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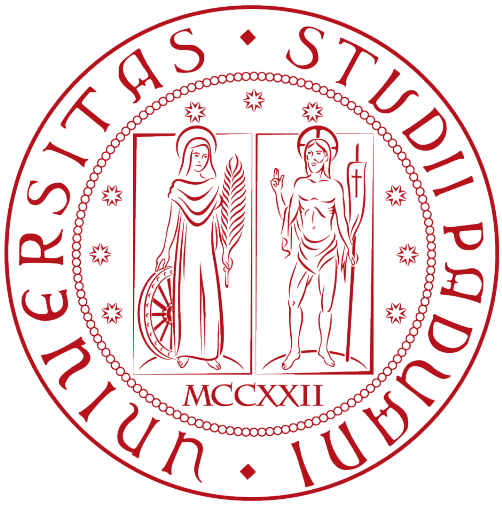

Stability and Stabilization of Positive Switched Systems with Application to HIV Treatment

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To my family and friends, with love.

"La saggezza non é comunicabile. La scienza si puó comunicare, ma la saggezza no. Si puó trovarla, viverla, si possono fare miracoli con essa, ma spiegarla e insegnarla non si puó."
dal libro "Siddharta" di *Hermann Hesse.*

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Abstract

HIV mutates rapidly and may develop resistance to specific drug therapies. There is no general agreement on how to optimally schedule the treatments for mitigating the effects of mutations. We examine different control strategies applied to two positive switched systems models of HIV under therapy. The smallest model of the two takes into account only four viral populations, whereas the greatest one also accounts for other immune cells involved in HIV infection. Simulation results show that model-based control approaches may outperform the common clinical treatment recommendations.

Contents

1 Introduction **1**

2 The Immune System and the HIV Model **3**
2.1 A brief overview of the immune system 3
2.1.1 Macrophages 5
2.1.2 Langerhans cells 5
2.1.3 Natural killer (NK) cells 6
2.1.4 T-helper cells 6
2.2 The HIV life cycle 6
2.3 The HIV and the HAARTs 8

3 Modeling the Three Stages in HIV Infection **11**
3.1 The three stages in HIV infection 11
3.2 Mathematical models 13
3.2.1 The HIV model, without therapy 13
3.2.2 Models of HIV with therapy 17
3.3 Solver ode113 in MATLAB® 24
3.4 Clinical treatments using the 4 variant, 2 drug combination model . 24
3.5 Clinical treatments using the 16 variant, 2 drug combination model . 33

4 Stability **35**
4.1 Stability of continuous-time positive switched systems 35
4.2 Exponential stability of continuous-time positive switched systems . 36
4.2.1 Lyapunov functions 38
4.2.2 Stability and periodic switching signals 41
4.2.3 Dual positive switched systems 42
4.2.4 Rate of convergence 43
4.3 Stability of the two models of HIV under therapy 44

5 Stabilization **47**
5.1 Stabilization of positive switched systems 47
5.2 Feedback stabilization and Lyapunov functions 49
5.3 Other feedback stabilization techniques 53
5.4 Lyapunov Metzler Inequalities (LMIs) 53
5.5 Picewise Linear Copositive Control Lyapunov functions 55
5.6 Stabilizability of the two HIV models under therapies models 55

6 Optimal and Suboptimal Control for p.s.s. 57
6.1 Optimal control 57
6.2 Guaranteed cost control 60
6.3 Applications to the 4 variant, 2 drug combination model 64
6.3.1 Using Optimal Control 64
6.3.2 Brute Force Algorithm 65
6.3.3 Dynamic Programming Approach 65
6.3.4 Using Guaranteed Cost Control over infinite horizon 69
6.3.5 Using Guaranteed Cost Control over finite horizon 70
6.3.6 Comparisons 70
6.4 Applications to the 16 variant, 2 drug combination model 72
6.4.1 Using the Luenberger observer 72
6.4.2 Model Predictive Control 74
6.4.3 Comparisons 75

7 Conclusions 79

Appendices 81

A Observability of linear continuous systems 83
A.1 Trivial Observer 84
A.2 Identity Observer 84
A.3 Reduced-Order Observer 85

References 87

List of Figures

2.1 Representation of the parts of the body which are involved in the immune system. 5
2.2 Representation of the structure of an HIV. 7
2.3 Representation of HIV life cycle. 9
2.4 Representation of the action of PIs. 10
2.5 Representation of the action of NrRTIs. 10

3.1 Representation of HIV progression, without any therapy. 12
3.2 HIV infection scheme. On the left a representation of a CD4+T cell and on the right of a macrophage. 14
3.3 Dynamics of the nonlinear model of HIV, without therapy. 16
3.4 Sixteen genotypes and two drug combination. The direction of the arrows means the effectiveness of the therapy. 17
3.5 Graph which represents the four variant, two drug combination model. The rectangles represent the effectiveness of the therapies. 23
3.6 Dynamics of the small model, with $k = 1$. 26
3.7 Dynamics of the small model, with $k = 2$. 27
3.8 Trajectories of the three scenarios, using the SWATCH rule. 30
3.9 Trajectories of the three scenarios, using the SVF rule. 31
3.11 SWATCH $\sigma(t)$. 32
3.10 SVF $\sigma(t)$ for the three scenarios. 32
3.12 Trajectories for the great nonlinear switched model of HIV, using SWATCH and SVF control law. 34

6.1 Optimal control for the small model. 68
6.2 Trajectories for the small model of HIV, using different control laws. 68
6.3 Switching law for the guaranteed cost approach over finite horizon. . 71
6.4 Scheme of the project, using the Luenberger Observer. 74
6.5 Model Predictive Control approach. 75
6.6 Scheme of the project, using the MPC approach. 76
6.7 Treatment scheduling based on MPC, using a Luenberger observer. Solid lines: the dynamics of the nonlinear model, under therapy. Dashed lines: the respective estimations. 77

Notation and Acronyms

$[\mathbf{x}]_i$	i-th entry of vector $\mathbf{x}$
$[a_{i,j}]$	matrix A
Δ_A	spectrum of the matrix A
$\mathbb{N}$	field of natural numbers
$\mathbb{R}$	field of real numbers
$\mathbb{R}^n$	set of n-dimensional real vectors
$\mathbb{R}^n_+$	set of n-dimensional real vectors
$\mathbb{R}^{m\times n}$	set of $m \times n$ real matrices
$\mathbf{x} > 0$	positive vector (if all entries are non-negative and at least one positive)
$\mathbf{x} \geq 0$	non-negative vector (if all entries are non-negative)
$\mathbf{x} \gg 0$	strictly positive vector (if all entries are strictly positive)
$\mathbf{0}_{m\times n}$	zero-matrix of dimension $m \times n$
$\mathbf{1}_n$	n-dimensional vector with all entries equal to 1
$\mathbf{e}_i$	i-th canonical vector
$\mathbf{x}^T$	transpose of $\mathbf{x}$
max_i	maximum with respect to i
min_i	minimum with respect to i
$\|\|\mathbf{x}\|\|$	Euclidean norm of vector $\mathbf{x}$
$\Re(\lambda)$	real part of the complex number λ
$A \otimes B$	Kronecker product
$A \prec \mathbf{0}$	matrix A is negative-definite
$A \preceq \mathbf{0}$	matrix A is seminegative-definite
$A \succ \mathbf{0}$	matrix A is positive-definite

$A \succeq \mathbf{0}$ matrix A is semipositive-definite

$A^{(i)}$ i-th column of matrix A

$a_{i,j}$ $(i,j)-$entry of matrix A

$argmax\ S$ index of the maximum element of ordered set S

$argmin\ S$ index of the minimum element of ordered set S

I_n identity matrix of order n

$ker_+(A)$ positive kernel of matrix A

p.s.s. positive switched system

u.e.s. uniformly exponentially stable

Chapter 1

Introduction

In this thesis we consider positive switched systems, which can be effectively used to model the dynamics of Human Immunodeficiency Virus (HIV) under therapy. We present two models of HIV under treatment. Highly Active Antiretroviral Therapies (HAARTs) are generally used to contrast HIV. They are constituted by treatments obtained by using different classes of medications. These treatments are more successful than the ARTs which only use one class of medication. However, they can still prove unsuccessful. We say that a HAART is not successful if it is unable to maintain HIV RNA load below a certain viral load level. Viral rebound is associated with the problem of resistance-conferring mutations within the viral genome and its result is that the mutated viruses are less susceptible to one or more therapies than the unaltered ones. This is caused by the reverse-transcription process of viral RNA into DNA, which can present errors.
Our purpose is to investigate the stabilizability problem of the two presented models of HIV under therapy and to find the best switching rule in order to maintain the viral load at low levels as long as possible. Thus, we especially investigate the Optimal control problem and the Suboptimal one for linear p.s.s..
In Chapter 2 we briefly explain the Immune System, and in particular we focus our attention on the cells involved in HIV disease. Successively, we describe the HIV life cycle and the HAARTs.
In Chapter 3 we illustrate a model of HIV without therapy, and the two models of HIV under therapy used throughout this thesis. The first one takes into account only four viral strains, while the second one takes into consideration sixteen genotypes and two types of immune cells that are infected by HIV (T-helper cells and macrophages). These infected cells can be infective, too. We then simulate the two models, applying commonly used treatments.
In Chapter 4 we give some information about stability of continuous-time p.s.s.. Moreover, we shortly investigate the stability of the two models of HIV under treatments introduced in Chapter 2. We then briefly investigate the stability of the two linear models of HIV under treatment.
In Chapter 5 we give some information about the stabilizability of continuous-time p.s.s., especially focusing on using the Linear Copositive Control Lyapunov functions and on the Lyapunov Metzler Inequalities (LMIs). Furthermore, we investigate the stabilizability of the two linear models of HIV under therapy introduced in Chapter 2.

In Chapter 6 we expose the Optimal and Suboptimal problem for p.s.s.. In the case of the small model, both controls are directly applied to it. In the case of the great model, we suppose that we can't have the full state vector at each decision time. Thus, we construct a Luenberger observer that takes as inputs signals which are outputs of the great nonlinear model. Having this information, we obtain the estimation of the state of linearised model. Having the estimate of the state, we compute a Suboptimal Control and apply it to the nonlinear model.
Moreover, we introduce the Model Predictive Control approach, a model-based approach which outperform the common clinical treatment recommendations. In Chapter 7 we give the conclusions of the thesis.

Chapter 2

The Immune System and the HIV Model

In this chapter we provide some key concepts about the immune system, the HIV (Human Immunodeficiency Virus), the ARTs (AntiRetroviral Therapies) and a possible model of HIV.
In particular we provide some basic information about the cells that constitute the immune system (their origin and function) and about the HIV (its structure and its life cycle). Together with HIV life cycle, we give information about the ARTs, because ARTs are strictly connected with the different stages of HIV's life.
In the end we introduce a model of HIV without therapy, which constitutes the base for the greater model (16 variant, 2 drug combination model in Section 3.2.2) that takes into consideration the treatments.

2.1 A brief overview of the immune system

The immune system is made by the so called *innate immune system* cells (which also invertebrates have), and the recently *adaptive immune system* ones (which only vertebrates present).
The principal functions of the immune system are:

- the recognition with subsequent elimination of foreign antigens,
- the formation of immunologic memory,
- the development of tolerance to self-antigens.

The immune system (in Figure 2.1 the parts are represented of the body which are involved in the immune system) can distinguish between healthy cells and unhealthy cells, by recognizing a number of signals, called *Danger Associated Molecular Patterns* (*DAMPs*). Cells may be unhealthy, because of infection or because of cellular damage, caused by non-infectious agents (e.g. cancer). *Pathogen Associated Molecular Patterns* (*PAMPs*) are cues which are recognised by the immune system and are released by infectious microbes (e.g. viruses and bacteria) [3]. The population that constitutes the immune system is made by *white cells*, also called *leukocytes*. Like

other components of the blood, they come from precursors (*pluripotent hematopoietic stem cells*) in the bone-marrow, and develop into mature cells in different parts of the body: in the bone-marrow itself, in the skin, in the blood stream, in the thymus and in the lymphatic system.
The skin is usually the first line of defence against microbes. Skin cells produce and secrete important antimicrobial proteins, and white cells can be found in specific layers of the skin. The *common myeloid progenitor stem cell* is a *precursor to innate immune* cells (e.g. neutrophilis, basilophilis, mast cells, monocytes, dendritic cells[1] and macrophages).
It is worth noticing that the *innate immune system* is the *first line of defence* against microbes. The *common lymphoid progenitor stem cell* is a *precursor to adaptive immune cells*: B-lymphocytes and T-lymphocytes.
B-lymphocytes derive from the bone-marrow itself, instead the T-lymphocytes develop in the thymus. Another group of lymphocytes consists in the natural-killer cells (NK cells) which are part of the innate immune system. Also these cells derive from the bone marrow, but the are unique in the sense that new ones are not generated throughout a human being's lifespan.
T-lymphocytes mediating the cellular immunity, along with B-lymphocytes arbitrating humoral immunity, provide adaptive immunity, which works in close collaboration with the innate immune system.
The majority of T-lymphocytes is made up by CD4+T cells (which are also called CD4+T cells, T helper lymphocytes and T4 cells) and CD8+T cells.
The CD4+T cells, after being activated and differentiated into distinct effector subtypes, play a major role in mediating immune response through the secretion of specific cytokines. These cells carry out multiple functions, e.g. the activation of the innate immune system's cells and a critical, opposite role in the suppression of immune reaction [38].

[1] Dendritic cells are antigen-presenting cells of the mammalian immune system.

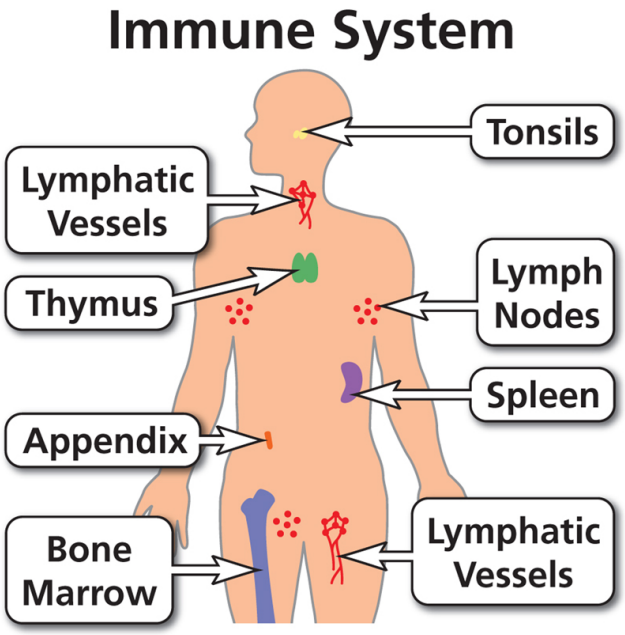


Figure 2.1: Representation of the parts of the body which are involved in the immune system.

In the next three subsection we provide some information about the immune cells which are included in the greatest HIV under treatments model used in this work. Most of the information is taken from [25].

2.1.1 Macrophages

These cells derive from *bone-marrow promonocytes* which, after differentation to *blood monocytes*, finally settle in the tissues as mature macrophages where they constitute the *mononuclear phagocyte system*.
They are present throughout the connective tissue and around the basement membrane of small blood vessels and are particularly concentrated in the lung (alveolar macrophages), liver, and lining of spleen sinusoids and lymph node medullary sinuses where they are strategically placed to filter off foreign material.
Macrophages are long-lived cells with significant rough-surfaced endoplastic reticulum and mitochondria, moreover they are the best in contrasting those bacteria, viruses and protozoa which are capable of living within the cells of the host.

2.1.2 Langerhans cells

Langerhans cells are dendritic cells (antigen-presenting cells) of the skin and mucosa, and contain organelles called Birbeck granules[2] They are present in all layers of the epidermis, except the stratum corneum[3], which protects against infections, and are almost prominent in the stratum spinosum[4]. These cells also occur in the papillary

[2]The Birbeck granules are cytoplasmic bodies which are rod and are solely found in Langerhans cells.

[3]The stratum corneum is the most external epidermic layer.

[4]The stratum spinosum is the epidermic layer before the basal one, which is the most internal one of the skin.

dermis (e.g. around blood vessels and in the mucosa of the mouth) and they can be found in the lymph nodes. Thus, the tissue which is in contact with the external environment has this type of cells. Langerhans cells are an important line of defence against viruses.

2.1.3 Natural killer (NK) cells

Viruses lack the apparatus for self-renewal so it is essential for them to penetrate the cells of the infected host in order to take over its replicative machinery. It is clearly in interest of the host to find a way to kill such infected cells before the virus has had a chance to reproduce. NK cells appear to do just that when studied in vitro.
They are large granular lymphocytes. They can recognize structures on high molecular weight glucoproteins which appear on the surface of virally infected cells and which allow them to be differentiated from normal cells. This recognition occurs through receptors on the NK cell surface. Activation of the NK cell ensures and leads to extracellular release of granule contents into the space between the two cells. Perhaps the most important of them is a perforin, or cytolysin, because it has the capacity to insert itself into the membrane of the target and associate to form a transmembrane pore with an annular structure, which induces the cell's death.

2.1.4 T-helper cells

T-helper cells are a subpopulation of T-lymphocytes, as previously said, which, if primed to that antigen, will recognize and bind to the combination of antigen with some particular molecules (called class II MHC molecules) and produce a variety of soluble factors called lymphokines, which constitute a subset of citokines. These include macrophage activating factors and bring about the death of intercellular micro-organisms.

2.2 The HIV life cycle

When a person is infected with HIV (a representation of the structure of an HIV is shown in Figure 2.2), the virus begins to attack and kill the CD4+T cells of the immune system [2]. Moreover HIV infects macrophages, even if it is a process which is slower than the infection of the CD4+T cells. As seen previously (in Section 2.1), CD4+T cells and macrophages are two types of white blood cells.

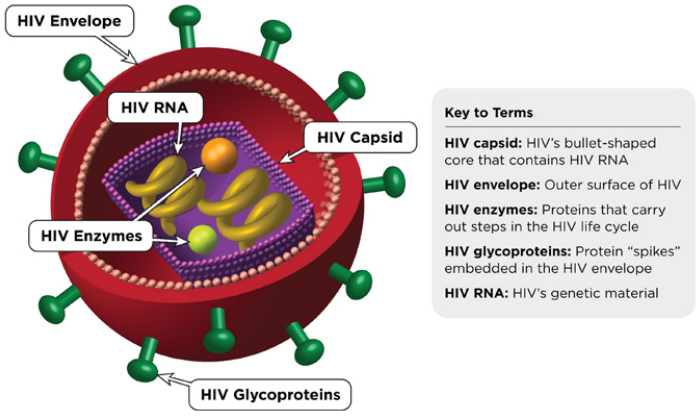


Figure 2.2: Representation of the structure of an HIV.

HIV uses the equipement of the cells to replicate and spread throughout the body, in particular HIV is able to infect CD4+T cells and macrophages. Supposing, for example, that the attacked cell is a CD4+T one, the HIV infection process (Figure 2.3) (called HIV life cycle too) is:

1) *binding* (or *attachment*):
HIV attacks itself to receptors on the surface of CD4+T cell;

2) *fusion*:
the HIV envelope and the CD4+T cell membrane fuse, which allows HIV to enter the CD4+T cell;

3) *reverse transcription*:
inside the CD4+T cell, HIV releases and uses the reverse transcriptase (an HIV enzyme) to convert its RNA (HIV genetic maerial) into HIV DNA (this conversion allows HIV to combine with the cell's genetic material);

4) *integration*:
inside the CD4+T cell nucleus, HIV releases integrase (an HIV enzyme) and uses it to insert its viral DNA into CD4+T's DNA;

5) *replication*:
HIV begins to use the CD4+T's machinery to make long chains of HIV proteins, which are the building blocks for more HIV;

6) *assembly*:
new HIV RNA moves to the cell's surface and noninfectious immature HIV is assembled;

7) *budding*:
the immature HIV goes out of the host cell and it releases protease (an HIV enzyme), which breacks up the long protein chains, so mature infectious HIV is formed.

Now, we introduce what we see in Section(2.3).
The drugs used to fight HIV are different, and they can be grouped in seven classes:

every medicine in each class is able to block one of the different steps of the HIV life cycle. An ART (AntiRetroviral therapy) is a therapy made by one class of medicines. Instead an HAART (Highly Active AntiRetroviral Therapy) is formed by a combinations of medicines of at least two different drug classes.
By taking into consideration the last observation, we decide to use an HIV mutation model ((3.3) in Section 3.2) which includes two drugs of two different classes:

- one therapy blocks the phase 3) of HIV life cycle, with NrRTIs (Nucleotide Reverse Transcriptase Inhibitors),
- the other therapy bocks the phase 7) of HIV life cycle, with PIs (Protease Inhibitors).

The genotype 1, g_1, in Figure **??** is the most prolific variant w.r.t. all the other genotypes, in absence of any drugs. Thus, it is called WTG (Wild Type Genotype). On the contrary, the genotype 16, g_{16}, is the least prolific variant w.r.t. all the other genotypes, in absence of any drugs. For this reason it is called Highly Resistant Genotype HRG.

2.3 The HIV and the HAARTs

In Section 2.2 we introduced the HAARTs which are therapies made by medicines of at least two drug classes.
As said in the end of the previous section, the genotype 1, g_1, in Figure **??** is the most prolific variant w.r.t. all the other genotypes, in absence of any drugs and it is called WTG (Wild Type Genotype). It is the most susceptible genotype w.r.t. all the other ones. For this reason it is the variant for which all the therapy combinations have been created in order to contrast it. Instead, the genotype 16, g_{16}, is the least prolific variant in absence of drugs w.r.t. all other genotypes and, as said, it is called HRG (Highly Resistant Genotype). Since it is the strain with the lowest prolification rate, it was not necessary for the drug therapies to be truly effective in fighting it. The therapies were designed consequently. Moreover, it represents the genotype that we obtain after several mutations.
AIDS info [2] suggests at least two nucleotide or nucleoside analogues[5]: either protease inhibitors (PIs) or nucleotide reverse transcriptase inhibitors.
The first type of inhibitors is used to combat the HIV, because without protease (Figure 2.4a and Figure 2.4b) the HIV is unable to become its infective form (or mature form). These type of inhibitors block the phase 7) of HIV life cycle (Section 2.2). In fact, when HIV infects a CD4+T cell, it copies its own genetic code into the cell's DNA, so when the CD4+T reproduces, it makes new HIV genetic material and HIV proteins (Figure 2.4a). The proteins must be cut up by the HIV protease to make functional new HIV copies and PIs block this process (Figure 2.4b)[2].
The second type of inhibitors includes Nucleotide Reverse Transcriptase InHibitors (NrRTIs) and Nucleoside Reverse Transcriptase Inhibitors (NRTIs) that interfere

[5]The nucleotide and the nucleoside analogs can be used in therapy drugs. They include a range of antiviral products used to prevent viral replication in infected cells, by stopping one phase of HIV life cycle [32] (see Figure 2.3).

