence by fixing certain parameters the optimisation routine could provide much better results.
- The acquired data-set was considered, and patients were selected to be included into this study based on how complete their datasets were.
- A cost-function was created to reflect the difference between the model and the data. The cost-function linked the model to the data by having at its base a least squares difference between model and data.
- The cost-function was refined with known information about the data-set and with optimisation goals in mind, such as the reaching of a steady-state (maximum derivative minimization) and, the fitting of data to the model and the actual value at steady-state.

- The terms in the cost-funtion were appropriately weighted to equalise the effect of the different optimisation criteria on the estimation outcome.
- Each step in the optimisation routine was discussed, and a layout of a complete simulation architecture was explained to implement this parameter optimisation.
- A GUI-tool was created alongside the simulation architecture to cater for response refinements and determining initial conditions.
- The simulation architecture was used to simulate a the complete set of patients, and to generate the results with specific goals in mind.
- A patient-benchmark was devised to compare the optimisation results of patients to one another. This benchmark was consequently used to select a few patients for case-studies on their responses.
- The model was verified by the latter optimisation and simulation by observing how well it fits to a patient with a fully-available dataset and one with a dataset containing a reduced number of samples. The model fits good to a full-dataset patient, and also very good (but not quite as well) to a patient with a reduced dataset. With a reduced data-set patient, however, the expectation never was that the response would be very good, as the identifiability study indicates the number of samples needed for identification of the identifiable parameters in the proposed model is at least 8 samples for the viral load, 7 samples for the CD8+ T-cells and 6 samples for the CD4+ T-cells.
- After the model was verified, the optimisation method was put to scrutiny. This was done by generating data from a patient's model response, and using this data as input to the exact same patient's optimisation again. The effect was that the optimisation routine could be verified as useable and efficient for generated datasets with high and low variances, and with datasets with a high number and a much lower number of samples. Across the spectrum of the available generated datasets, the optimisation routine could still provide parameters to the model such that the response was well-formed, reaching a steady-state and fitting in some cases almost perfectly to the generated data.
- Treatment was simulated for a single patient. The treatment simulation showed both the effect that changes in HIV has on TB, and the effect that changes in

TB has on HIV. It was found that, if TB was reduced after steady-state, HIV increased due to the resulting decrease in the number of macrophages. With a change in HIV at steady-state, however, no noticeable effect was found on the rest of the immune response.

- It was found that, when all the patients were compared to another, that the benchmark indicated similar values for at least 75 to 80% of the patients. This means that only a small handful of patients' models (about 6 of the 38) couldn't be well-optimised and showed a very low-valued benchmark (below 60%).
- As a final conclusion to the study, it must be said that the proposed model is by no means final and conclusive, even though it has been verified in this study. The true test for the model would be to use it on hundreds of patients (a large patient sample size), and verify that similar, refined results can be obtained for all the patients. After such stringent testing, the model would be ready for practical use by medical practitioners and doctors.
- One such model, known in this study as the 4-dimensional model proposed by [10] was used to generate

14.2. Continued Research Possibilities

Many new research possibilities stem from this co-infection model. They are listed here:

- The obvious next step would be to use the model to predict practical use-cases for specific patients. These use-cases will need to take the form of a treatment schedule to make a real difference. This implies that a controller for this model should be designed and a method devised to convert the controller-equations to physical medication scheme inputs to the system.
- The co-infection model can be extended to include the latest knowledge about tuberculosis and HIV. For tuberculosis, this would mean that the effects of drug-resistant TB would have to be considered, and the model accordingly adjusted for specific types of TB. A paper which discusses the control of multi-drug resistant TB is [13].

- A whole study could be made of finding the initial conditions specific to a patient.
- Co-infection should not be limited to tuberculosis only. Many other co-infection states exist which could be modelled, verified and simulated.
- Finally, the aim should always be to make practical use of studies such as this, to ensure that every bit of information that could help the individuals struggling with these terrible diseases to find comfort and happiness in their lives.

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A. Matlab Simulation Architecture

The simulation architecture (called *"HIVE"*, for HIV-emulator) that was built to obtain the results for this research is explained here. The main functionality of the architecture is described, as well as its operating procedure. The flow-diagram of the architecture is shown in Fig. A.1, and the complete code listing and program can be found on the accompanying CD.

The operating procedure for using the architecture needs to be followed exactly to obtain the correct outputs (a per-patient set of graphs and a per-patient set of optimised parameters).

Each section corresponds to a matlab M-file, and the appropriate functionality from the flow-diagram is pointed out in accordance with the M-file it is in.

A.1. Functionality

With HIVE, it is possible to

- Provide input patient data via a CSV (comma-separated-value) file in an input-directory
- Simulate a given patient's response
- Search for a patient's optimal parameter set. This optimum might be a local minimum, as the Nelder-Mead optimisation algorithm is used.
- Extend the simulation architecture by adding different plots to the code, for example CD4+ T-cells and CD8+ T-cells on one graph.

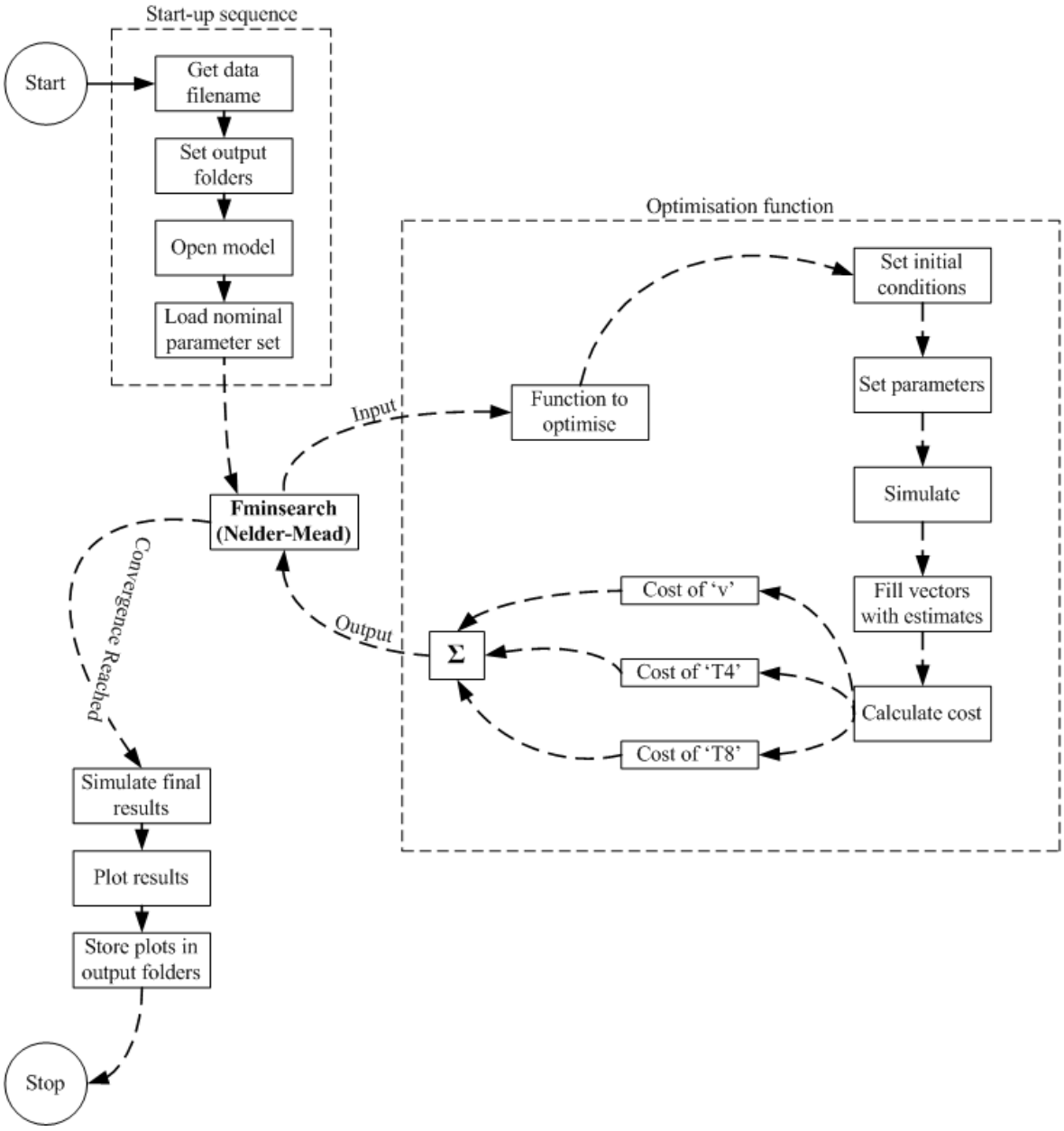

Figure A.1.: Simulation architecture.

A.2. Main Architecture Files

start.m

This file is the starting point for using the simulation architecture. It clears up variables from a previous simulation and closes any open graphs. Furthermore, it initialises the input data file, creates output folders for the specific simulation instance, opens the model, loads the nominal parameter set, en sets initial conditions. Finally it initiates

the main simulation loop.

main.m

As can be seen from the function definition (on the CD), the **start.m** file passes all the necessary initial conditions and information about the simulation environment to the main loop. Inside the main loop, the following things happen in sequence:

i. The input data file is parsed into several individual variables, which may then be used in the simulation environment (See **data_parser.m**)
ii. The Matlab function **fminsearch.m** is invoked with the function to be optimised. The optimisation function is in essence the total cost calculation from the difference between an instantaneous simulated point which falls on the same time as a field data point.
iii. **fminsearch.m** iterates the optimisation function until it converges to a solution
iv. The optimised state trajectory is plotted, and the optimal parameters are saved
v. All figures of the optimised state trajectory is saved to the relevant simulation output directory. A directory is named according to the date and time the simulation took place.

optimise.m

Within the optimisation function m-file, parameter constraints are enforced, the simulink model file is initialised with parameters, any known or fixed parameters are set before simulation and the model is integrated numerically. The results from the numerical integration are passed to the cost-function by means of sample and response vectors, and the value returned from the cost function is passed back from optimise.m.

fixed_parameters.m

This file contains the implementation of parameters constraints enforcing. The model is passed into this function, and the parameters are accordingly adjusted before the model is passed back to the calling routine.

parameter_constraints.m

Parameters contraints are limited between upper and lower-boundary values in this file. This is done and applied to the passed-in parameters array before the array is returned to the calling routine.

data_parser.m

Patient data is parsed in this file into vectors for each cell-type. If data is incomplete, the whole row of data is removed from the array for all the cell-types.

latexoutput.m

All simulated patients' optimised parameter sets are written to files in latex-table format by this file. This is useful for document (and dissertation!) automation, as any results obtained can be copied or linked directly into a latex-document.

A.3. Additional Files

Data files:

The various data-files include patient data in comma-separated-value format, like data13.csv, and generated data files called generated_data.csv. Nominal parameter sets are stored in files such as nominal.txt and nominal_test.txt.

Model files:

The simulink models for the co-infection model and a model for treatment-purposes are found in model.mdl and treatment_model.mdl respectively.

Output parameters:

Optimised parameters are written to files called parameters_optimisedXX. The XX is exchanged for the relevant patient number.

B. Matlab Simulation GUI Tool

A GUI tool was created to aid with the selection of initial conditions where they are unknown or incomplete. A screenshot of the tool is shown below:

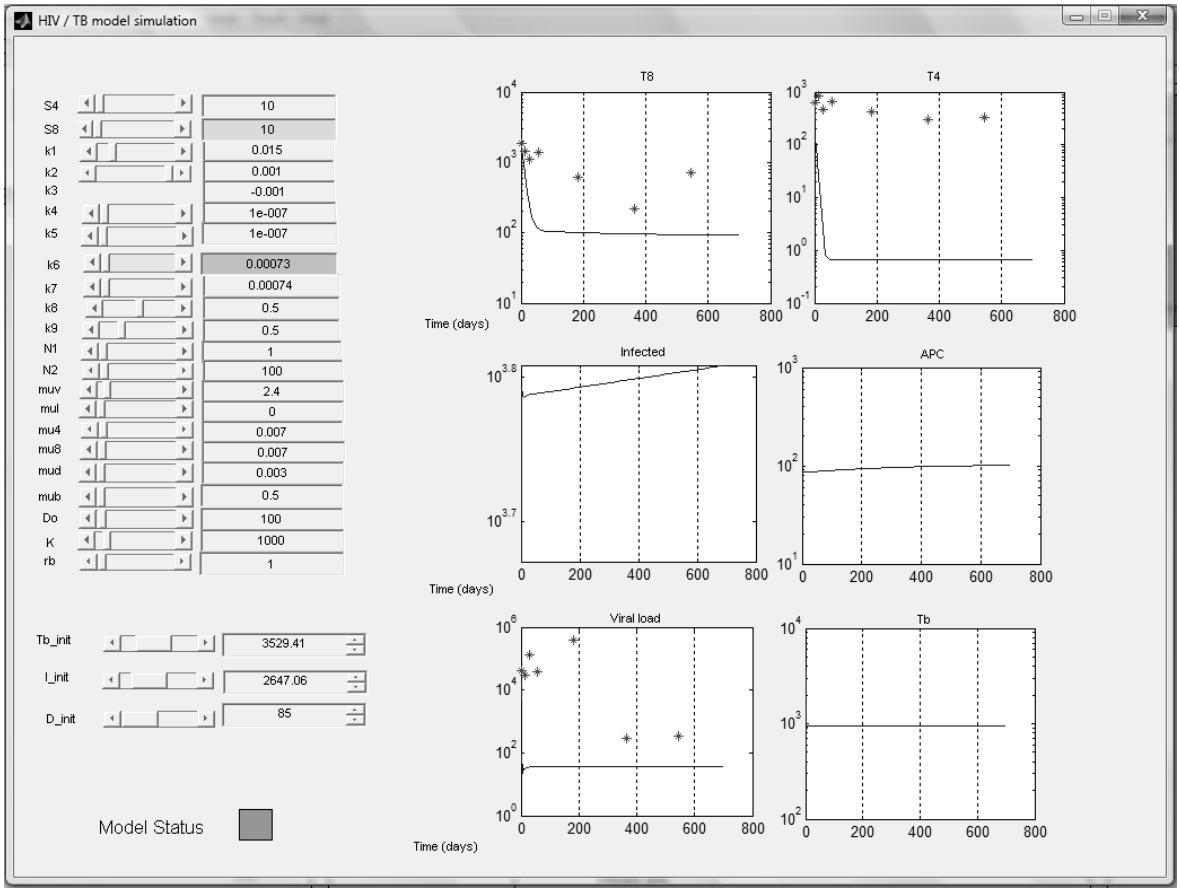

Figure B.1.: Simulation GUI tool.

The GUI-tool works in the following simple way:

- The parameters from a specific patient is programmed into the m-file code in Matlab
- The patient is simulated initially using the initial conditions set in the Matlab code
- The initial parameters are chosen from the patient's first data samples
- The GUI provides sliders to manipulate the parameters of the patient's model
- Sliders are also provided for the initial conditions of the bacterial load, macrophages and the infected cells.
- After a slider is adjusted, the model is automatically simulated with the new, updated parameters.
- The trend that is followed by the model can be visually inspected as a parameter or initial condition is changed.

C. Dataset Statistics

Table C.1.: Properties of the data-set : Individuals

Patient	HIV+	v	T_4	T_8	0 weeks?	78 weeks?	Useable ($\surd$ / $\emptyset$)
1	$\surd$	6	5	5	$\surd$	$\emptyset$	$\emptyset$
2	$\surd$	1	1	1	$\surd$	$\emptyset$	$\emptyset$
3	$\surd$	1	1	1	$\surd$	$\emptyset$	$\emptyset$
4	$\surd$	2	2	2	$\surd$	$\emptyset$	$\emptyset$
5	$\emptyset$	0	7	7	$\surd$	$\emptyset$	$\emptyset$
6	$\surd$	5	5	5	$\surd$	$\emptyset$	$\emptyset$
7	$\emptyset$	0	2	2	$\surd$	$\emptyset$	$\emptyset$
8	$\surd$	2	2	2	$\surd$	$\emptyset$	$\emptyset$
9	$\emptyset$	0	7	7	$\surd$	$\emptyset$	$\emptyset$
10	$\emptyset$	0	3	3	$\surd$	$\emptyset$	$\emptyset$
11	$\surd$	7	7	7	$\surd$	$\surd$	$\surd$
12	$\surd$	6	6	6	$\surd$	$\emptyset$	$\emptyset$
13	$\surd$	6	6	6	$\surd$	$\surd$	$\surd$
14	$\emptyset$	0	6	6	$\surd$	$\emptyset$	$\emptyset$
15	$\emptyset$	0	6	6	$\surd$	$\emptyset$	$\emptyset$
16	$\emptyset$	0	2	2	$\surd$	$\emptyset$	$\emptyset$
17	$\surd$	6	6	6	$\surd$	$\emptyset$	$\emptyset$
18	$\surd$	3	3	3	$\surd$	$\emptyset$	$\emptyset$
19	$\surd$	5	6	6	$\surd$	$\emptyset$	$\emptyset$
20	$\surd$	6	7	7	$\surd$	$\surd$	$\surd$
21	$\emptyset$	0	2	2	$\surd$	$\emptyset$	$\emptyset$
22	$\surd$	1	1	1	$\surd$	$\emptyset$	$\emptyset$
23	$\emptyset$	0	6	6	$\surd$	$\emptyset$	$\emptyset$
24	$\surd$	2	2	2	$\surd$	$\emptyset$	$\emptyset$
25	$\emptyset$	0	6	6	$\surd$	$\surd$	$\emptyset$
26	$\emptyset$	6	7	7	$\surd$	$\surd$	$\surd$
27	$\surd$	0	6	6	$\emptyset$	$\surd$	$\emptyset$
28	$\surd$	5	7	7	$\surd$	$\surd$	$\surd$

Table C.2.: Properties of the data-set : Individuals : continued

Patient	HIV+	v	T_4	T_8	0 weeks?	78 weeks?	Useable ($\surd$ / $\emptyset$)
29	$\emptyset$	0	4	4	$\surd$	$\emptyset$	$\emptyset$
30	$\surd$	7	7	7	$\surd$	$\surd$	$\surd$
31	$\emptyset$	0	7	7	$\surd$	$\surd$	$\emptyset$
32	$\surd$	4	4	4	$\surd$	$\emptyset$	$\emptyset$
33	$\surd$	7	7	7	$\surd$	$\surd$	$\surd$
34	$\surd$	7	7	7	$\surd$	$\surd$	$\surd$
35	$\surd$	7	7	7	$\surd$	$\surd$	$\surd$
36	$\emptyset$	1	7	7	$\surd$	$\surd$	$\emptyset$
37	$\surd$	5	6	6	$\surd$	$\surd$	$\surd$
38	$\surd$	7	7	7	$\surd$	$\surd$	$\surd$
39	$\emptyset$	0	7	7	$\surd$	$\surd$	$\emptyset$
40	$\surd$	7	7	7	$\surd$	$\surd$	$\surd$
41	$\surd$	7	7	7	$\surd$	$\surd$	$\surd$
42	$\surd$	4	4	4	$\surd$	$\emptyset$	$\emptyset$
43	$\emptyset$	0	7	7	$\surd$	$\surd$	$\emptyset$
44	$\surd$	7	7	7	$\surd$	$\surd$	$\surd$
45	$\surd$	7	6	6	$\surd$	$\surd$	$\surd$
46	$\emptyset$	0	7	7	$\surd$	$\surd$	$\emptyset$
47	$\surd$	7	6	6	$\surd$	$\surd$	$\surd$
48	$\emptyset$	0	6	6	$\surd$	$\surd$	$\emptyset$
49	$\surd$	4	4	4	$\surd$	$\emptyset$	$\emptyset$
50	$\surd$	7	6	6	$\surd$	$\surd$	$\surd$
51	$\emptyset$	0	7	7	$\surd$	$\surd$	$\emptyset$
52	$\surd$	7	7	7	$\surd$	$\surd$	$\surd$
53	$\surd$	5	5	5	$\surd$	$\emptyset$	$\emptyset$
54	$\emptyset$	0	7	7	$\surd$	$\surd$	$\emptyset$
55	$\surd$	6	7	7	$\surd$	$\surd$	$\surd$
56	$\surd$	4	4	4	$\surd$	$\emptyset$	$\emptyset$
57	$\surd$	7	7	7	$\surd$	$\surd$	$\surd$
58	$\surd$	6	7	7	$\surd$	$\surd$	$\surd$
59	$\emptyset$	0	7	7	$\surd$	$\surd$	$\emptyset$
60	$\surd$	6	7	7	$\surd$	$\surd$	$\surd$

Table C.3.: Properties of the data-set : Individuals : continued

Patient	HIV+	v	T_4	T_8	0 weeks?	78 weeks?	Useable ($\surd$ / $\emptyset$)
61	$\emptyset$	1	7	7	$\surd$	$\surd$	$\emptyset$
62	$\emptyset$	0	6	6	$\surd$	$\surd$	$\emptyset$
63	$\surd$	3	3	3	$\surd$	$\emptyset$	$\emptyset$
64	$\surd$	6	7	7	$\surd$	$\surd$	$\surd$
65	$\surd$	4	4	4	$\surd$	$\emptyset$	$\emptyset$
66	$\surd$	4	5	5	$\surd$	$\emptyset$	$\emptyset$
67	$\surd$	4	4	4	$\surd$	$\emptyset$	$\emptyset$
68	$\surd$	6	7	7	$\surd$	$\surd$	$\surd$
69	$\emptyset$	6	7	7	$\surd$	$\surd$	$\emptyset$
70	$\surd$	2	2	2	$\surd$	$\emptyset$	$\emptyset$
71	$\surd$	3	5	5	$\surd$	$\surd$	$\emptyset$
72	$\surd$	6	5	5	$\surd$	$\emptyset$	$\emptyset$
73	$\surd$	5	7	7	$\surd$	$\surd$	$\surd$
74	$\surd$	5	7	7	$\surd$	$\surd$	$\surd$
75	$\surd$	5	6	6	$\surd$	$\surd$	$\emptyset$
76	$\surd$	6	7	7	$\surd$	$\surd$	$\surd$
77	$\surd$	5	4	4	$\surd$	$\emptyset$	$\surd$
78	$\emptyset$	0	6	6	$\surd$	$\emptyset$	$\emptyset$
79	$\emptyset$	0	6	6	$\surd$	$\emptyset$	$\emptyset$
80	$\surd$	6	6	6	$\surd$	$\surd$	$\surd$
81	$\surd$	5	6	6	$\surd$	$\surd$	$\surd$
82	$\surd$	5	7	7	$\surd$	$\surd$	$\surd$
83	$\surd$	3	5	5	$\surd$	$\surd$	$\surd$
84	$\surd$	6	7	7	$\surd$	$\surd$	$\surd$
85	$\surd$	5	5	5	$\surd$	$\emptyset$	$\emptyset$
86	$\surd$	6	6	6	$\surd$	$\surd$	$\surd$
87	$\surd$	5	7	7	$\surd$	$\surd$	$\surd$
88	$\emptyset$	0	7	7	$\surd$	$\surd$	$\emptyset$
89	$\surd$	5	4	4	$\surd$	$\emptyset$	$\emptyset$
90	$\emptyset$	0	7	7	$\surd$	$\surd$	$\emptyset$

Table C.4.: Properties of the data-set : Individuals : continued

Patient	HIV+	v	T_4	T_8	0 weeks?	78 weeks?	Useable ($\surd$ / $\emptyset$)
91	$\surd$	4	6	6	$\surd$	$\surd$	$\surd$
92	$\surd$	5	5	5	$\surd$	$\emptyset$	$\emptyset$
93	$\surd$	5	7	7	$\surd$	$\surd$	$\surd$
94	$\surd$	6	7	7	$\surd$	$\surd$	$\surd$
95	$\emptyset$	1	7	7	$\surd$	$\surd$	$\emptyset$
96	$\emptyset$	0	6	6	$\surd$	$\surd$	$\emptyset$
97	$\emptyset$	0	7	7	$\surd$	$\surd$	$\emptyset$
98	$\surd$	6	7	7	$\surd$	$\surd$	$\surd$
99	$\surd$	6	6	6	$\surd$	$\emptyset$	$\emptyset$
100	$\surd$	4	6	6	$\surd$	$\emptyset$	$\emptyset$
101	$\surd$	5	6	6	$\surd$	$\emptyset$	$\emptyset$
102	$\emptyset$	0	6	6	$\surd$	$\surd$	$\emptyset$
103	$\emptyset$	0	6	6	$\surd$	$\emptyset$	$\emptyset$
104	$\surd$	4	4	4	$\surd$	$\emptyset$	$\emptyset$
105	$\surd$	1	1	1	$\surd$	$\emptyset$	$\emptyset$
106	$\surd$	6	6	6	$\surd$	$\emptyset$	$\emptyset$
107	$\surd$	6	6	6	$\surd$	$\emptyset$	$\emptyset$
108	$\emptyset$	0	6	6	$\surd$	$\emptyset$	$\emptyset$
109	$\emptyset$	6	6	6	$\surd$	$\emptyset$	$\emptyset$
110	$\emptyset$	0	6	6	$\surd$	$\emptyset$	$\emptyset$
111	$\surd$	3	4	4	$\surd$	$\emptyset$	$\emptyset$
112	$\emptyset$	0	6	6	$\surd$	$\emptyset$	$\emptyset$
113	$\surd$	5	6	6	$\surd$	$\emptyset$	$\emptyset$
114	$\emptyset$	0	4	4	$\surd$	$\emptyset$	$\emptyset$
115	$\surd$	5	6	6	$\surd$	$\emptyset$	$\emptyset$
116	$\surd$	5	6	6	$\surd$	$\emptyset$	$\emptyset$
117	$\emptyset$	0	6	6	$\surd$	$\emptyset$	$\emptyset$
118	$\surd$	5	5	5	$\surd$	$\emptyset$	$\emptyset$
119	$\surd$	5	6	6	$\surd$	$\emptyset$	$\emptyset$
120	$\surd$	5	6	6	$\surd$	$\emptyset$	$\emptyset$
121	$\surd$	5	6	6	$\surd$	$\emptyset$	$\emptyset$
122	$\emptyset$	0	6	6	$\surd$	$\emptyset$	$\emptyset$
123	$\surd$	6	6	6	$\surd$	$\emptyset$	$\emptyset$
124	$\emptyset$	0	6	6	$\surd$	$\emptyset$	$\emptyset$
125	$\emptyset$	0	6	6	$\surd$	$\emptyset$	$\emptyset$

Table C.5.: Properties of the data-set : Individuals : continued

Patient	HIV+	v	T_4	T_8	0 weeks?	78 weeks?	Useable ($\surd$ / $\emptyset$)
126	$\emptyset$	0	2	2	$\surd$	$\emptyset$	$\emptyset$
127	$\surd$	5	5	5	$\surd$	$\emptyset$	$\emptyset$
128	$\surd$	5	6	6	$\surd$	$\emptyset$	$\emptyset$
129	$\emptyset$	0	5	5	$\surd$	$\emptyset$	$\emptyset$
130	$\emptyset$	0	5	5	$\surd$	$\emptyset$	$\emptyset$
131	$\emptyset$	0	6	6	$\surd$	$\emptyset$	$\emptyset$
132	$\emptyset$	0	6	6	$\surd$	$\emptyset$	$\emptyset$
133	$\surd$	4	5	5	$\surd$	$\emptyset$	$\emptyset$
134	$\surd$	2	3	3	$\surd$	$\emptyset$	$\emptyset$
135	$\surd$	5	6	6	$\surd$	$\emptyset$	$\emptyset$
136	$\surd$	5	6	6	$\surd$	$\emptyset$	$\emptyset$
137	$\emptyset$	0	6	6	$\surd$	$\emptyset$	$\emptyset$

D. Patient Benchmarks

A benchmark was established to determine how well the data fits to the model, and to be able to compare how "well" the parameter optimisation fared for each of the patients. This is expressed in the form of a percentage for the specific subset of patients used, and calculated in the following way:

- The cost function in (6.1) is used as a starting-point. It is evaluated per patient.
- The value for a patient from the basic cost function is taken as the initial benchmark BM_1.
- The interim benchmark is calculated as:

$$BM_2 = BM_1 * \frac{7}{number\ of\ samples} \tag{D.1}$$

  The maximum number of actual field samples available for a patient in this study is 7, hence the benchmark is biased towards being better (a lower number) for a patient with more samples. Thus, for each sample that a patient has less than another, a seventh of the initial benchmark is added to itself towards reaching the interim benchmark. The deduction here is that, if a patient has all 7 samples intact, that the initial and interim benchmarks would be the same.
- The final benchmark is calculated by taking the worst interim benchmark (highest-valued) as 0%, and the best possible value (which is zero) as 100%
- The final benchmark (BM_f)is thus a percentage which is calculated from the specific set of patients used. It means that a very good mark is an indication that the patient's optimisation fared very well in relation to the best patient in the set. The complete results of patients' benchmarks can be found in table D.1.
- It should be qualified that, for this specific patient set, a low initial benchmark number is around 25, and a high initial benchmark is close to 1600. This evaluation

comes from the choice of basic cost function, shown in (6.1), and the weighting shown in table 6.3.