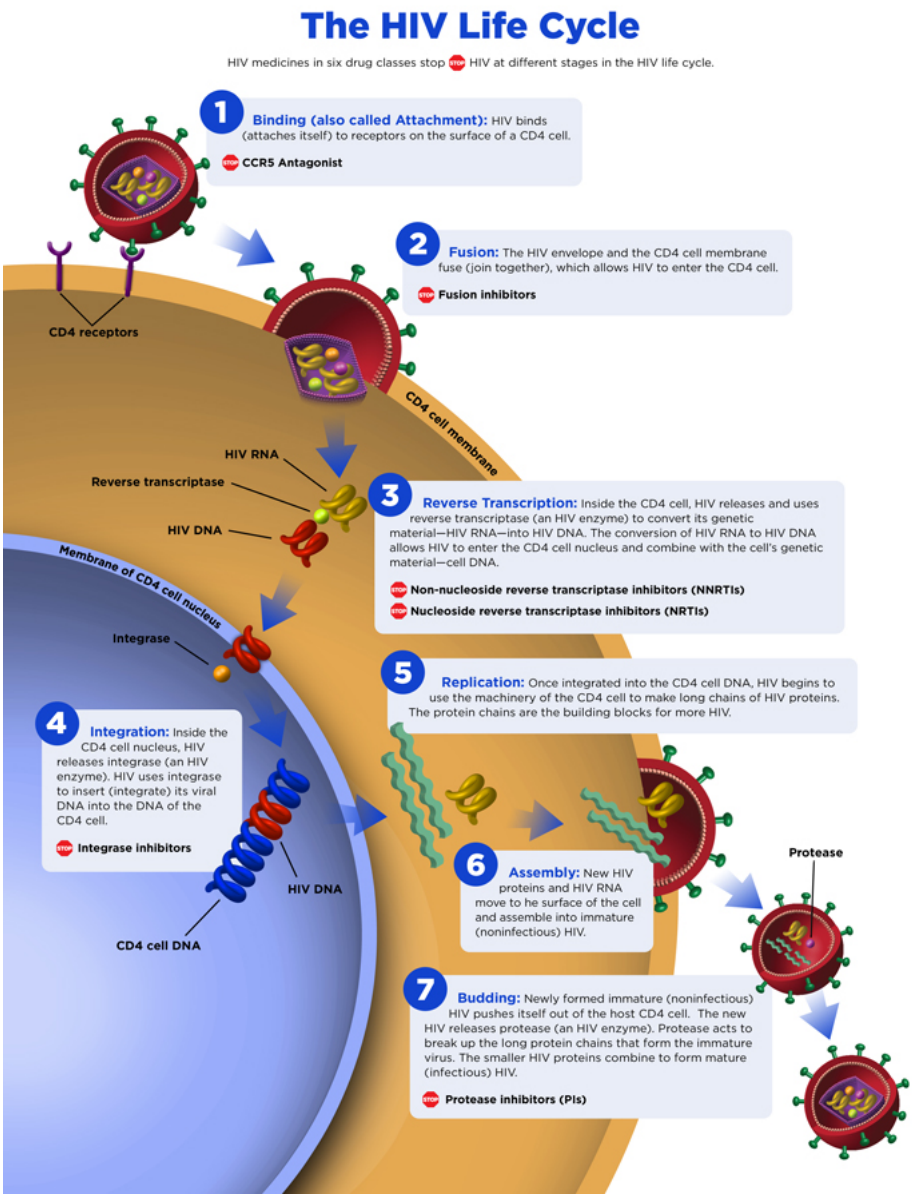
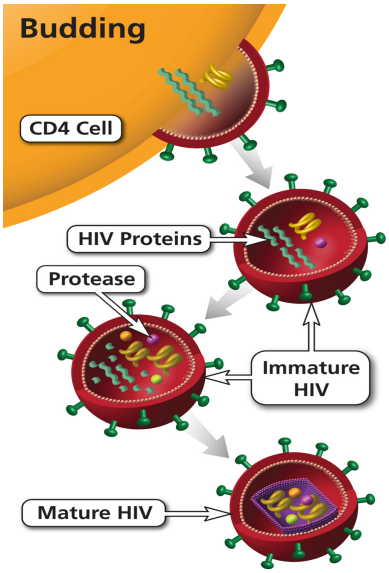


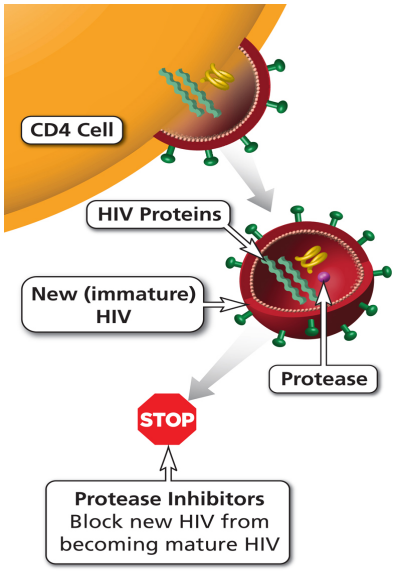
Figure 2.3: Representation of HIV life cycle.

with the HIV life cycle in the same way. Both block Reverse Transcription (Figure 2.5b), which is the third stage of HIV life cycle (Section 2.2). HIV uses Reverse Transcriptase (RT[6]) to convert its RNA into viral DNA: a process called reverse transcription, whose representation is in Figure 2.5a.

[6]Reverse Transcriptase (RT) is an enzyme found in HIV (and other retroviruses).

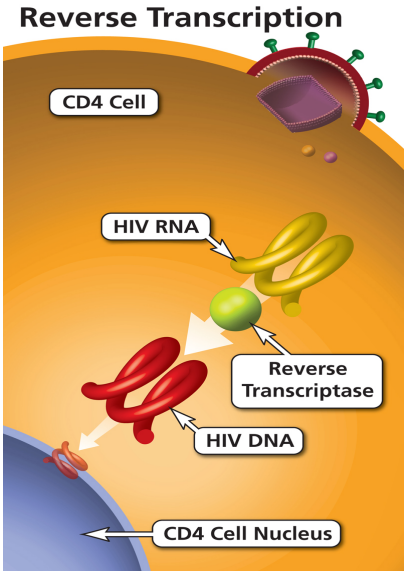


(a) Creation of a mature HIV copy.

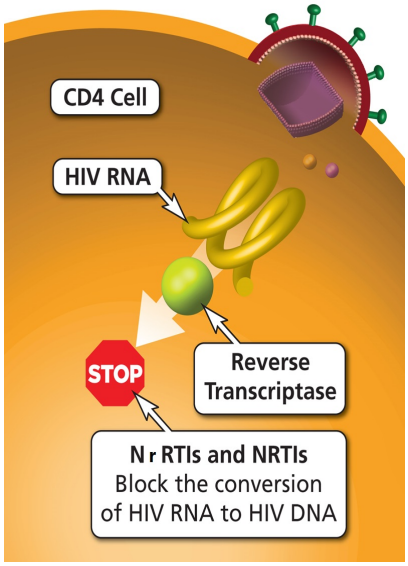


(b) PIs block the conversion of HIV RNA to HIV DNA.

Figure 2.4: Representation of the action of PIs.



(a) Reverse transcription.



(b) NRTIs and NrRTIs block the cutting up of proteins.

Figure 2.5: Representation of the action of NrRTIs.

Therefore, we consider therapies that are composed of both Protease Inhibitors (PIs), which alter the viral production constants p_T and p_M, and Reverse Transcriptase Inhibitors (RTIs) which change the infection constants k_T and k_M [22] (coefficients in Figure 3.2).

Chapter 3

Modeling the Three Stages in HIV Infection

In this chapter we provide some basic information about the three stages in HIV infection and the explanation of both models of HIV with treatments considered. The greatest is a 16 variant, 2 drug combination model, explained in Subsection 3.2.2), whereas the smallest one is a 4 variant, 2 drug combination model and it is introduced for its simplicity in Subsection 3.2.2.
It is preferable to explain the course of HIV in this chapter, because the structure of the biggest model is strictly connected with it.

3.1 The three stages in HIV infection

In HIV infection are involved two types of cells of the Immune System (see Chapter 2 for more information): CD4+T cells and macrophages [19]. These cells have an important role in the Immune System, so HIV infection may be destructive for the patient's health. CD4+T cell count and plasma viral levels are really important for monitoring the patient's health, because they are the clinical markers of the progression of HIV infection.

In the absence of antiretroviral treatment, the typical patient response to HIV infection includes three main phases [2] (Figure 3.1):

(i) A short period, during which there is an initial acute infection (*phase of Acute HIV Infection*);

(ii) A long asymptomatic period, which is called *period of Clinical Latency*, or *phase of Chronic (or Asymptomatic) HIV Infection*;

(iii) A final increase in viral load with a simultaneous collapse in healty CD4+T cells count, during which the *Acquired ImmunoDeficiency Syndrome* (*AIDS*) appears [8] (*phase of AIDS*).

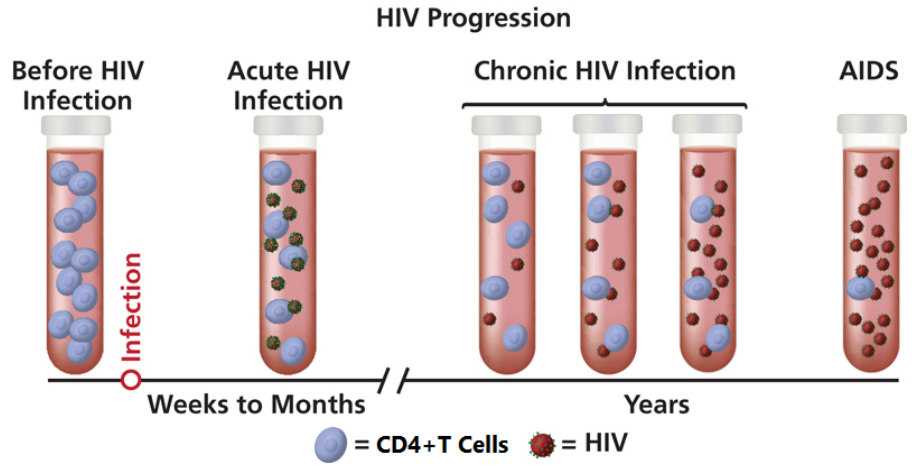


Figure 3.1: Representation of HIV progression, without any therapy.

During the first period, which lasts 2-10 weeks, there is an acute drop in the concentration of circulating CD4+T cells, and an high increase in the level of circulating free viruses. The bedridden person in this phase has an acute syndrome with symptoms such as fever, lymphadenopathy, pharyngitis, headache and rash.
In the second period, which lasts 7-10 years, the level of circulating CDT+4 cells returns almost to normality (the number of CD4+T cells is greater than 300 $[cells/mm^3]$), and the viral load decreases greatly. In this asymptomatic or latent period, the patient does not exhibit any symptoms of disease, even if HIV is continuously infecting new cells and actively replicating.
In the third period, phase of AIDS, the viral load rises rapidly with simultaneous drop in CD4+T cell count. An HIV-positive person is said to have AIDS when the CD4+T cells counts are below 200 $[cells/mm^3]$ or/and when his Immune System becomes so weak it can't fight off certain kinds of infections and cancers [1].
Several works only describe the first two stages of HIV infection, as the case of [34], [13] and [10]. Other works regard only the AIDS stage of infection [36].
Since the real dynamic system is complex and we are interested in analysing its stability and stabilization properties, we include in the model different types of cells involved in the HIV infection, to have a more accurate system's mathematical description. In fact, in the big model (Section 3.2.2) we consider both infected CD4+T cells and infected macrophages.
Macrophages have been known since the 1980s to be susceptible to HIV infection, but they have received little attention in the research literature w.r.t. the CD4+T cell host [8]. The big nonlinear model we use is taken from [19]. [19] is one of the first works which takes into consideration also the population of macrophages and in this manner it can explain the full HIV course, without time varying parameters.

3.2 Mathematical models

3.2.1 The HIV model, without therapy

The main problem of therapies against HIV is that there are latent cellular reservoirs[1] which may contribute to HIV persistence [14].
There are two main viral reservoirs: resting infected CD4+T cells and macrophages. The first type of cells is the major viral reservoir in case of HIV infection. Clinical observations [31] show that the viruses which are present in a patient undergoing interruption of a successful treatment[2] are genetically different from the ones which are present in the reservoirs CD4+T cells. Moreover, [19] infected macrophages may experience an increase in population which can be exponential, and this is consistent with studies in rhesus macaques [39]. However, it is worth underlining that the SHIV[3]'s dynamics are an exaggeration of the HIV's ones, but these help doctors to have an idea of the HIV's dynamics [39].
Moreover, [39] shows that the production of viruses is caused for 95% by infected macrophages and only 1 to 2% by infected CD4+T cells. [19], [34] and [5] show that the viral load explosion is not due to infected CD4+T cells. Furthermore, the final explosion of the viral load is due to infected macrophages [19].
So, the very slow dynamics observed in HIV infection, which show results in the AIDS stage, principally depend on the dynamics of macrophages' population [19].
Macrophages, together with Langerhans cells, appear to be the first cells infected with HIV, so their dynamics, despite being slow, begins at the starting moment of the infection, [11]. HIV isn't cytopathic[4] for macrophages, in fact healthy and infected macrophages could last for very long periods [29].
Thus, in order to explain all the three phases of HIV infection, it is necessary to have a model which takes into consideration the macrophages' dynamics.
Here we introduce a model with the following populations, [19]:

- $T \doteq$ healthy CD4+T cells,
- $M \doteq$ healthy macrophages,
- $T^* \doteq$ infected CD4+T cells,
- $M^* \doteq$ infected macrophages,
- $V \doteq$ the HIV population.

It is made by a connection of two feedback systems, see Figure 3.2.

[1] A reservior is a population of long-lived infected cells, that might permit viral replication even after many years of drug treatment.
[2] A successful treatment maintains the total viral load under or equal to 1000 $[copies/mL]$.
[3] Hybrid virus made by both HIV and SIV (Simian Immunodeficiency Virus). It permits both the infection of a simian and the contemporary valuation of the immune response to HIV [26].
[4] The term refers to structural changes in host cells caused by viral invasion.

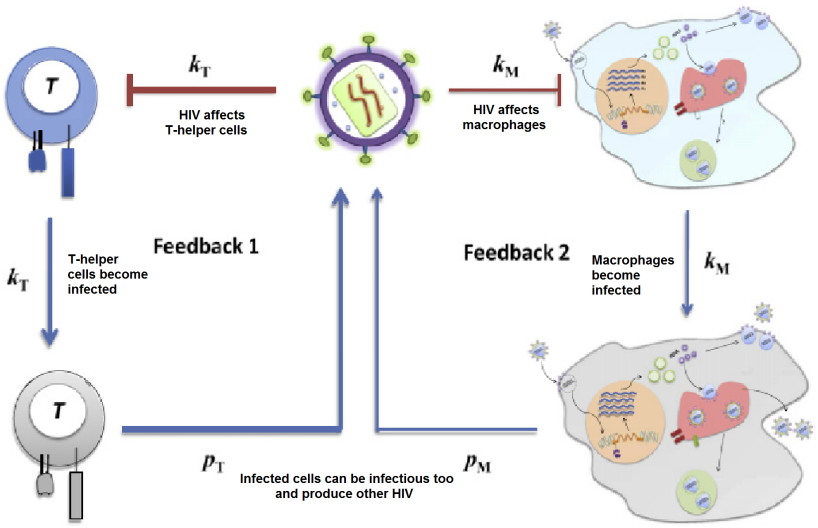


Figure 3.2: HIV infection scheme. On the left a representation of a CD4+T cell and on the right of a macrophage.

The first feedback models the fast dynamics for early stages of infection, as a result of a fast infection of CD4+T cells. The second feedback is for modelling the constant slow infection in macrophages.
In Figure 3.2, on the left there is a representation of a CD4+T cell, with k_T which is the CD4+T cells' infection constant and p_T which is the production constant of viruses, made by infected CD4+T cells.
Equivalently, in Figure 3.2, on the right there is a representation of a macrophage, with k_M which is the macrophages' infection constant, and p_M which is the production constant of viruses, made by infected macrophages.
The considered model of HIV without therapy, which presents all the populations previously introduced, is:

$$\begin{aligned}
\dot{T} &= s_T + \frac{\rho_T V}{C_T + V} T - k_T T V - \delta_T T, \\
\dot{M} &= s_M + \frac{\rho_M V}{C_M + V} M - k_M M V - \delta_M M, \\
\dot{T}^* &= k_T T V - \delta_{T^*} T^*, \\
\dot{M}^* &= k_M M V - \delta_{M^*} M^*, \\
\dot{V} &= p_T T^* + p_M M^* - \delta_V V,
\end{aligned} \tag{3.1}$$

where:

- k_T and k_M are the CD4+T infection rate (i.e. the rate at which free virus V infects CD4+T cells) and he macrophage infection rate (i.e. the rate at which free virus V infects macrophages);

- p_T and p_M are the rates of production per day of virus by T^* and by M^*, respectively;

- s_T and s_M are the source rates of $CD4{+}T$ cells and macrophages, respectively;
- ρ_T and ρ_M are the proliferation parameters of new $CD4+T$ cells and new macrophages, respectively;
- C_T and C_M are the concentrations of $CD4+T$ cells and macrophages, respectively;
- δ_T, δ_M, δ_{T^*}, δ_{M^*}, δ_V are the decay or death rates of healthy CD4+T cells, of healthy macrophages, of infected CD4+T cells, of infected macrophages and of viruses.

All the ranges of values of parameters which are in Table are taken from [19].
Looking at Table 3.1, the decay rate of the infected CD4+T cells is greater than

Parameter	Range or Value:
k_T	$\left[10^{-8}, 10^{-2}\right]$ $\left[\frac{mm^3}{day \cdot copies}\right]$
k_M	4.33×10^{-8} $\left[\frac{mm^3}{day \cdot copies}\right]$
p_T	$[0.24, 500]$ $\left[\frac{copies}{cell \cdot day}\right]$
p_M	$[0.05, 300]$ $\left[\frac{copies}{cell \cdot day}\right]$
s_T	10 $\left[\frac{cells}{mm^3 \cdot day}\right]$
s_M	0.15 $\left[\frac{cells}{mm^3 \cdot day}\right]$
ρ_T	0.01 $\left[day^{-1}\right]$
ρ_M	0.003 $\left[day^{-1}\right]$
C_T	300 $\left[\frac{copies}{mm^3}\right]$
C_M	220 $\left[\frac{copies}{mm^3}\right]$
δ_T	0.01 $\left[day^{-1}\right]$
δ_M	1×10^{-3} $\left[day^{-1}\right]$
δ_{T^*}	$[0.26, 1]$ $\left[day^{-1}\right]$
δ_{M^*}	1×10^{-3} $\left[day^{-1}\right]$
δ_V	$[2.06, 3.81]$ $\left[day^{-1}\right]$

Table 3.1: Ranges of parameter values for (3.1).

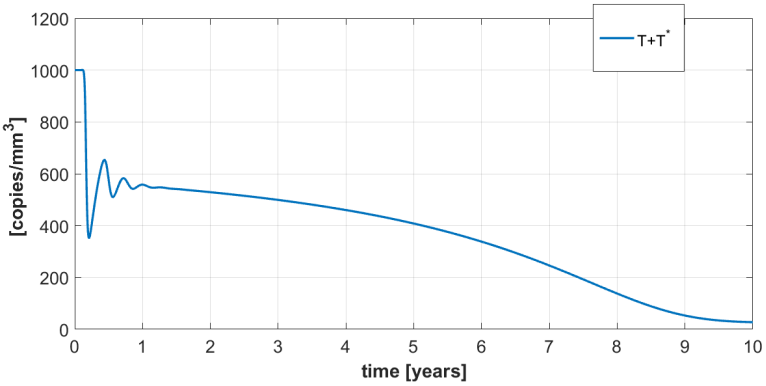
the macrophages' one of two orders of magnitude. It is coherent with the fact that macrophages can last for very long periods [11]. Moreover, the decay rates of healthy and infected macrophages are coincident, in fact we said that HIV is not cytopathic in the macrophages' case. Clearance of free viruses is the most rapid process, occurring on a time scale of hours, [11], [5] and [40].
The dynamics of the state variables of the nonlinear model (3.1), with initial state

$$\mathbf{x}(0)^T = [T(0)\ M(0)\ T^*(0)\ M^*(0)\ V(0)]^T =$$

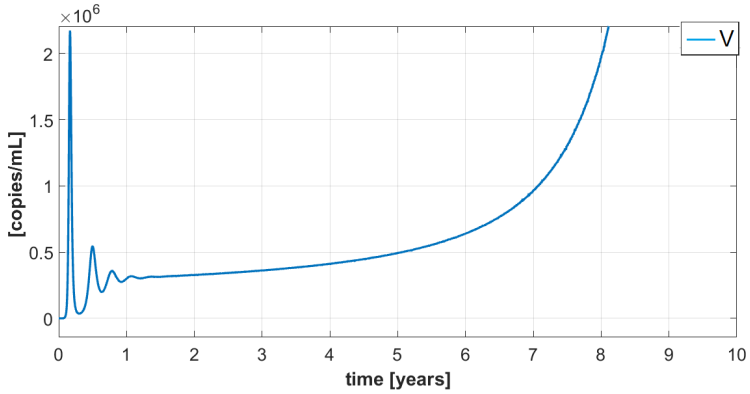
$$= \left[1000\left[\frac{copies}{mm^3}\right],\ 150\left[\frac{copies}{mm^3}\right],\ 0\left[\frac{copies}{mm^3}\right],\ 0\left[\frac{copies}{mm^3}\right],\ 10\left[\frac{copies}{mL}\right]\right]^T{}^{5},$$

are displayed in Figure 3.3. For initial condition values we consider the same values of [19], [11] and [33].

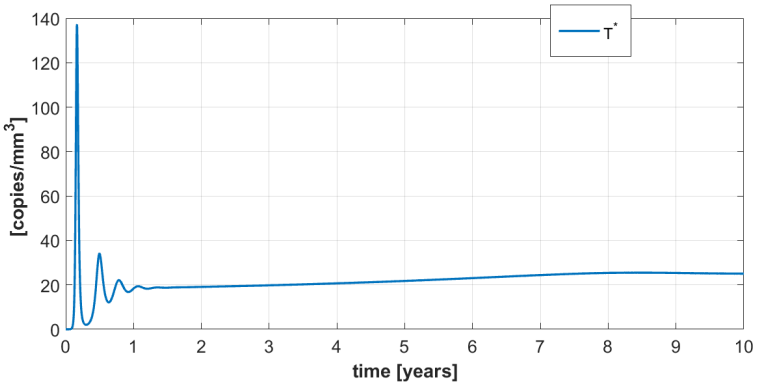
[5] To implement with MATLAB®, we use $\mathbf{x}(0)^T = [1000,\ 150,\ 0,\ 0,\ 0.01]^T\ \left[\frac{copies}{mm^3}\right]$.



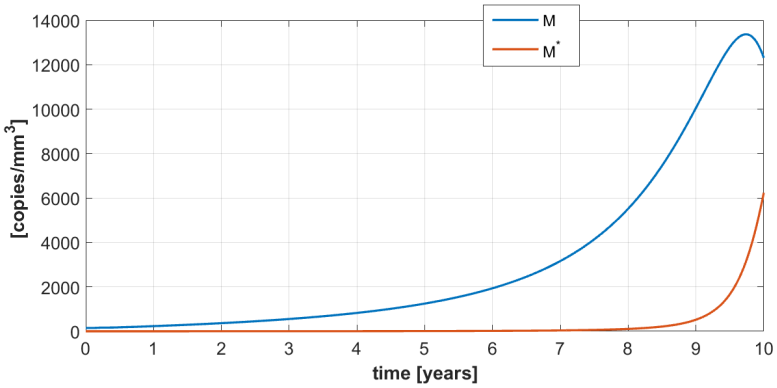
(a) Dynamics of $T + T^*$.



(b) Dynamics of V.



(c) Dynamics of T^*.



(d) Dynamics of M and M^*.

Figure 3.3: Dynamics of the nonlinear model of HIV, without therapy.

In Figure 3.3 it is visible that (3.1) matches reasonably well all the three stages of HIV infection. Figure 3.3b shows an initial peak in viral load and in Figure 3.3c it is visible the initial peak of infected $CD4+T$ cells. These features characterise the *phase of Acute Infection*. Then, there are lower concentrations of both viruses and infected $CD4+T$ cells, with a contemporary increase in macrophages' concentration. This is the *phase of Chronic HIV Infection*. Finally, Figure 3.3d shows the final increase infected macrophages, which leads to AIDS.
For more detailed information of HIV infection see Section 3.1.
The model (3.1) is moderately robust to parameters' variations.
For the wide diversity of resistant mutants, the HIV treatment problem may be not stabilizable [18].
As said, the aim of this thesis is to investigate the stabilizability (see Chapter 5) of the two models of HIV under treatment (which we introduce in this chapter), and to find switching rules that maintain the viral load under a certain upper bound (see Chapter 6).

3.2.2 Models of HIV with therapy

A 16 variant, 2 drug combination model

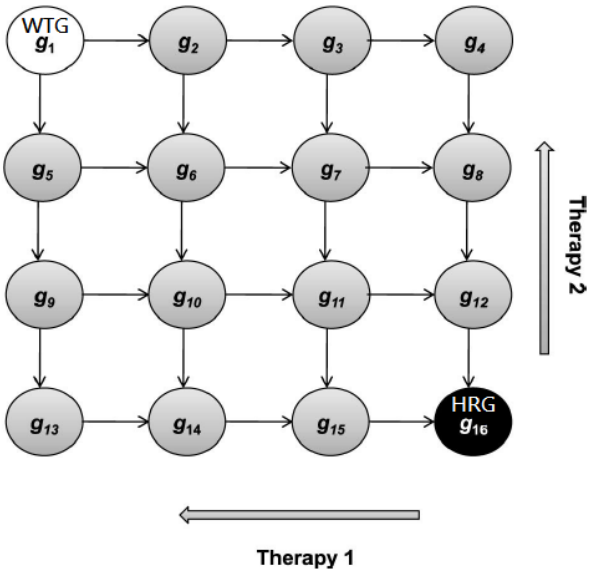


Figure 3.4: Sixteen genotypes and two drug combination. The direction of the arrows means the effectiveness of the therapy.

As said in Chapter 2, some of the parameters which we previously introduced are variable under therapies. These parameters are the infection constants k_T, k_M and the viral production constants p_T and p_M. Moreover, we consider separately the different n genotypes, which we name V_i and g_i $(i = 1, \ddots, n)$, equivalently.
The variation of some parameters during time leads to the construction of a switched

positive[6] nonlinear model which represents an oversimplified model of HIV under treatments:

$$\begin{aligned}
\dot{T} &= s_T + \frac{\rho_T V_T}{C_T + V_T} T - \sum_{i=1}^{n} k^i_{T,\sigma} T V_i - \delta_T T, \\
\dot{M} &= s_M + \frac{\rho_M V_T}{C_M + V_T} M - \sum_{i=1}^{n} k^i_{M,\sigma} M V_i - \delta_M M, \\
\dot{T}^*_i &= k^i_{T,\sigma} T V_i + \sum_{j=1}^{n} \mu m_{i,j} V_j T - \delta_{T^*} T^*_i, \\
\dot{M}^*_i &= k^i_{M,\sigma} M V_i + \sum_{j=1}^{n} \mu m_{i,j} V_j M - \delta_{M^*} M^*_i, \\
\dot{V}_i &= p^i_{T,\sigma} T^*_i + p^i_{M,\sigma} M^*_i - \delta_V V_i,
\end{aligned} \tag{3.2}$$

for $i = 1, \ldots, n$ and $k = 1, \ldots, M$.
And where V_i is the i-th genotype, T^*_i represents the infected activated CD4+T cells by V_i and M^*_i represents the infected macrophages by V_i. $m_{i,j}$ are the elements of the incidence matrix[7] of the graph in Figure 3.4. The graph represents all the possible mutations between genotypes.
Except to the parameters variable under therapy $\sigma(\cdot)$, all the parameters in (3.2) are exactly the same of the HIV model, without therapy (3.1):

- $k^i_{T,\sigma}$ and $k^i_{M,\sigma}$ are the CD4+T infection rate caused by the i-th strain V_i, and the macrophage infection rate caused by the i-th strain V_i;

- $p^i_{T,\sigma}$ and $p^i_{M,\sigma}$ are the rates of production per day of i-th virus V_i by T^* and by M^*, respectively.

As known, studying a linear model is simpler than studying a nonlinear one, especially the design of switching strategies for the nonlinear model (3.2) can be very demanding. As a matter of fact, under normal treatment conditions, typical clinical data suggest that macrophages M and CD4+T cells count T are approximately constant [5]. Thus, we assume constant

1. T (the uninfected CD4+T cells),

2. M (the uninfected macrophages).

These conditions allow us to use a linear model, otherwise we would have bilinear terms in differential equations (3.3).
We use the linearised model given by the following switched positive linear system,

[6] A positive state space model is a system whose state variables stay in the positive orthant. And it is a switching model when the parameters of the model changes at specific time instants.

[7] In graph theory an (unoriented) incidence matrix is a matrix which has dimension $n \times m$, with $n \doteq$ number of nodes and $m \doteq$ number of edges. $\xi_{i,j} = 1$ if the vertex v_i and edge e_j are incident and 0 otherwise.

[22]:

$$\begin{aligned}\dot{T}_i^* &= k_{T,\sigma}^i T V_i - \delta_{T^*} T_i^* + \sum_{j=1}^{n} \mu m_{i,j} V_j T,\\ \dot{M}_i^* &= k_{M,\sigma}^i M V_i - \delta_{M^*} M_i^* + \sum_{j=1}^{n} \mu m_{i,j} V_j M, \ for\ i = 1,\dots,n,\\ \dot{V}_i &= p_{T,\sigma}^i T_i^* + p_{M,\sigma}^i M_i^* - \delta_V V_i,\end{aligned} \tag{3.3}$$

for $i = 1,\dots,n$ and $k = 1,\dots,M$.
The previous equations (3.3) can be written in a matrix form:

$$\dot{\mathbf{x}} = \left(\begin{bmatrix} \Lambda_{1,\sigma} & \mathbf{0}_{3\times3} & \dots & \mathbf{0}_{3\times3} \\ \mathbf{0}_{3\times3} & \Lambda_{2,\sigma} & \dots & \mathbf{0}_{3\times3} \\ \mathbf{0}_{3\times3} & \dots & \ddots & \mathbf{0}_{3\times3} \\ \mathbf{0}_{3\times3} & \mathbf{0}_{3\times3} & \dots & \Lambda_{n,\sigma} \end{bmatrix} + \mu M_u \right) \mathbf{x}; \tag{3.4}$$

where $\mathbf{x} = [T_1^*\ M_1^*\ V_1\ \dots\ T_n^*\ M_n^*\ V_n]^T$, and

$$\Lambda_{i,\sigma} = \begin{bmatrix} -\delta_{T^*} & 0 & k_{T,\sigma}^i T \\ 0 & -\delta_{M^*} & k_{M,\sigma}^i M \\ p_{T,\sigma}^i & p_{M,\sigma}^i & -\delta_V \end{bmatrix} \tag{3.5}$$

For the 16-variant model we assume n = 16, and $\sigma \in \{1, 2\}$ (2 possible drugs).

The *mutation matrix* has the following form:

$$M_u = [m_{i,j}] \otimes \begin{bmatrix} 0 & 0 & T \\ 0 & 0 & M \\ 0 & 0 & 0 \end{bmatrix}, \tag{3.6}$$

where $\otimes$ denotes the Kronecker product[8].
The model above is an autonomous positive switched system (p.s.s.):

$$\dot{\mathbf{x}}(t) = A_{\sigma(t)}\mathbf{x}(t), \tag{3.7}$$

with $A_{\sigma(t)}$ a Metzler[9] matrix for each $\sigma(t) \in \{1, 2\}$.

As a matter of fact, the number of healthy CD4+T cells and healthy macrophages decreases in time until the beginning of the Acquired ImmunoDeficiency Syndrome (AIDS). The mentioned condition holds before the so called *Virologic Failure*, with *Virologic Failure* we mean a condition of detectable viremia (HIV RNA $>$ $1000\,[copies/mL] = 1\,[copies/mm^3]$) and of drug-resistant genotype identified [22].
Note that, the AIDS stage is characterized by both a decrease of healthy CD4+T cells and an high increase of the total viral load V_T. So, we use V_T as parameter to

[8]The Kronecker product $A \otimes B$, with $A \in \mathbb{R}^{n\times m}$ and $B \in \mathbb{R}^{p\times q}$ is the matrix

$$A \otimes B = \begin{bmatrix} a_{11}B & a_{12}B & \dots & a_{1m}B \\ \vdots & \dots & \ddots & \vdots \\ a_{n1}B & a_{n2}B & \dots & a_{nm}B \end{bmatrix},$$

where a_{ij}, for $i = 1,\dots,n$ and $j = 1,\dots,m$ are the entries of A

[9]A matrix is said to be Metzler if it is square and it has all off-diagonal entries non-negative.

understand if a therapy is effective[10].
Furthermore, we have that the constants in $\Lambda_{i,\sigma}$ can be written as:

- $k^i_{T,\sigma} = k_T f_i \eta^T_{\sigma,i}$,
- $k^i_{M,\sigma} = k_M f_i \eta^M_{\sigma,i}$,
- $p^i_{T,\sigma} = p_T f_i \theta^T_{\sigma,i}$,
- $p^i_{M,\sigma} = p_M f_i \theta^M_{\sigma,i}$,

where $\eta_{\sigma,i}$ is the infection efficiency for genotype V_i under σ, $\theta_{\sigma,i}$ is the production efficiency for genotype i V_i under σ. And f_i is the fitness of i-th genotype[11].
We consider the same initial values which we take for the model without therapy, but we suppose that the initial amount of the total viral load is made by only the WTG, thus, the initial state is

$$\mathbf{x}(0)^T = [T^*_1(0)\ M^*_1(0)\ V_1(0)\ \dots\ T^*_{16}(0)\ M^*_{16}(0)\ V_{16}(0)]^T =$$
$$= \left[0\left[\frac{copies}{mm^3}\right],\ 0\left[\frac{copies}{mm^3}\right],\ 10/16\left[\frac{copies}{mL}\right],\dots,0\left[\frac{copies}{mm^3}\right],\ 0\left[\frac{copies}{mm^3}\right],\ 0\left[\frac{copies}{mL}\right]\right]^T.$$

We take the constant values $T = 1000[copies/mm^3]$ and $M = 150[copies/mm^3]$.

The Wild Genotype Type (WTG, g_1 in the grid of Figure 3.4) is the most prolific variant in the absence of any medicines and it is also the variant that all drug combinations have been designed to combat, thus making it susceptible to all therapies. After several mutations the Highly Resistant Genotype (HRG, g_{16} in the grid of Figure 3.4) is a genotype with low proliferation rate, but resistant to all drug therapies.
[22] reports that mutation reduces the fitness of the genotype in absence of treatment and we assume that the same holds in case of therapy. In Figure 3.4 the graph which we use is asymmetric, and mutations occur in the direction of the arrows. So, for simplicity, we use linear decreasing fitness factors f_i, which decline in accordance with the orientations of the arrows. As seen in Section 2.2, inhibitors are more effective in CD4+T cells than in macrophages, so that $\eta^T_{\sigma,i} > \eta^M_{\sigma,i}$ and $\theta^T_{\sigma,i} > \theta^M_{\sigma,i}$.

For simulation purposes, we assume

- $f_i = [1, 0.95, 0.95, 0.95]$,
- $\eta^T_{\sigma=1} = \theta^T_{\sigma=1} = [0.2, 0.8, 0.9, 1]$,
- $\eta^T_{\sigma=2} = \theta^T_{\sigma=2} = [0.2, 0.4, 0.5, 1]$,
- $\eta^M_{\sigma=1} = \theta^M_{\sigma=1} = [0.25, 0.4, 0.5, 1]$,

[10] In fact, in Chapter 6 to study the Optimal control problem for the introduced model, we use the *cost function* proposed by Hernandez-Vargas [22]:

$$J \doteq \mathbf{c}^T \mathbf{x}(t_f),$$

with $\mathbf{c} = [0\ 0\ 1\ 0\ 0\ 1\ \dots 0\ 0\ 1\ ]^T$.
This cost functional is the total viral load V_T at a final time t_f.

[11] With fitness of i-th genotype, we mean the average contribution of i-th genotype to gene pool of next generation of viruses.

- $\eta^M_{\sigma=2} = \theta^M_{\sigma=2} = [0.1, 0.7, 0.8, 1]$.

Moreover, we assume (according to the parameter intervals shown in Table 3.1) the values of constant parameters shown in Table 3.2.

Parameter	Value		Value taken from:
p_T	38	$\left[\frac{copies}{cell \cdot day}\right]$	Fitted
k_M	4.33×10^{-8}	$\left[\frac{mm^3}{day} \cdot copies\right]$	[19]
p_T	38	$\left[\frac{copies}{cell \cdot day}\right]$	Fitted
p_M	35	$\left[\frac{copies}{cell \cdot day}\right]$	Fitted
δ_{T^*}	0.4	$[day^{-1}]$	[33]
δ_{M^*}	0.001	$[day^{-1}]$	[33]
δ_V	2.4	$[day^{-1}]$	[11]

Table 3.2: Parameter values used for (3.3).

A 4 variant, 2 drug combination model

For its simplicity, we use also the 4 variant, 2 drug combination model [20], obtained from the nonlinear model (3.2), upon assuming the following hypotheses:

1. Counts of macrophages and CD4+T cells are constant. The nonlinearities in the model (3.2) are bilinear and they involve, either the uninfected CD4+T cells, or the uninfected macrophages. As we assume to be under the normal treatment circumstances, i.e. that we are in the second or at the beginning of the third stage of HIV infection. In these phases, clinical data suggest that macrophage and CD4+T cell count are almost constant [22]. This hypotheses allow to simplify the nonlinear model to a linear one;

2. The dynamics for each genotype is a scalar one. The strains, called V_i or g_i for the 16 variant, 2 drug combination model in Section 3.2.2, are named x_i or G_i for the 4 variant, 2 drug combination model in this section (Section 3.2.2);

3. The viral decay rate δ_V is constant for each strain x_i and for each therapy $\sigma(t)$, $t \in \mathbb{R}^+$ (in reality the death rate depends on both the strain and the therapy);

4. The mutation rate μ is independent of both treatment and variant (in reality there are some relations between mutant, mutation rate and therapy);

5. The model used is deterministic.

Thus, we obtain the following model, [21]):

$$\dot{x}_i(t) = \rho_{i,\sigma(t)} x_i(t) - \delta_V x_i(t) + \sum_{i \neq j}^{n} \mu \zeta_{i,j} x_j(t), \tag{3.8}$$

with $i \in \{1, \dots, n\}$, $\sigma(t) \in \{1, \dots, M\}$, $\zeta_{i,j} \in \{0, 1\}$ for $i, j = 1, \dots, n$.
Morover,

- n is the number of different viral genotypes, with a viral population x_i, $i = 1, \dots, n$ and in this case $n = 4$,
- M is the number of different therapies and in this case $M = 2$,
- $\sigma(t)$ is the specific therapy at time $t \in \mathbb{R}_+$,
- $\rho_{i,\sigma(t)}$ is the growth rate of the genotype i under treatment $\sigma(t)$,
- δ_V ithe death rate of the genotypes, which is considered constant both w.r.t. the therapy and w.r.t. the type of virus,
- μ is the mutation rate, which represents the capacity of a genotype to mutate (in case the mutation is possible),
- $\zeta_{i,j}$ is an element of the incidence matrix of the graph (the graph here considered is in Figure 3.5).

Equations in (3.8) can be written in the vector form as:

$$\dot{\mathbf{x}}(t) = \left(R_{\sigma(t)} - \delta_V I_n\right) \mathbf{x}(t) + \mu Z \mathbf{x}(t), \tag{3.9}$$

where

$$R_{\sigma(t)} = \begin{bmatrix} \rho_{1,\sigma(t)} & 0 & 0 & 0 \\ 0 & \rho_{2,\sigma(t)} & 0 & 0 \\ 0 & 0 & \rho_{3,\sigma(t)} & 0 \\ 0 & 0 & 0 & \rho_{4,\sigma(t)} \end{bmatrix} \tag{3.10}$$

is a matrix which contains the growth rates of the 4 different genotypes under a certain therapy $\sigma(t)$ and

$$Z = \begin{bmatrix} 0 & 1 & 1 & 0 \\ 1 & 0 & 0 & 1 \\ 1 & 0 & 0 & 1 \\ 0 & 1 & 1 & 0 \end{bmatrix} \tag{3.11}$$

is the incidence matrix of the graph in Figure 3.5.
The model above is an autonomous positive switched system:

$$\dot{\mathbf{x}}(t) = A_{\sigma(t)} \mathbf{x}(t), \tag{3.12}$$

with $A_{\sigma(t)}$ a Metzler[12] matrix for each $\sigma(t) \in \{1, 2\}$. In fact, by elementary computations, we find the two state matrices of the p.s.s. (3.12):

$$A_k = \begin{bmatrix} \rho_{1,k} - \delta_V & 0 & 0 & 0 \\ 0 & \rho_{2,k} - \delta_V & 0 & 0 \\ 0 & 0 & \rho_{3,k} - \delta_V & 0 \\ 0 & 0 & 0 & \rho_{4,k} - \delta_V \end{bmatrix} + \mu \begin{bmatrix} 0 & 1 & 1 & 0 \\ 1 & 0 & 0 & 1 \\ 1 & 0 & 0 & 1 \\ 0 & 1 & 1 & 0 \end{bmatrix}, \quad k = 1, 2. \tag{3.13}$$

As in the 16 variant, 2 drug combination model of Section 3.2.2, in this simple model we have the HRG and the WTG, which respectively are the most prolific variant, and the most susceptible to the therapies. In Figure 3.5 we see G_1 which is the strain resistant to the therapy 1, but susceptible to therapy 2 and G_2 which is the strain resistant to the therapy 2, but susceptible to therapy 1.

[12] A matrix is said to be Metzler if it is square and it has all off-diagonal entries non-negative.

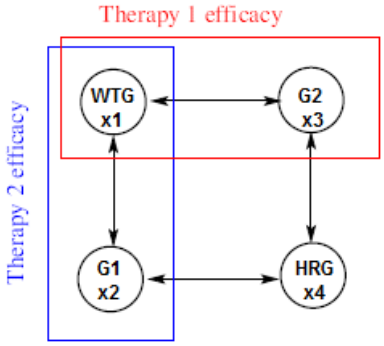


Figure 3.5: Graph which represents the four variant, two drug combination model. The rectangles represent the effectiveness of the therapies.

Muatation graph is symmetric and circular.
As a matter of fact, we allow only connections $WTG \leftrightarrow G_1$, $G_1 \leftrightarrow HRG$, $HRG \leftrightarrow G_2$ and $G_2 \leftrightarrow WTG$. All other connections would require double mutations and we hypothesize that they are of negligible probability.