Table D.1.: Patient benchmarks

Patient	BM_1 [%]	BM_2 [%]	BM_f [%]	Patient	BM_1 [%]	BM_2 [%]	BM_f [%]
64	22.02	25.69	97.73	47	78.87	92.02	91.86
44	25.83	25.83	97.71	33	97.15	97.15	91.40
38	30.48	30.48	97.3	37	87.43	122.4	89.17
40	31.06	31.06	97.25	41	124.44	124.44	88.99
35	38.78	38.78	96.57	91	72.27	126.47	88.81
28	29.30	41.03	96.37	87	93.63	131.08	88.40
94	38.79	45.26	95.99	30	141.5	141.5	87.48
20	46.89	54.71	95.16	98	144.49	168.58	85.08
45	48.80	56.94	94.96	73	130.15	182.21	83.88
34	63.78	63.78	94.36	83	79.39	185.26	83.61
13	50.77	71.08	93.71	11	201.38	201.38	82.18
26	60.96	71.12	93.71	76	172.77	201.57	82.16
93	50.84	71.17	93.70	68	253.02	295.20	73.88
74	52.47	73.46	93.50	50	437.30	510.26	54.85
82	52.86	74.01	93.45	60	464.74	542.19	52.03
55	64.08	74.76	93.38	86	320.28	560.50	50.41
79	66.22	77.25	93.16	58	512.73	598.19	47.07
81	45.16	79.04	92.01	80	807.26	1130.1	0.00
84	69.19	80.73	92.86				
57	83.07	83.07	92.65				

E. Complete Patient Simulations

This appendix provides the complete simulation results (after parameter-estimation) from the usable set of patient data. Usable data was selected based on whether the relevant set of data was complete over a period of 78 weeks. It was found that 39 patients' data was usable, and 99 unusable (The total number of patients in the dataset was thus 137) Subsequent sections are presented on a section-per-patient basis, and is structured in the following way:

i. A table containing the patient data
ii. Individual graphs of each of the model's state variables together with the data
iii. A graph grouping together the viral-load, CD4+ T-cells, CD8+ T-cells and the relevant data samples
iv. The patient's optimised parameter set
v. A short comment on the results

The method followed for reaching a simulated, optimised response for a patient is:

i. The first nominal parameter set was obtained from fitting the proposed model in (4.25) to data generated from the response of the 4-dimensional model in [10]. This process is shown in section 10.1. The nominal set is shown in table E.1
ii. Next, all patients are simulated using the first nominal parameter set obtained.
iii. The benchmark for all patients was obtained after simulation with the first nominal parameter set. The benchmarks can be seen in table D.1.
iv. The parameter set from the patient with the best benchmark was taken as the next nominal parameter set, or nominal parameter set 2. This set is shown in table E.2
v. All patients were simulated using the nominal parameter set 2.

vi. The simulations depicted in this appendix is the result of simulations done using the nominal parameter set 2.

vii. For the case studies in chapter 9, the following refinements were made for 5 selected patients: The GUI-tool described in appendix B was used to adjust the initial conditions for each patient, and the optimised parameter set for that specific patient (obtained in this appendix) was used as a nominal set for itself. Together, these refinements are show an improvement to the chosen patients' responses in chapter 9.

Table E.1.: Nominal co-infection model parameters : 4-dimensional model fit.

Parm.	Description	Value	Units
S_4	Source - Healthy T_4 cells	679.8	/day
S_8	Src - T_8 cells	19.567	/day
k_1	Rate - T_4 cells	$1.10\text{x}10^{-3}$	/day-vir.
k_2	Rate - T_4 cells by APC's	$1.064\text{x}10^{-5}$	/day-cell
k_3	Rate - T_8 cells by APC's	$4.2264\text{x}10^{-9}$	/day-cell
k_4	Recr. - APC's by HIV	$4.2049\text{x}10^{-8}$	/day
k_5	Recr. - APC's by Mtb	$1.1488\text{x}10^{-5}$	/day
k_6	Dth rate : virus by APC's	$4.114\text{x}10^{-5}$	mm^3d^{-1}
k_7	Dth rate : virus by T_8	$8.4292\text{x}10^{-3}$	mm^3d^{-1}
k_8	Dth rate : tb by T_4	$6.235\text{x}10^{-1}$	mm^3d^{-1}
k_9	Dth rate : tb by APCs	$4.6878\text{x}10^{-1}$	mm^3d^{-1}
N_1	Free vir. by inf. cells	6264.51	none
N_2	Free vir. by APCs	5241.39	none
μ_v	Natural death rate - HIV	2.5152	/day
μ_I	Nat. death : inf. cells	$8.7109\text{x}10^{-3}$	/day
μ_4	Natural death rate - T_4 cells	$4.0712\text{x}10^{-3}$	/day
μ_8	Natural death rate - T_8 cells	$8.9932\text{x}10^{-2}$	/day
μ_d	Natural death rate - Dendr. cells	$3.868\text{x}10^{-3}$	/day
μ_b	Natural death rate - tb	$5.9768\text{x}10^{-1}$	/day
D_o	APCs equilib. value	2383	mm^{-3}
K	Carry. cap.: tb pop.	9637.3	mm^{-3}
r_b	Max. tb prolif. rate	23.987	/day

Initial conditions provided per patient contain the first sample of the viral load, CD4+ T-cell count and the CD8+ T-cell count. The initial values for the macrophages, the bacterial load and the number of infected cells were chosen on a trial-and-error basis, and in some instances aided by using the GUI tool described in appendix B. This means that whenever it seemed the cost-function was not properly minimized, the three parameters TB_INIT, I_INIT and D_INIT (TB, infected cells, macrophages) were changed after looking at the model response and adapting the initial conditions based on inspection of the model itself. For instance, if the viral load model response values seemed generally below the actual samples, increasing the initial infected cell count and the macrophages would have an increasing effect on it.

Table E.2.: Nominal parameter set 2 : Best-benchmark patient's optimised parameters

Parm.	Description	Value	Units
S_4	Source - Healthy T_4 cells	1261.66	/day
S_8	Src - T_8 cells	14.16	/day
k_1	Rate - T_4 cells	$5.585\text{x}10^{-4}$	/day-vir.
k_2	Rate - T_4 cells by APC's	$3.135\text{x}10^{-6}$	/day-cell
k_3	Rate - T_8 cells by APC's	$3.236\text{x}10^{-9}$	/day-cell
k_4	Recr. - APC's by HIV	$7.463\text{x}10^{-8}$	/day
k_5	Recr. - APC's by Mtb	$8.016\text{x}10^{-6}$	/day
k_6	Dth rate : virus by APC's	$8.256\text{x}10^{-5}$	mm^3d^{-1}
k_7	Dth rate : virus by T_8	$1.187\text{x}10^{-2}$	mm^3d^{-1}
k_8	Dth rate : tb by T_4	$5.158\text{x}10^{-1}$	mm^3d^{-1}
k_9	Dth rate : tb by APCs	$7.973\text{x}10^{-1}$	mm^3d^{-1}
N_1	Free vir. by inf. cells	3369.01	none
N_2	Free vir. by APCs	9107.90	none
μ_v	Natural death rate - HIV	2.476	/day
μ_I	Nat. death : inf. cells	$1.626\text{x}10^{-2}$	/day
μ_4	Natural death rate - T_4 cells	$6.142\text{x}10^{-4}$	/day
μ_8	Natural death rate - T_8 cells	$1.069\text{x}10^{-2}$	/day
μ_d	Natural death rate - Dendr. cells	$1.8808\text{x}10^{-3}$	/day
μ_b	Natural death rate - tb	$4.734\text{x}10^{-1}$	/day
D_o	APCs equilib. value	1781	mm^{-3}
K	Carry. cap.: tb pop.	6246.8	mm^{-3}
r_b	Max. tb prolif. rate	33.16	/day

E.1. Patient 11

Table E.3.: Patient 11 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.628154	42477.01599	640	1862	T_4	640
2	4.489902	30895.98176	839	1437	T_8	1862
4	5.11807	131241.1418	461	1117	v	42477.0159
8	4.570192	37169.95198	643	1372	T_b	2800
26	5.575584	376343.1364	424	624	I	28000
52	5.341431	219498.2186	294	222	D	700
78	4.908828	81063.99447	333	718		

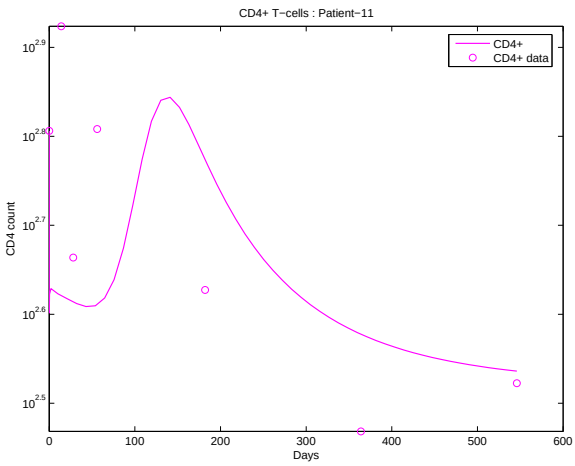

Figure E.1.: CD4+ T-Cells

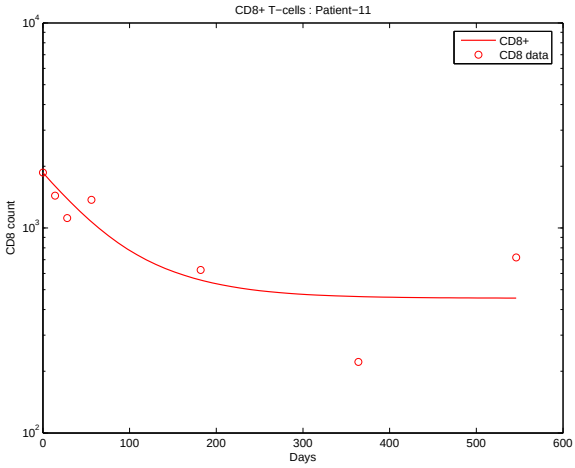

Figure E.2.: CD8+ T-Cells

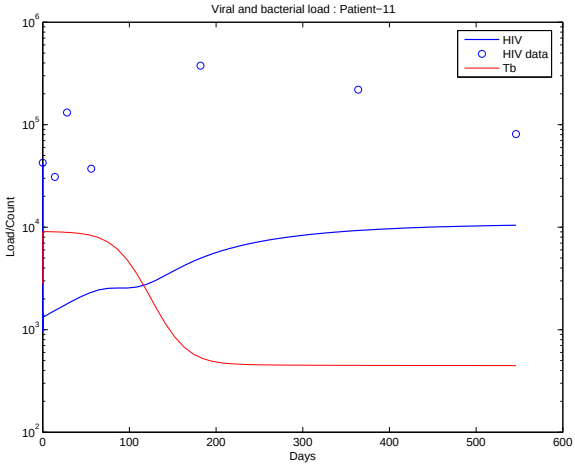

Figure E.3.: Viral and bacterial load

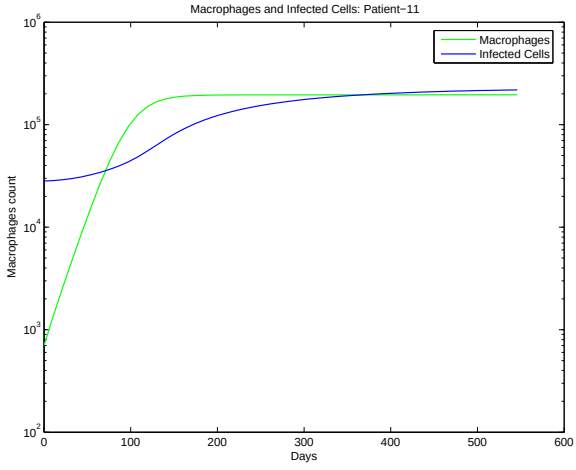

Figure E.4.: Macrophages and infected cells

Table E.4.: Optimised parameter set : Patient11

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	2693.2148	/day
S_8	Src - T_8 cells	6.1628	/day
k_1	Rate - T_4 cells	0.00029021	/day-vir.
k_2	Rate - T_4 cells by APCs	2.0228e-008	/day-cell
k_3	Rate - T_8 cells by APCs	3.453e-009	/day-cell
k_4	Recr. - APCs by HIV	1.2308e-008	/day
k_5	Recr. - APCs by Mtb	9.7248e-006	/day
k_6	Dth rate : virus by APCs	0.00011307	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.0073092	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.48524	mm^3d^{-1}
k_9	Dth rate : tb by APCs	1.2114	mm^3d^{-1}
N_1	Free vir. by inf. cells	7958.2288	none
N_2	Free vir. by APCs	4780.0053	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.0010004	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.013038	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1903.4418	mm^{-3}
K	Carry. cap.: tb pop.	8163.3506	mm^{-3}
r_b	Max. tb prolif. rate	22.9096	/day

Comments:

The response of the CD4+ T-cells and CD8+ T-cells seem to fit the data very well, but the viral load is not close to fitting to the sample data. This patient's response is refined in section 9. In the latter section, the GUI tool is used to establish a better initial conditions for the macrophages, infected cells and TB cell-types. It should further be noted that this patient has a large viral infection of order 10^5. With the GUI-tool, the initial condition for the infected cells will be adjusted to lift the response for the viral load to the correct level.

E.2. Patient 13

Table E.5.: Patient 13 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.420137	26310.97852	516	899	T_4	516
2	4.683605	48261.96496	657	1072	T_8	899
4			648	1189	v	26310.97852
8	4.193236	15604.0021	529	919	T_b	2900
26	3.816175	6549.000144	599	1175	I	1020
52	4.044853	11087.99445	470	817	D	5000
78	3.873611	7474.996609				

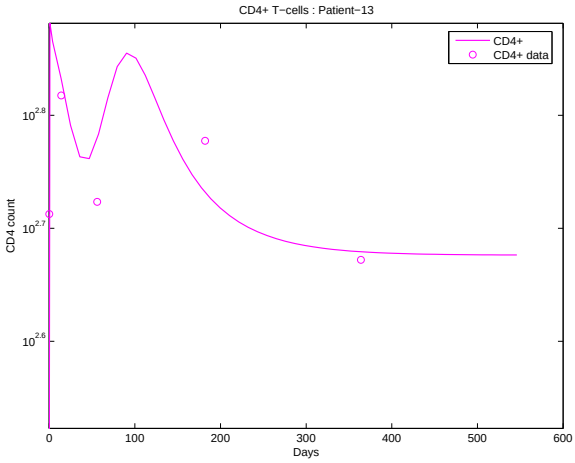

Figure E.5.: CD4+ T-Cells

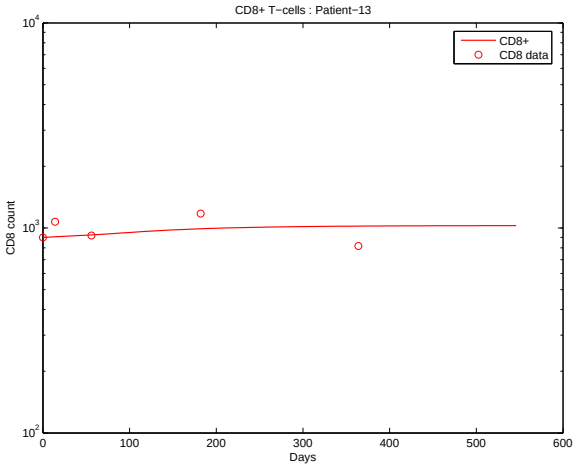

Figure E.6.: CD8+ T-Cells

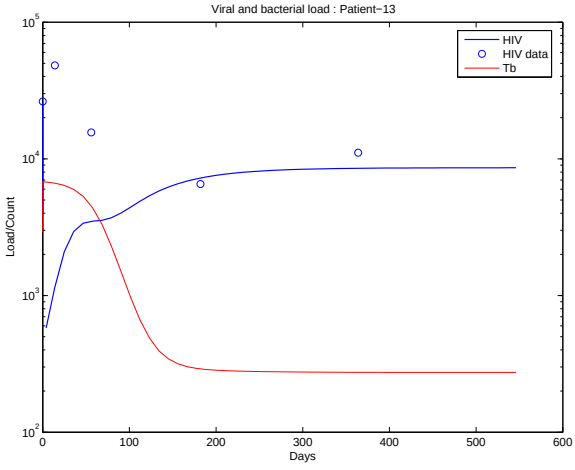

Figure E.7.: Viral and bacterial load

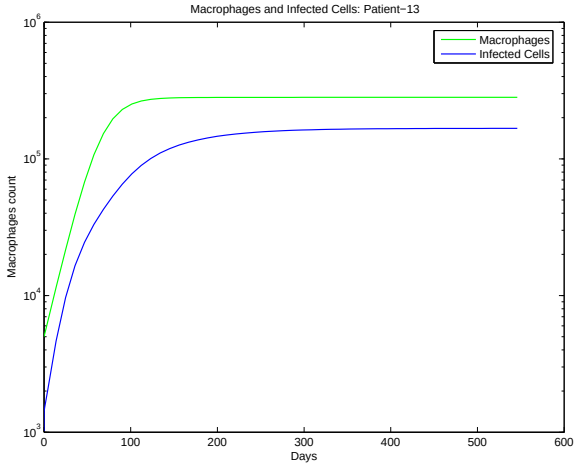

Figure E.8.: Macrophages and infected cells

Table E.6.: Optimised parameter set : Patient13

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	1735.8644	/day
S_8	Src - T_8 cells	12.3872	/day
k_1	Rate - T_4 cells	0.00029341	/day-vir.
k_2	Rate - T_4 cells by APCs	6.5126e-006	/day-cell
k_3	Rate - T_8 cells by APCs	2.977e-009	/day-cell
k_4	Recr. - APCs by HIV	6.7928e-008	/day
k_5	Recr. - APCs by Mtb	4.8011e-006	/day
k_6	Dth rate : virus by APCs	6.393e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.012017	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.28517	mm^3d^{-1}
k_9	Dth rate : tb by APCs	1.2022	mm^3d^{-1}
N_1	Free vir. by inf. cells	7746.8966	none
N_2	Free vir. by APCs	1057.3111	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.015878	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.012472	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	2187.8813	mm^{-3}
K	Carry. cap.: tb pop.	6268.5353	mm^{-3}
r_b	Max. tb prolif. rate	13.4855	/day

Comments:

Patient 13's response fits very well to the field data. All the cell-types reach a steady-state, and although the viral load does not initially fit the first few samples, it settles on a value inbetween the last two samples. Once again, this patient's response is refined in section 9, to refine and better the viral load response.

E.3. Patient 20

Table E.7.: Patient 20 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	5.120577	132000.9327	136	364	T_4	136
2	5.134856	136413.0754	122	505	T_8	364
4	5.344359	220983.0686	126	596	v	132000.9327
8	4.695534	49605.97613	104	719	T_b	2206
26			67	592	I	41000
52	4.548807	35384.006	50	765	D	4530
78	4.991204	97995.01867	26	595		

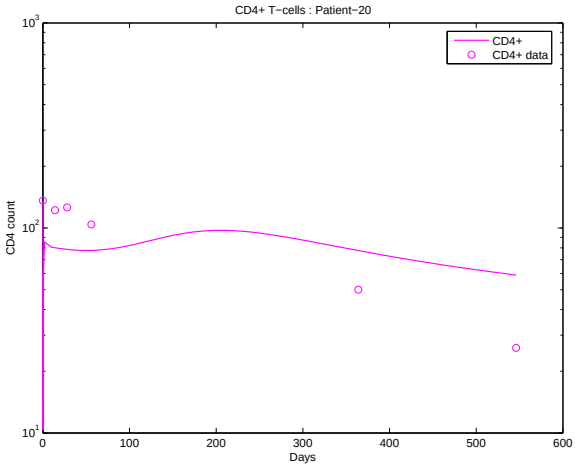

Figure E.9.: CD4+ T-Cells

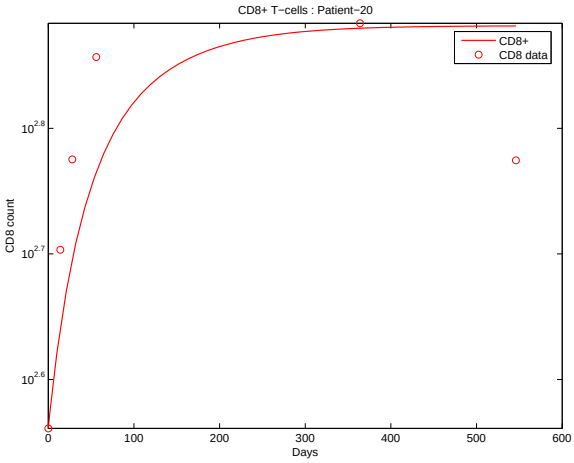

Figure E.10.: CD8+ T-Cells

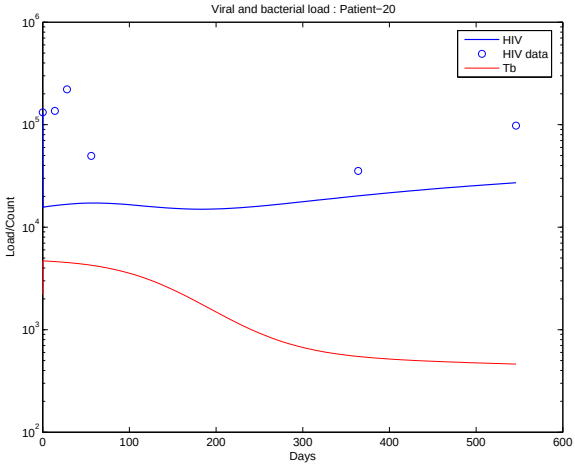

Figure E.11.: Viral and bacterial load

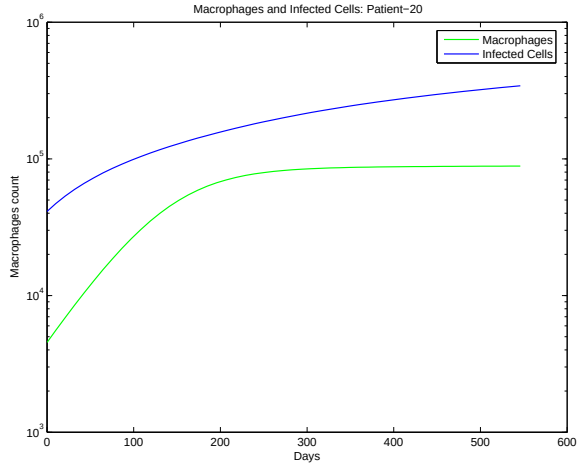

Figure E.12.: Macrophages and infected cells

Table E.8.: Optimised parameter set : Patient20

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	817.4102	/day
S_8	Src - T_8 cells	11.3956	/day
k_1	Rate - T_4 cells	0.00048717	/day-vir.
k_2	Rate - T_4 cells by APCs	4.8177e-006	/day-cell
k_3	Rate - T_8 cells by APCs	4.9256e-009	/day-cell
k_4	Recr. - APCs by HIV	3.1368e-008	/day
k_5	Recr. - APCs by Mtb	4.68e-006	/day
k_6	Dth rate : virus by APCs	8.5342e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.010238	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.40861	mm^3d^{-1}
k_9	Dth rate : tb by APCs	1.7246	mm^3d^{-1}
N_1	Free vir. by inf. cells	5915.5846	none
N_2	Free vir. by APCs	6669.7509	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.0010047	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.0154	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1405.8877	mm^{-3}
K	Carry. cap.: tb pop.	4926.6257	mm^{-3}
r_b	Max. tb prolif. rate	34.2196	/day

Comments:

With patient 20 it seems that, due to the nature of the field data, the only responses that reaches a steady state within 78 weeks is the macrophages and the CD8+ T-cells. From the response, the CD4+ T-cells are declining and the viral load is increasing.

E.4. Patient 26

Table E.9.: Patient 26 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	3.886434	7698.994334	199	518	T_4	199
2	2.346353	222.0000131	358	1007	T_8	518
4	2.133539	136.0000287	414	1204	v	7698.994334
8	3.03583	1086.000437	446	1196	T_b	2900
26	2.867467	736.9991721	417	1331	I	10020
52			401	854	D	5000
78	2.951823	894.9999272	385	966		

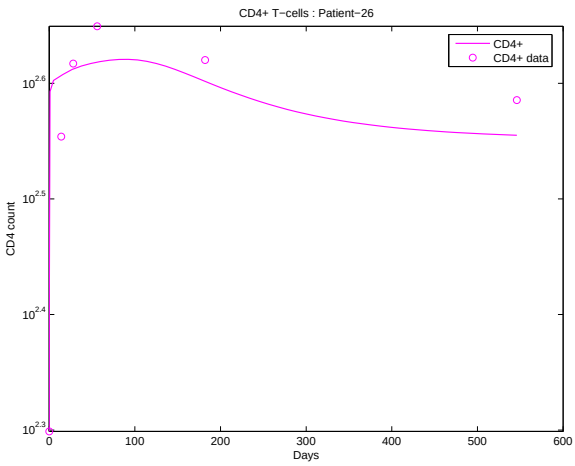

Figure E.13.: CD4+ T-Cells

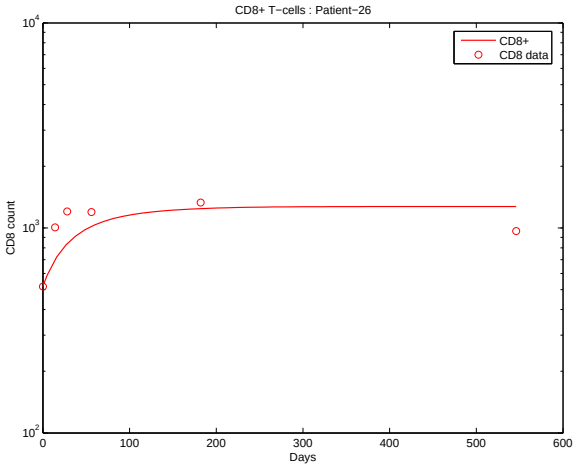

Figure E.14.: CD8+ T-Cells

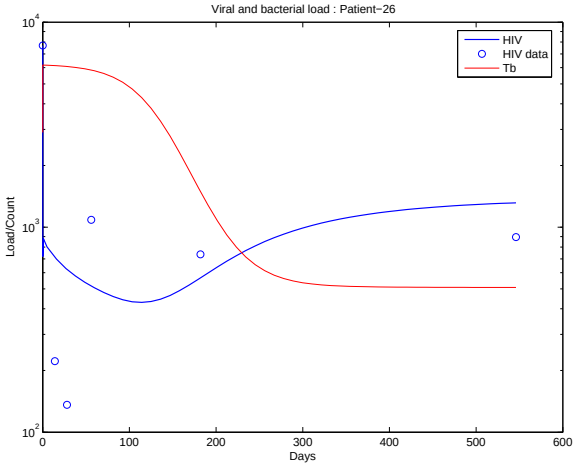

Figure E.15.: Viral and bacterial load

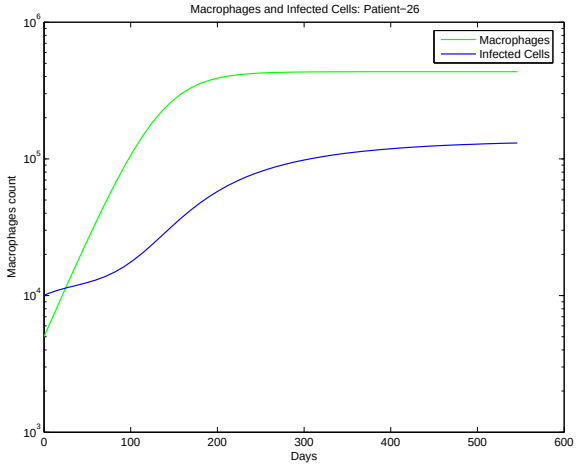

Figure E.16.: Macrophages and infected cells

Table E.10.: Optimised parameter set : Patient26

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	1124.9979	/day
S_8	Src - T_8 cells	25.7245	/day
k_1	Rate - T_4 cells	0.00039842	/day-vir.
k_2	Rate - T_4 cells by APCs	5.5284e-006	/day-cell
k_3	Rate - T_8 cells by APCs	9.8597e-010	/day-cell
k_4	Recr. - APCs by HIV	5.6535e-008	/day
k_5	Recr. - APCs by Mtb	5.7423e-006	/day
k_6	Dth rate : virus by APCs	1.8463e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.025976	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.069785	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.69015	mm^3d^{-1}
N_1	Free vir. by inf. cells	3746.7317	none
N_2	Free vir. by APCs	4269.7121	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.0076817	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.020647	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1257.7306	mm^{-3}
K	Carry. cap.: tb pop.	6245.1391	mm^{-3}
r_b	Max. tb prolif. rate	52.2433	/day

Comments:

Patient 26's response fits very well to the supplied data. However, at the end of the period, around 78 weeks, the viral load hasn't completely reached a steady-state, and seems to be on the increase. Also, the CD4+ T-cells are decreasing.

E.5. Patient 28

Table E.11.: Patient 28 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.885887	76893.03446	106	1616	T_4	106
2	5.015975	103746.8693	106	1189	T_8	1616
4	4.836153	68572.97634	113	1224	v	76893.03446
8	5.129406	134711.9119	88	1005	T_b	2033
26	4.986351	96906.07419	80	983	I	30000
52			111	977	D	8983
78			62	1774		

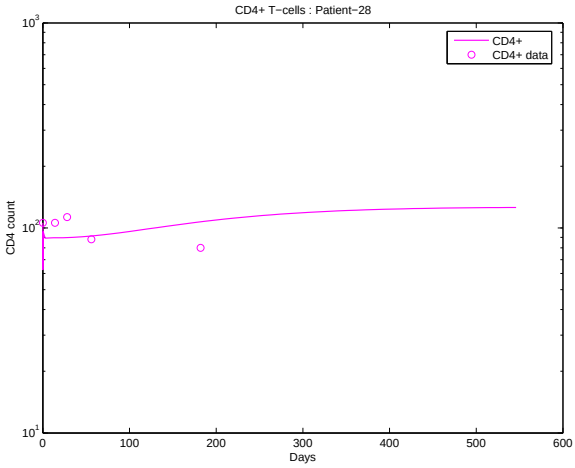

Figure E.17.: CD4+ T-Cells

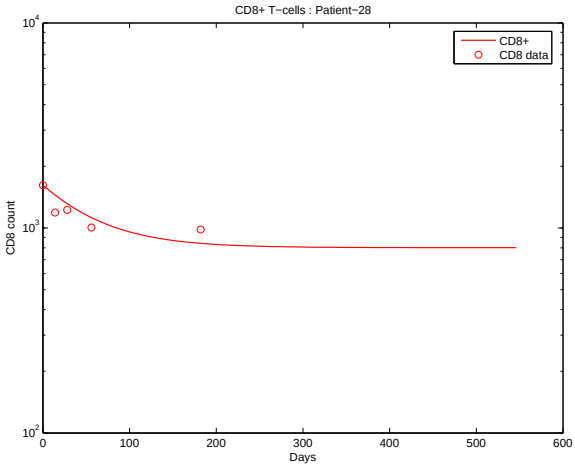

Figure E.18.: CD8+ T-Cells

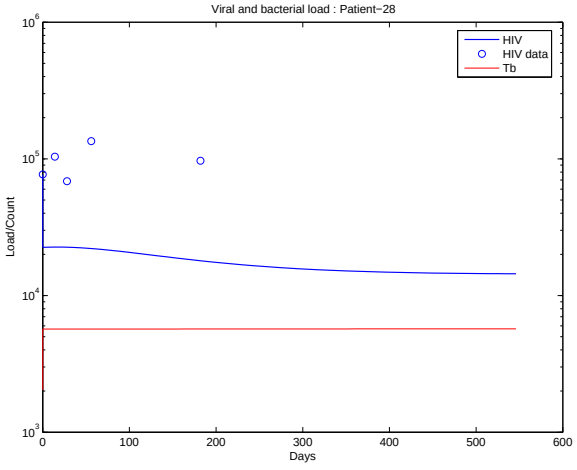

Figure E.19.: Viral and bacterial load

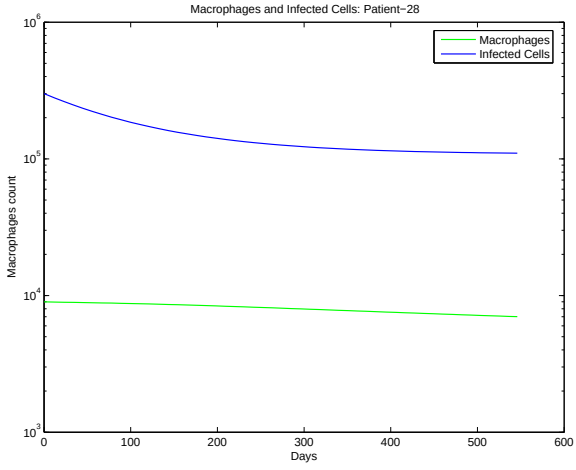

Figure E.20.: Macrophages and infected cells

Table E.12.: Optimised parameter set : Patient28

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	4087.3602	/day
S_8	Src - T_8 cells	21.3856	/day
k_1	Rate - T_4 cells	0.00072155	/day-vir.
k_2	Rate - T_4 cells by APCs	7.4965e-007	/day-cell
k_3	Rate - T_8 cells by APCs	4.4467e-009	/day-cell
k_4	Recr. - APCs by HIV	1.0204e-008	/day
k_5	Recr. - APCs by Mtb	1.0003e-007	/day
k_6	Dth rate : virus by APCs	0.00020057	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.0073997	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.17152	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.35929	mm^3d^{-1}
N_1	Free vir. by inf. cells	6441.2969	none
N_2	Free vir. by APCs	8267.0906	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.022309	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.023727	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1009.7222	mm^{-3}
K	Carry. cap.: tb pop.	5691.6519	mm^{-3}
r_b	Max. tb prolif. rate	44.1253	/day

Comments:

This patient's response is refined in section 9. The CD4+ T-cells and CD8+ T-cells response fits to the field data, but the viral load doesn't.

E.6. Patient 30

Table E.13.: Patient 30 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	2.582063	381.9996808	726	1125	T_4	726
2	4.278044	18968.98093	834	1903	T_8	1125
4	2.91803	827.9993579	747	1803	v	381.9996808
8	3.04454	1108.000611	1095	1382	T_b	1710
26	1.869232	74.00004776	1029	1388	I	4010
52	2.897077	788.9999942	921	1209	D	5290
78	3.371806	2353.997515	922	1349		

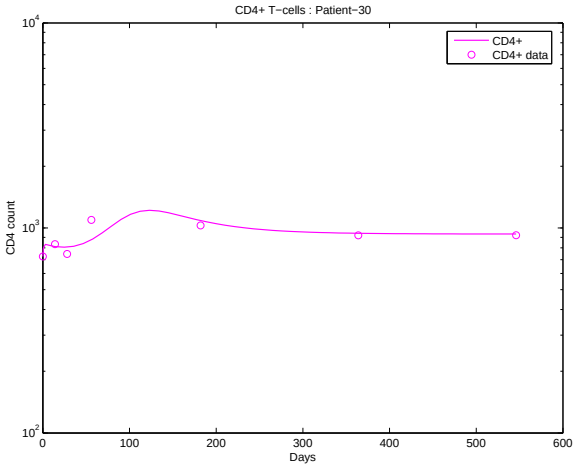

Figure E.21.: CD4+ T-Cells

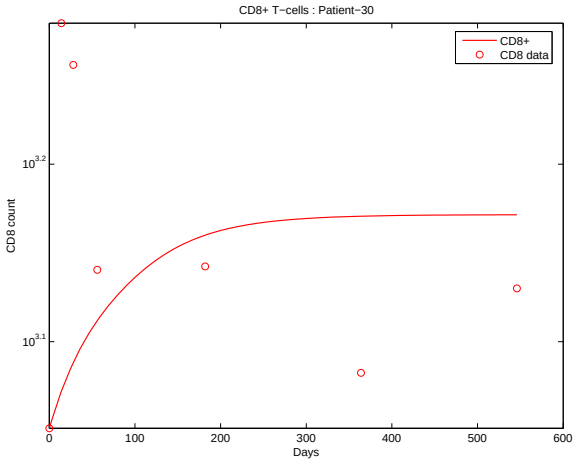

Figure E.22.: CD8+ T-Cells

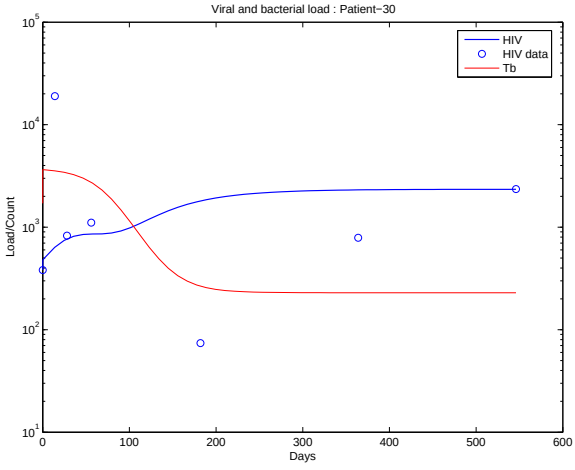

Figure E.23.: Viral and bacterial load

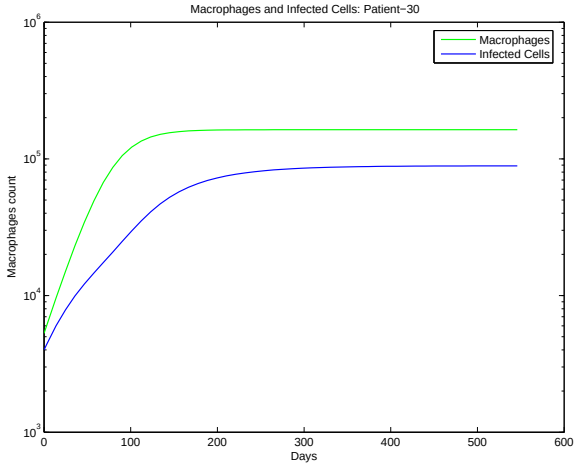

Figure E.24.: Macrophages and infected cells

Table E.14.: Optimised parameter set : Patient30

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	1382.6544	/day
S_8	Src - T_8 cells	14.4762	/day
k_1	Rate - T_4 cells	0.00051918	/day-vir.
k_2	Rate - T_4 cells by APCs	3.571e-006	/day-cell
k_3	Rate - T_8 cells by APCs	3.3441e-009	/day-cell
k_4	Recr. - APCs by HIV	7.0711e-008	/day
k_5	Recr. - APCs by Mtb	8.7176e-006	/day
k_6	Dth rate : virus by APCs	8.2112e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.012341	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.50759	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.96108	mm^3d^{-1}
N_1	Free vir. by inf. cells	3664.3445	none
N_2	Free vir. by APCs	8646.6517	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.015356	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.010751	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1825.6973	mm^{-3}
K	Carry. cap.: tb pop.	3573.674	mm^{-3}
r_b	Max. tb prolif. rate	31.9077	/day

Comments:

The model response for patient 30 fits very well to the field data.

E.7. Patient 33

Table E.15.: Patient 33 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.584105	38380.00262	165	750	T_4	165
2	4.893662	78282.01572	176	789	T_8	750
4	4.945946	88297.01054	196	962	v	38380.00262
8	5.077793	119617.0259	133	795	T_b	3000
26	5.18942	154674.9556	154	624	I	620
52	5.69897	499999.995	128	774	D	2000
78	5.084373	121443.1434	135	811		

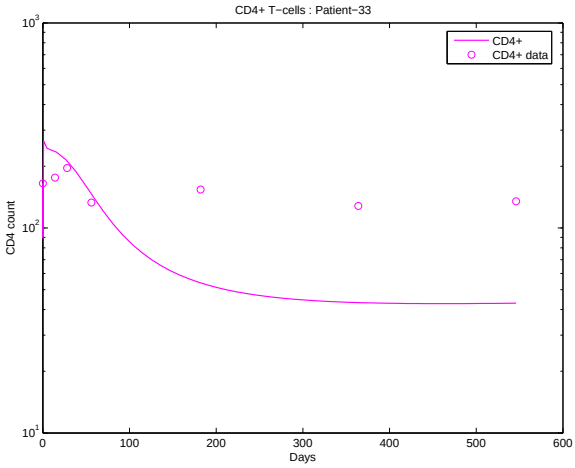

Figure E.25.: CD4+ T-Cells

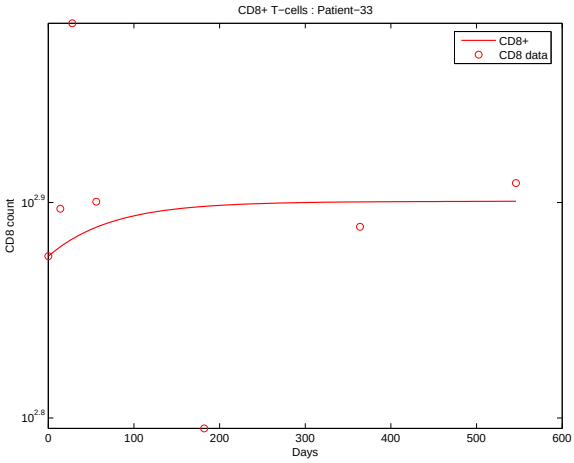

Figure E.26.: CD8+ T-Cells

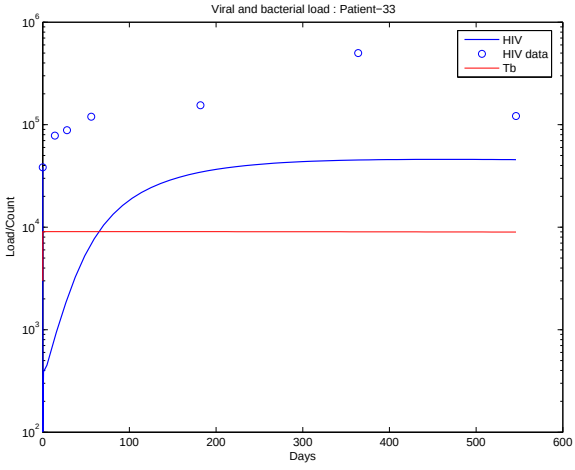

Figure E.27.: Viral and bacterial load

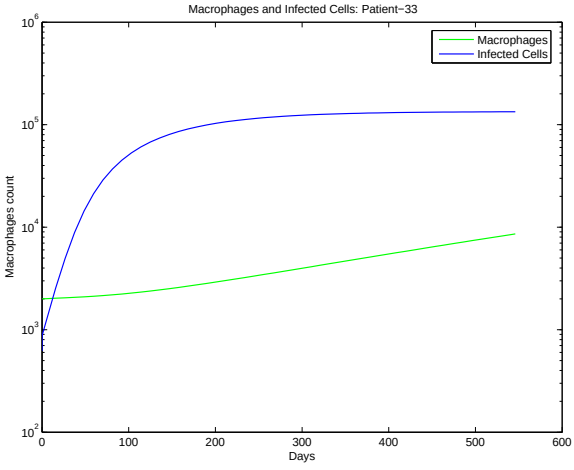

Figure E.28.: Macrophages and infected cells

Table E.16.: Optimised parameter set : Patient33

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	2035.1836	/day
S_8	Src - T_8 cells	10.5546	/day
k_1	Rate - T_4 cells	0.00086721	/day-vir.
k_2	Rate - T_4 cells by APCs	4.0546e-006	/day-cell
k_3	Rate - T_8 cells by APCs	1.1916e-009	/day-cell
k_4	Recr. - APCs by HIV	6.8687e-008	/day
k_5	Recr. - APCs by Mtb	2.8855e-007	/day
k_6	Dth rate : virus by APCs	0.0001169	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.017224	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.32214	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.77365	mm^3d^{-1}
N_1	Free vir. by inf. cells	6772.4458	none
N_2	Free vir. by APCs	38.8206	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.012676	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.013278	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	800.6372	mm^{-3}
K	Carry. cap.: tb pop.	9076.584	mm^{-3}
r_b	Max. tb prolif. rate	60.1079	/day

Comments:

Patient 33's response settles at a steady-state in all cell-types except the macrophages, which are increasing. The steady-state values do not align to the field data in the case of the CD4+ T-cells and the viral load.

E.8. Patient 34

Table E.17.: Patient 34 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.181844	15200.01442	509	2000	T_4	509
2	3.711638	5147.99362	574	1966	T_8	2000
4	3.67431	4724.001208	651	2000	v	15200.01442
8	4.195014	15668.01577	506	1963	T_b	2900
26	3.90531	8040.99885	427	1632	I	1020
52	4.127053	13398.40188	541	1967	D	5000
78	4.010597	10247.00622	458	1018		

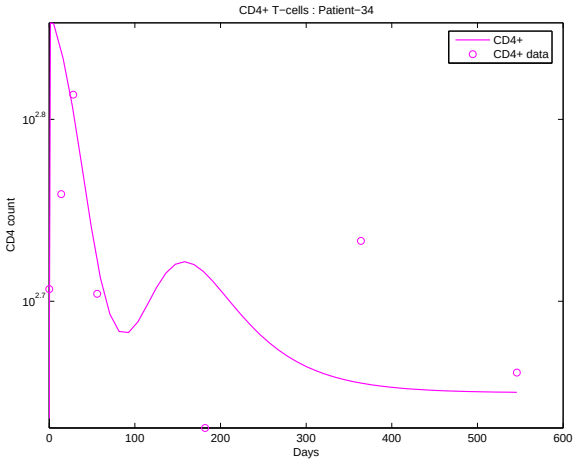

Figure E.29.: CD4+ T-Cells

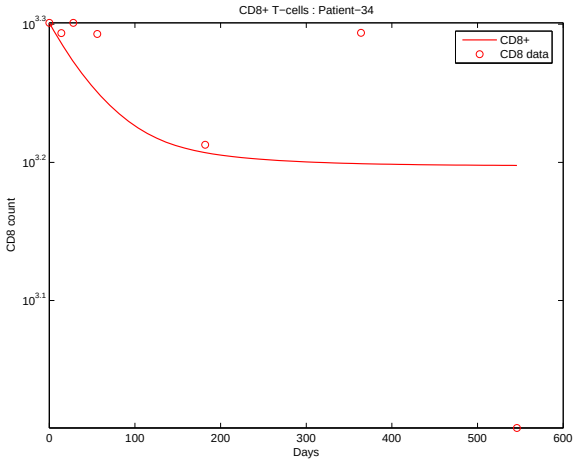

Figure E.30.: CD8+ T-Cells

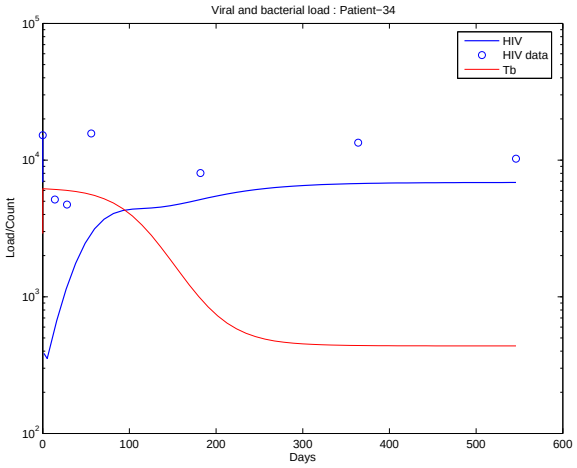

Figure E.31.: Viral and bacterial load

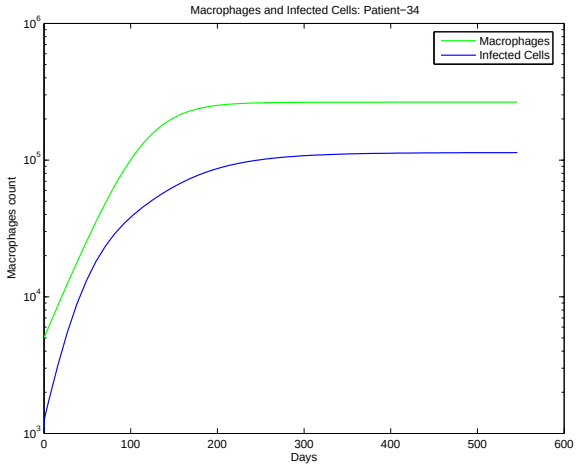

Figure E.32.: Macrophages and infected cells

Table E.18.: Optimised parameter set : Patient34

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	1984.0078	/day
S_8	Src - T_8 cells	14.7764	/day
k_1	Rate - T_4 cells	0.00042342	/day-vir.
k_2	Rate - T_4 cells by APCs	5.0729e-006	/day-cell
k_3	Rate - T_8 cells by APCs	2.2088e-009	/day-cell
k_4	Recr. - APCs by HIV	5.9504e-008	/day
k_5	Recr. - APCs by Mtb	5.886e-006	/day
k_6	Dth rate : virus by APCs	3.2947e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.0054057	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.73267	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.80617	mm^3d^{-1}
N_1	Free vir. by inf. cells	7018.6582	none
N_2	Free vir. by APCs	1860.9421	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.016721	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.0099631	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1883.2902	mm^{-3}
K	Carry. cap.: tb pop.	6297.3324	mm^{-3}
r_b	Max. tb prolif. rate	36.5595	/day

Comments:

Patient 34's response fits very well to the field data. The viral load almost reaches the correct steady-state value, while the CD4+ T-cells and CD8+ T-cells reach a value lower than the required value.

E.9. Patient 35

Table E.19.: Patient 35 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.221258	16644.01122	349	1036	T_4	349
2	4.179178	15106.99203	336	880	T_8	1036
4	4.019449	10458.00873	327	947	v	16644.01122
8	4.157336	14366.00456	378	1035	T_b	2900
26	4.339948	21874.99689	277	689	I	1020
52	4.124113	13308.00637	292	767	D	5000
78	4.328319	21297.02791	188	522		

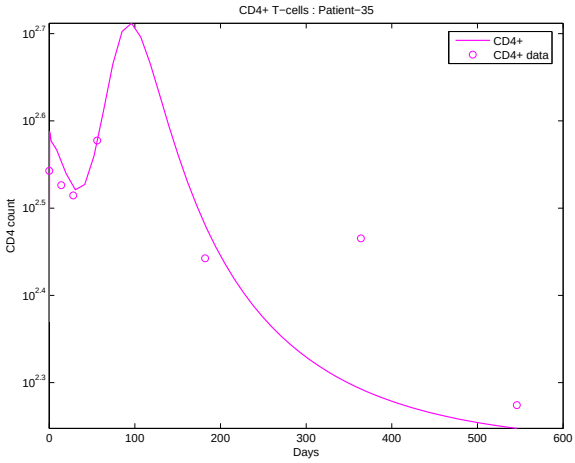

Figure E.33.: CD4+ T-Cells

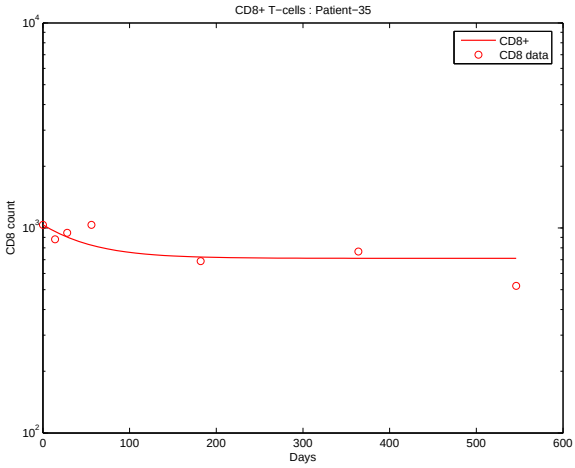

Figure E.34.: CD8+ T-Cells

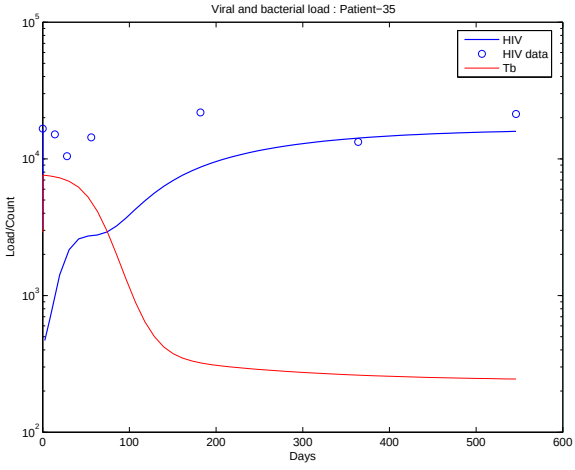

Figure E.35.: Viral and bacterial load

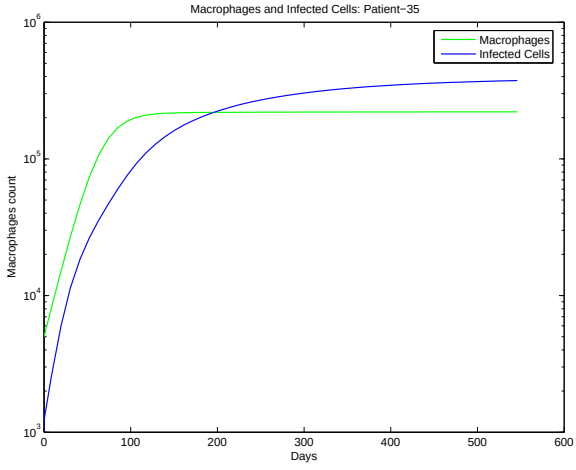

Figure E.36.: Macrophages and infected cells

Table E.20.: Optimised parameter set : Patient35

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	2618.5564	/day
S_8	Src - T_8 cells	13.4115	/day
k_1	Rate - T_4 cells	0.00086251	/day-vir.
k_2	Rate - T_4 cells by APCs	3.9977e-006	/day-cell
k_3	Rate - T_8 cells by APCs	1.0269e-011	/day-cell
k_4	Recr. - APCs by HIV	6.7577e-008	/day
k_5	Recr. - APCs by Mtb	7.8245e-006	/day
k_6	Dth rate : virus by APCs	5.0639e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.012057	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.26507	mm^3d^{-1}
k_9	Dth rate : tb by APCs	1.2595	mm^3d^{-1}
N_1	Free vir. by inf. cells	5600.6112	none
N_2	Free vir. by APCs	6130.0575	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.0065797	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.018864	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1124.7519	mm^{-3}
K	Carry. cap.: tb pop.	7779.4383	mm^{-3}
r_b	Max. tb prolif. rate	36.9083	/day

Comments:

Patient 35's response fits the field data very well. The CD4+ T-cell count seems to be still declining at 78 weeks, and the steady-state value goals of the CD8+ T-cells and viral load are reached.

E.10. Patient 37

Table E.21.: Patient 37 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.2944	19696.99615	190	950	T_4	190
2	4.256309	18043.01042	153	547	T_8	950
4	4.478985	30129.0196	131	695	v	19696.99615
26	4.037436	10900.23849	92	585	T_b	2900
52	4.579967	38016.05086	73	541	I	1020
78			67	729	D	5000

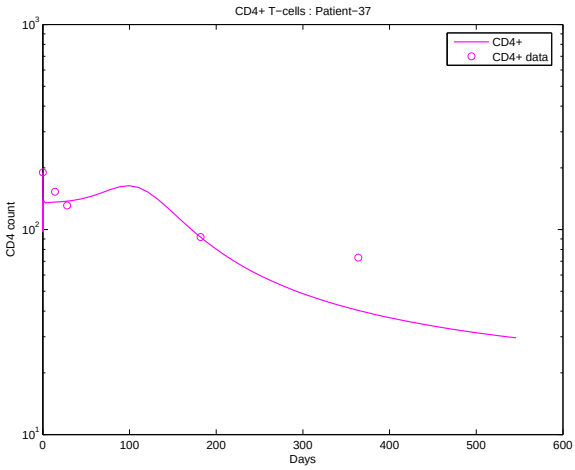

Figure E.37.: CD4+ T-Cells

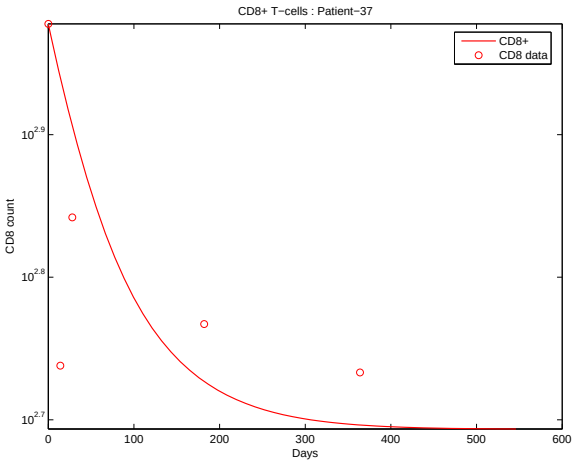

Figure E.38.: CD8+ T-Cells

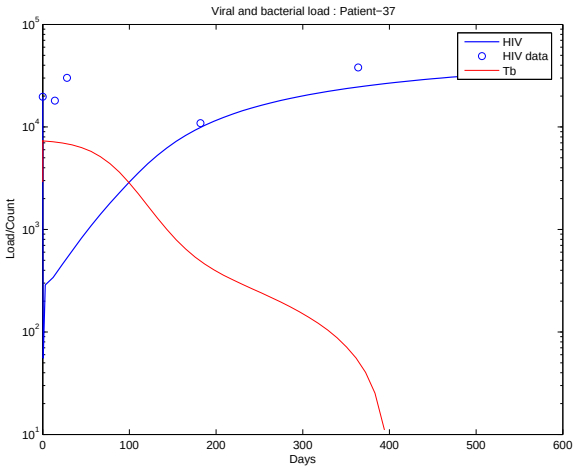

Figure E.39.: Viral and bacterial load

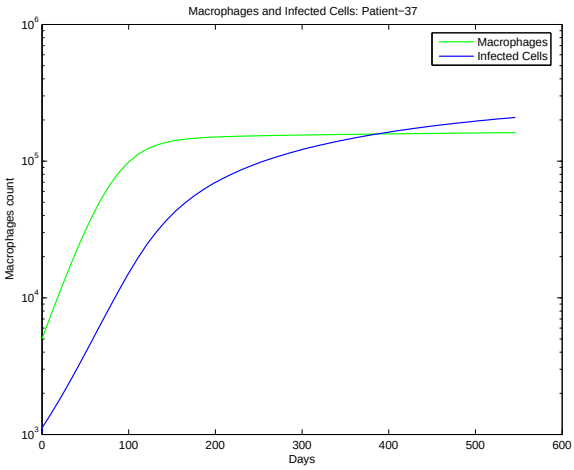

Figure E.40.: Macrophages and infected cells

Table E.22.: Optimised parameter set : Patient37

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	758.7298	/day
S_8	Src - T_8 cells	6.1429	/day
k_1	Rate - T_4 cells	0.0007388	/day-vir.
k_2	Rate - T_4 cells by APCs	3.9602e-006	/day-cell
k_3	Rate - T_8 cells by APCs	3.157e-009	/day-cell
k_4	Recr. - APCs by HIV	1.1684e-007	/day
k_5	Recr. - APCs by Mtb	5.6891e-006	/day
k_6	Dth rate : virus by APCs	2.4675e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.01707	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.90344	mm^3d^{-1}
k_9	Dth rate : tb by APCs	1.503	mm^3d^{-1}
N_1	Free vir. by inf. cells	5751.6606	none
N_2	Free vir. by APCs	595.0697	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.002385	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.012955	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1157.3341	mm^{-3}
K	Carry. cap.: tb pop.	7549.0165	mm^{-3}
r_b	Max. tb prolif. rate	31.5308	/day

Comments:

The responses generated for this patient fits reasonably well to the field data, although the goals of reaching a steady-state on the viral load and CD4+ T-cells haven't been reached.