We use $\delta_V = 0.24\,[day^{-1}]$, which corresponds assuming viruses' half life of almost three days and the mutation rate μ equal to 10^{-4} $\left[\frac{mm^3}{day \cdot copies}\right]$. And we suppose three scenarios, characterized by different values of growth rates $\rho_{i,\sigma(t)}$, with $i = 1, 2, 3, 4$ and $\sigma(t) \in \{1,\ 2\}$ (see Table 3.3).
As initial condition we take $\mathbf{x}(0) = [\mathbf{x}_1(0),\ \mathbf{x}_2(0),\ \mathbf{x}_3(0),\ \mathbf{x}_4(0)]^T =$

$$[250\ 250\ 250\ 250]^T\ \ [copies/mL].$$

Case	Therapy $\sigma(t)$	WTG (x_1)	G_1 (x_2)	G_2 (x_3)	HRG (x_4)
I	1	$\rho_{1,1} = 0.05$	$\rho_{2,1} = 0.245$	$\rho_{3,1} = 0.05$	$\rho_{4,1} = 0.245$
Symmetric	2	$\rho_{1,2} = 0.05$	$\rho_{2,2} = 0.05$	$\rho_{3,2} = 0.245$	$\rho_{4,2} = 0.245$
II	1	$\rho_{1,1} = 0.05$	$\rho_{2,1} = 0.255$	$\rho_{3,1} = 0.01$	$\rho_{4,1} = 0.245$
Partially symmetric	2	$\rho_{1,2} = 0.05$	$\rho_{2,2} = 0.175$	$\rho_{3,2} = 0.225$	$\rho_{4,2} = 0.245$
III	1	$\rho_{1,1} = 0.05$	$\rho_{2,1} = 0.235$	$\rho_{3,1} = 0.01$	$\rho_{4,1} = 0.265$
Asymmetric	2	$\rho_{1,2} = 0.01$	$\rho_{2,2} = 0.125$	$\rho_{3,2} = 0.225$	$\rho_{4,2} = 0.245$

Table 3.3: Different scenarios for (3.9).

The first scenario is a symmetric case in the growth rates of the different genotypes, even if in reality it is really unlikely a context like this one. In fact the growth rate of WTG and the replication rate of the HRG are, respectively, the same under both therapies. Moreover, the growth rate of G_1 under therapy 1 is equal to the growth rate of G_2 under therapy 2, and viceversa. The second scenario has the same growth rate under both therapies in the case of the WTG and of the HRG, and asymmetric growth rates for what concerns G_1 and G_2 under therapies. The last case is the

more realistic case, it is completely asymmetric, in the sense that all the genotypes have a different dynamics under the same therapy.
The values in Table 3.3 are idealized, but they are chosen by taking into consideration clinical data and the following general principles:

1. genetic distance from the Wild Type Genotype reduces fitness:
   in the absence of any medicine, we expect that the Wild Type Genotype is the most prolific genotype, which means that it is the most fit. We suppose that the fitness decreases with the distance of the genotype from the Wild Type Genotype;

2. therapy is at best 90% effective. Without therapy we expect that the viruses increase very quickly, and from typical clinical data we suppose that without treatments the viruses' growth rates are $\rho_i = 0.5\left[day^{-1}\right]$, for $i = 1, \ldots, 4$.

3.3 Solver ode113 in MATLAB®

We use Solver ode113 in MATLAB® for computing the simulations of the two previously introduced models of HIV under treatments, because it is the Solver used for problems with stringent tolerance or that are computationally intensive. In fact, Solver ode113 has an high accuracy. Moreover, the problem type for which it is built are nonstiff ones.
It is worth noticing that, for a linear constant coefficient system, stiffness occurs if all its eigenvalues have negative real parts and the stiffness ratio is large[13] (see (**??**)). The considered models' dynamic matrices have eigenvalues with non-negative real parts. Hence, from previous definition of a stiff linear system we can conclude that we deal with nonstiff systems.

3.4 Clinical treatments using the 4 variant, 2 drug combination model

AIDsinfo [2] suggests to alternate therapies to combat the HIV and propose two ways of alternating:

1. *Switch on Virologic Failure (SVF)*:
   introduce a new regimen if there is a detectable viremia (HIV RNA $> 1000\ [copies/mL]$) and a drug-resistant genotype identified,

2. *SWitching Antiretroviral Therapy Combinations against HIV (SWATCH)*:
   alternate between two regimens every three months.

[13] Given a linear homogeneous system $\dot{\mathbf{x}} = A\mathbf{x}$, we suppose that all the real parts of eigenvalues of the dynamic matrix are negative, i.e. $\forall\lambda \in \Delta_A \implies \mathcal{R}(\lambda) < 0$. Let $\bar{\lambda}$ and $\hat{\lambda} \in \Delta_A$, defined by $\left|\mathcal{R}(\hat{\lambda})\right| \geq |\mathcal{R}(\lambda)| \geq \left|\mathcal{R}(\bar{\lambda})\right|$, $\forall\lambda \in \Delta_A$.
Thus, stiffness ratio is defined as

$$\left|\frac{\mathcal{R}(\hat{\lambda})}{\mathcal{R}(\bar{\lambda})}\right|.$$

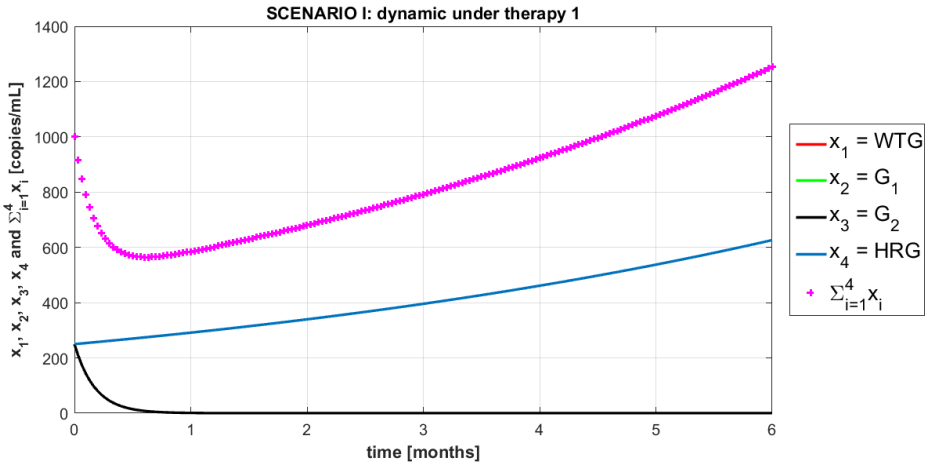
[22] shows that proactive switching (SWATCH) seems to be a more effective switching therapy than SVF one.
We carry out simulations of one year, involving the application of these two types of treatments (see Table **??**) for the smaller model in Subsection 3.2.2).
We plot the dynamics of HIV under monotherapy for only six months, because the whole trajectories aren't so interesting. Differential equations given by (3.12) and (3.13) are solved in MATLAB® using the solver ode113, as just said.

Switch on Virologic Failure (SVF):
if $\mathbf{x}(t+\tau) > 1000[copies/mL]$
if $\sigma(t) = 1$
$\sigma(t+\tau) = 2$
elseif $\sigma(t) = 2$
$\sigma(t+\tau) = 1$
endif
endif

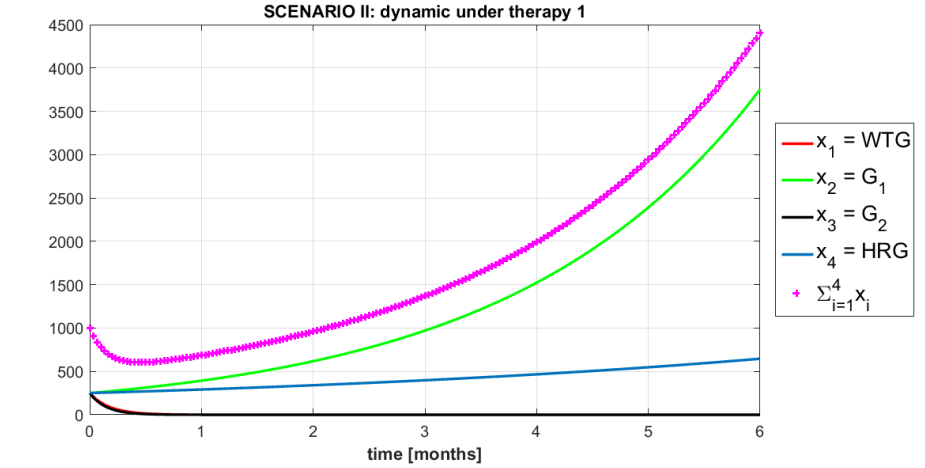
SWitch Antiretroviral Therapy Combinations against HIV (SWATCH):
switch every three months

Table 3.4: SVF and SWATCH rule.

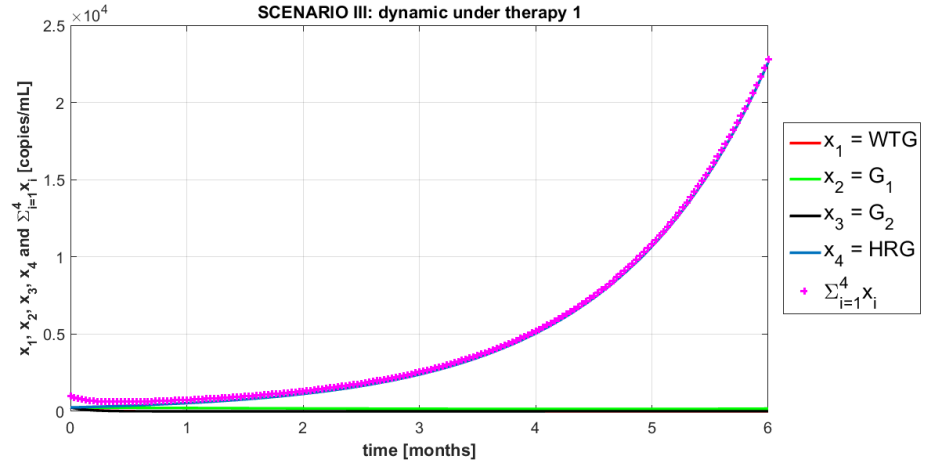
We can see by Figure 3.6a that G_2 is susceptible to therapy 1. Its trajectory coincides with WTG's one. Instead, HRG isn't suppressed under therapy 1, indeed it is continuously growing during months, as G_1 which isn't affected by therapy 1. It is the symmetric case (see Table 3.3) of the model's parameters and it is the reason why the trajectories of WTG and G_2 are equal and the same holds for the case of HRG and G_1.
The total viral concentration, for the symmetric scenario, at the end of the year is 3139 $[copies/mL]$.
For what concerns the trajectories in Figure 3.6b, it is visible that G_1 isn't affected by therapy 1, in fact it is the strain which is the most increasing during time. HRG is the genotype which hasn't an high growth rate, but it is continuously replicating during time. Therapies are projected to combat WTG, in fact it decreases. Also G_2 decreases during therapy 1, as expected.
The total viral load, for the partially asymmetric scenario under therapy 1, after one year is $5.8 \cdot 10^4$ $[copies/mL]$.
In the end, we can see in Figure 3.6c that the principal problem during therapy 1 for the asymmetric case of model's parameters is the HRG which is continuously replicating during time and it is the greatest factor of the total viral load. It is coherent with clinical data.
The total viral load, for the asymmetric scenario under therapy 1, after one year is $2.033 \cdot 10^6$ $[copies/mL]$.
All the values of viral load in the three scenarios, after one year of therapy 1, are in Table 3.5.
In Figures 3.7a, 3.7b and 3.7c are plotted the trajectories of the three cases of Table 3.3 of genotypes' growth rates under therapy 2. It is visible that the therapy can effectively combat WTG and G_1, but can't very well fight against HRG and G_2. But in the case of therapy 2, with parameters of the partially asymmetric scenario, it is possible to see that the greatest contribute to the total viral load, after one



(a) Scenario I

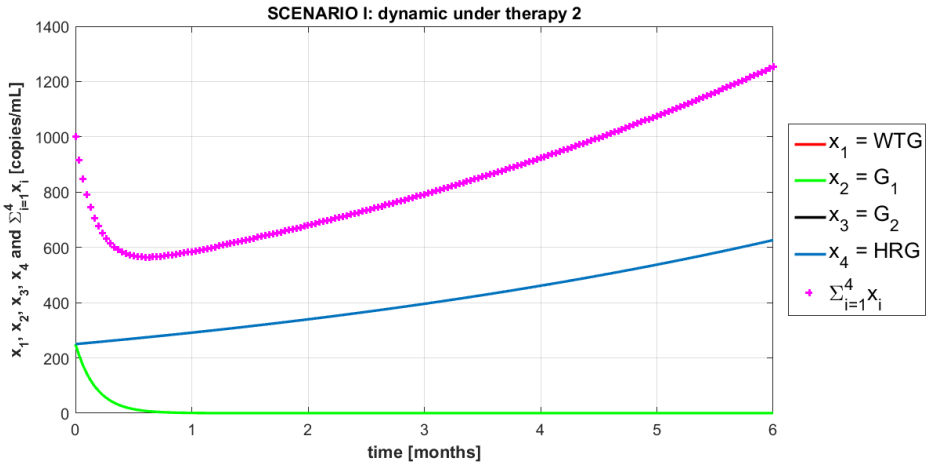


(b) Scenario II

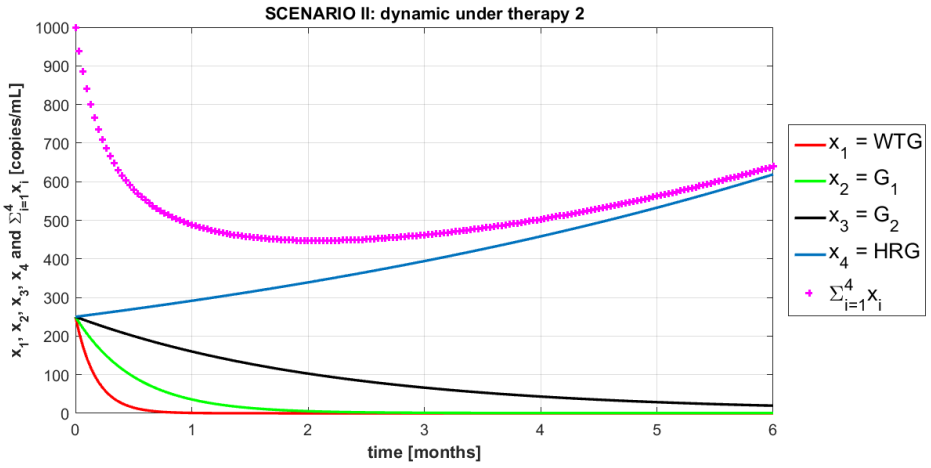


(c) Scenario III

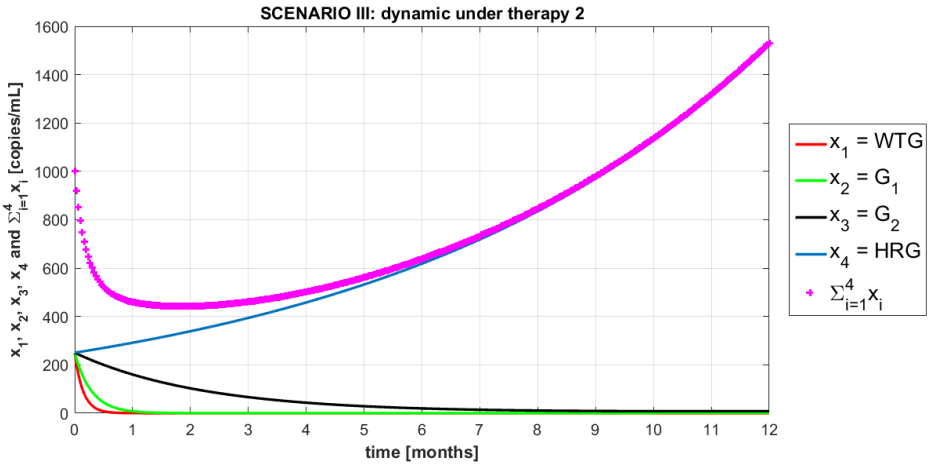
Figure 3.6: Dynamics of the small model, with $k = 1$.



(a) Scenario I



(b) Scenario II



(c) Scenario III

Figure 3.7: Dynamics of the small model, with $k = 2$.

year, is given by the HRG. It is coherent with the parameter chosen, indeed, looking at Table 3.3, we can see that $\rho_{3,2}$ (the growth rate of G_2) is smaller than $\rho_{4,2}$ (the growth rate of HRG). Instead in the case of therapy 1, with parameters of the partially asymmetric scenario, $\rho_{2,1}$ (the growth rate of G_1) is greater than $\rho_{4,1}$ (the growth rate of HRG), see Figure 3.6b. In the end, in the case of using the parameters of the asymmetric scenario, we can see that under both the two therapies the greatest contribute to the total viral load is given by the HRG, see Figure 3.6c and 3.7c.
The total viral load after one year of therapy 2 in the symmetric case is 3139 $[copies/mL]$, in the partially asymmetric case is 1533 $[copies/mL]$ and in the asymmetric case is 1532 $[copies/mL]$, see Table 3.5. Comparing the trajectories with the values of

Scenario	Virus load after 12 months with th.1 $[copies/mL]$	Virus load after 12 months with th.2 $[copies/mL]$
Symmetric	3139	3139
Partially symmetric	$5.8 \cdot 10^4$	1533
Asymmetric	$2.033 \cdot 10^6$	1532

Table 3.5: Values referring to the model (3.9), with $k = 1, 2$.

model's parameters in Table (3.3), we can see the curves are coherent with the growth rates $\rho_{i,k}$, for $i = 1,\ 2,\ 3$ and 4 and $k = 1,\ 2$. There is this strict connection because the graph of Figure 3.5 is cyrcular and symmetric, moreover the mutation rate μ is equal for all the state variables, as the decay rate δ_V.

Scenario	Virus load after 12 months $[copies/mL]$	Month of the 1^{rst} virologic failure	Month of the 2^{nd} virologic failure
Symmetric	1547	5-th	10-th
Partially symmetric	1533	3-th	10-th
Asymmetric	$7.633 \cdot 10^4$	2-th	3-th

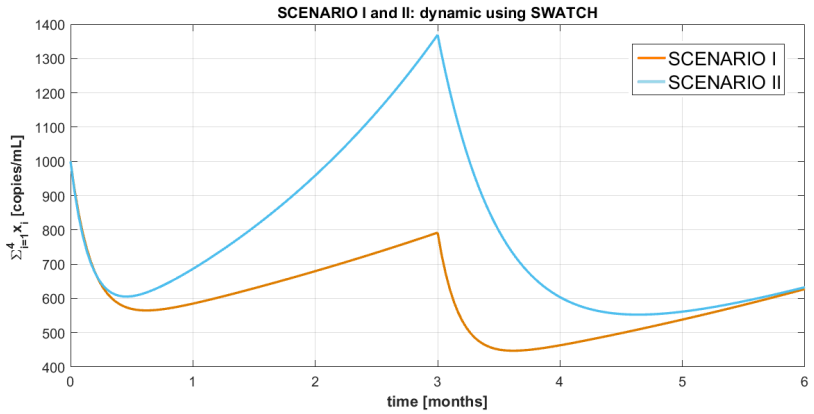
Table 3.6: Values referring to the model (3.9), using the SVF rule.

Scenario	Virus load after 12 months $[copies/mL]$	Month of the 1^{rst} virologic failure	Month of the 2^{nd} virologic failure
Symmetric	1543	9-th	10-th
Partially symmetric	1550	2-th	9-th
Asymmetric	$5.56 \cdot 10^4$	2-th	3-th

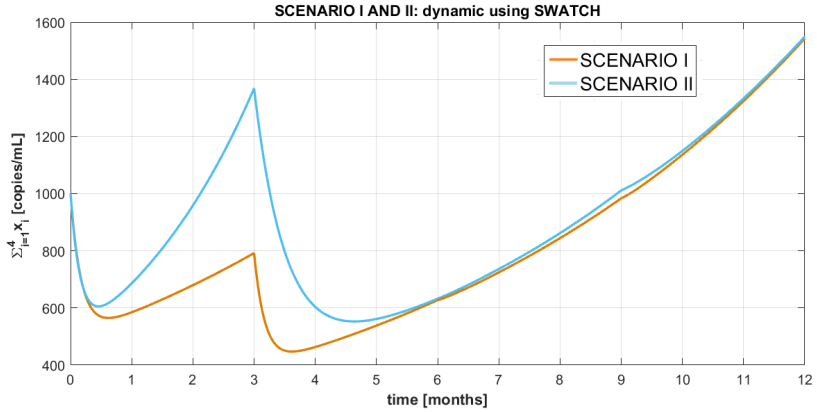
Table 3.7: Values reffering to the model (3.9), using the SWATCH rule.