E.11. Patient 38

Table E.23.: Patient 38 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	3.547898	3531.002296	168	614	T_4	168
2	3.514946	3272.99996	157	579	T_8	614
4	2.869232	740.0004776	154	532	v	3531.002296
8	3.234264	1714.999509	187	787	T_b	2800
26	3.593175	3918.997622	200	962	I	120
52	3.864393	7318.010023	258	1564	D	700
78	4.013848	10324.0001	300	1797		

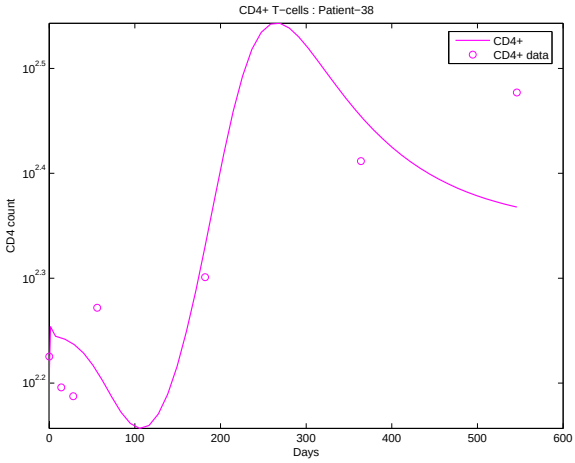

Figure E.41.: CD4+ T-Cells

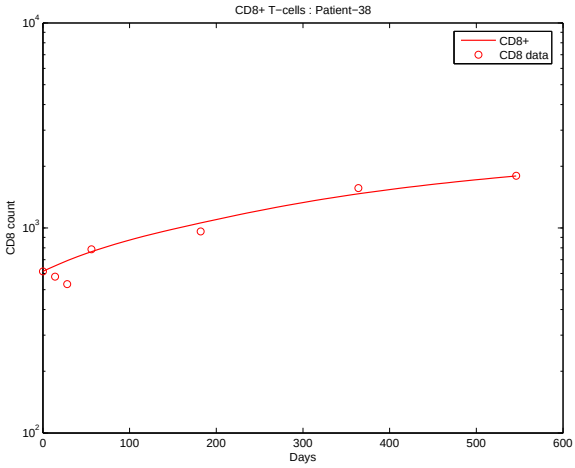

Figure E.42.: CD8+ T-Cells

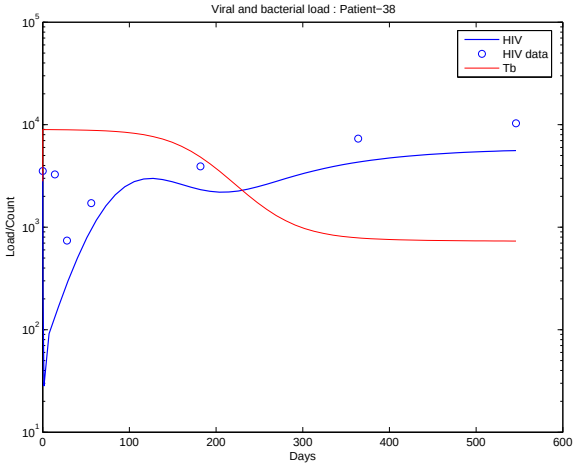

Figure E.43.: Viral and bacterial load

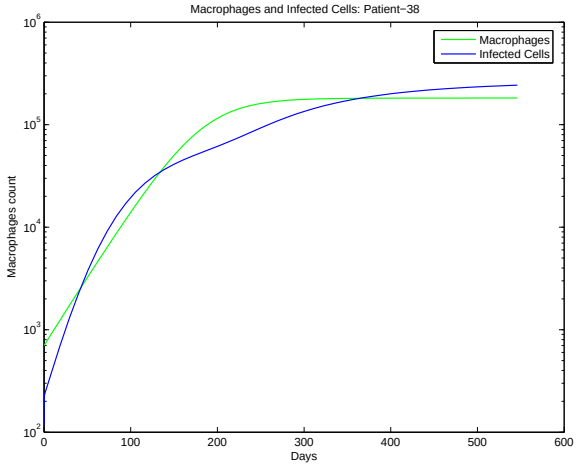

Figure E.44.: Macrophages and infected cells

Table E.24.: Optimised parameter set : Patient38

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	2461.6801	/day
S_8	Src - T_8 cells	4.3404	/day
k_1	Rate - T_4 cells	0.0015489	/day-vir.
k_2	Rate - T_4 cells by APCs	4.086e-006	/day-cell
k_3	Rate - T_8 cells by APCs	4.4005e-009	/day-cell
k_4	Recr. - APCs by HIV	5.2834e-008	/day
k_5	Recr. - APCs by Mtb	3.6985e-006	/day
k_6	Dth rate : virus by APCs	0.00019518	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.0081167	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.0085121	mm^3d^{-1}
k_9	Dth rate : tb by APCs	1.6651	mm^3d^{-1}
N_1	Free vir. by inf. cells	1316.4845	none
N_2	Free vir. by APCs	3735.1089	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.0083673	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.0023606	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	226.1829	mm^{-3}
K	Carry. cap.: tb pop.	8986.0741	mm^{-3}
r_b	Max. tb prolif. rate	36.729	/day

Comments:

This patient's response is reasonable in comparison with the provided data. The CD4+ T-cells does not settle at a steady-state within 78 weeks, but it can be seen that the data is also varying as 78 weeks is approached. The viral load and CD8+ T-cells fit very well to the provided data.

E.12. Patient 40

Table E.25.: Patient 40 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	3.375481	2374.00156	427	1137	T_4	427
2	3.202216	1593.000822	397	839	T_8	1137
4	3.348305	2230.000703	433	1067	v	2374.00156
8	2.886491	770.0004873	541	1161	T_b	2900
26	2.783904	608.000589	512	858	I	1020
52	3.777209	5986.996441	541	1255	D	5000
78	3.516139	3282.003199	508	1092		

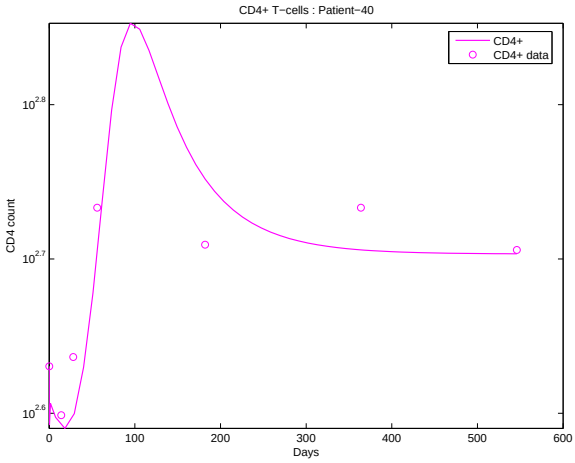

Figure E.45.: CD4+ T-Cells

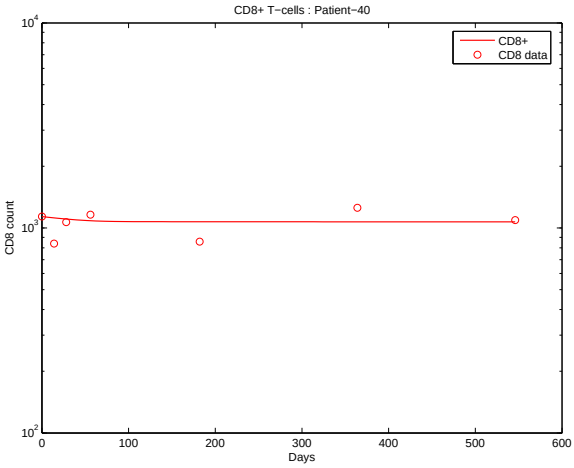

Figure E.46.: CD8+ T-Cells

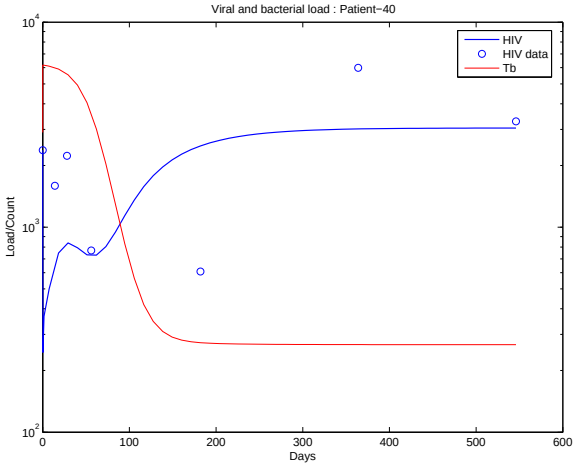

Figure E.47.: Viral and bacterial load

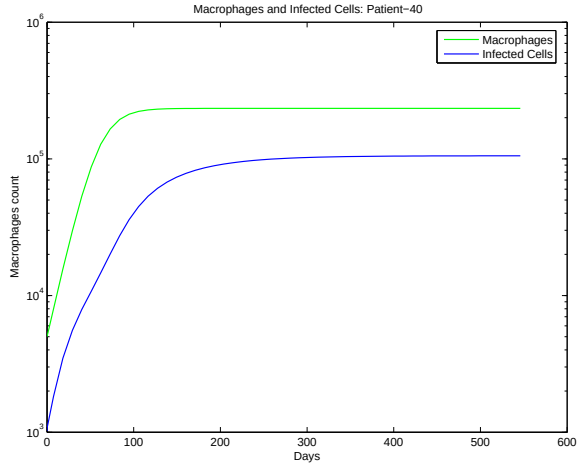

Figure E.48.: Macrophages and infected cells

Table E.26.: Optimised parameter set : Patient40

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	1801.7954	/day
S_8	Src - T_8 cells	10.6806	/day
k_1	Rate - T_4 cells	0.0006819	/day-vir.
k_2	Rate - T_4 cells by APCs	5.5563e-006	/day-cell
k_3	Rate - T_8 cells by APCs	2.64e-009	/day-cell
k_4	Recr. - APCs by HIV	5.3503e-008	/day
k_5	Recr. - APCs by Mtb	1.0554e-005	/day
k_6	Dth rate : virus by APCs	0.00011187	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.0074249	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.32997	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.90877	mm^3d^{-1}
N_1	Free vir. by inf. cells	6205.5979	none
N_2	Free vir. by APCs	8749.2435	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.016195	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.010587	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1271.238	mm^{-3}
K	Carry. cap.: tb pop.	6310.1671	mm^{-3}
r_b	Max. tb prolif. rate	35.2508	/day

Comments:

The response for patient 40 can be used a prime example of how well the model response should fit to the data. The proper steady-state values are reached.

E.13. Patient 41

Table E.27.: Patient 41 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.51594	32804.99682	334	914	T_4	334
2	4.696487	49714.9492	375	779	T_8	914
4	5.510376	323873.9366	201	412	v	32804.99682
8	4.930496	85211.06631	332	932	T_b	2900
26	4.696889	49760.98861	239	486	I	1020
52	5.177698	150555.9765	354	782	D	5000
78	4.878275	75557.05117	267	650		

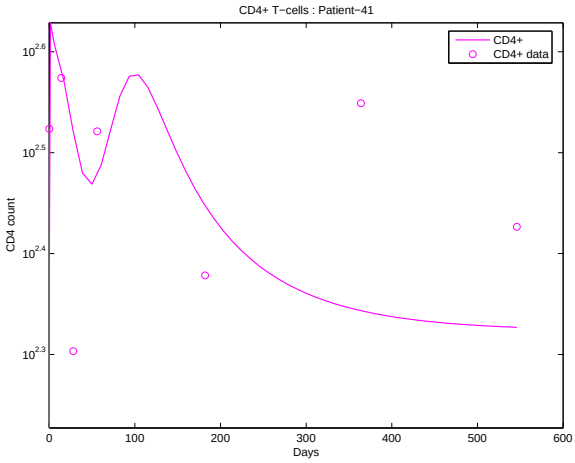

Figure E.49.: CD4+ T-Cells

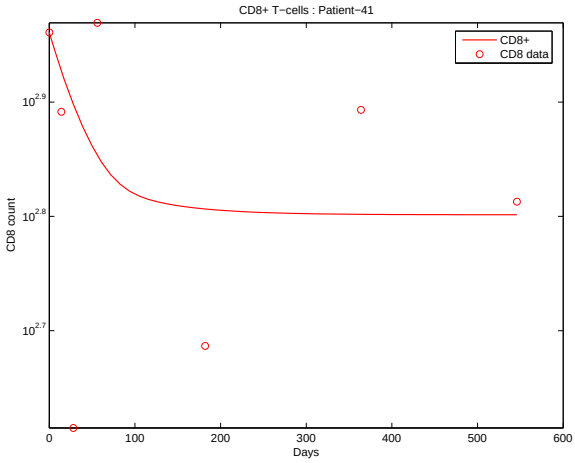

Figure E.50.: CD8+ T-Cells

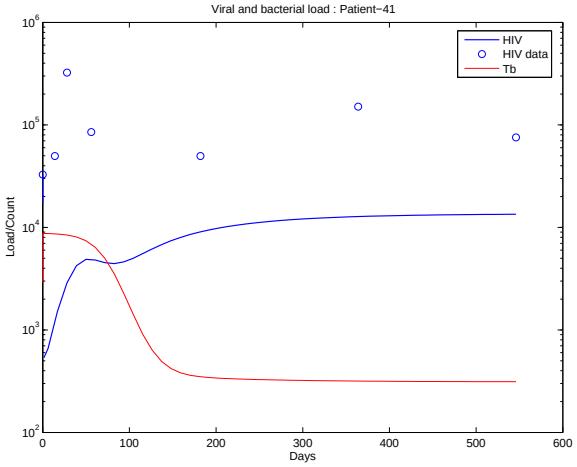

Figure E.51.: Viral and bacterial load

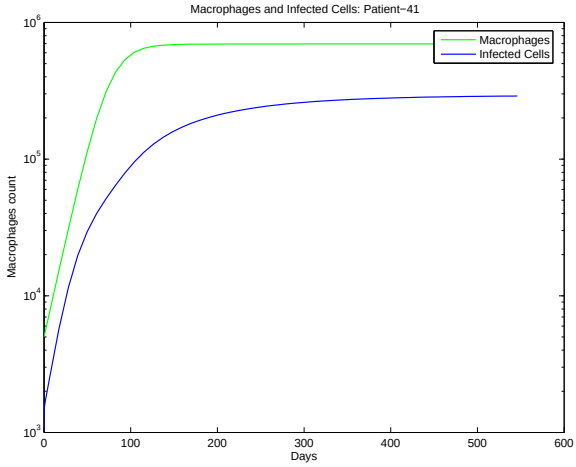

Figure E.52.: Macrophages and infected cells

Table E.28.: Optimised parameter set : Patient41

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	2849.6363	/day
S_8	Src - T_8 cells	8.3592	/day
k_1	Rate - T_4 cells	0.00074516	/day-vir.
k_2	Rate - T_4 cells by APCs	4.5479e-006	/day-cell
k_3	Rate - T_8 cells by APCs	2.6617e-009	/day-cell
k_4	Recr. - APCs by HIV	4.4344e-008	/day
k_5	Recr. - APCs by Mtb	7.672e-006	/day
k_6	Dth rate : virus by APCs	8.1191e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.0094589	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.61746	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.53576	mm^3d^{-1}
N_1	Free vir. by inf. cells	4205.8664	none
N_2	Free vir. by APCs	78.854	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.0095653	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.015059	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1493.9265	mm^{-3}
K	Carry. cap.: tb pop.	8808.1858	mm^{-3}
r_b	Max. tb prolif. rate	43.9427	/day

Comments:

With patient 41, only the CD8+ T-cells reach the proper steady-state value, although the CD4+ T-cells fit the data reasonably well. This patient is used in section 9 to indicate how the response can be refined.

E.14. Patient 44

Table E.29.: Patient 44 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.054077	11326.01155	404	443	T_4	404
2	4.101507	12633.01466	410	523	T_8	443
4	4.201807	15915.01308	380	525	v	11326.01155
8	3.997386	9939.991202	326	402	T_b	2900
26	3.851136	7098.000082	304	401	I	1020
52	3.988202	9731.997753	379	419	D	5000
78	3.957511	9067.989321	348	452		

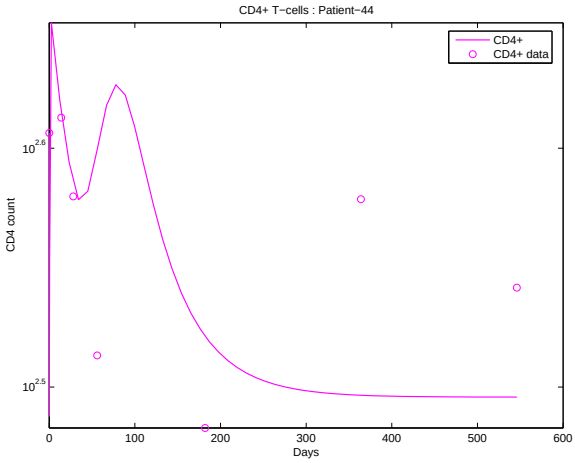

Figure E.53.: CD4+ T-Cells

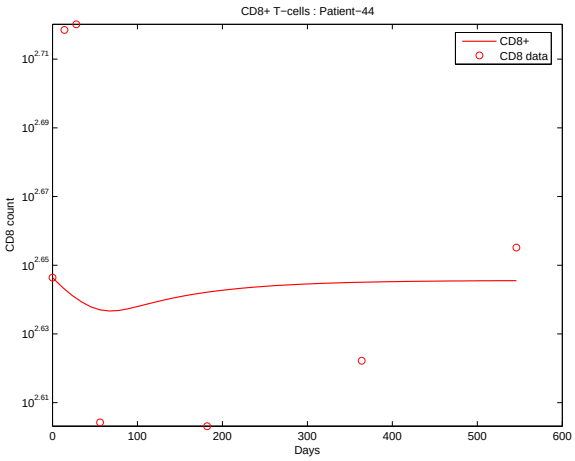

Figure E.54.: CD8+ T-Cells

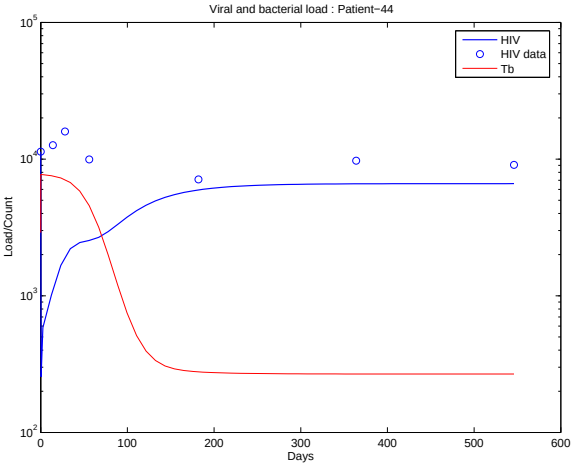

Figure E.55.: Viral and bacterial load

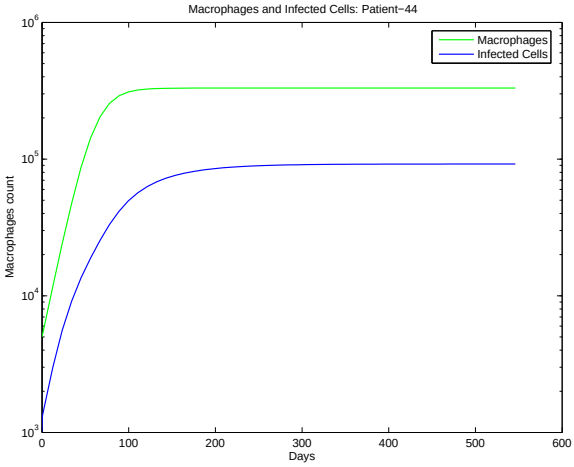

Figure E.56.: Macrophages and infected cells

Table E.30.: Optimised parameter set : Patient44

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	1805.2861	/day
S_8	Src - T_8 cells	4.4841	/day
k_1	Rate - T_4 cells	0.00049419	/day-vir.
k_2	Rate - T_4 cells by APCs	7.1137e-006	/day-cell
k_3	Rate - T_8 cells by APCs	1.7575e-009	/day-cell
k_4	Recr. - APCs by HIV	8.3228e-008	/day
k_5	Recr. - APCs by Mtb	9.0722e-006	/day
k_6	Dth rate : virus by APCs	8.4865e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.0088669	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.52434	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.78233	mm^3d^{-1}
N_1	Free vir. by inf. cells	5070.2839	none
N_2	Free vir. by APCs	12.1649	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.019138	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.010723	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	2517.0038	mm^{-3}
K	Carry. cap.: tb pop.	7831.7202	mm^{-3}
r_b	Max. tb prolif. rate	34.2869	/day

Comments:
This patient's model response fits well to the provided data.

E.15. Patient 45

Table E.31.: Patient 45 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.299246	19918.01247	331	1250	T_4	331
2	4.370198	23452.97821	317	954	T_8	1250
4	4.301291	20012.02331	196	689	v	19918.01247
8	3.921843	8353.009974	285	787	T_b	2900
26	4.2352	17186.99695	288	882	I	1020
52	4.322798	21028.00153			D	5000
78	4.6784	47686.99981	303	1014		

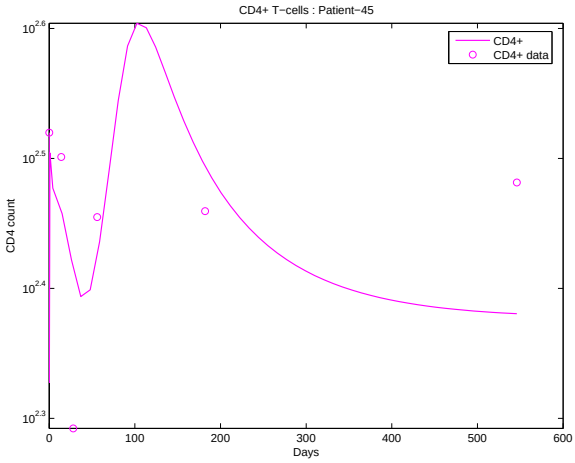

Figure E.57.: CD4+ T-Cells

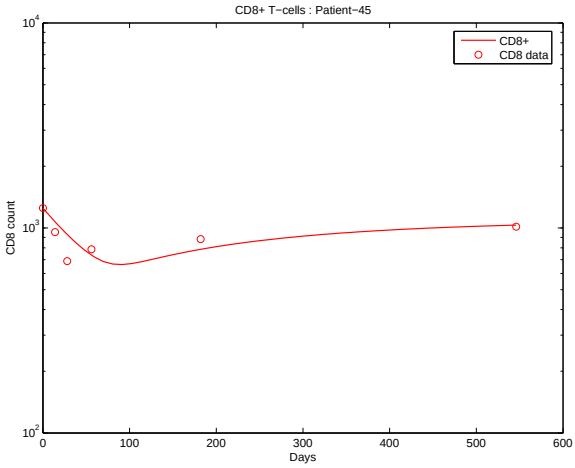

Figure E.58.: CD8+ T-Cells

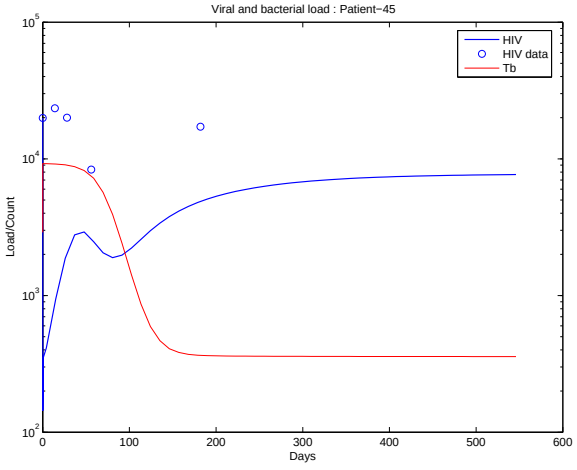

Figure E.59.: Viral and bacterial load

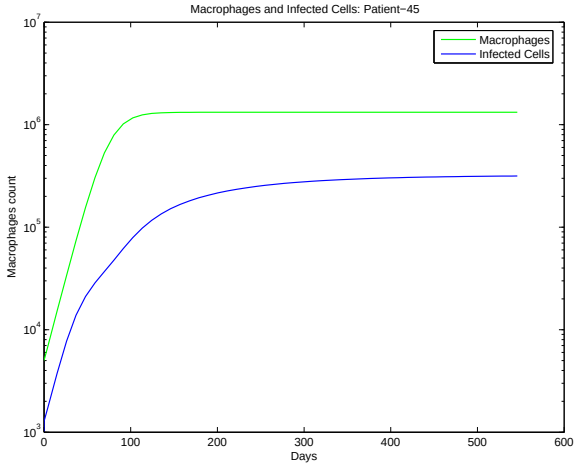

Figure E.60.: Macrophages and infected cells

Table E.32.: Optimised parameter set : Patient45

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	2991.1563	/day
S_8	Src - T_8 cells	4.8849	/day
k_1	Rate - T_4 cells	0.0010263	/day-vir.
k_2	Rate - T_4 cells by APCs	3.179e-006	/day-cell
k_3	Rate - T_8 cells by APCs	8.1613e-009	/day-cell
k_4	Recr. - APCs by HIV	1.0455e-008	/day
k_5	Recr. - APCs by Mtb	8.1587e-006	/day
k_6	Dth rate : virus by APCs	0.00010219	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.012643	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.30112	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.44543	mm^3d^{-1}
N_1	Free vir. by inf. cells	4401.2868	none
N_2	Free vir. by APCs	2541.7218	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.0090501	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.015263	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	810.3047	mm^{-3}
K	Carry. cap.: tb pop.	9265.5917	mm^{-3}
r_b	Max. tb prolif. rate	66.1393	/day

Comments:

The viral load response does not quite reach the same value as that of the last sample, but the CD8+ T-cells response matches the data very well.