It is worth noticing that using only, for example therapy 1, the values of the viral load in the three aforementioned cases are always of 10^4 $[day^{-1}]$, as order of magnitude (see Table 3.5). We use for the three cases also the two switching rules which we introduced previously, which are the Switching on Virologic Failure

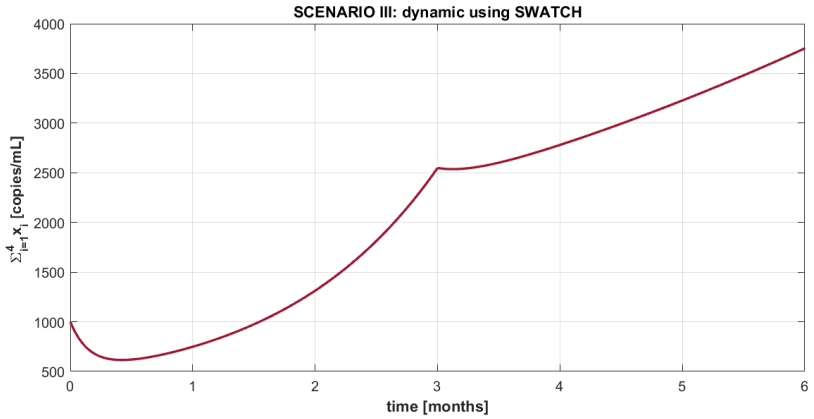
rule (SVF), i.e. switch if $V_T \geq 1000[copies/mL]$ and the SWitching Antriretroviral Therapy Combinations against HIV (SWATCH), i.e. switch every three months. In Figures 3.8 and 3.9 are depicted the trajectories, using the SWATCH rule and the SVF one, respectively. Looking at Tables 3.5, 3.6 and 3.7 it is visible that using a switching rule to treat a person affected with HIV, is better than using the same therapy throughout time. This result is coherent with clinical data [1] and [2]. In fact, by using the SWATCH rule we have decreasing in the total viral load in all the cases from 50% to two orders of magnitude. There is only the case of monotherapy with therapy 2 which has the total viral amount at the end of the year that is smaller of one order of magnitude than the viral amount under SWATCH. Probably this fact arises for the SWATCH control law isn't the best control rule in the case of the asymmetric scenario. In Figure 3.10 and Figure 3.11 the SVF rules for the three cases and the SWATCH rule are depicted.
It is worth noticing that the introduced model (given by (3.12) and (3.13)) is not robust to parameter variations: slight changes of the growth rates of the genotypes lead to strong variations of the trajectories. Clearly, the trajectories have almost the same shape, but can differ by orders of magnitude. It is reasonable to expect that a so simple model has this kind of behaviour.



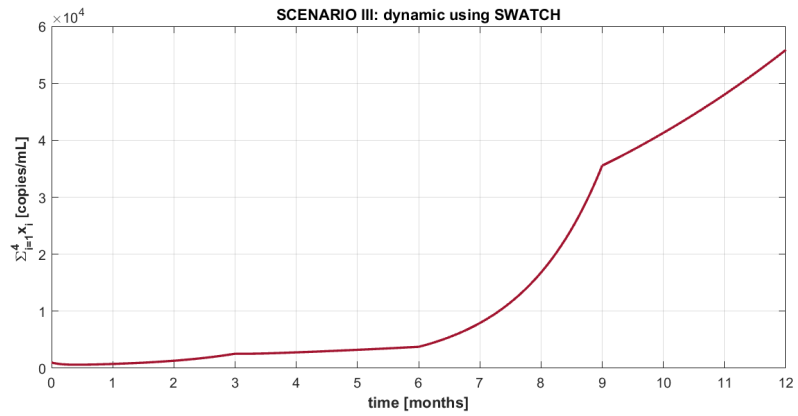
(a) Zoom of the first six months.



(b) One year of treatment.

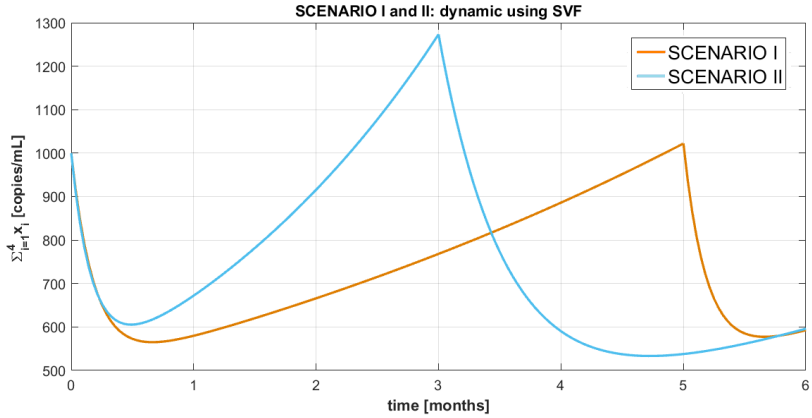


(c) Zoom of the first six months.

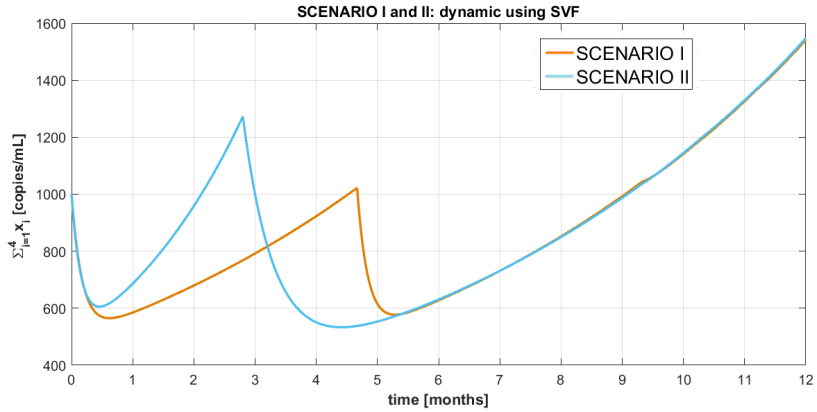


(d) One year of treatment.

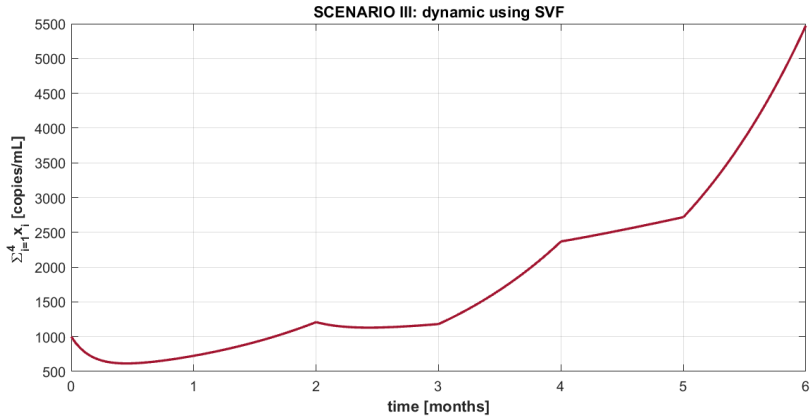
Figure 3.8: Trajectories of the three scenarios, using the SWATCH rule.



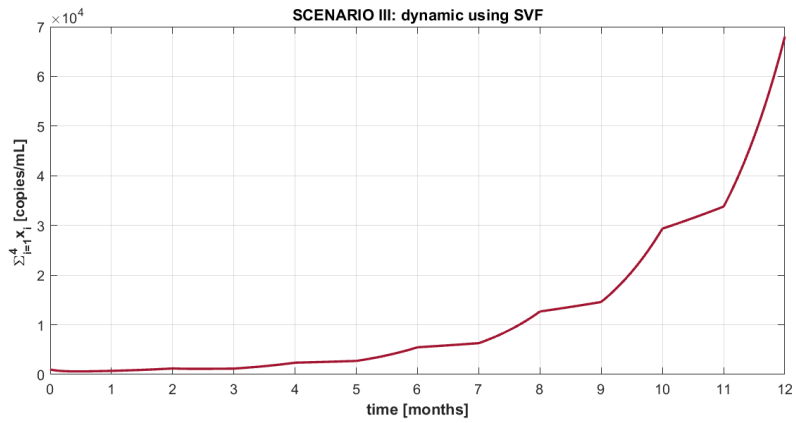
(a) Zoom of the first six months.



(b) One year of treatment.



(c) Zoom of the first six months.



(d) One year of treatment.

Figure 3.9: Trajectories of the three scenarios, using the SVF rule.

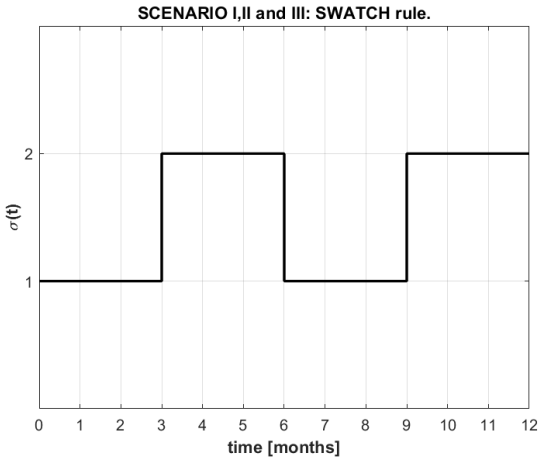


Figure 3.11: SWATCH $\sigma(t)$.

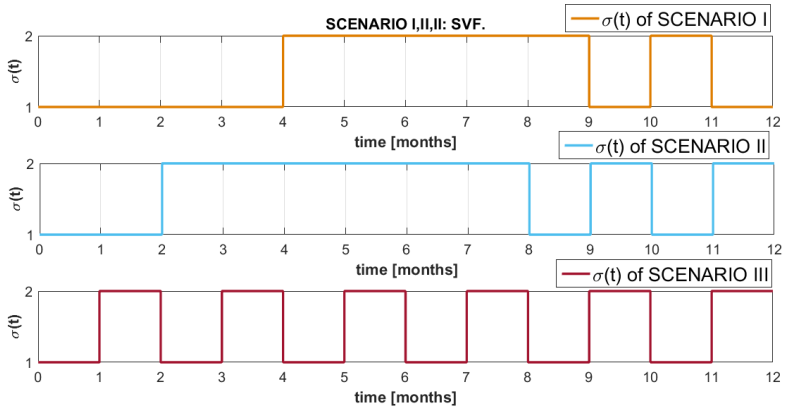
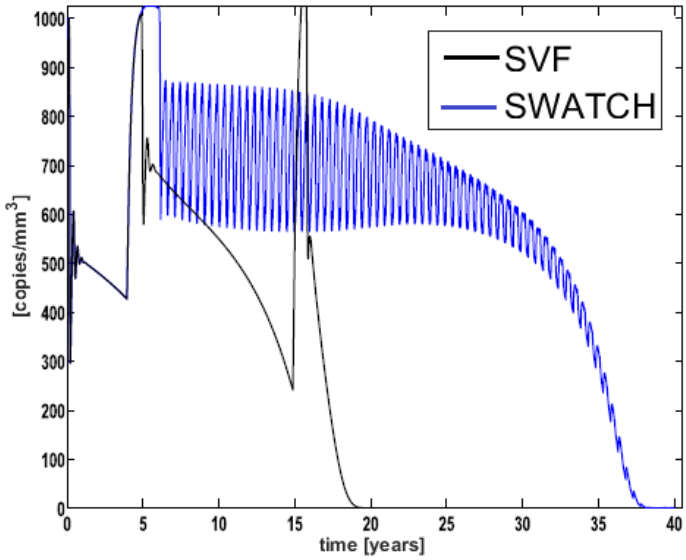


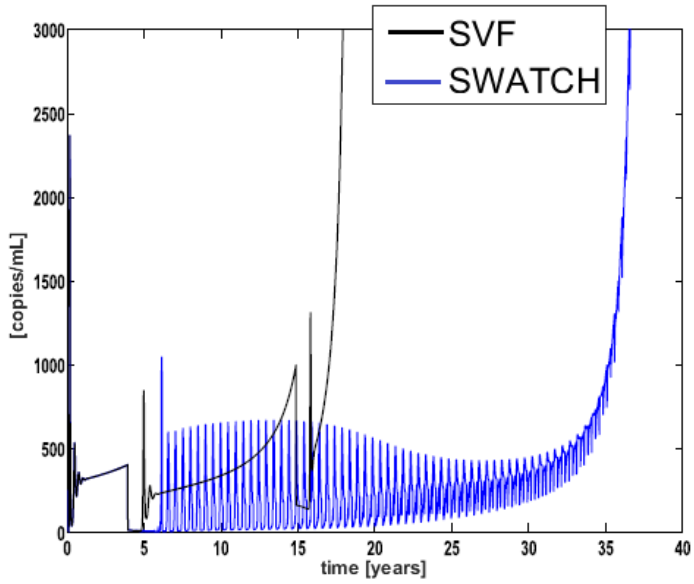
Figure 3.10: SVF $\sigma(t)$ for the three scenarios.

3.5 Clinical treatments using the 16 variant, 2 drug combination model

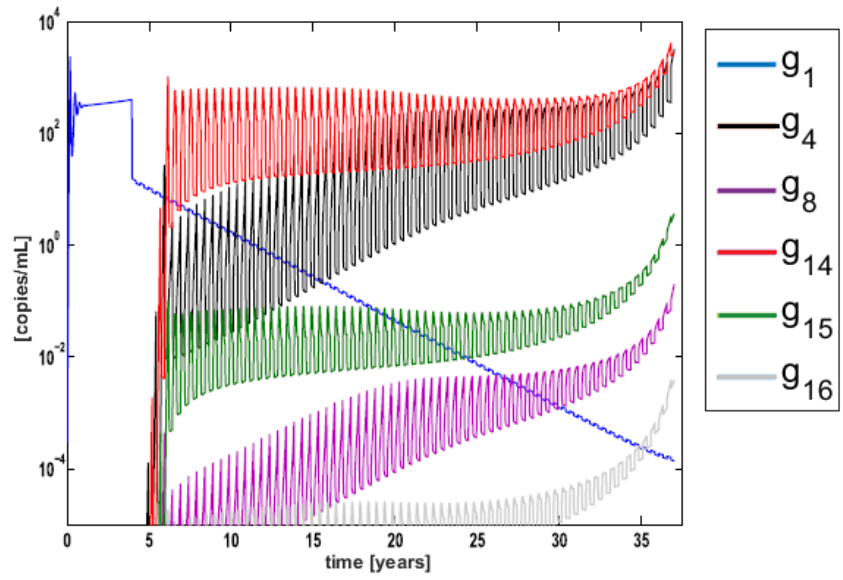
For what concerns the great model of HIV under treatment, we hypothesise to introduce treatment after four years of infection, as [2] recommends antiretroviral therapy for patients with CD4+T counts in the range $[350, 500]$ $[cells/mm^3]$ (see Figure 3.3).
We compute the trajectories using SWATCH and SVF control law. In Figure 3.12 we plot the trajectory of CD4+T cells' concentration, of total viral load and of some genotypes' concentration, using the nonlinear switched model (3.2).
Figure 3.12 shows that SVF provides a fast recovery in $CD4 + T$ count and a fast sharp drop in viral load, which is consistent with clinical observations. Moreover, it is worth noticing that, before the first virological failure the CD4+T cell's concentration is coherent with real data, in fact it is of 500 $[cells/mm^3]$. It is visible that the first virological failure is after 10 years of therapy, thus it is necessary to switch the therapy (using SVF control law) and, due to the presence of long-term reservoirs, there is another virological failure after three years.
Using the SWATCH control law, there is the first virological failure after approximately 37 years. Furthermore, in Figure 3.12 we can see that there is a normal range in CD4+T cell counts of $500 - 1500$ $\left[cells/mm^3\right]$. We can see by Figure 3.12 that, using the SWATCH control law, the final viral escape is not due to the HRG g_{16}, as we would expect. It seems that periodic oscillation promotes other genotypes to escape.
In the end it is clear that switching between therapies is better than to use only a therapy, also in the case of the great model.



(a) Dynamics of T .



(b) Dynamics of V_T.



(c) Dynamics of V_i, with $i = 1, 4, 8, 14, 15$ and 16.

Figure 3.12: Trajectories for the great nonlinear switched model of HIV, using SWATCH and SVF control law.

Chapter 4

Stability

In this chapter we introduce key concepts and theorems about the stability of p.s.s. [24] and we investigate the stability of the models of HIV under therapies introduced so far.
The stability problem of positive systems is different from the one of standard systems and the main difference is that in the first case the state variables are confined to the positive orthant (i.e. $\mathbf{x}(t) \in \mathbb{R}^n_+$, for $t \in \mathbb{R}_+$).
We discuss the stability under arbitrary switching (and the relation with the existence of certain Lyapunov functions), the stability under periodic switching and stability based on dual positive switched systems. We also discuss the equivalence, which is disproved for systems of dimension $n \geq 3$, of the stability under arbitrary switching and the Hurwitz robustness (i.e. all the matrices in the convex hull of the family of system matrices are Hurwitz[1]). Consequently, Hurwitz robustness is only a necessary condition to have stability under arbitrary switching.
In the end, we apply some theorems and notions presented in this chapter to investigate the stability of the introduced models of HIV under therapy.

4.1 Stability of continuous-time positive switched systems

A *continuous-time positive switched system* is a continuous system of type

$$\dot{\mathbf{x}}(t) = A_{\sigma(t)}\mathbf{x}(t), \quad t \in \mathbb{R}_+, \tag{4.1}$$

where $\sigma(t)\colon \mathbb{R}_+ \to \mathcal{I} \doteq \{1, 2, \ldots, M\}$ is the piecewise constant switching signal and $0 = t_0 < t_1 < \ldots$ the switching instants. Moreover, the dynamic matrices A_k, for $k \in \mathcal{I}$, are all Metzler[2].
We define with $\mathcal{D}_0$ the set of switching signals $\mathcal{D}_0 \doteq \{\sigma(\cdot) : \mathbb{R}_+ \to \{1, \ldots, M\}\, s.t.$ $\sigma(t) = const\ \forall t \in [t_k, t_{k+1}),\ and\ 0 = t_0 < t_1 < \cdots < \lim_k t_k = +\infty\}$.
Furthermore, a function $\mathbf{x} : \mathbb{R}_+ \to \mathbb{R}^n$ is a solution of (4.1) if it is continous, piecewise continuously differentiable and there is a switching signal $\sigma(t)$ such that (4.1) holds at every $t \in \mathbb{R}^+$, except at the switching istants. So, $\forall k \in \mathcal{I}$ (4.1) is an autonomous continous-time positive switched system.

[1] A square matrix is Hurwitz if and only if all its eigenvalues lie in the open left haf plane

[2] A Metzler matrix is a matrix which has non-negative diagonal elements.

Given an initial state $\mathbf{x}(\tau) = \mathbf{x}_0 \in \mathbb{R}^n_+$, a switching signal $\sigma : \mathbb{R}_+ \to \mathcal{I}$ and a pair of instants $t \geq \tau \geq 0$ the subsequent relation holds

$$\mathbf{x}(t) = \Phi(t, \tau, \sigma)\mathbf{x}_0, \tag{4.2}$$

where $\Phi(t, \tau, \sigma)$ is the *state transition matrix* in $[\tau, t]$ of the p.s.s. (4.1).
The state transiton matrix in $[\tau, t]$ is given by

$$\Phi(t, \tau, \sigma) = e^{A_{i_l}(t-t_l)} \dots e^{A_{i_1}(t_2-\tau)}, \tag{4.3}$$

where t_l are the switching istants with $l = 1, 2, \dots$.
Morover, referring to the p.s.s. (4.1), the switching istants t_l (for $l = 0, 1, \dots$) can be all isolated, so the switching signal $\sigma(t)$ is constant in $[t_l, t_{l+1})$ (for $l = 0, 1, \dots$), otherwise the switching instants are not all isolated and we talk about sliding switching signals. As a matter of fact, to study a system of type (4.1) sliding switching signals is more difficult than studing one with all isolated switching instants.
To study the stability of system (4.1), it is convenient to embed the system (4.1) and use the *bilinear system*

$$\dot{\mathbf{x}}(t) = \left(\sum_{k=1}^{M} A_k [\mathbf{u}(t)]_k \right) \mathbf{x}(t), \tag{4.4}$$

where $\mathbf{u}(t) \in \mathcal{U}_{li}^M$ is the class of locally integrable M-dimensional vector functions in the simplex $\mathcal{A}_M$[3]. The dual system (4.4) has solutions absolutely continuous almost everywhere and are coincident with the solutions of (4.1).

4.2 Exponential stability of continuous-time positive switched systems

In the whole chapter we focus on the uniform exponential stability of the origin as an equilibrium point of (4.1), because we know that attractivity, uniform attractivity, asymptotic stability, uniform asymptotic stability and, in the end, the exponential stability and the uniform exponential stability are equivalent for systems of type (4.1). We refer the interested reader to [41].

Definition 4.1. *The system (4.1) is uniformly exponentially stable (u.e.s.) if exists two real constants $C > 0$ and $\beta > 0$ such that*

$$||\mathbf{x}(t; \mathbf{x}(0), \sigma)|| \leq Ce^{-\beta t}||\mathbf{x}(0)||, \tag{4.5}$$

for every $\mathbf{x}(0) \in \mathbb{R}^n_+$, $t \in \mathbb{R}_+$ and every switching signal $\sigma \in \mathcal{D}_0$.
If (4.5) holds for every $\mathbf{x}(0) \in \mathbb{R}^n$, then, a fortiori, it holds true for every initial conditions. Viceversa, if (4.5) holds $\forall \mathbf{x}(0) \in \mathbb{R}^n_+$, we can always do the decomposition

$$\mathbf{x}(0) = \mathbf{x}_+ - \mathbf{x}_-, \tag{4.6}$$

with $\mathbf{x}_+$ and $\mathbf{x}_-$ whose entries are respectively

$$[\mathbf{x}_+]_i \doteq \begin{cases} [\mathbf{x}(0)]_i & if\ [\mathbf{x}(0)]_i > 0 \\ 0, & otherwise \end{cases}$$

[3] *Simplex* $\mathcal{A}_n \doteq \{\alpha = (\alpha_1, ..., \alpha_n) \in \mathbb{R}^n_+ : \sum_{i=1}^n \alpha_i = 1\}$.

and

$$[\mathbf{x}_-]_i \doteq \begin{cases} -[\mathbf{x}(0)]_i \;\; if \;\; [\mathbf{x}(0)]_i < 0 \\ 0, \; otherwise \end{cases} .$$

Using the linearity and the norm property, we obtain

$$\begin{aligned} &||\mathbf{x}(t;\mathbf{x}(0),\sigma)|| = ||\mathbf{x}(t;\mathbf{x}_+,\sigma) - \mathbf{x}(t;\mathbf{x}_-,\sigma)|| \\ &\leq ||\mathbf{x}(t;\mathbf{x}_+,\sigma)|| + ||\mathbf{x}(t;\mathbf{x}_-,\sigma)|| \\ &\leq Ce^{-\beta t}||\mathbf{x}_+|| + Ce^{-\beta t}||\mathbf{x}_-|| \\ &\leq 2Ce^{-\beta t}||\mathbf{x}(0)|| \end{aligned} \tag{4.7}$$

.

The condition (4.5) holds $\forall \mathbf{x}(0) \in \mathbb{R}^n$*, if C is replaced by 2C, for (4.7).*

This simple remark allows one to inherit all the results alredy derived for standard switched systems [12], [37] and [41]. First of all, an obvious necessary condition for uniform exponential stability is that all matrices A_k, for $k \in \mathcal{I}$ are Hurwitz.

Proposition 4.1. *The system (4.1) is uniformly exponentially stable (u.e.s.) only if each* $\dot{\mathbf{x}}(t) = A_k\mathbf{x}(t)$*,* $k \in \mathcal{I}$ *is u.e.s. , i.e.* $\forall A_k$*, with k in*$\mathcal{I}$ *is a Metzler and Hurwitz matrix.*

The necessary condition given by Proposition 4.1 can be strengthened, since a necessary condition for uniform exponential stability (u.e.s.) is that all convex combinations of the state matrices A_k, with $k = 1, \ldots, M$ are Metzler and Hurwitz.

Proposition 4.2. *[12] The continuous time positive switched system (p.s.s.) (4.1) is uniformly exponentially stable (u.e.s.) only if* $A(\alpha)$ [4] *is Metzler Hurwitz,* $\forall \alpha \in \mathcal{A}_M$*.*

The Proposition 4.2 is a necessary condition for the stability of a p.s.s., but it is not a sufficient condition for uniform exponential stability for p.s.s.. In fact, [30] provided the following three-dimensional counterxample.

Example

Consider the continous-time positive switched system (4.1), with $M = 2$ and $n = 3$,

$$A_1 = \begin{bmatrix} -1 & 0 & 0 \\ 10 & -1 & 0 \\ 0 & 0 & -10 \end{bmatrix} \text{ and } A_2 = \begin{bmatrix} -10 & 0 & 10 \\ 0 & -10 & 0 \\ 0 & 10 & -1 \end{bmatrix}.$$

All convex combinations of A_1 and A_2 are Hurwitz, however [30] shows that the positive switched system is not uniformly exponentially stable.

Remark. *There are classes of systems for which the condition in the Proposition 4.2 is necessary and sufficient. For example, certain classes of positive switched systems whose matrices* A_k*, with* $k \in \mathcal{I}$ *are rank one deficent*[5] *[17].*

[4] $A(\alpha) \doteq sum_{k=1}^{M} \alpha_k A_k$.

[5] Two matrices of same dimensions A and B are said to be rank one deficent when $rank(A-B) = 1$.

It is worth noticing that the particular class of matrices which have rank one difference is interesting also for what concerns the stabilizability of the p.s.s. of type (4.1). Matrices, in order to be of rank one difference, must have a particular structure. We do not show any of the theorems on p.s.s. with state matrices of rank one difference, because the state matrices of both the considered models have not such particular structure. We refer the interested reader to [16]. The connection between the exponential stability of original p.s.s. and its dual is given by the following

Proposition 4.3. *The p.s.s. (4.1) is exponentially stable if and only if the associated bilinear system (4.4) is exponentially stable, [7] and [35].*

Proposition 4.4. *[24] Uniform exponential stability of (4.4) is equivalent to uniform exponential stability of its transpose, which is*

$$\dot{\mathbf{x}}(t) = \left(\sum_{k=1}^{M} A_k^T [\mathbf{u}(t)]_k \right) \mathbf{x}(t). \tag{4.8}$$

For the previous proposition, dual conditions can be derivered from those worked out for system (4.1) by transposition, i.e. considering the matrices A_k^T, $k \in \mathcal{I}$.

4.2.1 Lyapunov functions

In this context we are interested in global stability, and so we search for positive definite functions, whose derivatives along the system trajectories are decreasing for every choice of initial condition $\mathbf{x}(0)$ and for every choice of switching signal $\sigma(t)$, with $t \in \mathbb{R}_+$.

Definition 4.2. *[24] A differentiable function $V(\mathbf{x})\colon \mathbb{R}^n \to \mathbb{R}$ is a Lyapunov function for the continous-time (positive) switched system (4.1) if it is positive definite and*

$$\begin{aligned} &\nabla V(\mathbf{x}) A_k \mathbf{x} < 0, \\ &\forall \mathbf{x} \in \mathbb{R}^n,\ \mathbf{x} \neq 0,\ \forall k \in \mathcal{I}, \end{aligned} \tag{4.9}$$

where $\nabla V(\mathbf{x}) \doteq \left[\frac{\partial V(\mathbf{x})}{\partial x_1}, \ldots, \frac{\partial V(\mathbf{x})}{\partial x_n} \right]$ is the gradient of $V(\mathbf{x})$.

Theorem 4.1. *[24] The following facts are equivalent*[6]*:*

i) the system (4.1) is u.e.s.,

ii) there exists a differentiable Lyapunov function $V(\mathbf{x})$ for the switched system (4.1), homogeneous of order 2[7]*,*

iii) there exists an infinitely differentiable (smooth) and convex Lyapunov function for the switched system (4.1).

[6] Note that these facts hold true for standard switched systems.
[7] $V(\alpha \mathbf{x}) = \alpha^2 V(\mathbf{x})$, for every $\alpha > 0$ and every $\mathbf{x} \in \mathbb{R}^n$

A polyhedral function is a function which can be written in the form

$$V(\mathbf{x}) = \max_{i\in\{1,\dots,s\}} [F\mathbf{x}]_i, \tag{4.10}$$

for some $s \times n$ full column rank matrix F.
In particular, choosing $F = W$, a symmetric polyhedral function is $V(\mathbf{x}) = ||Wx||_\infty$, or in dual form as $V(\mathbf{x}) = min\{||\mathbf{z}||_1 : \mathbf{z} > 0 \ s.t. \ \mathbf{x} = X\mathbf{z}\}$, where X is a matrix whose columns represent the vertices of the unit ball of $V(\mathbf{x})$.
These types of functions are continuous and positive definite [24].

Proposition 4.5. *The following facts are equivalent:*

i) the continous stable p.s.s. (4.1) is u.e.s.,

ii) there exists $s \in \mathbb{Z}_+$, a full row rank non-negative $n \times s$ matrix X and $s \times s$ square Metzler matrices P_k, $k \in \mathcal{I}$, s.t.

$$A_k X = X P_k, \ \mathbf{1}_s^T P_k \ll 0, \tag{4.11}$$

iii) there $s \in \mathbb{Z}_+$ full column rank non-negative $s \times n$ matrix W and $s \times s$ square Metzler matrices Q_k, $k \in \mathcal{I}$, s.t.

$$W A_k = Q_k W, \quad Q_k \mathbf{1}_s \ll 0. \tag{4.12}$$

Proposition 4.5 suggests how to compute a Polyhedral Lyapunov function for (4.1), however it can be computationally demanding, because s is a priori unknown.

It is worth noticing that the main advantage of p.s.s. is that we have to consider the non-negative orthant and for this propriety it is possible to weak the constraints on Lyapunov functions.
For p.s.s., a Lyapunov function is only:

1) differentiable,

2) copositive ($V(\mathbf{x}) > 0, \ \forall \mathbf{x} > 0$ and $V(\mathbf{x}) = 0, \ if \ \mathbf{x} = 0$).

The general search of copositive Lyapunov functions is computionally intractable, so it is better to focus on particular classes of copositive Lyapunov functions:

1. linear Lyapunov functions,

2. quadratic Lyapunov functions.

Definition 4.3. *A differentiable copositive function $V(\mathbf{x}) : \mathbb{R}^n \to \mathbb{R}$ is*

i) linear if $V(\mathbf{x}) = \mathbf{v}^T\mathbf{x}$, for some $\mathbf{v} \in \mathbb{R}^n, \ \mathbf{v} \gg 0$,

ii) quadratic copositive if $V(\mathbf{x}) = \mathbf{x}^T P \mathbf{x}$, for some matrix $P = P^T \in \mathbb{R}^{n\times n}$, such that $\mathbf{x}^T P \mathbf{x} > 0, \forall \mathbf{x} > 0$,

iii) quadratic positive definite if $V(\mathbf{x}) = \mathbf{x}^T P \mathbf{x} > 0$, for some matrix $P = P^T \succ 0 \in \mathbb{R}^{n\times n}$, $\forall \mathbf{x} \neq 0$.

Definition 4.4. *A copositive Lyapunov function is said to be*

1. *a Linear Copositive Lyapunov Function (LCLF) for (4.1) if and only if*
$$\begin{aligned} &\mathbf{v}^T A_k \mathbf{x} < 0, \ \forall k \in \mathcal{I} \text{ and } \forall \mathbf{x} > 0, \text{ which implies:} \\ &\mathbf{v}^T A_k \ll 0, \quad \forall k \in \mathcal{I}. \end{aligned} \tag{4.13}$$

2. *a Quadratic Copositive Lyapunov Function (QCLF) for (4.1) if and only if*
$$\mathbf{x}^T [A_k^T P + P A_k] \mathbf{x} < 0 \ \forall k \in \mathcal{I} \text{ and } \forall \ \mathbf{x} > 0. \tag{4.14}$$

3. *a Quadratic Positive Definite Lyapunov Function (QPDLF) for (4.1) if and only if*
$$\mathbf{x}^T [A_k^T P + P A_k] \mathbf{x} < 0, \ \forall k \in \mathcal{I} \text{ and } \forall \mathbf{x} > 0. \tag{4.15}$$

Theorem 4.2. *[24] Given a system of type (4.1), the following facts are equivalent:*

i) there exists $\mathbf{v} \gg 0$ *s.t.* $\mathbf{v}^T A(\alpha) = \mathbf{v}^T \sum_{k=1}^M \alpha_k A_k \ll 0, \forall \alpha = (\alpha_1, \dots, \alpha_M) \in \mathcal{A}_M$,

ii) there exists $\mathbf{v} \gg 0$ *s.t.* $V(\mathbf{x}) = \mathbf{v}^T \mathbf{x}$ *is an LCLF for (4.1),*

iii) there exists $P = P^T$ *of rank 1 s.t.* $V(\mathbf{x}) = \mathbf{x}^T P \mathbf{x}$ *is a QCLF for (4.1),*

iv) for each map $\pi \colon \{1, 2, \dots, n\} \to \mathcal{I}$ *the matrix* $A_\pi \doteq \left[col_1(A_{\pi(1)}) \ col_2(A_{\pi(2)}) \ \dots \ col_n(A_{\pi(n)})\right]$ *is Hurwitz,*

v) the convex hull of the columns of $\mathbb{A} \doteq [A_1 \dots A_M] \in \mathbb{R}^{n \times nM}$ *does not intersect the positive orthant of* $\mathbb{R}^n$,

vi) for every choice of M non-negative diagonal matrices D_k, $k \in \mathcal{I}$, *with* $\sum_{k=1}^M D_k = I_n$, *so* $\sum_{k=1}^M A_k D_k$ *is a Metzler Hurwitz.*

Now we see what is the relationship between LCLF, QPDLF and QCLF.

Theorem 4.3. *Given a system of type (4.1) we have:*
if there exists a LCLF for (4.1), implies that there exists a QPDLF for (4.1) and, in turn, this implies the existence a QCLF for (4.1).

Proof. 1) $\implies$ 2) Let $\mathbf{v} \gg 0$ be such that $V(\mathbf{x}) = \mathbf{v}^T \mathbf{x}$ is an LCLF for (4.1). Define $P \doteq \mathbf{v}\mathbf{v}^T + \xi I_n$, where ξ is a positive parameter to be chosen. We want to show that $V(\mathbf{x}) = \mathbf{x}^T P \mathbf{x}$ is a QPDLF for (4.1). We have that P is symmetric and positive definite $P = P^T \succ 0$, since $\mathbf{x}^T P \mathbf{x} = (\mathbf{v}^T \mathbf{x})^2 + \xi ||\mathbf{x}||^2 \geq 0$ and
$$\mathbf{x}^T P \mathbf{x} = (\mathbf{v}^T \mathbf{x})^2 + \xi ||\mathbf{x}||^2 = 0 \iff \mathbf{x} = 0.$$
Finally, for every $\mathbf{x} > 0$ and every $k \in \{1, \dots, M\}$,
$$\mathbf{x}^T (A_k^T P + P A_k) \mathbf{x} = (\mathbf{x}^T A_k^T \mathbf{v})(\mathbf{v}^T \mathbf{x}) + (\mathbf{x}^T \mathbf{v})(\mathbf{v}^T A_k \mathbf{x}) + \mathbf{x}^T [A_k \xi + \xi A_k] \mathbf{x}.$$
Set $K \doteq \{\mathbf{x} \in \mathbb{R}^n_+ : ||\mathbf{x}|| = 1\}$. K is a compact set and hence, by the Weiestrass theorem, there exist
$$-\alpha \doteq max_{\mathbf{x} \in K, k \in \{1, \dots, M\}} (\mathbf{v}^T \mathbf{x})(\mathbf{v}^T A_k \mathbf{x}) < 0$$
and
$$\beta \doteq max_{\mathbf{x} \in K, k \in \{1, \dots, M\}} \left| \mathbf{x}^T A_k \mathbf{x} \right| \geq 0.$$

If $\xi \in (0, \alpha/\beta)$, then for every $\mathbf{x} \in K$

$$\mathbf{x}^T(A_k^T P + P A_k)\mathbf{x} = 2(\mathbf{v}^T\mathbf{x})(\mathbf{v}^T A_k \mathbf{x}) + 2\xi\left(\mathbf{x}^T A_k \mathbf{x}\right) \leq -2\alpha + 2\xi\beta < 0.$$

On the other hand, for any $\mathbf{x} \in \mathbb{R}^n_+$, $\mathbf{x} \neq 0$, we have $\mathbf{x} = ||\mathbf{x}|| \cdot \bar{\mathbf{x}}$, with $\bar{\mathbf{x}} \doteq \mathbf{x}/||\mathbf{x}|| \in K$. Therefore,

$\mathbf{x}^T(A_k^T P + P A_k)\mathbf{x} = ||\mathbf{x}||^2\left(2(\mathbf{v}^T\bar{\mathbf{x}})(\mathbf{v}^T A_k \bar{\mathbf{x}}) + 2\xi\bar{\mathbf{x}}^T A_k \bar{\mathbf{x}}\right) \leq ||\mathbf{x}||^2(-2\alpha + 2\xi\beta) < 0,$

and so it is concluded the proof.

2) $\implies$ 3) is obvious.

□

Note that the existence of an LCLF is a more restrictive condition with respect to the existence of a QPDLF, as shown in the following example.

Example

Consider the 2-dimensional positive switched system (4.1), with $M = 2$ and matrices

$$\begin{bmatrix} -1 & 1 \\ 1 & -3 \end{bmatrix} \text{ and } \begin{bmatrix} -3 & 1 \\ 1 & -1 \end{bmatrix}.$$

It is not possible to find LCLF, since the matrix

$$A_\pi = [col_1(A_1)\ \ col_2(A_2)] = \begin{bmatrix} -1 & 1 \\ 1 & -1 \end{bmatrix}$$

is not Hurwitz. However it is possible to verify that both $A_1 + A_1^T \prec 0$ and $A_2 + A_2^T \prec 0$, which means that $V(\mathbf{x}) = ||\mathbf{x}||^2 = \mathbf{x}^T\mathbf{x}$ is a QPDLF.

Remark. *The existence of a QCLF for the p.s.s. (4.1) of size n is also induced by the existence of a LCLF in an extended space of size n^2.*

Stability under arbitrary switching can be checked via linear programming techniques by searching for LCLFs for systems of type (4.1).

4.2.2 Stability and periodic switching signals

Can we focus only on periodic switching signals in $\mathcal{D}_0$?

The question is if we can focus on periodic switching signals σ only, in the case of positive switched system of type (4.1), to say that it is exponentially stable.

For a continuous-time system it is proved that for low-dimension systems, periodic stability is sufficient for uniform exponential stability [35].

In the general case, periodic stability doesn't ensure uniform exponential stability. However, if the switched system is periodically exponentially stable with some finite "robustness margin" ξ, then it is u.e.s., as stated by the following theorem:

Theorem 4.4. *[24] A switched linear system is u.e.s. under arbitrary switching, if and only if there exists $\xi > 0$ such that for every period $T > 0$ and every periodic switching signal $\sigma \in \mathcal{D}_0$ of period T, the spectral-radius of $\Phi(T, 0, \sigma)$ is smaller than $1 - \xi$.*

In the following part, with the notation $\sigma = \bar{\sigma}$, we mean that we are taking a

specific switching signal $\bar{\sigma}$.

Proposition 4.6. *Assuming $\sigma = \bar{\sigma}$ and $\mathbf{q}$ a strictly positive vector, $\mathbf{q} \gg 0$, the time-varying system (4.1) corresponding to $\bar{\sigma}$ is u.e.s. if and only if the differential inequalities*

$$\dot{\mathbf{r}}(t)^T + \mathbf{r}(t)^T A_{\bar{\sigma}(t)} \ll -\mathbf{q}^T \tag{4.16}$$

have a solution $\mathbf{r}(t) \in \mathbb{R}^n_+$, differentiable almost everywhere, and s. t.

$$\bar{\mathbf{r}} < \mathbf{r}(t) < \hat{\mathbf{r}}, \quad t \geq 0, \tag{4.17}$$

for some $\bar{\mathbf{r}} \gg 0$ and $\hat{\mathbf{r}} \gg 0$.

Proof. Let $\mathbf{r}(t)$ be a solution of (4.16) with the mentioned proprieties, and let $\gamma > 0$ be such that $\bar{\mathbf{r}} \ll \gamma \mathbf{1}_n$. $V(\mathbf{x}, t) = \mathbf{r}^T(t)\mathbf{x}(t)$ is a time-varying copositive function and it is worth noticing that it is well defined since $V(\mathbf{x}, t) \leq \hat{\mathbf{r}}^T \mathbf{x}(t)$, $\forall t \geq 0$. Standard computations show that $\dot{V}(\mathbf{x}, t) < -\xi\gamma^{-1} V(\mathbf{x}, t)$, $\forall t \geq 0, \forall \mathbf{x} > 0$, where ξ is any positive number such that $\mathbf{q} \gg \xi \mathbf{1}_n$.
For, $V(\mathbf{x}, t) \gg \bar{\mathbf{r}}^T \mathbf{x}(t)$, $\mathbf{x}(t) > 0$, the uniform exponential stability follows.
On the contrary, assume that the system (4.1), for $\sigma = \bar{\sigma}$, is uniformly exponentially stable, and define

$$\mathbf{r}(t) \doteq \int_t^\infty \Phi(\tau, t, \bar{\sigma})(\mathbf{q} + \xi \mathbf{1}_n) d\tau,$$

where $\Phi(\tau, t, \bar{\sigma})$ is the state transition matrix associated with $A_{\bar{\sigma}(t)}$, and $\xi > 0$. The exponential stability of the time-varying system ensures that there exist $C > 0$ and $\beta > 0$ such that $||\Phi(\tau, t, \bar{\sigma})||_\infty < Ce^{-\beta(\tau - t)}$, for every $\tau > t \geq 0$. Taking the infinity norm of $\mathbf{r}(t)$, one gets $||\mathbf{r}(t)||_\infty \leq \frac{C}{\beta} ||\mathbf{q} + \xi \mathbf{1}_n||_\infty$ and hence $\mathbf{r}(t) < \hat{\mathbf{r}} \doteq \frac{C}{\beta}(\mathbf{q} + \xi \mathbf{1}_n)$, $t \geq 0$. So $\mathbf{r}(t)$ exists and is uniformly bounded. Also, as $A_{\sigma(t)}$ is Metzler at every time $t \geq 0$, $\Phi(\tau, t, \bar{\sigma})$ is positive at every $\tau > t \geq 0$ and there exists $\bar{\mathbf{r}} \gg 0$ such that $\mathbf{r}(t) > \bar{\mathbf{r}}$, $t \geq 0$.
In the end, a long computation shows that $\mathbf{r}(t)$ satisfies

$$\dot{\mathbf{r}}(t)^T + \mathbf{r}(t)^T A_{\bar{\sigma}(t)} = -(\mathbf{q}^T + \xi \mathbf{1}_n^T) \ll -\mathbf{q}^T. \tag{4.18}$$

□

4.2.3 Dual positive switched systems

In this subsection we give some information about the connections between the uniform exponential stability of the positive switched system (4.1) and the uniform exponential stability of the *dual system* of (4.1), namely the positive switched system

$$\dot{\mathbf{z}}(t) = A^T_{\sigma(t)} \mathbf{z}(t), \tag{4.19}$$

whose k-th subsystem is described by the Metzler Hurwitz matrix A_k^T, which is the transposed version of the one characterizing the k-th subsystem of (4.1).
Considering both the Proposition 4.3 and Proposition 4.4, we can conslude that the u.e.s. of the dual system (4.19) of (4.1) is a necessary and sufficient condition for the u.e.s. of (4.1). Thus the existence of an LCLF for the dual system (4.19) ensures the uniform exponential stability of (4.1), but the viceversa doesn't hold.

Proposition 4.7. *The existence of a LCLF for (4.1) doesn't ensure the existence of a LCLF for dual one (4.19), as shown in the following*

Example
Consider the two matrices

$$A_1 = \begin{bmatrix} -1 & 1/2 \\ 1 & -2 \end{bmatrix} \text{ and } A_2 = \begin{bmatrix} -3 & 1 \\ 1/3 & -1 \end{bmatrix}.$$

It is easly seen that no LCLF can be found, but the dual system has the LCLF $\tilde{V}(\mathbf{z}) = [1\ 1]^T\mathbf{z}$.

Proposition 4.8. *[24] Given a continous-time positive switched system (4.1), if there exist* $\mathbf{v},\ \xi \in \mathbb{R}^n_+$ *for which holds*

$$\mathbf{v}^T A_k \ll 0 \text{ and } A_k\xi \ll 0,\ \forall k \in \mathcal{I};,$$

then

$$D := diag\left(\frac{[\mathbf{v}]_1}{[\xi]_1}, \ldots, \frac{[\mathbf{v}]_M}{[\xi]_M}\right)$$

is positive definite and holds $A_k^T D + DA_k \prec 0,\ \forall k \in \mathcal{I}$.