E.16. Patient 47

Table E.33.: Patient 47 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	3.662852	4600.997529	151	531	T_4	151
2	4.085861	12185.99512	175	621	T_8	531
4	3.761176	5770.002482	246	820	v	4600.997529
8	2.428135	268.0001271	287	1120	T_b	2900
26	4.874899	74971.98334			I	1020
52	3.89483	7849.283225	255	773	D	5000
78	4.030964	10739.0039	200	624		

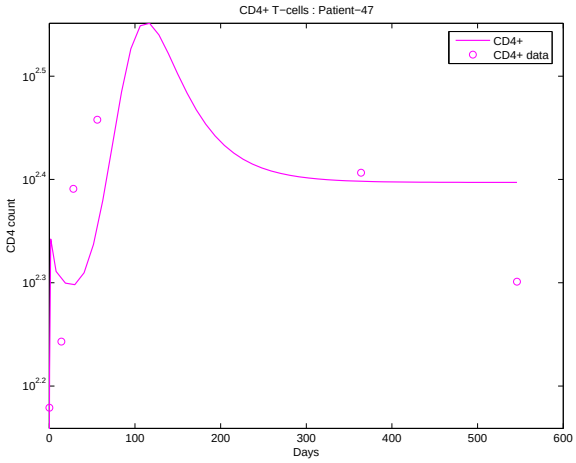

Figure E.61.: CD4+ T-Cells

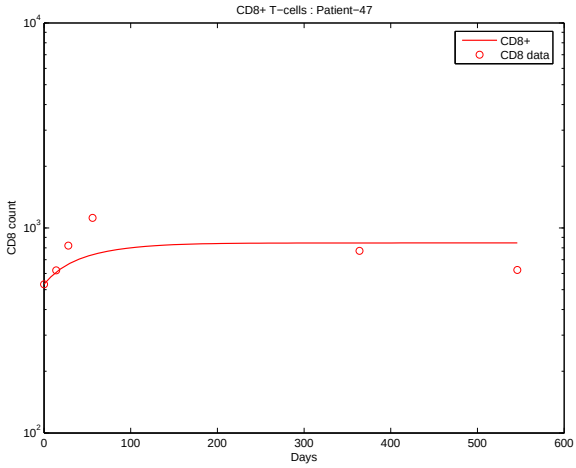

Figure E.62.: CD8+ T-Cells

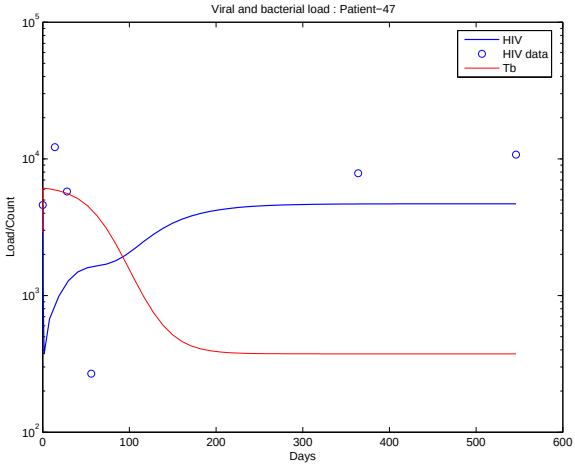

Figure E.63.: Viral and bacterial load

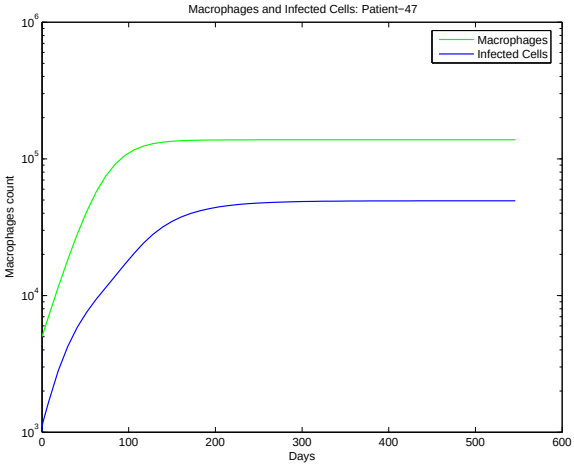

Figure E.64.: Macrophages and infected cells

Table E.34.: Optimised parameter set : Patient47

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	1229.7025	/day
S_8	Src - T_8 cells	17.9474	/day
k_1	Rate - T_4 cells	0.00089814	/day-vir.
k_2	Rate - T_4 cells by APCs	2.699e-006	/day-cell
k_3	Rate - T_8 cells by APCs	3.5666e-009	/day-cell
k_4	Recr. - APCs by HIV	1.0479e-008	/day
k_5	Recr. - APCs by Mtb	7.7729e-006	/day
k_6	Dth rate : virus by APCs	8.3629e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.0036717	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.42257	mm^3d^{-1}
k_9	Dth rate : tb by APCs	1.5611	mm^3d^{-1}
N_1	Free vir. by inf. cells	2456.4424	none
N_2	Free vir. by APCs	4202.4789	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.023197	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.021727	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1884.9399	mm^{-3}
K	Carry. cap.: tb pop.	6336.3164	mm^{-3}
r_b	Max. tb prolif. rate	36.1025	/day

Comments:

The viral-load response steady-state is slightly below the target value, but both the CD4+ T-cells and the CD8+ T-cells fit the provided data very well.

E.17. Patient 50

Table E.35.: Patient 50 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.753951	56748.05749	720	1521	T_4	720
2	1	1010	1967	0	T_8	1521
4	3.764176	5809.998229	1637	2168	v	56748.05749
6	3.829304	6750.003531			T_b	2900
8	3.661529	4587.002745	552	1142	I	1020
26	3.253232	1791.562651	732	1020.5	D	5000
52	3.527372	3367.999358				
78	3.995854	9904.989055	537	750		

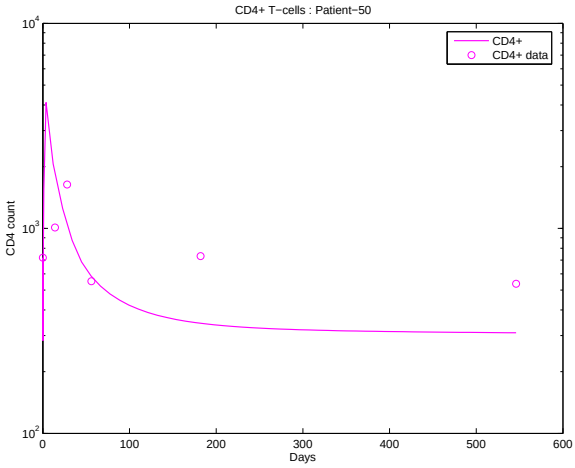

Figure E.65.: CD4+ T-Cells

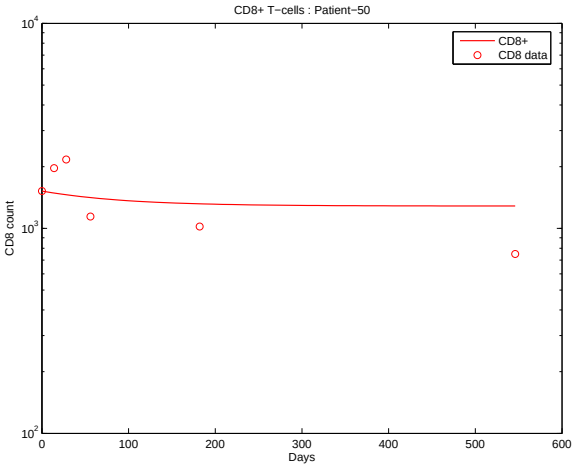

Figure E.66.: CD8+ T-Cells

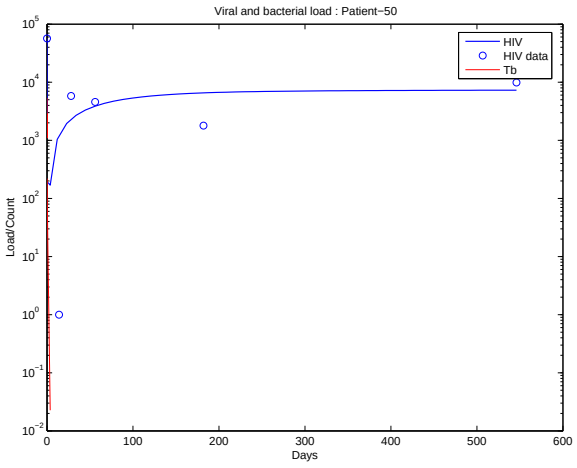

Figure E.67.: Viral and bacterial load

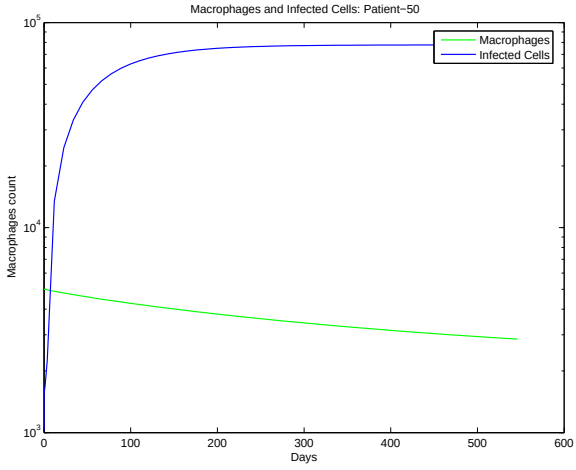

Figure E.68.: Macrophages and infected cells

Table E.36.: Optimised parameter set : Patient50

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	1263.8284	/day
S_8	Src - T_8 cells	14.1048	/day
k_1	Rate - T_4 cells	0.00055625	/day-vir.
k_2	Rate - T_4 cells by APCs	3.1405e-006	/day-cell
k_3	Rate - T_8 cells by APCs	3.2421e-009	/day-cell
k_4	Recr. - APCs by HIV	7.4743e-008	/day
k_5	Recr. - APCs by Mtb	8.027e-006	/day
k_6	Dth rate : virus by APCs	8.2681e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.011896	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.52188	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.79723	mm^3d^{-1}
N_1	Free vir. by inf. cells	3374.3409	none
N_2	Free vir. by APCs	9119.3473	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.016211	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.010985	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1784.6144	mm^{-3}
K	Carry. cap.: tb pop.	6240.936	mm^{-3}
r_b	Max. tb prolif. rate	33.1757	/day

Comments:

A very good model-data fit can be seen for patient 50.

E.18. Patient 55

Table E.37.: Patient 55 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.525939	33569.04606	272	583	T_4	272
2	5.030859	107364.0783	300	657	T_8	583
4	4.591009	38995.00676	241	453	v	33569.04606
8			258	472	T_b	2900
26	4.640193	43670.98625	192	550	I	1020
52	4.939916	87079.5147	199	476	D	5000
78	4.642761	43929.97944	202	501		

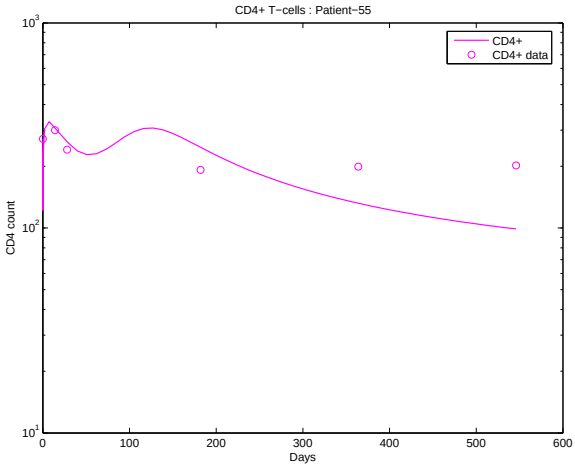

Figure E.69.: CD4+ T-Cells

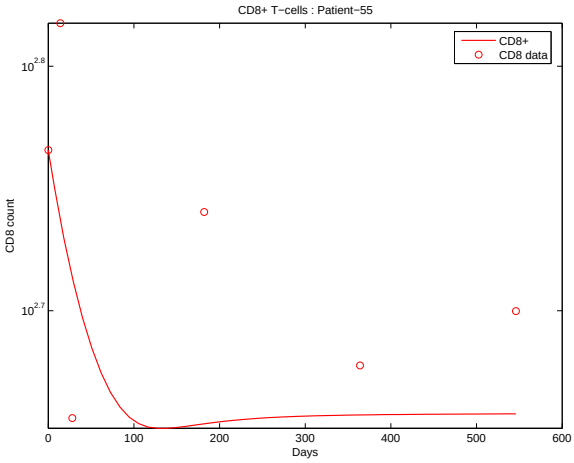

Figure E.70.: CD8+ T-Cells

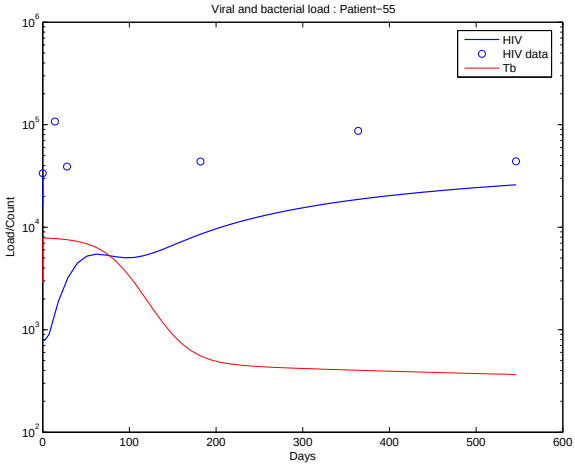

Figure E.71.: Viral and bacterial load

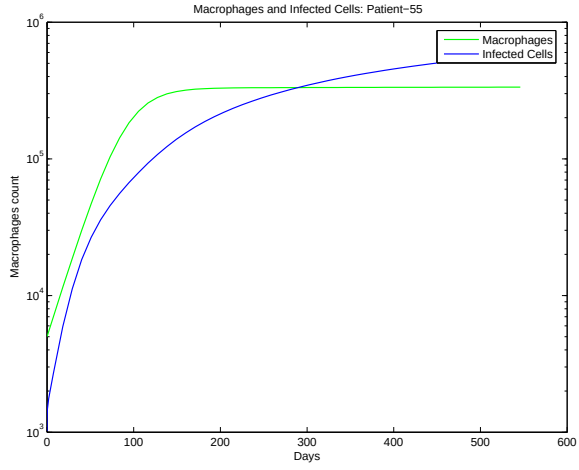

Figure E.72.: Macrophages and infected cells

Table E.38.: Optimised parameter set : Patient55

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	1929.1888	/day
S_8	Src - T_8 cells	7.1983	/day
k_1	Rate - T_4 cells	0.00067972	/day-vir.
k_2	Rate - T_4 cells by APCs	4.9324e-006	/day-cell
k_3	Rate - T_8 cells by APCs	4.9689e-009	/day-cell
k_4	Recr. - APCs by HIV	2.951e-008	/day
k_5	Recr. - APCs by Mtb	6.1324e-006	/day
k_6	Dth rate : virus by APCs	7.5408e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.010553	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.4451	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.95253	mm^3d^{-1}
N_1	Free vir. by inf. cells	4935.0276	none
N_2	Free vir. by APCs	4332.4806	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.0019777	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.017488	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1678.9645	mm^{-3}
K	Carry. cap.: tb pop.	7960.5167	mm^{-3}
r_b	Max. tb prolif. rate	42.0003	/day

Comments:

This patient's viral load response does not fit so well to the provided data. Also, the CD4+ T-cells response fits well to the data, but it doesn't reach a steady-state. The response for the CD8+ T-cells reach a steady-state though.

E.19. Patient 57

Table E.39.: Patient 57 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.609808	40720.02163	242	842	T_4	242
2	5.013911	103254.9784	321	820	T_8	842
4	5.07739	119506.0797	355	750	v	40720.02163
8	5.387087	243829.9222	166.5	647	T_b	2900
26	5.543949	349904.0747	195	524	I	1020
52	4.806275	64014.00508	233	553	D	5000
78	4.56921	37086.00051	261	544		

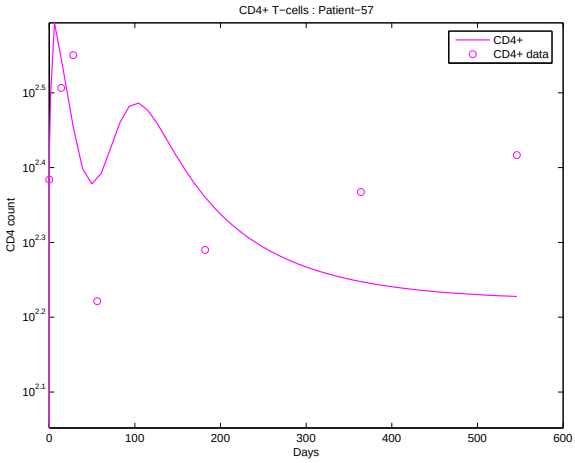

Figure E.73.: CD4+ T-Cells

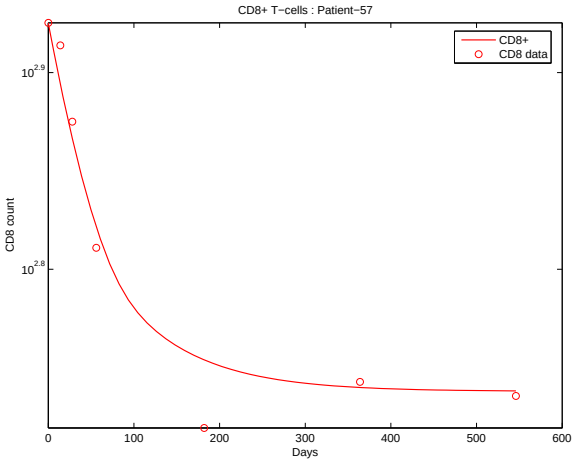

Figure E.74.: CD8+ T-Cells

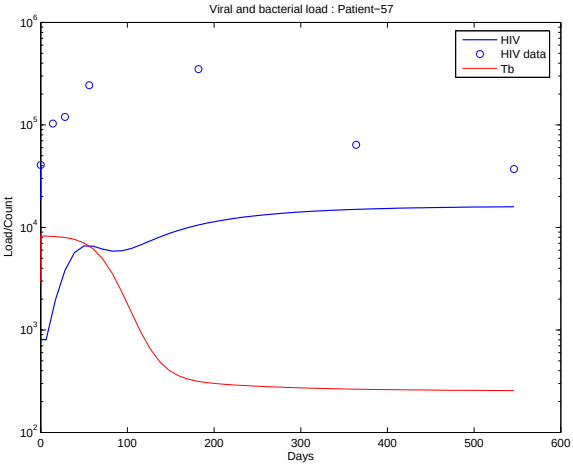

Figure E.75.: Viral and bacterial load

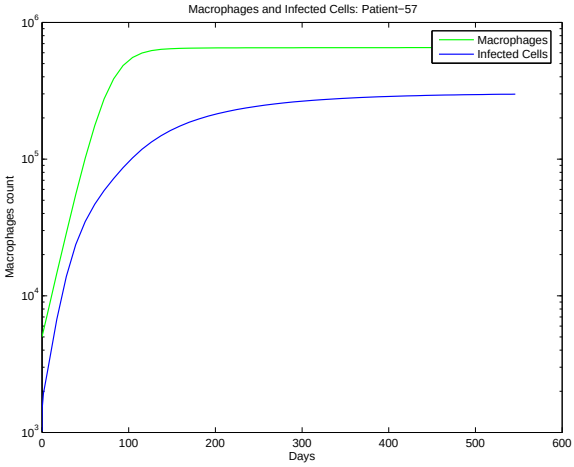

Figure E.76.: Macrophages and infected cells

Table E.40.: Optimised parameter set : Patient57

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	2730.3008	/day
S_8	Src - T_8 cells	6.1955	/day
k_1	Rate - T_4 cells	0.00080023	/day-vir.
k_2	Rate - T_4 cells by APCs	4.9154e-006	/day-cell
k_3	Rate - T_8 cells by APCs	2.1847e-009	/day-cell
k_4	Recr. - APCs by HIV	6.216e-008	/day
k_5	Recr. - APCs by Mtb	7.8259e-006	/day
k_6	Dth rate : virus by APCs	7.2848e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.010457	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.41786	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.52385	mm^3d^{-1}
N_1	Free vir. by inf. cells	4338.0843	none
N_2	Free vir. by APCs	227.7046	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.0088958	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.012757	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1983.1782	mm^{-3}
K	Carry. cap.: tb pop.	8324.3046	mm^{-3}
r_b	Max. tb prolif. rate	42.4863	/day

Comments:

The reason that this patient's response do not fit too well to the data when it comes to the viral load and CD4+ T-cells, is because of the high variability of the data. The viral load data doesn't reach a steady-state, but rather it continues to vary at 78 weeks to the order of 10^4. The response reaches a steady-state for all cell-types though.

E.20. Patient 58

Table E.41.: Patient 58 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	5.459334	287961.2168	327	1146	T_4	327
2	5.69897	499999.995	429	1939	T_8	1146
4	5.362121	230208.3118	327	1349	v	287961.2168
8			357	1596	T_b	2900
26	5.69897	499999.995	164	791	I	1020
52	3.595386	3939.000174	582	2328	D	5000
78	4.430623	26953.9861	302	1037		

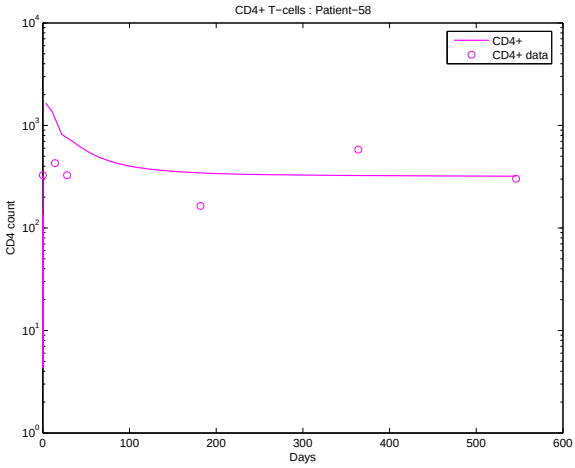

Figure E.77.: CD4+ T-Cells

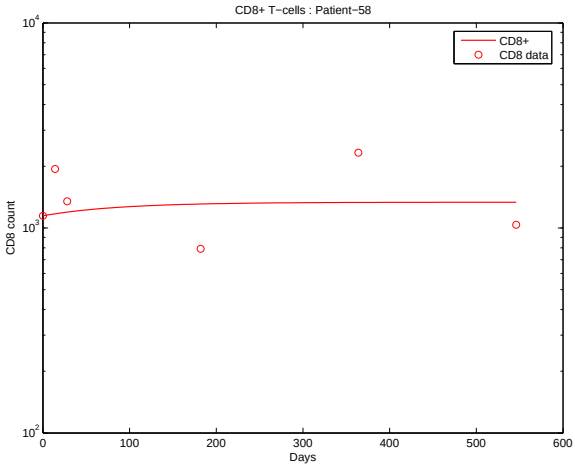

Figure E.78.: CD8+ T-Cells

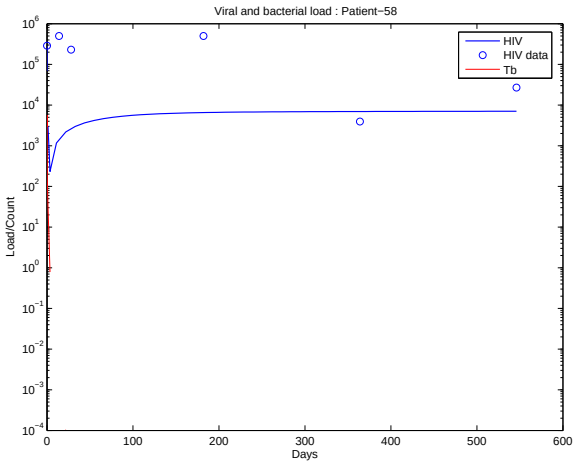

Figure E.79.: Viral and bacterial load

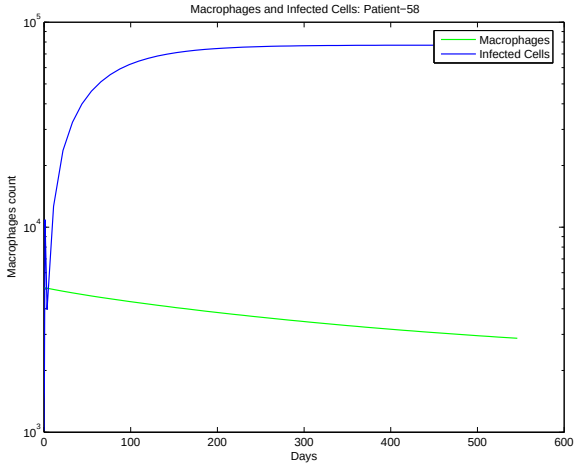

Figure E.80.: Macrophages and infected cells

Table E.42.: Optimised parameter set : Patient58

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	1266.137	/day
S_8	Src - T_8 cells	14.256	/day
k_1	Rate - T_4 cells	0.00055716	/day-vir.
k_2	Rate - T_4 cells by APCs	3.144e-006	/day-cell
k_3	Rate - T_8 cells by APCs	3.2516e-009	/day-cell
k_4	Recr. - APCs by HIV	7.4716e-008	/day
k_5	Recr. - APCs by Mtb	8.015e-006	/day
k_6	Dth rate : virus by APCs	8.255e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.011857	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.51857	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.83158	mm^3d^{-1}
N_1	Free vir. by inf. cells	3355.499	none
N_2	Free vir. by APCs	9217.7805	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.016369	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.01065	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1788.7933	mm^{-3}
K	Carry. cap.: tb pop.	6220.508	mm^{-3}
r_b	Max. tb prolif. rate	33.2554	/day

Comments:

This patient's response fits very well to the provided data, except in the case of the viral load, which doesn't reach the proper steady-state value. This patient's responses are refined in section 9.

E.21. Patient 60

Table E.43.: Patient 60 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	3.576687	3773.001692	335	967	T_4	335
2	4.145196	13969.98694	221	1266	T_8	967
4	3.67071	4685.004367	366	1537	v	3773.001692
8	3.720159	5249.996332	429	1625	T_b	2900
26	4.532398	34072.02926	533	2978	I	1020
52	3.995328	9892.999793	505	379	D	5000
78			302	1875		

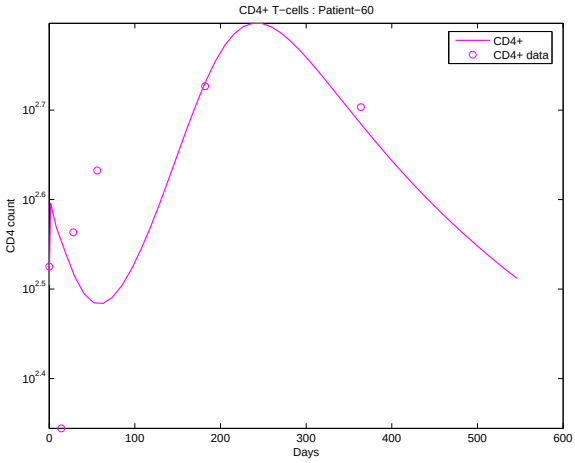

Figure E.81.: CD4+ T-Cells

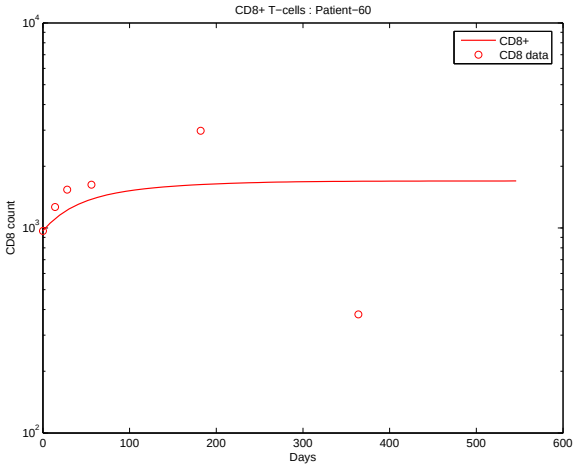

Figure E.82.: CD8+ T-Cells

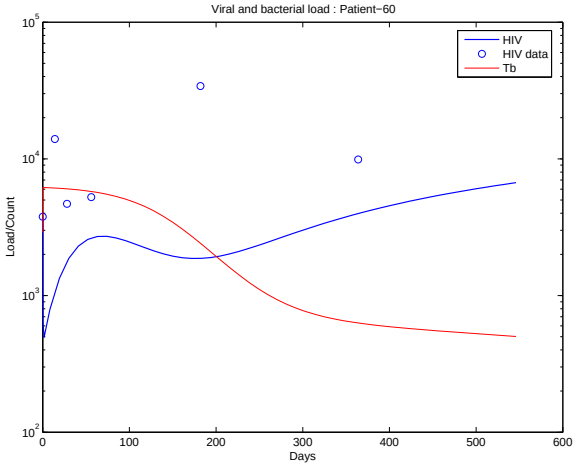

Figure E.83.: Viral and bacterial load

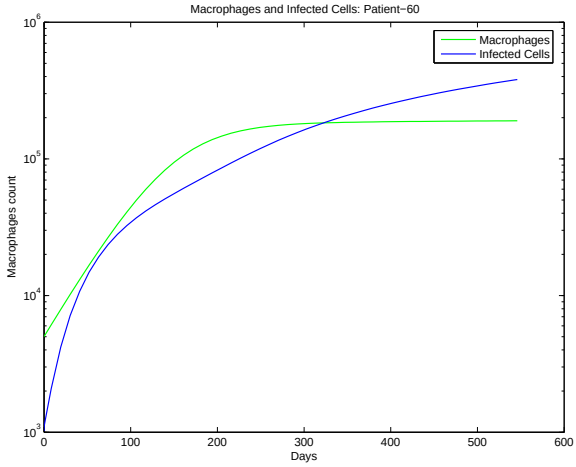

Figure E.84.: Macrophages and infected cells

Table E.44.: Optimised parameter set : Patient60

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	1288.7494	/day
S_8	Src - T_8 cells	28.0174	/day
k_1	Rate - T_4 cells	0.00049842	/day-vir.
k_2	Rate - T_4 cells by APCs	1.9574e-006	/day-cell
k_3	Rate - T_8 cells by APCs	3.3006e-009	/day-cell
k_4	Recr. - APCs by HIV	1.4405e-007	/day
k_5	Recr. - APCs by Mtb	4.1616e-006	/day
k_6	Dth rate : virus by APCs	6.8057e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.00010463	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.35439	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.95703	mm^3d^{-1}
N_1	Free vir. by inf. cells	6345.1662	none
N_2	Free vir. by APCs	5998.2636	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.0010005	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.017147	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	2293.2307	mm^{-3}
K	Carry. cap.: tb pop.	6334.4549	mm^{-3}
r_b	Max. tb prolif. rate	31.1901	/day

Comments:

The model responses for patient 60 reflects what can be said of the data : it varies significantly over time, especially close to the end of the simulation period, which is 78 weeks. Only the CD8+ T-cells response reach a steady-state value.