Example
Consider the two matrices

$$A_1 = \begin{bmatrix} -1 & 0 & 0 \\ 1/16 & -1 & 1 \\ 1/100 & 1/10 & -1 \end{bmatrix} \text{ and } A_2 = \begin{bmatrix} -1 & 0 & 0 \\ 1/100 & -1 & 1 \\ 1/100 & 1/100 & -1 \end{bmatrix}.$$

By considering $\mathbf{v} = [1\ 1\ 1]^T$ and $\xi = [1\ 1\ 2]^T$ we get both $\mathbf{v}^T A_k \ll 0$ and $A_k\xi \ll 0$, for $k = 1, 2$. On the other hand, $P = diag\{1, 1, 1/2\}$ is a QPDLF for the positive switched system described by these two matrices.

4.2.4 Rate of convergence

In some cases, verifying the exponential stability of the system is not enough. Nonetheless, it is meaningful to understand if the convergence to zero of the system trajectories is sufficiently fast.

Proposition 4.9. *Given an exponentially stable positive switched system (4.1), we say that it is exponentially stable with rate of convergence* $\bar{\beta}$ *if and only if the perturbed positive switched system*

$$\dot{\mathbf{x}}_\beta(t) = [\beta I_n + A_\sigma]\,\mathbf{x}_\beta(t)$$

is exponentially stable $\forall \beta < \bar{\beta}$.
The solutions of the perturbed system and the unperturbed one, corresponding to the same initial condition $\mathbf{x}_0$ *and to the same switching signal* σ, *named* $\mathbf{x}_\beta(t; \mathbf{x}_0, \sigma)$ *and* $\mathbf{x}(t; \mathbf{x}_0, \sigma)$ *respectively, are related as follows:*

$$\mathbf{x}_\beta(t; \mathbf{x}_0, \sigma) = e^{\beta t}\mathbf{x}(t; \mathbf{x}_0, \sigma),\ \forall t \geq 0.$$

4.3 Stability of the two models of HIV under therapy

In this subsection, we study the stability of the two models of HIV under therapy, proposed in Section 3.2.2 and in Section 3.2.2.
By using the Proposition 4.1, we find that the necessary condition for the simpler model, with state matrices given by (3.13), do not hold. In fact

1. both the state matrices are Metzler, but

2. both the state matrices are not Hurwitz.

For what concerns 1. it is sufficient to analyse the structure of the state matrices.

$$A_k = \begin{bmatrix} \rho_{1,k} - \delta_V & 0 & 0 & 0 \\ 0 & \rho_{2,k} - \delta_V & 0 & 0 \\ 0 & 0 & \rho_{3,k} - \delta_V & 0 \\ 0 & 0 & 0 & \rho_{4,k} - \delta_V \end{bmatrix} + \mu \begin{bmatrix} 0 & 1 & 1 & 0 \\ 1 & 0 & 0 & 1 \\ 1 & 0 & 0 & 1 \\ 0 & 1 & 1 & 0 \end{bmatrix}, \quad k = 1, 2.$$

have the off-diagonals entries which are non-negative. In fact, all the non diagonal terms of matrices A_k, with $k = 1, 2$, are the mutation rate μ, equal to 10^{-4} $\left[\frac{mm^3}{day \cdot copies}\right]$, therefore greater than zero.
For what concerns 2. we compute the eigenvalues of A_k, with $k = 1, 2$, with the help of MATLAB® , and we find that the mentioned eigenvalues do not stay in the left s-plane. In fact, we obtain that

1. in SCENARIO I,
   $\Delta_{A_1} = \{-0.1901,\ 0.0049001,\ 0.0049001,\ 0.0051001\}$ and
   $\Delta_{A_2} = \{-0.1901,\ 0.0049001,\ 0.0049001,\ 0.0051001\}$,

2. in SCENARIO II,
   $\Delta_{A_1} = \{-0.23,\ 0.004999,\ 0.004999,\ 0.015001\}$ and
   $\Delta_{A_2} = \{-0.19,\ -0.015,\ -0.015,\ 0.0050006\}$,

3. in SCENARIO III,
   $\Delta_{A_1} = \{-0.23,\ -0.0050003,\ -0.0050003,\ 0.025\}$ and
   $\Delta_{A_2} = \{-0.23,\ -0.015,\ -0.015,\ 0.0050006\}$.

We can conclude that the necessary stability condition given by Proposition 4.1 does not hold, the system given by both the equations (4.1) and (3.13) is not stable, when using the parameter values of the three cases in Table 3.3.
By making the same considerations for the great model in subsection 3.2.2, with the help of MATLAB®, we obtain that both the state matrices are Metzler. However, the necessary condition of the Proposition 4.1 does not hold, because both the state matrices are not Hurwitz.
In fact, by defining

- $\tilde{\Delta}_{A_1} \doteq$ the set of elements in Δ_{A_1} which have real part strictly greater than zero and

- $\tilde{\Delta}_{A_2} \doteq$ the set of elements in Δ_{A_2} which have real part strictly greater than zero,

we have
$\tilde{\Delta}_{A_1} = \{0.0179,\ 0.1073,\ 0.2042,\ 0.0179,\ 0.1073,\ 0.2042,\ 0.0179,\ 0.1073,\ 0.2042,\ 0.0179,\ 0.1073,\ 0.2042\}$
and

$$\tilde{\Delta}_{A_2} = \{0.2042,\ 0.2042,\ 0.2042,\ 0.2042\}.$$

Since $\tilde{\Delta}_{A_1}$ and $\tilde{\Delta}_{A_2}$ are nonempty sets, A_1 and A_2 are not Hurwitz.

Chapter 5

Stabilization

In this chapter we provide some basic concepts about the stabilization problem of p.s.s. and we investigate the stabilizability of the models of HIV under therapies introduced in Chapter 3.
The stabilization problem is a fundamental problem which is of great interest in control theory, because the capacity of stabilizing a system is one of the main goals of control theory. However, it is worth highlighting that it is not a simple problem.

5.1 Stabilization of positive switched systems

The stabilization problem consists in finding a control input which drives the system trajectory from an initial state $\mathbf{x}(0)$ to the null state at infinite time, namely the state-trajectoriy has to converge to zero.
With the constraint of dealing with the important class of p.s.s. of the type of (4.1), the standard stabilization problem becomes the so-called *standard stabilization problem for positive switched systems*.
The main restraint of the stabilization problem for positive switched systems w.r.t. the general case stabilization one (i.e. stabilization of a non-necessarily positive system), is that the initial state $\mathbf{x}(0)$ and the system trajectory $\mathbf{x}(t)$, for $t \in \mathbb{R}_+$, have to stay in the positive orthant, for $t \in \mathbb{R}_+$. Moreover the control input in the case of p.s.s. of the type of (4.1) is the switching signal σ, and, as in the standard systems, the control input has to be choosen in an appropriate manner. Thus in many cases the switching signal σ is not a completely arbitrary switching signal.
It is worth noticing that in the case in which we want to choose σ such that the trajectory $\mathbf{x}(t)$, for $t \in \mathbb{R}_+$, converges to zero with a guaranteed rate of convergence $\bar{\beta}$, we can reduce this problem to the *standard stabilization problem*, by using the perturbed system $\dot{\mathbf{x}}_\beta(t) = \left[A_{\sigma(t)} + \beta I_n\right] \mathbf{x}_\beta(t)$ and by demonstrating that it is stabilizable $\forall \beta < \bar{\beta}$.
In order to stabilize the continous-time p.s.s. of type (4.1) we can either resort to the open loop stabilization or to the closed loop stabilization (which is also called feedback stabilization). In the case of the open loop stabilization we have that the switching signal $\sigma(t)$ depends only on the time ($\sigma(t) = \Psi(t)$), indeed, in the case of the feedback stabilization, the switching singnal $\sigma(t)$ depends on both the time t and the state value at the same time t, namely the switching signal $\sigma(t)$ is a function

of kind $\sigma(t) = \Psi(\mathbf{x}(t), t)$.
There is an interesting propriety of p.s.s. which makes them differ from the standard switched systems. In a p.s.s. the open loop stabilization and feedback stabilization are equivalent, as a consequence of the following theorems.

Theorem 5.1. *[24] For p.s.s. the following statements are equivalent:*

(i) there exists $\bar{\mathbf{x}}_0 \gg 0$ *and* $\bar{\sigma}(t),\ t \in \mathbb{R}_+$, *such that the corresponding trajectory* $\bar{\mathbf{x}}(t)$ *converges to zero,*

(ii) the p.s.s. is feedback stabilizable, which means that there exists $\sigma(t) = \Psi(\mathbf{x}(t), t)$ *such that* $\forall\ \mathbf{x}_0 > 0$ *the corresponding trajectory* $\mathbf{x}(t)$ *converges to zero,*

(iii) the p.s.s. is consistently stabilizable, which means that $\forall\ \mathbf{x}_0 > 0 \exists \sigma(t)$ *such that the corresponding trajectory* $\mathbf{x}(t)$ *converges to zero.*

In the following we refer to p.s.s. that satisfy any of the equivalent conditions in Theorem 5.1 with the term *stabilizable*.

Theorem 5.2. *[24] If a standard switched system is consistently stabilizable, then it is open-loop stabilizable. Moreover if a system is consistently stabilizable, then it can be stabilized by resorting to periodic switching signal* $\sigma(t),\ t \geq 0$. *And open loop stabilization (when achievable) can be always obtained by resorting to periodic switching signal* $\sigma(t),\ t \geq 0$.

From [15] we have the subsequent

Proposition 5.1. *Given a family* $\mathcal{A} = \{A_1, \ldots, A_M\}$ *of* $n \times n$ *matrices, the following statements are equivalent:*

i) there exists a LCLF for the family $\mathcal{A}$, *i.e. there exists a vector* $\mathbf{v} \gg 0$ *such that the function* $V(x)$ *is LCLF for all the subsystem with state matrices* A_k, *for* $k \in \mathcal{I} = \{1, \ldots, M\}$,

ii) $ker_+ [I_n| - A_1| - A_2| - A_3| \ldots | - A_M] = \{0\}$[1],

iii) the convex hull of the vector family $\mathcal{C}_{\mathcal{A}} \doteq \{col_j(A_k)\colon\ j \in \{1, \ldots, n\}, k \in \mathcal{I}\}$ *does not intersect the positive orthant* $\mathbb{R}^n_+$.

Proof. i) $\Longleftrightarrow$ ii) First of all, we notice that

$$\{\mathbf{v} \gg 0 : A_k^T \mathbf{v} \ll 0, \forall k \in \{1 \ldots, M\} = \left\{ \mathbf{v} \in \mathbb{R}^n_+ : \begin{bmatrix} I_n \\ -A_1^T \\ \vdots \\ -A_M^T \end{bmatrix} \mathbf{v} \gg 0 \right\}.$$

[1]The positive kernel of a matrix A is the intersection of its kernel and the positive orthant, namely $ker_+ A = ker A \cap \mathbb{R}^n_+$.

On the other hand, the set of right-hand side in the previous identity is the interior of the closed convex cone

$$\mathcal{K}^* \doteq \left\{ \mathbf{v} \in \mathbb{R}^n_+ : \begin{bmatrix} I_n \\ -A_1^T \\ \vdots \\ -A_M^T \end{bmatrix} \mathbf{v} \geq 0 \right\},$$

which, in turn is the dual cone of the polyhedral cone

$$\mathcal{K} \doteq Cone[I_n \ -A_1 \ \dots \ -A_M].$$

Thus, the set $\{\mathbf{v} \gg 0 : A_k^T \mathbf{v} \ll 0, \ \forall k \in \mathcal{I}\}$ is nonempty if and only if the dual cone $\mathcal{K}^*$ is solid, and this happens if and only if the cone $\mathcal{K}$ is pointed. However, as $[I_n \ -A_1 \ \dots \ -A_M]$ is devoid of zero columns, it easly seen that $\mathcal{K}$ is pointed if and only if the only non-negative vector in the kernel of $[I_n \ -A_1 \ \dots \ -A_M]$. So i) and ii) are equivalent statements.
ii) $\Longleftrightarrow$ iii) There exists a positive vector in $ker[I_n \ -A_1 \ \dots \ -A_M]$ if and only if there exist non-negative vectors $\mathbf{y}, \ \mathbf{x}_1, \dots, \ \mathbf{x}_M$ not all of them equal to zero, such that

$$\mathbf{y} = \sum_{k=1}^{M} A_k \mathbf{x}_k = \sum_{k=1}^{M} \sum_{j=1}^{n} col_j(A_k)[\mathbf{x}_k]_j.$$

Possibly rescaling $\mathbf{y}$ and the several non-negative coefficients $[\mathbf{x}_k]_j$, we can assume $\sum_{k=1}^{M} \sum_{j=1}^{n} [\mathbf{x}_k]_j = 1$, which amounts to saying that the convex hull of the family vectors $\mathcal{C}_{\mathcal{A}}$ includes a non-negative vector. So we can deduce that ii) and iii) are equivalent statements.

□

5.2 Feedback stabilization and Lyapunov functions

To choose a feedback stabilization strategy is better than to choose an open loop stabilization one. In fact the first type is more robust to parameter variations than the second one, because the feedback stabilization design takes into consideration the actual state at time t, $\mathbf{x}(t)$, and in this way it has infomation about the real parameter values of the system.

Definition 5.1. *A function $V(\mathbf{x})$ is a Copositive Control Lyapunov Function (CCLF) for the continuous-time p.s.s. $\dot{\mathbf{x}}(t) = A_{\sigma(t)}\mathbf{x}(t)$ of type (4.1) if exists a suitable feedback switching law $\sigma(t) = \Psi(\mathbf{x}(t), t)$ such that $V(\mathbf{x})$ is a copositive Lyapunov function for $\dot{\mathbf{x}}(t) = A_{\sigma(t)}\mathbf{x}(t)$ of type (4.1).*

It is equivalent to require:

1) *$V(\mathbf{x}) > 0, \forall \mathbf{x} > 0$ and $V(0) = 0$,*

2) *$D_{A_\sigma \mathbf{x}} V(\mathbf{x}) < 0$, with $D_{A_\sigma \mathbf{x}} V(\mathbf{x}) \doteq \lim_{h \to 0^+} \frac{V(\mathbf{x} + h A_\sigma \mathbf{x}) - V(\mathbf{x})}{h} < 0$, using a suitable feedback switching law $\sigma(t) = \Psi(\mathbf{x}(t), t)$, for $t \in \mathbb{R}^n_+$.*

For a standard switched system the existence of convex control Lyapunov functions is a sufficient condition for the stabilizability:
if exists a convex control Lyapunov function the standard switched system is stabilizable, but if we can't find functions of the mentioned type, the standard switched system can be stabilizable. We ask ourselves if there exists a class of control Lyapunov functions whose existence ensure the stabilizability of continuous-time p.s.s., namely we try to understand if exists a necessary and sufficient condition to have stabilizability of a p.s.s. of type (4.1).
First of all, we give a theorem that provides a necessary condition to have stabilizability of a p.s.s. of type (4.1).

Theorem 5.3. *If the p.s.s. (4.1) is stabilizable, then it admits a concave copositive control Lyapunov function $V(\mathbf{x})$, positively homogeneous of order one (i.e. $V(\alpha\mathbf{x}) = \alpha V(\mathbf{x})$, with $\alpha > 0$).*

The existence of a concave copositive control Lyapunov function $V(\mathbf{x})$, positively homogeneous of order one, is a necessary condition for having a stabilizable p.s.s..
For standard switched system, we have that a necessary condition for stabilizability is that the standard switched system admits a smooth[2], convex copositive Lyapunov function, so we ask orselves if to have a smooth copositive concave homogeneous Lyapunov function (of order one) is a sufficient condition to have stabilizability of a p.s.s.. It is proved to be true only for two-dimensional systems.

Theorem 5.4. *[23] For a p.s.s. of type (4.1) the following statements are equivalent and sufficient, but in general not necessary for exponential stabilizability:*

i) The system admits a copositive, positively homogeneous of order one, smooth control Lyapunv function s.t.

$$\min_{k\in\{1,\dots,M\}} \nabla V(\mathbf{x}) A_k \mathbf{x} \leq -\beta^* V(\mathbf{x}),\ \forall \mathbf{x} > 0,\ \textit{for some } \beta^* > 0; \tag{5.1}$$

ii) there exists $\alpha \in A_M$ s.t. $A(\alpha) = \sum_{k=1}^{M} \alpha_k A_k$ is Hurwitz,

iii) the system admits a linear copositive control Lyapunv function $V_L(\mathbf{x}) = \mathbf{v}^T\mathbf{x}$, with $\mathbf{v} \gg 0$.

Proof. For semplicity, we suppose that the state matrices are irreducible[3]. The standard case may be deduced from the irreducible one, by considering the irreducible matrices $A_k + \xi \mathbf{1}_n \mathbf{1}_n^T$, with $\xi > 0$ and then considering $\xi \to 0^+$.
i) $\Rightarrow$ *iii)* Suppose that there exists an Hurwitz convex combination

$$A(\alpha) = \sum_{k=1}^{M} \alpha_k A_k, \quad \alpha_k \geq 0, \quad \sum_{k=1}^{M} \alpha_k = 1,$$

and let $\mathbf{v} \gg 0$ be the strictly positive left eigenvector of $A(\alpha)$ associated with the Frobenius eigenvalue $\lambda_F < 0$[4]. For the hypothesis that all the state matrices

[2] With "smooth", we mean continously differentiable.

[3] A Metzler matrix is irreducible when there not exist a permutation matrix Π s.t.

$$\Pi^T A \Pi = \begin{bmatrix} A_{11} & A_{12} \\ 0 & A_{22} \end{bmatrix},$$

A_{11} ed A_{22} are square nonvacous matrices.

[4] $\lambda_F \in \Delta_A \doteq$ the Frobenius eigenvalue which is such that $\Re(\lambda_F) > \Re(\lambda)$, $\forall \lambda \in \Delta_A$ and $\lambda \neq \lambda_F$.

are irreducible, all the matrices $A(\alpha)$ are irreducible. By considering the linear copositive Lyapunov function $V_L(\mathbf{x}) = \mathbf{v}^T\mathbf{x}$, by linearity for every $\mathbf{x} > 0$ we have

$$\min_{k=1,\dots,M} \mathbf{v}^T A_k\mathbf{x} \leq \mathbf{v}^T A(\alpha)\mathbf{x} = \lambda_F \mathbf{v}^T\mathbf{x} = \lambda_F V_L(\mathbf{x}),$$

with $\lambda_F < 0$.
So we can conclude that the switching strategy $\sigma(t) = arg\ min_k \mathbf{v}^T A_k\mathbf{x}(t)$ is stabilizing. This shows that $V_L(\mathbf{x}) = \mathbf{v}^T\mathbf{x}$ is a linear copositive control Lyapunov function.
iii) $\Rightarrow$ *ii)* It is obvious, since a linear copositive Lyapunov function is smooth and positively homogeneous of order one, and satisfies (5.1).
i) $\Rightarrow$ *ii)* Here we report only a draft of the proof and for the whole proof see [23]. Assume that there exists a copositive, positively homogeneous of order one, smooth control Lyapunov function, for which

$$\min_k \nabla V(\mathbf{x}) A_k\mathbf{x} \leq -\beta^* V(\mathbf{x}),$$

for some positive $\beta^* > 0$. For any $\beta < \beta^*$, consider the following "relaxed condition":

$$\min_{\alpha\in\mathcal{A}_M} \nabla V(\mathbf{x}) A(\alpha)\mathbf{x} \leq -\beta V(\mathbf{x}). \tag{5.2}$$

For each $\mathbf{x} > 0$ define the convex set-valued map,

$$\Omega(\mathbf{x}) = \{\alpha \in \mathcal{A}_M : \nabla V(\mathbf{x}) A(\alpha)\mathbf{x} \leq \beta V(\mathbf{x})\}.$$

The set Ω has a non-empty relative interior in $\mathcal{A}_M$ for any $\mathbf{x} > 0$, because we choose $\beta < \beta^*$, and by the continuity of the gradient, it is a convex continuous set-valued map. Therefore, there exists a continuous function $\bar{\alpha}(\mathbf{x})$, such that $\bar{\alpha}(\mathbf{x}) \in \Omega(\mathbf{x})$, for all $\mathbf{x} \gg 0$.
Now we take the following two functions respectively from $\mathcal{A}_n$ to $\mathcal{A}_M$ and vice versa:

$$\mathbf{x} \to \bar{\alpha}(\mathbf{x})$$

and

$$\alpha \to \mathbf{v}_F(\alpha),$$

where $\mathbf{v}_F(\alpha)$ is the strictly positive Frobenius eigenvector associated with $A(\alpha)$, normalized such that $\mathbf{1}_n^T\mathbf{v}_F(\alpha) = 1$. Note that $\mathbf{v}_F(\alpha)$ is a positive continuous function of α. The composed map from $\mathcal{A}_n$ to $\mathcal{A}_M$

$$\mathbf{x} \to \bar{\alpha}(\mathbf{x}) \to \mathbf{v}_F(\bar{\alpha}(\mathbf{x}))$$

is continuous and admits a fixed point $\tilde{\mathbf{x}}$, because $\mathcal{A}_n$ is convex and compact. For such point we have

$$\nabla V(\tilde{\mathbf{x}}) A(\tilde{\alpha})\tilde{\mathbf{x}} = \tilde{\lambda}_F \nabla V(\tilde{\mathbf{x}})\tilde{\mathbf{x}} \leq -\beta V(\tilde{\mathbf{x}}),$$

where $\tilde{\alpha} \doteq \bar{\alpha}(\tilde{\mathbf{x}})$ and $\tilde{\lambda}_F$ is the Frobenoius eigenvalue associated with $A(\tilde{\alpha})$. On the other hand, any positively homogeneous smooth function is such that

$$V(\mathbf{x}) = \nabla V(\mathbf{x})\mathbf{x}.$$

This implies that the last inequality can be written as

$$\lambda_F V(\tilde{\mathbf{x}}) \leq -\beta V(\tilde{\mathbf{x}})$$

and so $\lambda_F < 0$. This ensures that $A(\tilde{\alpha})$ is Hurwitz.