E.22. Patient 64

Table E.45.: Patient 64 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	3.496653	3138.000439	484	682	T_4	484
2	3.15045	1414.001923	361	484	T_8	682
4	3.630224	4267.995963	368	459	v	3138.000439
8	3.664172	4615.003131	373	404	T_b	2900
26	3.414973	2599.997917	328	442	I	1020
52	3.851791	7108.713314	354	529	D	5000
78			424	580		

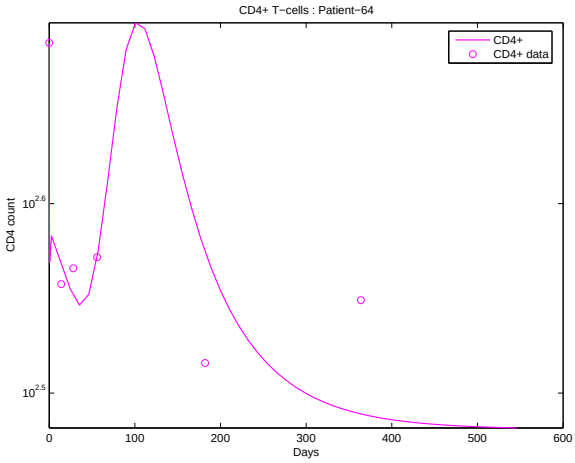

Figure E.85.: CD4+ T-Cells

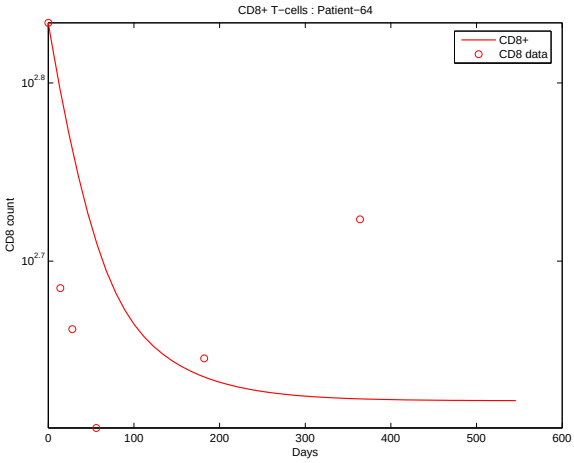

Figure E.86.: CD8+ T-Cells

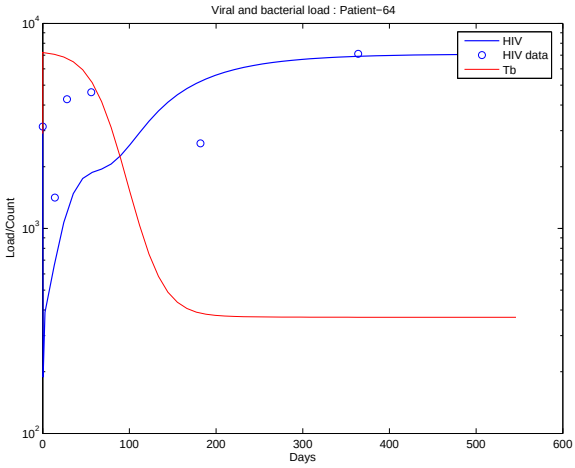

Figure E.87.: Viral and bacterial load

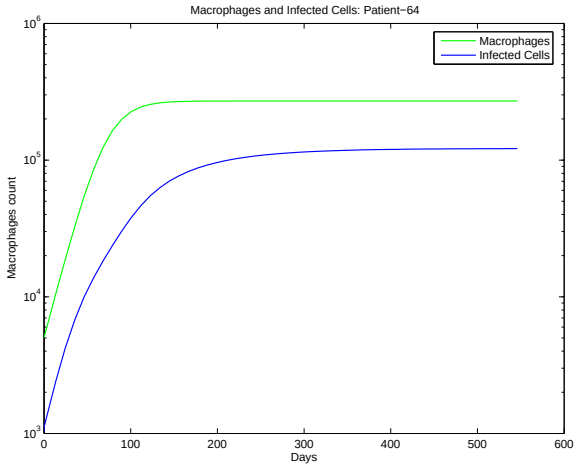

Figure E.88.: Macrophages and infected cells

Table E.46.: Optimised parameter set : Patient64

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	1697.37	/day
S_8	Src - T_8 cells	5.8119	/day
k_1	Rate - T_4 cells	0.0005851	/day-vir.
k_2	Rate - T_4 cells by APCs	4.5774e-006	/day-cell
k_3	Rate - T_8 cells by APCs	4.8177e-009	/day-cell
k_4	Recr. - APCs by HIV	1.0001e-008	/day
k_5	Recr. - APCs by Mtb	7.905e-006	/day
k_6	Dth rate : virus by APCs	6.412e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.008002	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.36994	mm^3d^{-1}
k_9	Dth rate : tb by APCs	1.0002	mm^3d^{-1}
N_1	Free vir. by inf. cells	4234.2712	none
N_2	Free vir. by APCs	7127.7865	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.013402	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.015194	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1453.1017	mm^{-3}
K	Carry. cap.: tb pop.	7337.715	mm^{-3}
r_b	Max. tb prolif. rate	38.8709	/day

Comments:

All the responses for this patient reach a steady-state value similar to that of the data. This patient has a very good model response.

E.23. Patient 68

Table E.47.: Patient 68 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.679909	47852.9813	119	642	T_4	119
2	4.275473	18857.01732	146	721	T_8	642
4	4.851735	71077.96742	118	620	v	47852.9813
8	5.020651	104869.9353	109	496	T_b	2800
26	4.801383	63296.98151	66	325	I	120
52	5.264348	183801.0551	63	1112	D	700
78			42	1360		

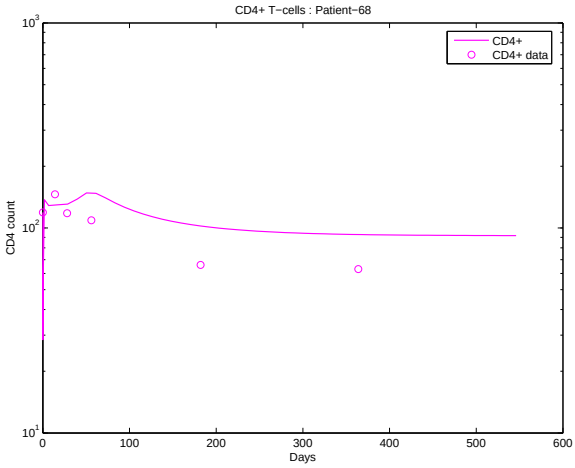

Figure E.89.: CD4+ T-Cells

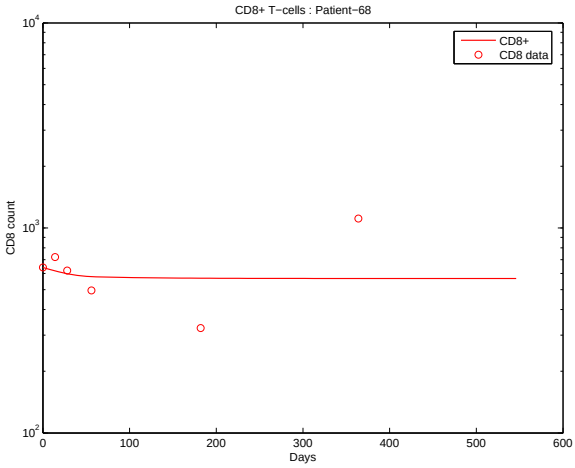

Figure E.90.: CD8+ T-Cells

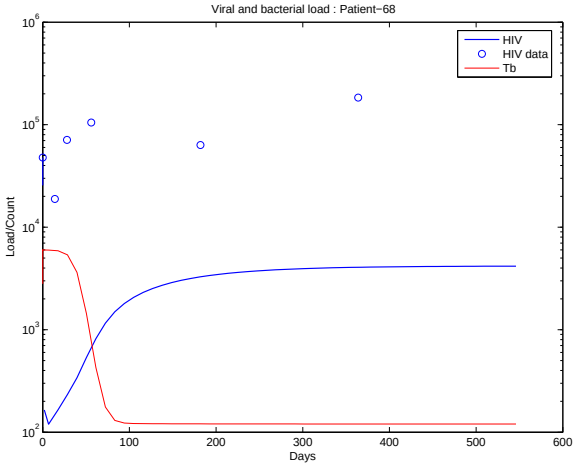

Figure E.91.: Viral and bacterial load

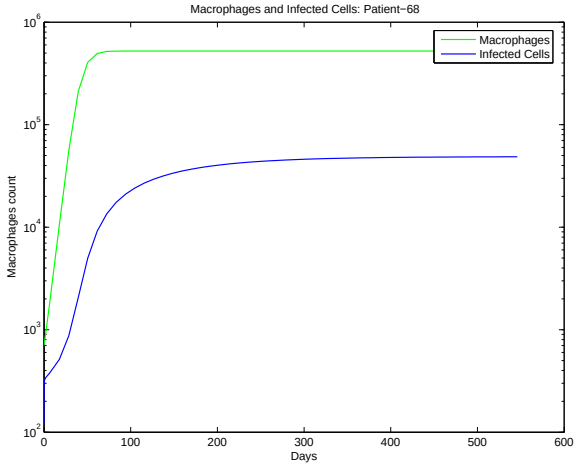

Figure E.92.: Macrophages and infected cells

Table E.48.: Optimised parameter set : Patient68

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	552.1003	/day
S_8	Src - T_8 cells	7.637	/day
k_1	Rate - T_4 cells	0.0006929	/day-vir.
k_2	Rate - T_4 cells by APCs	5.807e-006	/day-cell
k_3	Rate - T_8 cells by APCs	2.7323e-009	/day-cell
k_4	Recr. - APCs by HIV	1.0089e-008	/day
k_5	Recr. - APCs by Mtb	2.4602e-005	/day
k_6	Dth rate : virus by APCs	1.6577e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.0095407	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.71252	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.32172	mm^3d^{-1}
N_1	Free vir. by inf. cells	4095.9955	none
N_2	Free vir. by APCs	3133.2799	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.011138	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.014903	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	4.2585	mm^{-3}
K	Carry. cap.: tb pop.	6007.4471	mm^{-3}
r_b	Max. tb prolif. rate	28.5922	/day

Comments:

This patient is refined in section 9, because its viral-load response steady-state does not reach the required value. All other responses for this patient fits the provided data very well.

E.24. Patient 73

Table E.49.: Patient 73 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0			272	983	T_4	272
2	5.223994	167491.9736	285	1613	T_8	983
4	4.025879	10613.99796	311	1238	v	167491.9736
8	4.414455	25968.98646	371	2000	T_b	2900
26	4.766301	58384.96175	333	1500	I	1020
52	4.708473	51106.13055	428	1621	D	5000
78			387	1695		

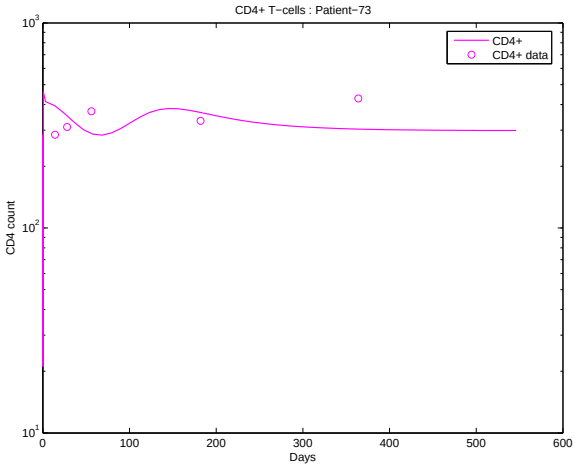

Figure E.93.: CD4+ T-Cells

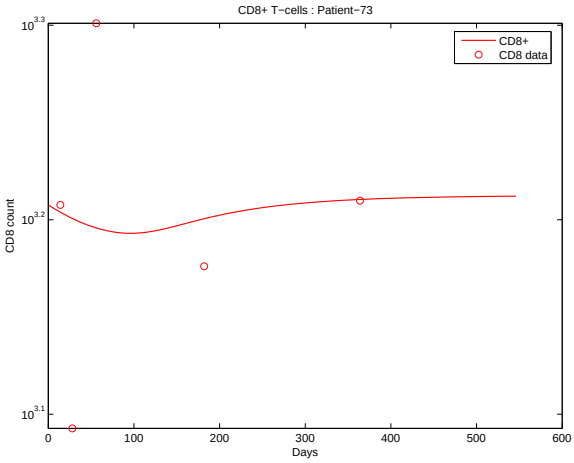

Figure E.94.: CD8+ T-Cells

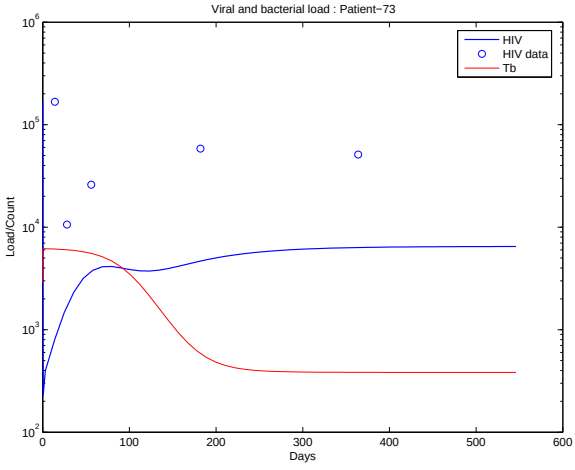

Figure E.95.: Viral and bacterial load

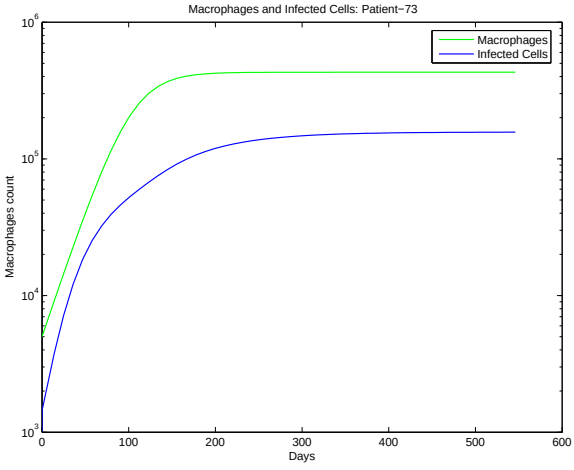

Figure E.96.: Macrophages and infected cells

Table E.50.: Optimised parameter set : Patient73

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	2368.7381	/day
S_8	Src - T_8 cells	16.091	/day
k_1	Rate - T_4 cells	0.00085966	/day-vir.
k_2	Rate - T_4 cells by APCs	4.7003e-006	/day-cell
k_3	Rate - T_8 cells by APCs	1.8309e-009	/day-cell
k_4	Recr. - APCs by HIV	3.1158e-008	/day
k_5	Recr. - APCs by Mtb	7.2739e-006	/day
k_6	Dth rate : virus by APCs	9.4428e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.012122	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.087662	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.22251	mm^3d^{-1}
N_1	Free vir. by inf. cells	6009.112	none
N_2	Free vir. by APCs	4632.7291	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.014438	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.010654	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1856.2962	mm^{-3}
K	Carry. cap.: tb pop.	6246.3481	mm^{-3}
r_b	Max. tb prolif. rate	16.3388	/day

Comments:

According to the data-inclusion criteria from section 5.3, this patient shouldn't have been included into the study. The reason for its inclusion is to show that, even if the first sample of a cell-type, in this case the viral load, is missing, the next available sample will be taken as the initial condition for simulation purposes. This patient consequently fits well to the data with the CD4+ T-cells and CD8+ T-cells responses, but the viral load response doesn't fit well to the data. The response can be refined according to the procedure described at the start of this appendix.

E.25. Patient 74

Table E.51.: Patient 74 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.686618	48597.95561	275	1012	T_4	275
2	4.88475	76691.98877	143	925	T_8	1012
4	4.38421	24222.00001	172	955	v	48597.95561
8			181	1147	T_b	2900
26	5.69897	499999.995	131	874	I	1020
52	5.552197	356612.8596	118	809	D	5000
78			77	741		

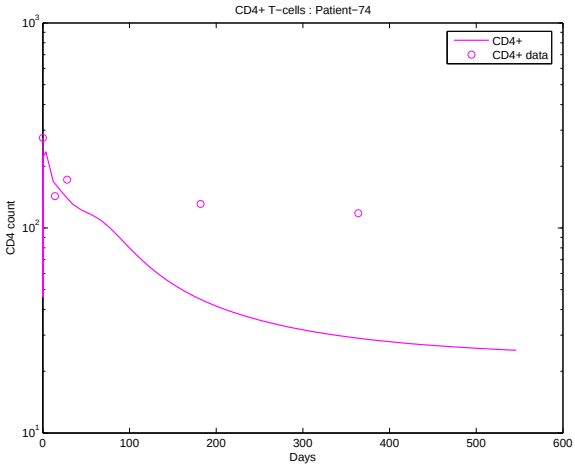

Figure E.97.: CD4+ T-Cells

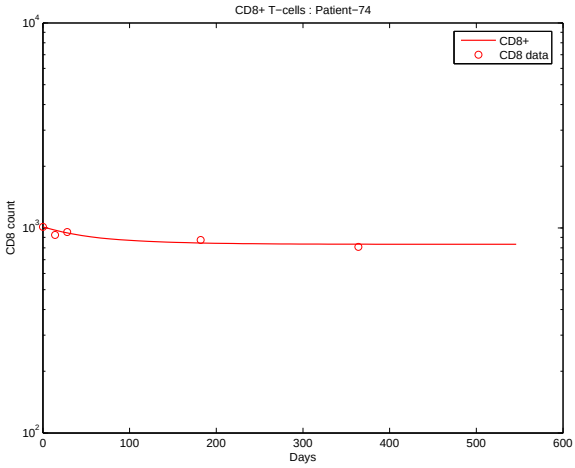

Figure E.98.: CD8+ T-Cells

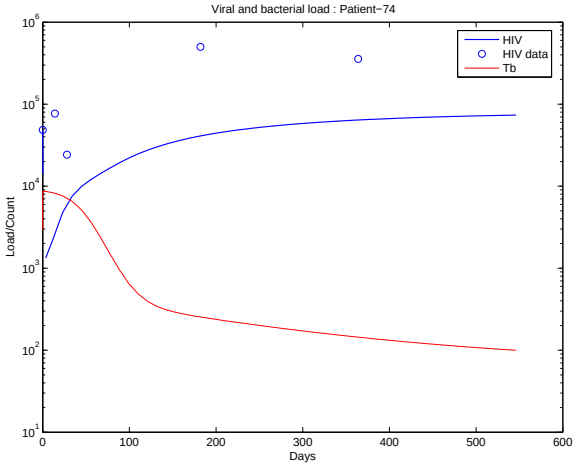

Figure E.99.: Viral and bacterial load

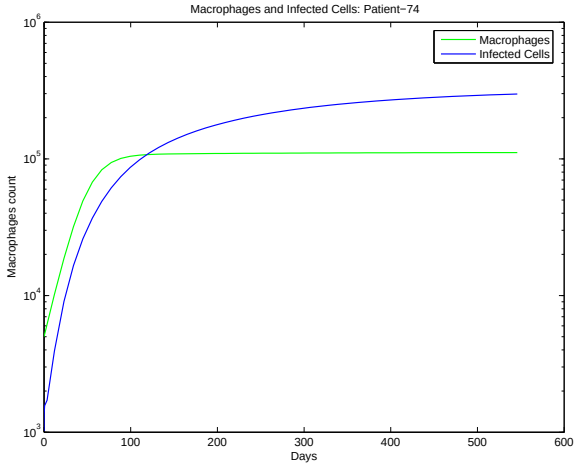

Figure E.100.: Macrophages and infected cells

Table E.52.: Optimised parameter set : Patient74

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	1589.8477	/day
S_8	Src - T_8 cells	10.9656	/day
k_1	Rate - T_4 cells	0.00084239	/day-vir.
k_2	Rate - T_4 cells by APCs	6.2293e-006	/day-cell
k_3	Rate - T_8 cells by APCs	4.7427e-009	/day-cell
k_4	Recr. - APCs by HIV	3.0937e-008	/day
k_5	Recr. - APCs by Mtb	7.154e-006	/day
k_6	Dth rate : virus by APCs	0.00013173	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.0056668	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.47023	mm^3d^{-1}
k_9	Dth rate : tb by APCs	1.4446	mm^3d^{-1}
N_1	Free vir. by inf. cells	6464.3117	none
N_2	Free vir. by APCs	59.0026	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.0048727	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.0137	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	929.1029	mm^{-3}
K	Carry. cap.: tb pop.	9149.2685	mm^{-3}
r_b	Max. tb prolif. rate	17.7495	/day

Comments:

This patient's viral load and CD4+ T-cells responses do not fit too well with the provided data. This patient's response is refined in section 9.

E.26. Patient 76

Table E.53.: Patient 76 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	2.093422	124.0000899	572	1268	T_4	572
2	4.338257	21789.98845	471	1073	T_8	1268
4	3.264582	1839.001147	738	2000	v	124.0000899
8	1.973128	94.00003169	724	1875	T_b	2900
26	3.020361	1047.999318	734	1175	I	1020
52	2.585461	385.0002398	700	2000	D	5000
78			623	1752		

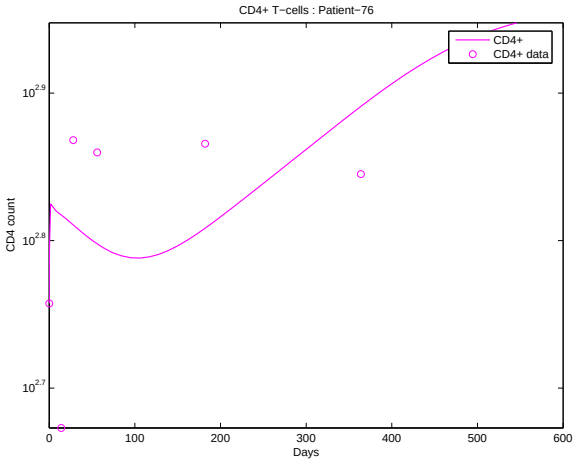

Figure E.101.: CD4+ T-Cells

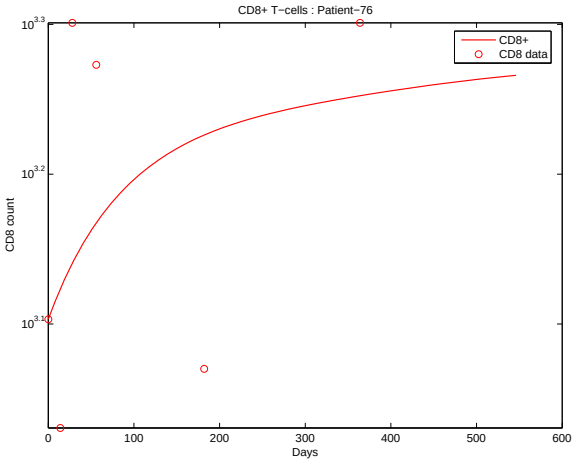

Figure E.102.: CD8+ T-Cells

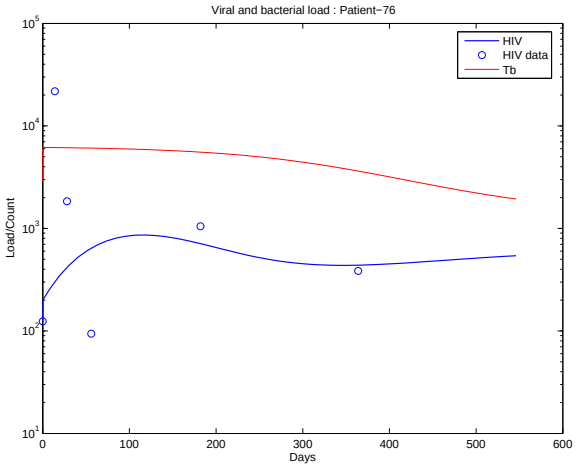

Figure E.103.: Viral and bacterial load

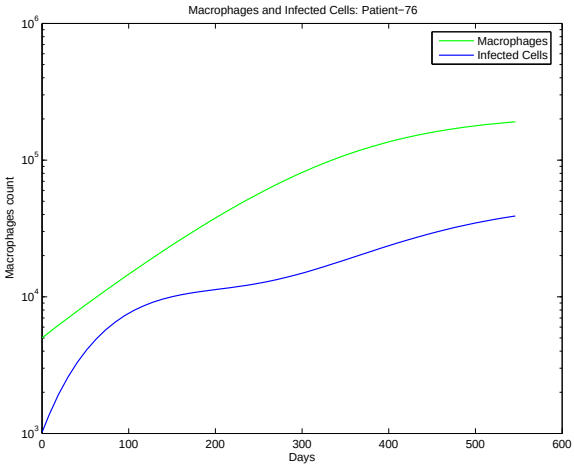

Figure E.104.: Macrophages and infected cells

Table E.54.: Optimised parameter set : Patient76

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	1514.5395	/day
S_8	Src - T_8 cells	16.1209	/day
k_1	Rate - T_4 cells	0.00035241	/day-vir.
k_2	Rate - T_4 cells by APCs	4.3429e-006	/day-cell
k_3	Rate - T_8 cells by APCs	2.5264e-009	/day-cell
k_4	Recr. - APCs by HIV	7.0025e-008	/day
k_5	Recr. - APCs by Mtb	2.1164e-006	/day
k_6	Dth rate : virus by APCs	0.00012492	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.0021885	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.27363	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.75325	mm^3d^{-1}
N_1	Free vir. by inf. cells	4524.5113	none
N_2	Free vir. by APCs	6327.1285	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.020951	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.0090937	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	2252.8724	mm^{-3}
K	Carry. cap.: tb pop.	6289.1761	mm^{-3}
r_b	Max. tb prolif. rate	33.0342	/day

Comments:

This patient's responses do not fit the data very well.

E.27. Patient 79

Table E.55.: Patient 79 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.008558	10199.00959	262	1396	T_4	262
2	3.703205	5048.99569	293	1789	T_8	1396
4	4.190276	15498.01226	345	1935	v	10199.00959
8	3.266215	1845.929031	578	1262.5	T_b	2900
26	3.790567	6174.005329	297	1367	I	1020
52	3.928498	8481.994763	361	1666	D	5000
78			337	2000		

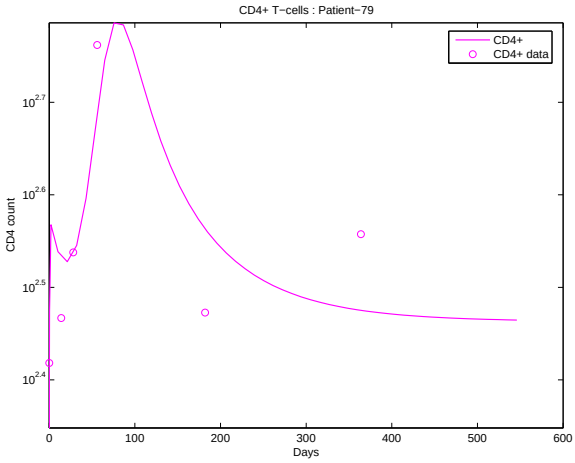

Figure E.105.: CD4+ T-Cells

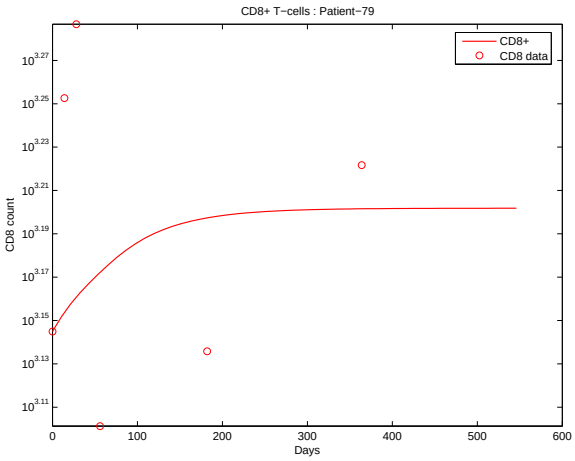

Figure E.106.: CD8+ T-Cells

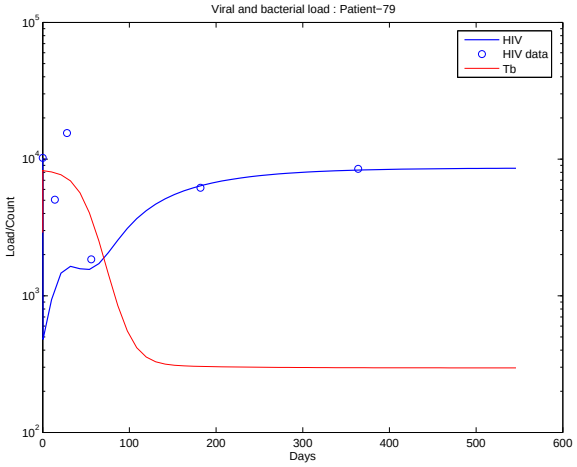

Figure E.107.: Viral and bacterial load

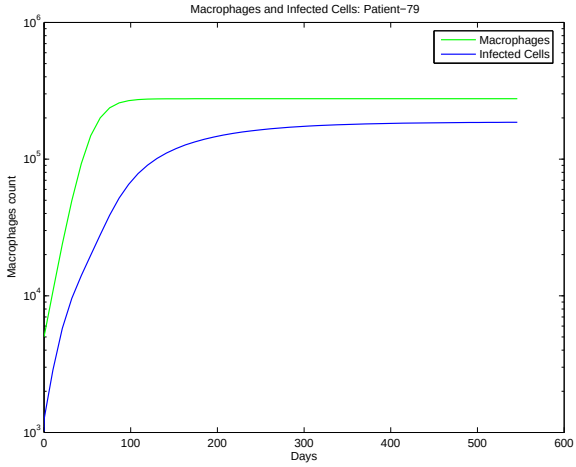

Figure E.108.: Macrophages and infected cells

Table E.56.: Optimised parameter set : Patient79

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	2190.2358	/day
S_8	Src - T_8 cells	24.5028	/day
k_1	Rate - T_4 cells	0.00069794	/day-vir.
k_2	Rate - T_4 cells by APCs	4.7632e-006	/day-cell
k_3	Rate - T_8 cells by APCs	1.9524e-009	/day-cell
k_4	Recr. - APCs by HIV	2.4181e-008	/day
k_5	Recr. - APCs by Mtb	9.2983e-006	/day
k_6	Dth rate : virus by APCs	0.00011719	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.0027467	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.69032	mm^3d^{-1}
k_9	Dth rate : tb by APCs	1.0177	mm^3d^{-1}
N_1	Free vir. by inf. cells	3947.9799	none
N_2	Free vir. by APCs	3063.9601	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.011391	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.015936	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	3094.0669	mm^{-3}
K	Carry. cap.: tb pop.	8379.9531	mm^{-3}
r_b	Max. tb prolif. rate	34.8645	/day

Comments:

The model responses for patient 79 fits very well to the provided data. Although the data variance on the CD8+ T-cells seems to show that the model doesn't fit the data well, the scale to which the graph is drawn is very small: all samples fall within the order $10^3.11$ to $10^3.27$. Thus if the scale was drawn differently, the response wouldn't seem to far from the data. The viral load response fits its data very well.

E.28. Patient 80

Table E.57.: Patient 80 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.893856	78316.99223	738	3444	T_4	738
2	4.504987	31987.99357	1577	5560	T_8	3444
4	4.426592	26704.96419	687	2000	v	78316.99223
8	4.215876	16439.02288			T_b	2900
26	3.990321	9779.597931	543	1281	I	1020
52	4.479575	30169.97845	383	864	D	5000
78			4401330			

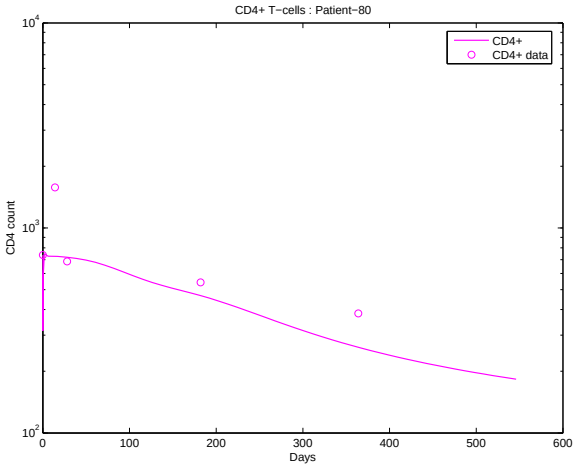

Figure E.109.: CD4+ T-Cells

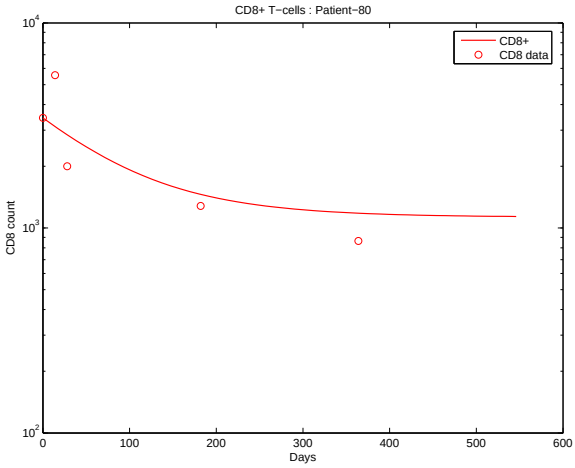

Figure E.110.: CD8+ T-Cells

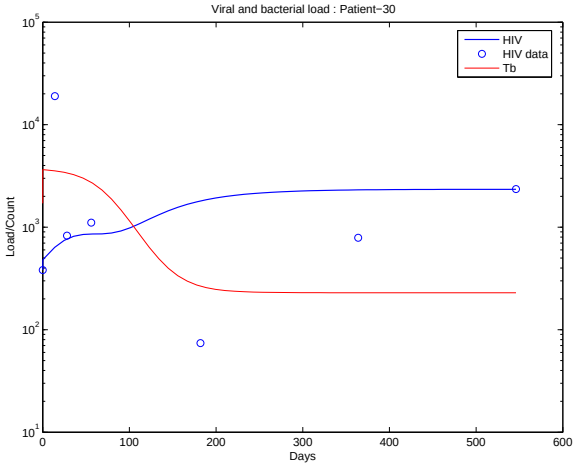

Figure E.111.: Viral and bacterial load

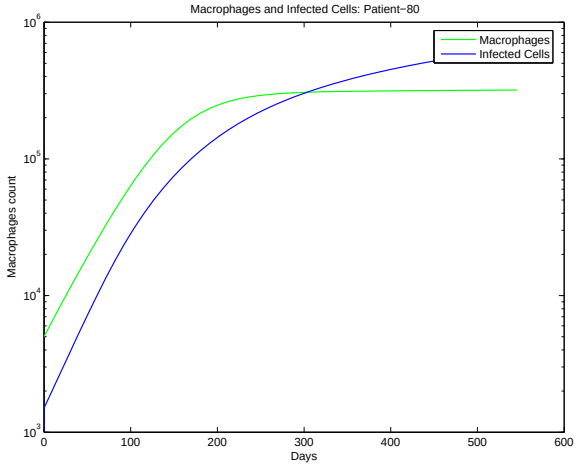

Figure E.112.: Macrophages and infected cells

Table E.58.: Optimised parameter set : Patient80

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	2028.7523	/day
S_8	Src - T_8 cells	11.2544	/day
k_1	Rate - T_4 cells	0.00043914	/day-vir.
k_2	Rate - T_4 cells by APCs	6.0418e-006	/day-cell
k_3	Rate - T_8 cells by APCs	1.379e-009	/day-cell
k_4	Recr. - APCs by HIV	5.7303e-008	/day
k_5	Recr. - APCs by Mtb	4.8131e-006	/day
k_6	Dth rate : virus by APCs	0.00010373	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.0094576	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.3872	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.50123	mm^3d^{-1}
N_1	Free vir. by inf. cells	4402.0454	none
N_2	Free vir. by APCs	782.2365	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.0012476	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.010402	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	2301.3451	mm^{-3}
K	Carry. cap.: tb pop.	6238.5792	mm^{-3}
r_b	Max. tb prolif. rate	27.3411	/day

Comments:

This patient's responses fit the data very well, but the CD4+ T-cells do not settle at a steady-state after 78 weeks. Also, the infected CD4+ T-cells count seems to rise, thus the infection process is fluctuating, and new infections are still occurring after 78 weeks.

E.29. Patient 81

Table E.59.: Patient 81 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.135037	13646.99398	289	2000	T_4	289
2	4.849665	70739.99096	348	2000	T_8	2000
4	4.017951	10421.99835	369	2000	v	13646.99398
8	4.33163	21460.01395			T_b	2900
26			327	2000	I	1020
52	4.435685	27269.99134	247	2000	D	5000
78			207	1689		

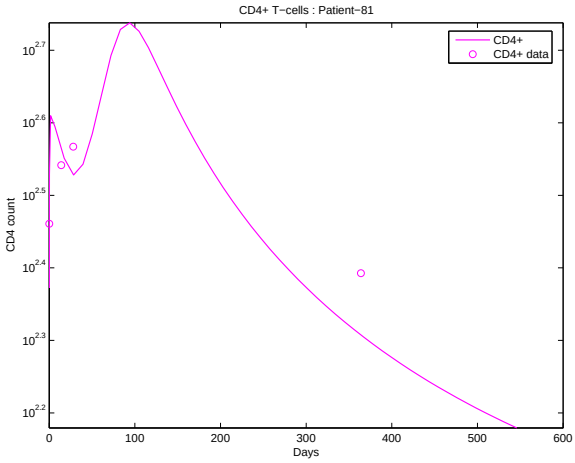

Figure E.113.: CD4+ T-Cells

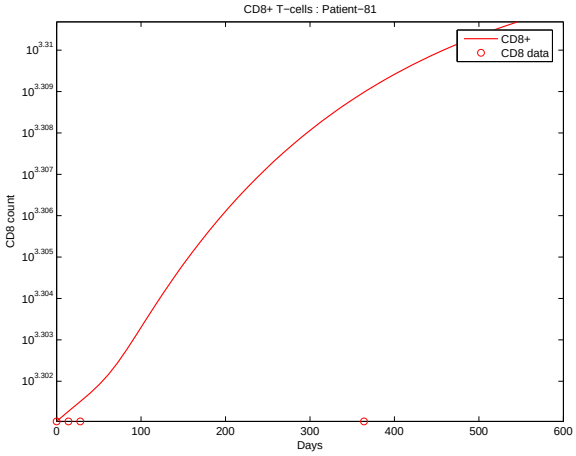

Figure E.114.: CD8+ T-Cells

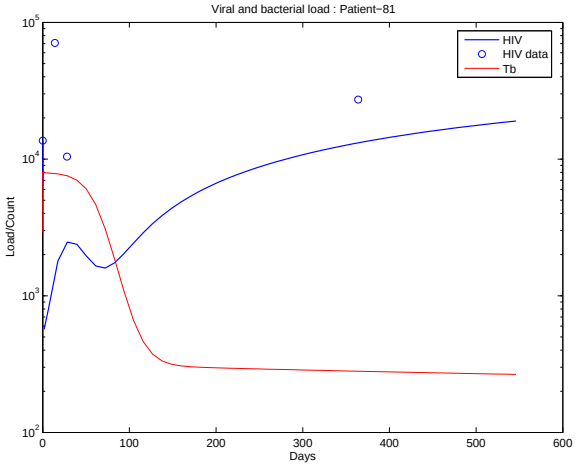

Figure E.115.: Viral and bacterial load

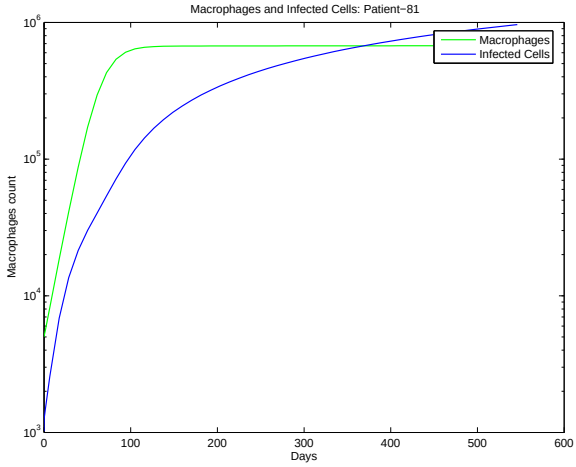

Figure E.116.: Macrophages and infected cells

Table E.60.: Optimised parameter set : Patient81

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	2706.1173	/day
S_8	Src - T_8 cells	7.5059	/day
k_1	Rate - T_4 cells	0.00078479	/day-vir.
k_2	Rate - T_4 cells by APCs	4.1353e-006	/day-cell
k_3	Rate - T_8 cells by APCs	8.5453e-011	/day-cell
k_4	Recr. - APCs by HIV	2.3429e-008	/day
k_5	Recr. - APCs by Mtb	9.6162e-006	/day
k_6	Dth rate : virus by APCs	8.163e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.004218	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.80961	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.563	mm^3d^{-1}
N_1	Free vir. by inf. cells	5324.8334	none
N_2	Free vir. by APCs	9209.1598	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.0012599	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.003713	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1548.7272	mm^{-3}
K	Carry. cap.: tb pop.	8016.1481	mm^{-3}
r_b	Max. tb prolif. rate	49.0862	/day

Comments:

This patient's responses do not fit the provided data very well at all. The data is reduced due to incomplete samples, hence the total number of complete sample sets available for this patient is 4.

E.30. Patient 82

Table E.61.: Patient 82 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	2.25042	177.9999991	549	1240	T_4	549
2	1.69897	49.9999995	588	1005	T_8	1240
4	1.69897	49.9999995	632	1614	v	177.9999991
8			768	1881	T_b	2900
26	2.049218	111.9999942	575	1604	I	1020
52	3.328176	2129.00166	512	1285	D	5000
78			662	1001		

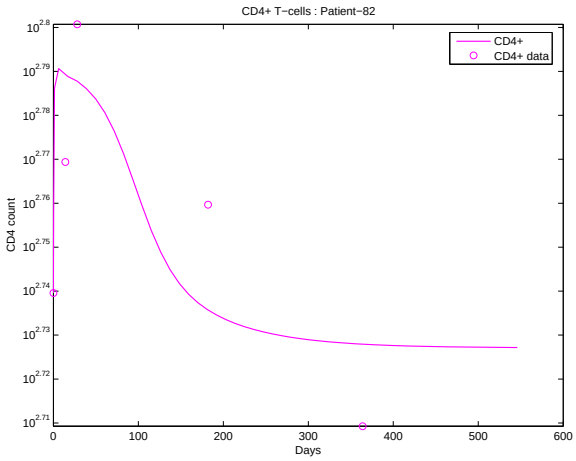

Figure E.117.: CD4+ T-Cells

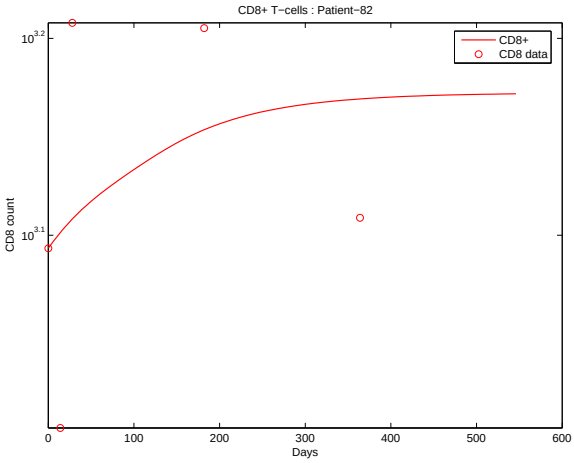

Figure E.118.: CD8+ T-Cells

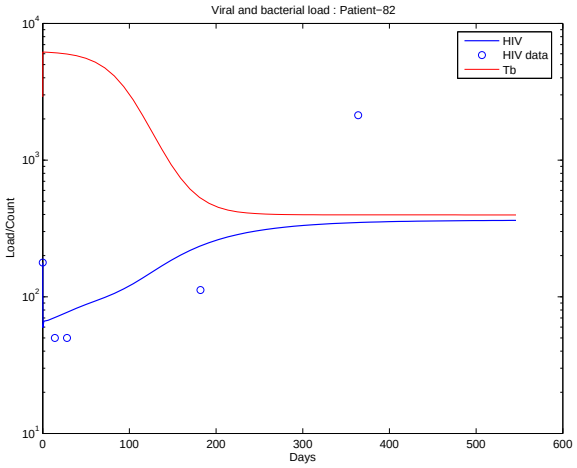

Figure E.119.: Viral and bacterial load

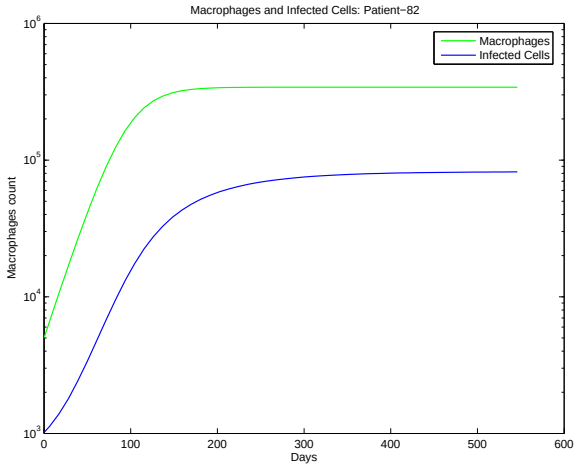

Figure E.120.: Macrophages and infected cells

Table E.62.: Optimised parameter set : Patient82

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	1084.3708	/day
S_8	Src - T_8 cells	14.5311	/day
k_1	Rate - T_4 cells	0.00027629	/day-vir.
k_2	Rate - T_4 cells by APCs	5.3138e-006	/day-cell
k_3	Rate - T_8 cells by APCs	1.5639e-009	/day-cell
k_4	Recr. - APCs by HIV	8.6812e-008	/day
k_5	Recr. - APCs by Mtb	7.4267e-006	/day
k_6	Dth rate : virus by APCs	9.0008e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.011512	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.39939	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.72649	mm^3d^{-1}
N_1	Free vir. by inf. cells	4837.5894	none
N_2	Free vir. by APCs	8505.407	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.012418	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.010305	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	2161.2441	mm^{-3}
K	Carry. cap.: tb pop.	6268.1316	mm^{-3}
r_b	Max. tb prolif. rate	42.3166	/day

Comments:

This patient's complete sample sets are limited to 5. The responses all reach steady-state values, but not that of the final data sample.

E.31. Patient 83

Table E.63.: Patient 83 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.072397	11814.00091	247	540	T_4	x
8			372	1194	T_8	
26	4.326192	21192.97862	328	1272	v	
52	4.203413	15973.97499	225	665	T_b	
78			289	769	I	
					D	

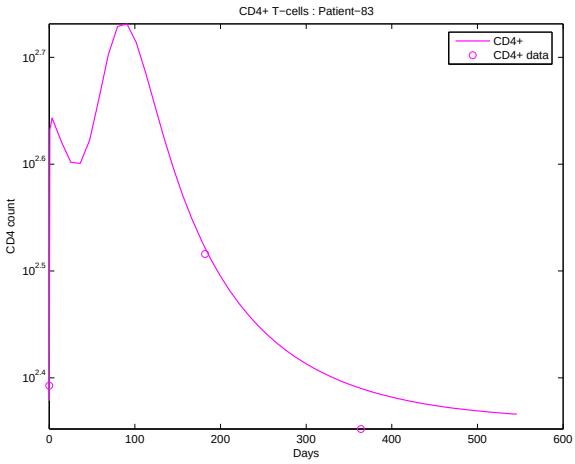

Figure E.121.: CD4+ T-Cells

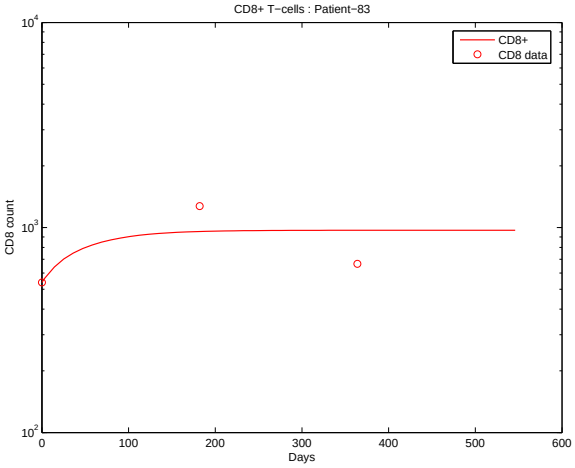

Figure E.122.: CD8+ T-Cells

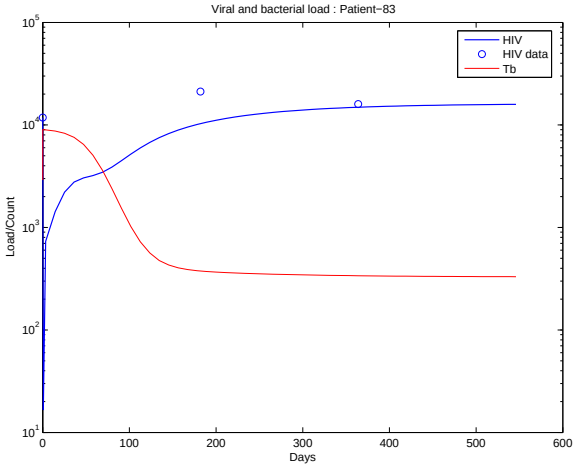

Figure E.123.: Viral and bacterial load

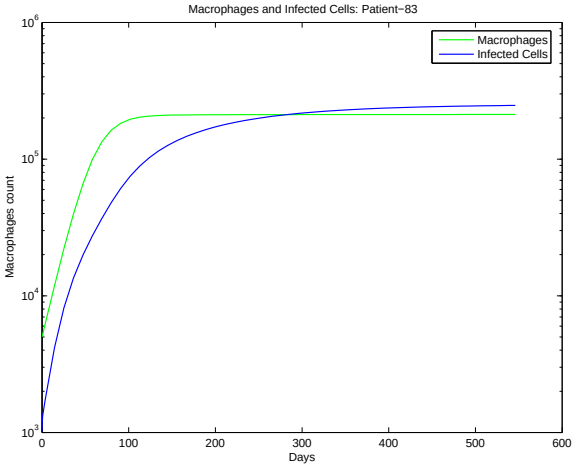

Figure E.124.: Macrophages and infected cells

Table E.64.: Optimised parameter set : Patient83

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	2201.4148	/day
S_8	Src - T_8 cells	19.1411	/day
k_1	Rate - T_4 cells	0.00051245	/day-vir.
k_2	Rate - T_4 cells by APCs	5.4554e-006	/day-cell
k_3	Rate - T_8 cells by APCs	2.7182e-009	/day-cell
k_4	Recr. - APCs by HIV	4.3303e-008	/day
k_5	Recr. - APCs by Mtb	6.9265e-006	/day
k_6	Dth rate : virus by APCs	6.3716e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.0059583	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.3521	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.70671	mm^3d^{-1}
N_1	Free vir. by inf. cells	5366.4112	none
N_2	Free vir. by APCs	2284.1719	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.0085918	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.020302	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1567.38	mm^{-3}
K	Carry. cap.: tb pop.	9228.7266	mm^{-3}
r_b	Max. tb prolif. rate	16.8557	/day

Comments:

The number of available sample sets for this patient is 3. Nonetheless, the model still fits well to the provided data. This confirms that, even with a reduced dataset and limited samples, the optimisation routine is robust enough to minimize the cost-function properly.

E.32. Patient 84

Table E.65.: Patient 84 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.252319	17878.00276	506	990	T_4	506
2	4.843918	69810.05819	530	888	T_8	990
4	4.745621	55669.97163	527	902	v	17878.00276
8	4.711638	51479.9362	512	1156	T_b	2900
26	4.069261	11729.00037	576	911	I	1020
52	3.774152	5945.001931	337	902	D	5000
78			503	1178		

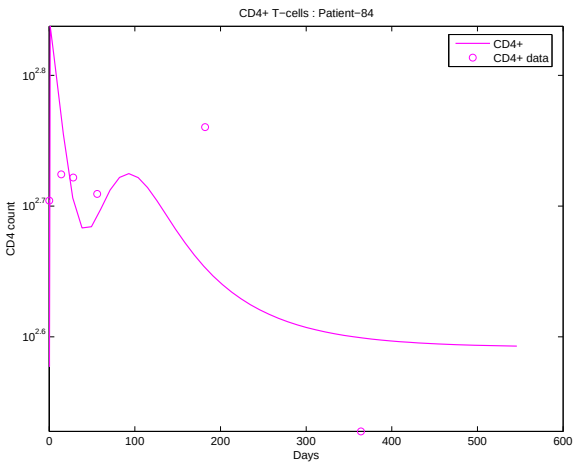

Figure E.125.: CD4+ T-Cells

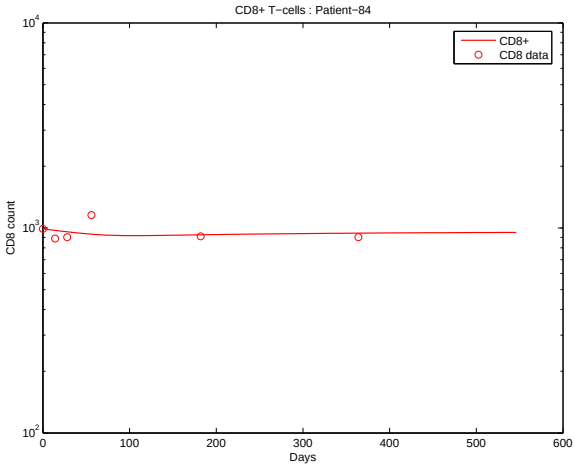

Figure E.126.: CD8+ T-Cells

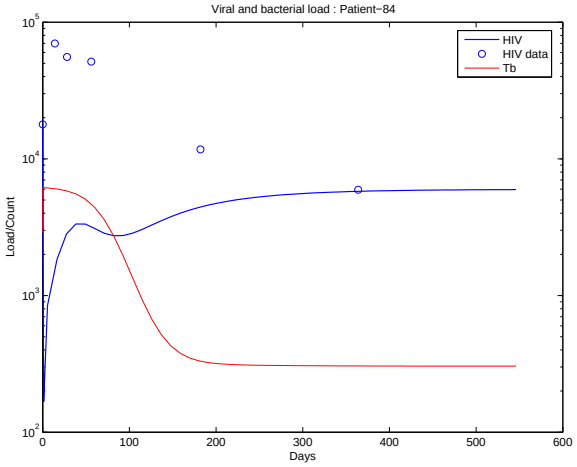

Figure E.127.: Viral and bacterial load

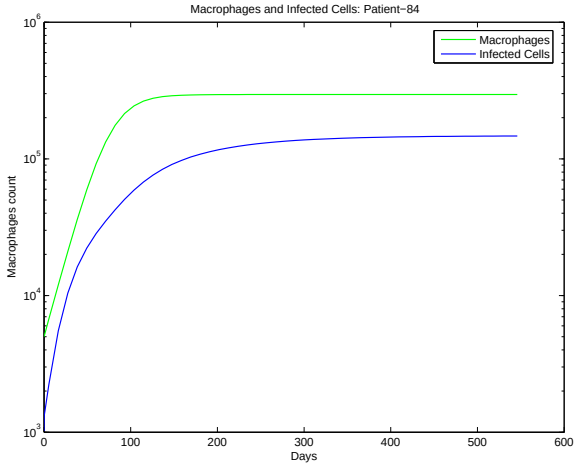

Figure E.128.: Macrophages and infected cells

Table E.66.: Optimised parameter set : Patient84

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	1748.8959	/day
S_8	Src - T_8 cells	4.2904	/day
k_1	Rate - T_4 cells	0.00037989	/day-vir.
k_2	Rate - T_4 cells by APCs	7.0312e-006	/day-cell
k_3	Rate - T_8 cells by APCs	3.9661e-009	/day-cell
k_4	Recr. - APCs by HIV	4.1263e-008	/day
k_5	Recr. - APCs by Mtb	9.0172e-006	/day
k_6	Dth rate : virus by APCs	3.3579e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.0048251	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.95347	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.94357	mm^3d^{-1}
N_1	Free vir. by inf. cells	8829.0896	none
N_2	Free vir. by APCs	5386.8781	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.01152	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.0056548	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1017.9219	mm^{-3}
K	Carry. cap.: tb pop.	6273.882	mm^{-3}
r_b	Max. tb prolif. rate	46.8264	/day

Comments:

The correct steady-state values are reached with the CD8+ T-cells and the viral load model responses.

E.33. Patient 86

Table E.67.: Patient 86 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0			126	885	T_4	126
2	5.470196	295254.1428	170	977	T_8	885
4	5.308603	203518.0815	162	677	v	295254.1428
8	5.357981	228024.2311	199	741	T_b	2900
26	4.711174	51424.96443	160	1125	I	1020
52	5.564632	366971.2152			D	5000
78			30	517		

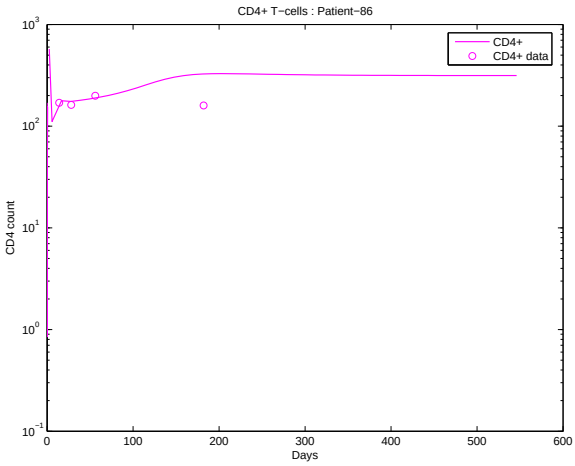

Figure E.129.: CD4+ T-Cells

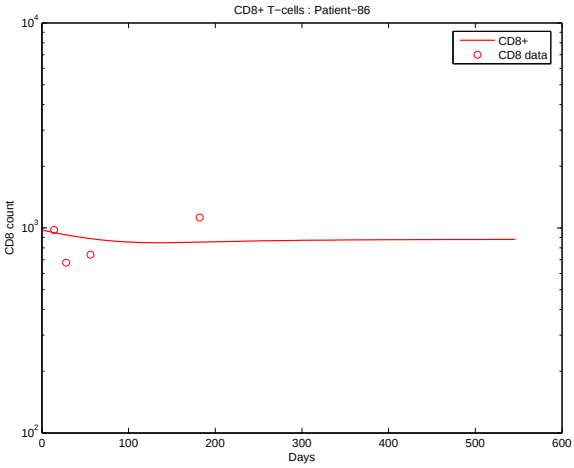

Figure E.130.: CD8+ T-Cells

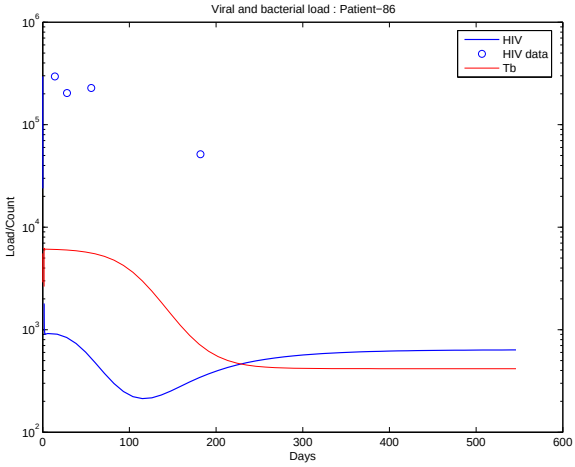

Figure E.131.: Viral and bacterial load

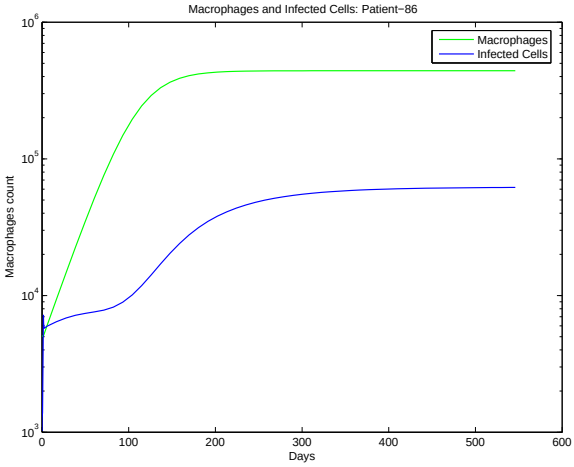

Figure E.132.: Macrophages and infected cells

Table E.68.: Optimised parameter set : Patient86

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	928.2393	/day
S_8	Src - T_8 cells	8.0023	/day
k_1	Rate - T_4 cells	0.00076289	/day-vir.
k_2	Rate - T_4 cells by APCs	4.8558e-006	/day-cell
k_3	Rate - T_8 cells by APCs	2.9876e-009	/day-cell
k_4	Recr. - APCs by HIV	7.4316e-008	/day
k_5	Recr. - APCs by Mtb	7.0657e-006	/day
k_6	Dth rate : virus by APCs	7.2613e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.012323	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.5599	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.63697	mm^3d^{-1}
N_1	Free vir. by inf. cells	3603.4743	none
N_2	Free vir. by APCs	6770.2068	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.013314	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.010409	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1706.0969	mm^{-3}
K	Carry. cap.: tb pop.	6181.3606	mm^{-3}
r_b	Max. tb prolif. rate	48.7815	/day

Comments:

This patient is similar to patient 73 in that it shouldn't have been included due to the inclusion criteria on the availability of the first sample. Nonetheless, all responses except the viral load fit their data very well.

E.34. Patient 87

Table E.69.: Patient 87 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.153693	14246.00197	478	1822	T_4	478
2	4.179466	15117.01347	674	1988	T_8	1822
4	3.891537	7789.991791	623	1526	v	14246.00197
8			571	1165	T_b	2900
26	4.188225	15424.99387	581	1202	I	1020
52	4.490464	30935.98867	688	1656	D	5000
78			633	1299		

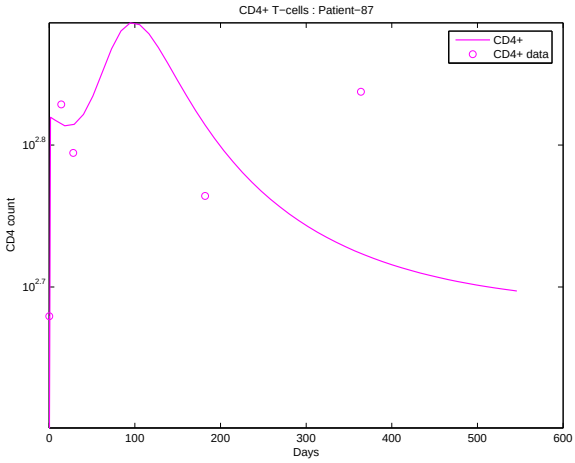

Figure E.133.: CD4+ T-Cells

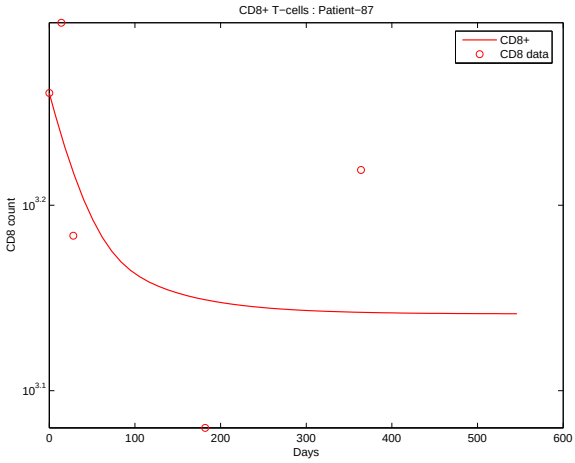

Figure E.134.: CD8+ T-Cells

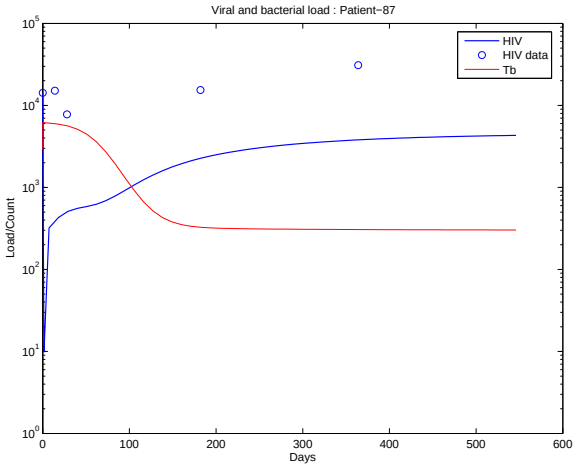

Figure E.135.: Viral and bacterial load

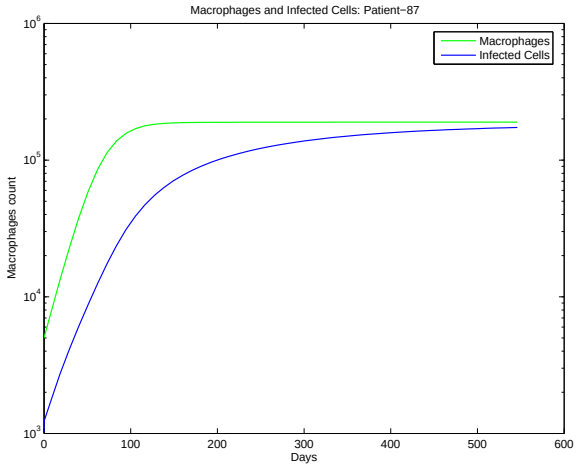

Figure E.136.: Macrophages and infected cells

Table E.70.: Optimised parameter set : Patient87

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	1181.2165	/day
S_8	Src - T_8 cells	16.2699	/day
k_1	Rate - T_4 cells	0.00027291	/day-vir.
k_2	Rate - T_4 cells by APCs	5.8268e-006	/day-cell
k_3	Rate - T_8 cells by APCs	6.6051e-009	/day-cell
k_4	Recr. - APCs by HIV	5.4332e-008	/day
k_5	Recr. - APCs by Mtb	9.0481e-006	/day
k_6	Dth rate : virus by APCs	7.0634e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.0016259	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.96247	mm^3d^{-1}
k_9	Dth rate : tb by APCs	1.0885	mm^3d^{-1}
N_1	Free vir. by inf. cells	5133.4333	none
N_2	Free vir. by APCs	3697.0776	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.0062033	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.013001	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1770.6814	mm^{-3}
K	Carry. cap.: tb pop.	6348.6326	mm^{-3}
r_b	Max. tb prolif. rate	34.2233	/day

Comments:

This patient is included in the case-studies in section 9 to improve its viral load response steady-state value.

E.35. Patient 91

Table E.71.: Patient 91 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	3.512551	3255.000053	182	328	T_4	182
2			252	321.5	T_8	328
4	5.128053	134292.8838	269	278	v	3255.000053
8	4.736882	54560.95961	271	506	T_b	2900
52	4.615666	41272.99644	201	396	I	1020
78			167	587	D	5000

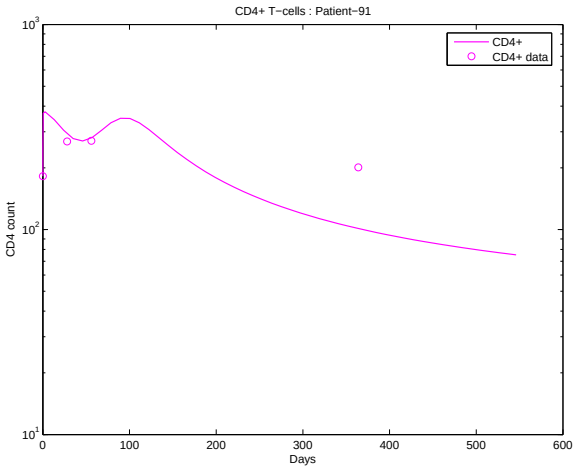

Figure E.137.: CD4+ T-Cells

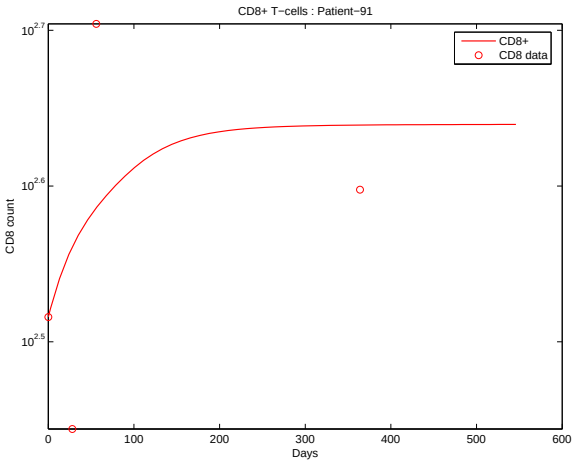

Figure E.138.: CD8+ T-Cells

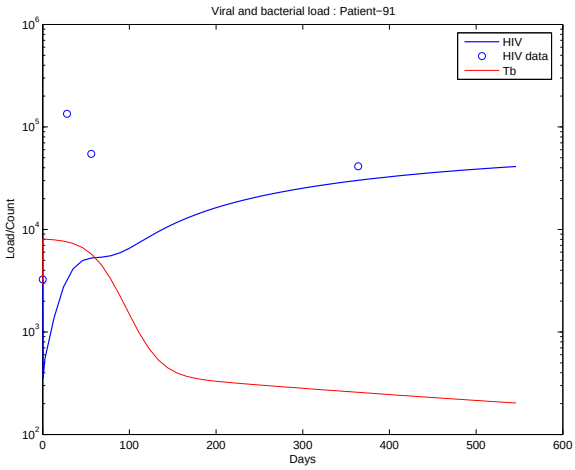

Figure E.139.: Viral and bacterial load

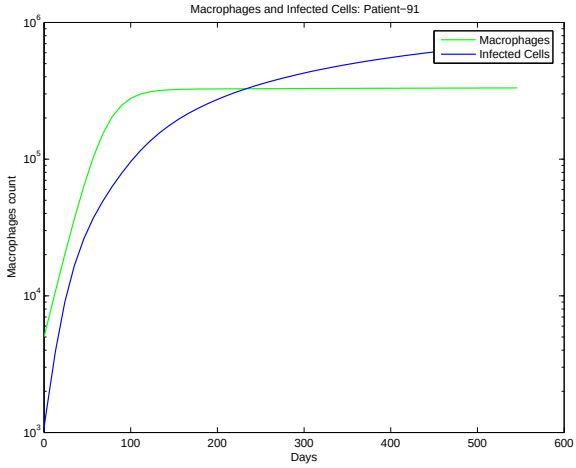

Figure E.140.: Macrophages and infected cells

Table E.72.: Optimised parameter set : Patient91

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	2244.8175	/day
S_8	Src - T_8 cells	8.3423	/day
k_1	Rate - T_4 cells	0.00069749	/day-vir.
k_2	Rate - T_4 cells by APCs	2.9601e-006	/day-cell
k_3	Rate - T_8 cells by APCs	3.7616e-009	/day-cell
k_4	Recr. - APCs by HIV	3.6317e-008	/day
k_5	Recr. - APCs by Mtb	7.5098e-006	/day
k_6	Dth rate : virus by APCs	0.00010436	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.011684	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.7261	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.68702	mm^3d^{-1}
N_1	Free vir. by inf. cells	3903.2709	none
N_2	Free vir. by APCs	343.9589	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.0019412	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.020376	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	1781.99	mm^{-3}
K	Carry. cap.: tb pop.	8188.8994	mm^{-3}
r_b	Max. tb prolif. rate	28.5555	/day

Comments:

With only 4 samples available, this patient's viral load response and CD4+ T-cells count doesn't settle after 78 weeks.

E.36. Patient 93

Table E.73.: Patient 93 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.593351	39205.86138	150	419	T_4	150
2	4.255948	18028.0187	140	358	T_8	419
4	4.854075	71461.97259	143	379	v	39205.86138
8			194	483	T_b	2900
26	4.388421	24458.00334	116	481	I	1020
52	4.588977	38812.98103	146	721	D	5000
78			132	469		

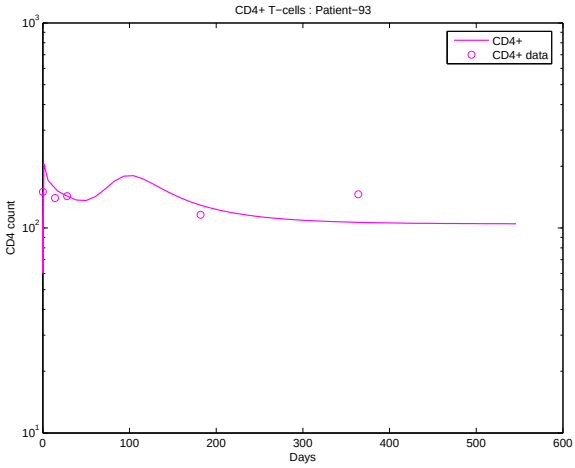

Figure E.141.: CD4+ T-Cells

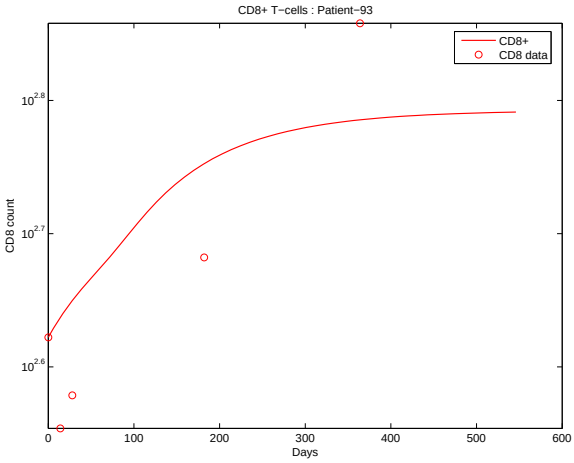

Figure E.142.: CD8+ T-Cells

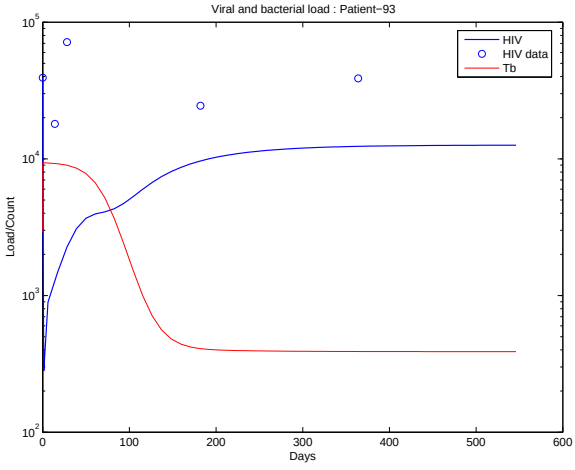

Figure E.143.: Viral and bacterial load

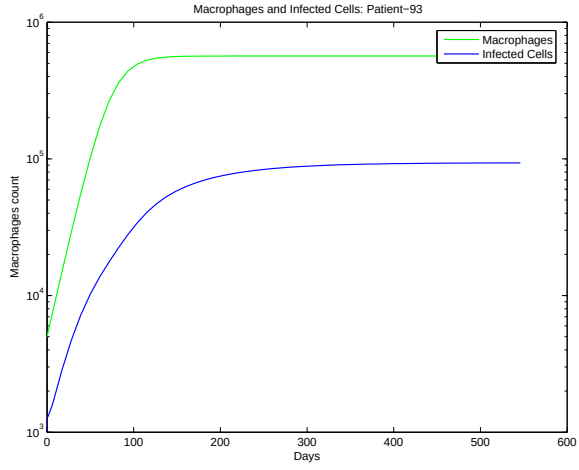

Figure E.144.: Macrophages and infected cells

Table E.74.: Optimised parameter set : Patient93

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	1241.5888	/day
S_8	Src - T_8 cells	5.7581	/day
k_1	Rate - T_4 cells	0.00076295	/day-vir.
k_2	Rate - T_4 cells by APCs	3.4177e-006	/day-cell
k_3	Rate - T_8 cells by APCs	3.1553e-009	/day-cell
k_4	Recr. - APCs by HIV	2.2172e-008	/day
k_5	Recr. - APCs by Mtb	6.9754e-006	/day
k_6	Dth rate : virus by APCs	1.6221e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.015131	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.35453	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.66451	mm^3d^{-1}
N_1	Free vir. by inf. cells	6661.4444	none
N_2	Free vir. by APCs	1330.2716	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.012911	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.011069	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	2054.6381	mm^{-3}
K	Carry. cap.: tb pop.	9445.3781	mm^{-3}
r_b	Max. tb prolif. rate	41.5335	/day

Comments:

This patient's viral load response doesn't reach the required value. It is included into the refinement section of a case-study in section 9.

E.37. Patient 94

Table E.75.: Patient 94 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	3.660486	4575.999834	441	790	T_4	441
2	4.304813	20174.97476	408	618	T_8	790
4	4.320022	20894.01971	390	687	v	4575.999834
8	4.447499	28021.99169	376	592	T_b	2900
26	3.98313	9619.001667	385	776	I	1020
52	3.949536	8902.992346	459	899	D	5000
78			429	751		

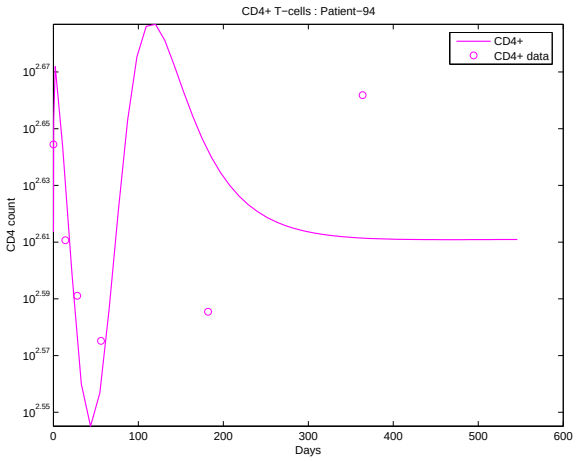

Figure E.145.: CD4+ T-Cells

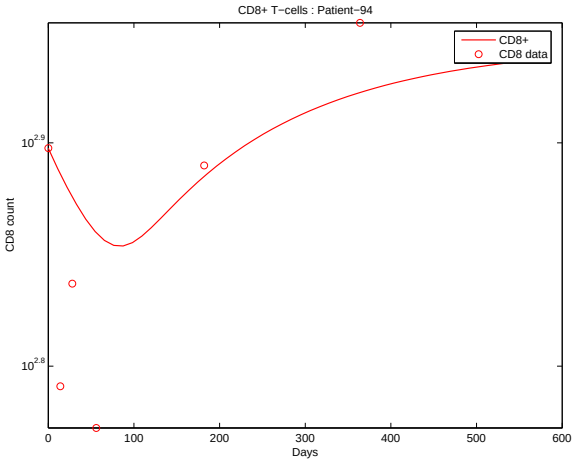

Figure E.146.: CD8+ T-Cells

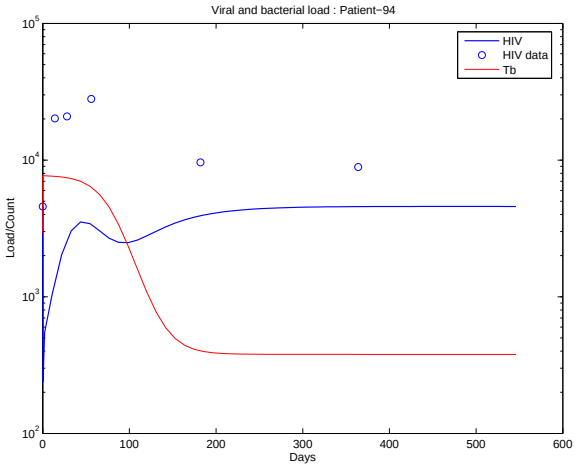

Figure E.147.: Viral and bacterial load

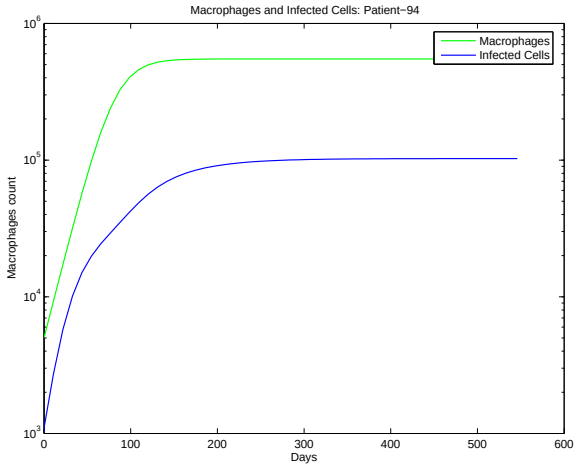

Figure E.148.: Macrophages and infected cells

Table E.76.: Optimised parameter set : Patient94

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	2032.1592	/day
S_8	Src - T_8 cells	4.6092	/day
k_1	Rate - T_4 cells	0.0005269	/day-vir.
k_2	Rate - T_4 cells by APCs	4.2908e-006	/day-cell
k_3	Rate - T_8 cells by APCs	4.7494e-009	/day-cell
k_4	Recr. - APCs by HIV	1.3833e-008	/day
k_5	Recr. - APCs by Mtb	7.752e-006	/day
k_6	Dth rate : virus by APCs	0.00011295	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.01232	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.4443	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.52229	mm^3d^{-1}
N_1	Free vir. by inf. cells	9980.9593	none
N_2	Free vir. by APCs	5600.335	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.018988	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.007847	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	81.6549	mm^{-3}
K	Carry. cap.: tb pop.	7763.6863	mm^{-3}
r_b	Max. tb prolif. rate	38.9019	/day

Comments:

With patient 94, the CD4+ T-cells and CD8+ T-cells seem to fit well to the field data. The viral load doesn't quite reach the correct steady-state value. This correction can be made by refining the initial conditions.

E.38. Patient 98

Table E.77.: Patient 98 data

Week	$log(v)$	v	T_4	T_8	Dep. Var.	Initial Count
0	4.442213	27682.99027	145	852	T_4	145
2	4.749659	56189.99585	160	1391	T_8	852
4	4.829053	67461.03501	192	939	v	27682.99027
8	4.888179	77299.91209	216	1289	T_b	2900
26	4.974438	94284.00018	398	1999	I	1020
52	4.931448	85398.05904	87	1290	D	5000
78			69	657		

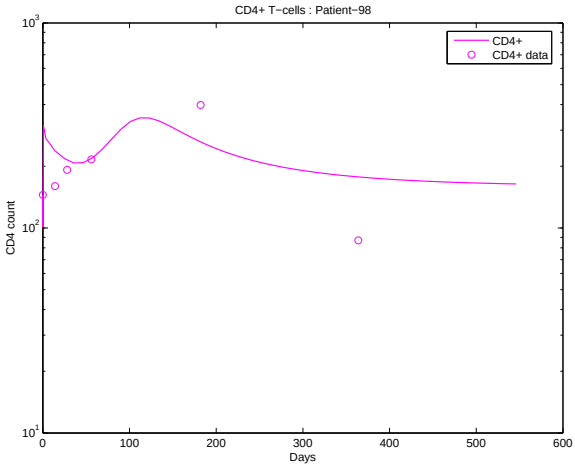

Figure E.149.: CD4+ T-Cells

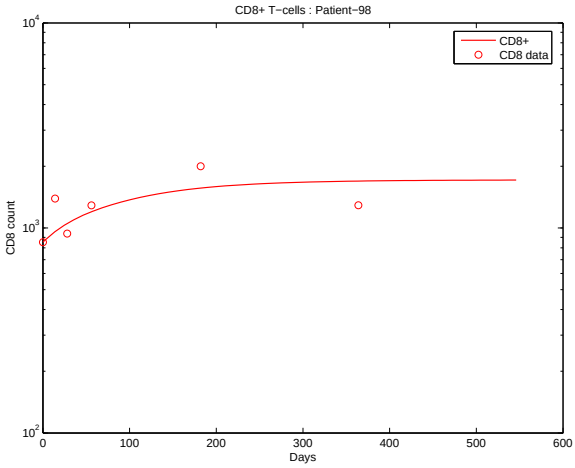

Figure E.150.: CD8+ T-Cells

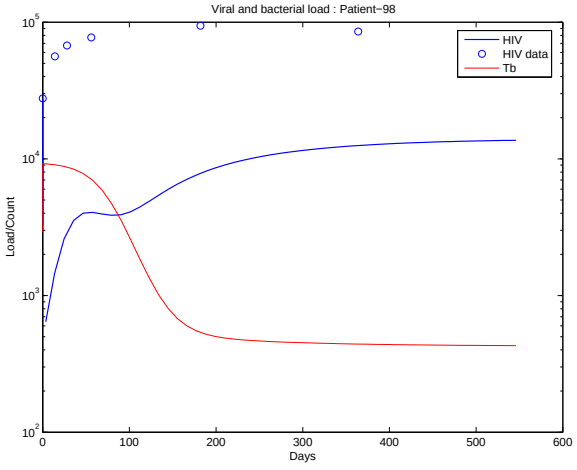

Figure E.151.: Viral and bacterial load

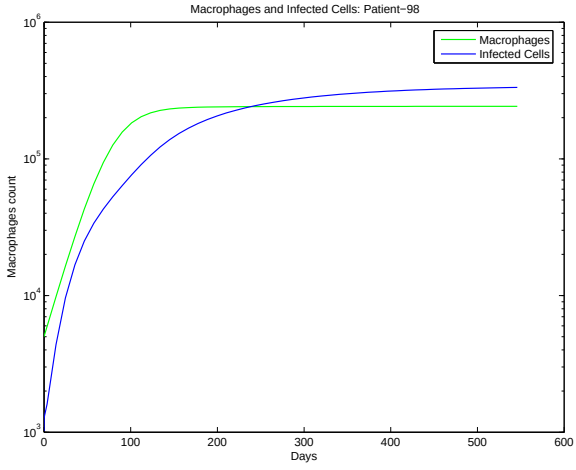

Figure E.152.: Macrophages and infected cells

Table E.78.: Optimised parameter set : Patient98

Parm.	Description	Values	Units
S_4	Source - Healthy T_4 cells	2822.5282	/day
S_8	Src - T_8 cells	17.9615	/day
k_1	Rate - T_4 cells	0.001126	/day-vir.
k_2	Rate - T_4 cells by APCs	5.4372e-006	/day-cell
k_3	Rate - T_8 cells by APCs	3.6977e-009	/day-cell
k_4	Recr. - APCs by HIV	4.4374e-008	/day
k_5	Recr. - APCs by Mtb	5.5148e-006	/day
k_6	Dth rate : virus by APCs	6.6393e-005	mm^3d^{-1}
k_7	Dth rate : virus by T_8	0.010227	mm^3d^{-1}
k_8	Dth rate : tb by T_4	0.3816	mm^3d^{-1}
k_9	Dth rate : tb by APCs	0.11078	mm^3d^{-1}
N_1	Free vir. by inf. cells	4937.8069	none
N_2	Free vir. by APCs	9236.2588	none
μ_v	Natural death rate - HIV	2.5	/day
μ_I	Nat. death : inf. cells	0.0080104	/day
μ_4	Natural death rate - T_4 cells	0.007	/day
μ_8	Natural death rate - T_8 cells	0.011363	/day
μ_d	Natural death rate - Dendr. cells	0.003	/day
μ_b	Natural death rate - tb	0.5	/day
D_o	APCs equilib. value	2009.9385	mm^{-3}
K	Carry. cap.: tb pop.	9446.1588	mm^{-3}
r_b	Max. tb prolif. rate	2.9835	/day

Comments:

With this patient, the viral load does not fit well to the field data, but the CD4+ T-cells and CD8+ T-cells responses are acceptable in terms of their data fit.