□

A stabilizing strategy is $\sigma(t) \in \{\sigma(t)\ s.t.\ arg\ \min_{k\in\mathcal{I}} \mathbf{v}^T A_k\mathbf{x}(t)\}$.

Proposition 5.2. *A second order continuous-time p.s.s. is stabilizable if and only if exists $\alpha \in A_M$ such that $A(\alpha)$ is Hurwitz, [23].*

For the following part, for semplicity we assume that A_k, with $k \in \{1, \dots, M\}$, have to be irreducible.
The previous discussion suggests that have two cases:

1. *Lucky case*: If we find a Hurwitz convex combination of the systems' matrices $A_k,\ k \in \mathcal{I}$, then a linear control Lyapunov functions can be inferred from its left Frobenius eigenvector.

2. *Unucky case:* We can't find a Hurwitz convex combination of the systems' matrices $A_k,\ k \in \mathcal{I}$, then we can't find a smooth, positively homogeneous of order one, control Lyapunov function, so we have to find more general classes of control Lyapunov functions, as the minimum of linear copositive Lyapunov functions.

It is because we negate one of the equivalent conditions that we have in the previous theorem (Theorem 5.4) is equivalent: to negate (ii) is equivalent to negate (i).
The existence of linear copositive control Lyapunov function can be known by using *linear programming techniques.*

Definition 5.2. *$V_L(\mathbf{x}) = \mathbf{v}^T\mathbf{x}$ is a Linear Copositive Control Lyapunov Function (LCCLF), with $\mathbf{v} \gg 0$, a strictly positive vector, if and only if for any vector $\boldsymbol{x}$ in the closed positive simplex $\mathcal{A}_n$, there is at least one choice of the matrix A_k such the derivative of V_L along the k-th subsystem is negative:*

$$\min_{k=1,\dots,M} \mathbf{v}^T A_k \mathbf{x} < 0,\ \forall \mathbf{x} \in \mathcal{A}_n.$$

The previous condition is not verified if and only if the sets $\mathcal{P}_k := \left\{\mathbf{x} \in \mathcal{A}_n \colon \mathbf{v}^T A_k \mathbf{x} \geq 0\right\}$, for $k = 1, \dots, M$, have a non-empty intersection with the positive orthant.

It is worth exploring what is the relation between the existence of copositive control linear, quadratic positive definite and quadratic Lyapunov functions.
All these functions are smooth and the condition that the functions are decreasing along the systems' trajectories can be checked by verifying that

$$\min_{k=1,\dots,M} \nabla V(\mathbf{x}) A_k \mathbf{x} < 0,\ \forall \mathbf{x} > 0.$$

Theorem 5.5. *If exists a LCCLF, then exists a QCCPDLF and this, in turn, implies the existence of a QCCLF.*

We introduce the definition of the convex hull of vectors $\mathbf{v}_1,\ \dots,\ \mathbf{v}_n$ in $\mathbb{R}^n$, because it will be useful subsequently.

Definition 5.3. *The convex hull of vectors $\mathbf{v}_1,\ \dots,\ \mathbf{v}_n$ in $\mathbb{R}^n$ is the set of vectors*

$$\left\{ \sum_{k=1}^{n} \alpha_k \mathbf{v}_k : (\alpha_1, \dots, \alpha_n) \in \mathcal{A}_n \right\},$$

where $\mathcal{A}_n$ is the simplex set[5].

[5] *Simplex* $\mathcal{A}_n \triangleq \left\{\alpha = (\alpha_1, ..., \alpha_n) \in \mathbb{R}^n_+ : \sum_{i=1}^n \alpha_i = 1\right\}$.

5.3 Other feedback stabilization techniques

The purpose of this subsection is to provide additional stabilization techniques for positive switched systems with respect to the ones investigated previously, in order to drive the state to zero starting from any positive initial condition.
In particular, we consider two feedback stabilization techniques:

1. one based on *Lyapunov Metzler inequalities*, the feasibility of such inequalities is a sufficient condition for stabilizability (of continuous-time p.s.s.), but their existence is not necessary;

2. one based on piecewise LCCLF (Linear Copositive Control Lyapunov Function), the existence of such functions is a sufficient condition for stabilizability (of continuous-time p.s.s.).

5.4 Lyapunov Metzler Inequalities (LMIs)

Previously we focused our attention on linear and quadratic copositive control Lyapunov functions, but this strategy is too restrictive.
A different approach to the stabilization problem consists in searching for sufficient conditions for the existence of copositive control Lyapunov functions of the type:

$$V(\mathbf{x}) = \min_{k=1,\dots,M} V_k(\mathbf{x}),$$

with $V_k(\mathbf{x})$ suitable smooth functions and $\forall\ \mathbf{x} > 0\ \exists k \in \mathcal{I}$ such that $\dot{V}_k(\mathbf{x}) < 0$.
Lyapunov inequalities parametrized by the entries of a Metzler matrix (this idea was first proposed by [27]) can be seen as quadratic matrix inequalities, which are named *Lyaunov Metzler inequalities*.
We denote with $\mathcal{P}_M := \left\{\Lambda \in \mathbb{R}^{M\times M} : \Lambda \mathbf{1}_M = \mathbf{0}\right\}$, with Λ a Metzler matrix.
The following theorem is taken from [23].

Theorem 5.6. *If exist strictly positive vectors $\mathbf{v}_k \gg 0$, $k \in \mathcal{I}$ and $M(M-1)$ non-negative parameters λ_{kj}, with $k, j = 1,\dots,M$ with $k \neq j$ s.t. the following Lyapunov Metzler inequalities hold:*

$$A_k^T \mathbf{v}_k + \sum_{j=1, j\neq k}^{M} \lambda_{kj}(\mathbf{v}_j - \mathbf{v}_k) \ll 0,\ k = 1,\dots,M, \tag{5.3}$$

then the continuous-time p.s.s. of type (4.1) is stabilizable. If it is the case, the stabilizing state feedback laws are given by

$$\sigma(t) \in \{\sigma(t)\ s.t.\ arg \min_{l=1,\dots,M} \mathbf{v}_l^T \mathbf{x}(t)\}. \tag{5.4}$$

Proof. Consider the proposed piecewise linear copositive control Lyapunov function $V(\mathbf{x}) = min_{k=1,\dots,M} \mathbf{v}_k^T \mathbf{x}$. Let $\mathcal{I}(\mathbf{x})$ be the sets of all indices l such that $\mathbf{v}_l^T \mathbf{x} \leq \mathbf{v}_r^T \mathbf{x}$ (i.e. $(\mathbf{v}_l - \mathbf{v}_r)^T \mathbf{x} \leq 0$) for every $r \neq l$. If k is the active mode at time t, $\sigma(t) = k$, computing the Dini derivative of $V(\mathbf{x})$ leads to

$$D^+ V(\mathbf{x}) = \min_{r\in\mathcal{I}(\mathbf{x})} \mathbf{v}_r^T A_k \mathbf{x} \leq \mathbf{v}_k^T A_k \mathbf{x},$$

and

$$D^+V(\mathbf{x}) < \sum_{j=1,j\neq k}^{M} \lambda_{kj}(\mathbf{v}_k - \mathbf{v}_j)^T\mathbf{x} \leq 0.$$

□

We do some observations about the previous theorem:

i) the compact form of the LMIs is $\mathbf{v}^T\tilde{A} \ll 0$, where $\mathbf{v}$ is an nM-dimensional vector whose k-th block is $\mathbf{v}_k,\ k \in \{1,\dots,M\}$ and

$$\tilde{A} = \begin{bmatrix} A_1 & \lambda_{21}I_n & \dots & \lambda_{M1}I_n \\ \lambda_{12}I_n & A_2 & \dots & \lambda_{M2}I_n \\ \vdots & \vdots & \dots & \vdots \\ \lambda_{1M}I_n & \lambda_{2M}I_n & \dots & A_M \end{bmatrix},$$

ii) the LMIs are linear when we fix the Metzler matrix Λ,

iii) the search of $\Lambda \in \mathcal{P}_M$ is equivalent to have that the associated augmented matrix $\tilde{A}$ is Hurwitz.

Proposition 5.3. *The continuous-time p.s.s. is stabilizable if there exists $\Lambda \in \mathcal{P}_M$, vectors $\mathbf{v}_k \gg 0,\ k \in \{1,\dots,M\}$, and a scalar $\mathcal{T} > 0$, s.t.*

$$\mathbf{v}_k^T A_k + \sum_{j=1,j\neq k}^{M} \lambda_{kj}(\mathbf{v}_j^T e^{A_j\mathcal{T}} - \mathbf{v}_k^T) \ll 0,\ k = 1,\dots,M.$$

Let $t_l,\ l = 0,1,\dots$ denote the switching istants with $t_0 = 0$. Then it is proved that the system is stabilizable, by choosing

$$\sigma(t) = \begin{cases} \sigma(t^-), & t - t_l \leq \mathcal{T} \text{ or } \mathbf{v}_k^T x \leq \mathbf{v}_j e^{A_j\mathcal{T}}\mathbf{x},\ \forall j \neq k; \\ arg\ min_k \mathbf{v}_k^T e^{A_k\mathcal{T}}\mathbf{x}, & otherwise. \end{cases}$$

Note that the switching laws are a mixed of open-loop switching rules and closed-loop ones.

5.5 Picewise Linear Copositive Control Lyapunov functions

Now we provide a necessary and sufficient condition for positive exponential stabilizability.

Proposition 5.4. *A continuous-time p.s.s. is exponentially stabilizable if and only if exists* $N \in \mathbb{Z}_+$ *and exist* $\mathbf{v}_k \gg 0,\ k \in \{1, \dots, N\}$ *s.t.*

$$V(\mathbf{x}) = min_{k\in\{1,\dots,N\}} \mathbf{v}_k^T \mathbf{x}$$

is a control copositive Lyapunov function.

It is worth noticing that all the sufficient conditions for stabilizability of p.s.s. which we have seen in the previous sections are based on the existence of Lyapunov functions, or on the feasibility of the LMIs. And the existence conditions are very difficult to verify or, vice versa, it is very hard to demonstrate that these type of conditions don't hold.

5.6 Stabilizability of the two HIV models under therapies models

In this section, we apply some theorems which we presented in the previous sections to try to find out if the HIV under therapies models are stabilizable, or not.
For clinical data, we expect that sufficient conditions for stabilizability of the introduced HIV under therapies models don't hold.
For Proposition 5.1, we know that if we find that $ker_+[I_n| - A_1| - A_2]$ doesn't contain only the null-vector it is equivalent to the nonexistence of LCLFs for the family $\mathcal{A} = \{A_1, A_2\}$.
Thus, with MATLAB®, we compute the orthonormal basis of the kernel of the matrix

$$[I_n \,|-A_1\,|-A_2]\,.$$

We only report the results for the smaller model (the 4 variant, 2 drug combination model in Section 3.2.2). We do not report the computations for the case of the great model[6] (the 16 variant, 2 drug combination model in Section 3.2.2), because it entails formulas which are too big.
Using the parameters of the symmetric scenario of Table 3.3, we obtain:

$$= ker_+ [I_n \,|-A_1\,|-A_2] = [\mathbf{v}_1\ \mathbf{v}_2\ \dots \mathbf{v}_{12}] =$$

$$= ker_+ \begin{bmatrix} 1 & 0 & 0 & 0 & 0,1900 & -0,0001 & -0,0001 & 0 & 0,1900 & -0,0001 & -0,0001 & 0 \\ 0 & 1 & 0 & 0 & -0,0001 & -0,0050 & 0 & -0,0001 & -0,0001 & 0,1900 & 0 & -0,0001 \\ 0 & 0 & 1 & 0 & -0,0001 & 0 & 0,1900 & -0,0001 & -0,0001 & 0 & -0,0050 & -0,0001 \\ 0 & 0 & 0 & 1 & 0 & -0,0001 & -0,0001 & -0,0050 & 0 & -0,0001 & -0,0001 & -0,0050 \end{bmatrix}.$$

[6]It is possible to prove that there exists a non-null vector in $ker_+ [I_n \,|-A_1\,|-A_2]$, using A_σ, $\sigma = 1, 2$ of the great model.

We compute an orthonormal basis of the $ker[I_4 \mid -A_1 \mid -A_2]$, whose vectors we display in the following matrix:

$$\begin{bmatrix} -1.0000 & 0 & -0.0022 & 0 \\ 0.0016 & -0.7071 & -0.7071 & -0.0005 \\ 0.0016 & 0.7071 & -0.7071 & -0.0005 \\ 0 & 0 & 0.0007 & -1.0000 \end{bmatrix} \doteq [\tilde{\mathbf{v}}_1|\tilde{\mathbf{v}}_2|\tilde{\mathbf{v}}_3|\tilde{\mathbf{v}}_4]\,.$$

Now, we try to find non-null vectors in $ker_+[I_4|-A_1|-A_2]$.
The first elements of vectors $\tilde{\mathbf{v}}_k$, with $k = 1, \ldots, 4$, are negative or null. Thus, to obtain $ker_+[I_4|-A_1|-A_2]$, we compute the linear combinations

$$\hat{\alpha}\tilde{\mathbf{v}}_1 + \hat{\beta}\tilde{\mathbf{v}}_2 + \hat{\gamma}\tilde{\mathbf{v}}_3 + \hat{\delta}\tilde{\mathbf{v}}_4,$$

with $\hat{\alpha} = \hat{\gamma} = 0$ or with $\hat{\alpha} < 0$ and $\hat{\gamma} < 0$.
Thus, considering the first case, we obtain

$$\hat{\beta}\tilde{\mathbf{v}}_2 + \hat{\delta}\tilde{\mathbf{v}}_4.$$

By choosing $\hat{\beta} = \hat{\delta} = -1$, we obtain a positive vector which is non-null: $\hat{\beta}\tilde{\mathbf{v}}_2 + \hat{\delta}\tilde{\mathbf{v}}_4 \in \mathbb{R}^4_+/\{\mathbf{0}\}$.
So, by applying the Proposition 5.1, if we find a non-null positive vector which belongs to $ker_+ [I_n \mid -A_1 \mid -A_2]$. This is equivalent to the nonexistence of a LCLF[7] for the family $\mathcal{A} = \{A_1,\ A_2\}$. Thus, by using Theorem 5.4, we can infer that a sufficient condition for stabilizability doesn't hold.

[7]It is worth noticing that some articles' authors, as E. Fornasini, use CLCLF to identify a common linear Lyapunov function for the M subsystems which is a linear copositive Lyapunov function for each of them. For Definition 4.13 is Section 4.2.1, it is easy to verify that the definition of LCLF used in this work is equivalent to the Fornasini's definition.

Chapter 6

Optimal and Suboptimal Control for p.s.s.

In the following chapter, we address the problem of Highly Active Antiretroviral Therapy (HAART) scheduling, using a control theoretic approach.
First of all, we deal with the optimal control problem and we also explain its great criticality, which is the computation the optimal solution. The computation of the optimal law is a hard task to be accomplished, even numerically. For this reason, looking for suboptimal solutions may be convenient. In this regard, two different approaches are considered. Firstly, switching strategies designed by means of CLFs are tested using the 4 variant, 2 drug combination model. Secondly, a Luenberger observer is designed in order to obtain an approximation of the state, by exploiting information given by the output of the nonlinear model. Thus, we find out a suboptimal control based on the state estimate (a Guaranteed Cost control) and we apply it to the nonlinear model. Finally, we briefly explain another way to compute an optimal control law, which is the Model Predictive Control (MPC). We use the state estimate to compute the MPC, then we apply it to the nonlinear model. Most of the information in this chapter is taken from [6] and [22].

6.1 Optimal control

We consider the switched positive system on a finite time interval,

$$\begin{aligned} \dot{\mathbf{x}}(t) &= A_{\sigma(t)}\mathbf{x}(t), \quad t \in \mathbb{R}_+, \\ \mathbf{x}(0) &= \mathbf{x}_0. \end{aligned} \tag{6.1}$$

Where $\mathbf{x}(t) \in \mathbb{R}_n^+$ is the state variable vector, $\sigma(t)$ the switching signal, $\mathbf{x}_0 \in \mathbb{R}_+^n$ the initial condition and A_k, for $k = 1, \ldots, M$ are Metzler matrices.
We introduce the cost functional which is the tool to compute the optimal control. The cost functional, in this kind of problems, has to be minimized over all admissible switching sequences and is given by

$$J(\mathbf{x}_0, \mathbf{x}, \sigma) = \int_0^{t_f} \mathbf{q}_{\sigma(t)}^T \mathbf{x}(t)dt + \mathbf{c}^T \mathbf{x}(t_f), \tag{6.2}$$

where $\mathbf{x}(t)$ is a solution of (6.1) and $\sigma(t)$ is a switching signal. Vectors $\mathbf{q}_k$, $k = 1, \ldots, M$ and $\mathbf{c}$ are assumed to be positive.

The optimal switching signal, the corresponding trajectory and the optimal cost functional are named as $\sigma^o(t, \mathbf{x}_0)$, $\mathbf{x}^o(t)$ e $J(\mathbf{x}_0, \mathbf{x}^o, \sigma^o)$, respectively.

Theorem 6.1. *Let $\sigma^o(t, \mathbf{x}_0) : [0, t_f] \times \mathbb{R}^n_+ \to \mathcal{I} = \{1, \ldots, M\}$ be an admissible switching signal relative to $\mathbf{x}_0$, and $\mathbf{x}^o(t)$ be the corresponding trajectory. Let $\pi^o(t)$ denote a positive vector solution of the system of differential equations (the Pontryagin equations)*

$$\dot{\mathbf{x}}^o(t) = A_{\sigma^o(t,\mathbf{x}_o)}\mathbf{x}^o(t) \tag{6.3}$$

$$-\dot{\pi}^o(t) = A^T_{\sigma^o(t,\mathbf{x}_o)}\pi^o(t) + \mathbf{q}_{\sigma^o(t,\mathbf{x}_o)} \tag{6.4}$$

$$\sigma^o(t, \mathbf{x}^o) = arg\min_{k\in\mathcal{I}} \left\{ \pi^{oT}(t) A_k \mathbf{x}^o(t) + \mathbf{q}_k^T \mathbf{x}^o(t) \right\}, \tag{6.5}$$

with the boundary conditions $\mathbf{x}^o(0) = \mathbf{x}_0$ and $\pi^o(t_f) = \mathbf{c}$. Then $\sigma^o(t, \mathbf{x}_0)$ is an optimal switching signal relative to $\mathbf{x}_0$ and the value of the optimal cost functional is

$$J(\mathbf{x}_0, \mathbf{x}^o, \sigma^o) = \pi^{oT}(0)\mathbf{x}_o. \tag{6.6}$$

Proof. The scalar function

$$\mathbf{v}(\mathbf{x}, t) = \pi^{oT}(t)\mathbf{x} \tag{6.7}$$

is the generalized solution of the Hamilton-Jacobi-Bellman (HJB) equation

$$0 = \frac{\partial \mathbf{v}}{\partial t} + H\left(\mathbf{x}(t), \sigma^o(t, \mathbf{x}_0), \frac{\partial \mathbf{v}}{\partial \mathbf{x}}(\mathbf{x}, t)^T\right), \tag{6.8}$$

where

$$H(\mathbf{x}, \sigma, \pi) = \mathbf{q}_\sigma^T \mathbf{x}(t) + \pi^T(t) A_\sigma \mathbf{x}(t). \tag{6.9}$$

Notice that the triple $(\mathbf{x}^o, \sigma^o, \pi^o)$ satisfies the necessary condition of the Pontryagin principle, since

$$H(\mathbf{x}^o, \sigma^o, \pi^o) \leq H(\mathbf{x}^o, \sigma, \pi^o), \text{ for } \sigma = 1, \ldots, M. \tag{6.10}$$

Moreover,

$$\frac{\partial \mathbf{v}}{\partial \mathbf{x}}(\mathbf{x}, t) = \pi^o(t)^T \tag{6.11}$$

$$\frac{\partial \mathbf{v}}{\partial t}(\mathbf{x}, t) = \dot{\pi}^o(t)^T \mathbf{x} \tag{6.12}$$

so that, for almost all $t \in [0, t_f]$

$$\dot{\pi}(t)^T \mathbf{x}^o(t) + \mathbf{q}^T_{\sigma^o(t,\mathbf{x}_0)} \mathbf{x}^o(t) + \pi^o(t)^T A_{\sigma^o(t,\mathbf{x}_0)} \mathbf{x}^o(t) = 0. \tag{6.13}$$

Moreover it satisfies the boundary condition

$$v(\mathbf{x}^o(t_f), t_f) = \pi^o(t_f)^T \mathbf{x}^o(t_f) = \mathbf{c}^T \mathbf{x}^o(t_f) \tag{6.14}$$

and so the proof is completed. □

Notice that the computation of the optimal control law, as seen in Theorem 6.1, is quite demanding. This is due to the two points boundary value problem that requires a forward integration of the system (6.3), with a given initial condition, and a back integration of (6.4), with fixed final condition.

Theorem 6.1 is a generalization of the optimal control problem for autonomous linear switched positive systems (6.1) on a finite time interval $[0, t_f]$ which uses the subsequent cost functional to be minimized overall admissible switching sequences [6]

$$J(\mathbf{x}_0, \mathbf{x}, \sigma) = \int_0^{t_f} \mathbf{q}^T \mathbf{x}(t) dt + \mathbf{c}^T \mathbf{x}(t_f), \tag{6.15}$$

where $\mathbf{x}(t)$ is a solution of (6.1) and $\sigma(t)$ is a switching signal. Vectors $\mathbf{q}$ and $\mathbf{c}$ are assumed to be strictly positive. (6.15) is a particular case of (6.2), as the weight-vector $\mathbf{q}$ is constant w.r.t. the system A_k, for $k = 1, \ldots, M$ which is active at a specific instant $t \in \mathbb{R}^+$.
The optimal switching signal, the corresponding trajectory and the optimal cost functional are identified as previously.
The Hamiltonian function relative to system (6.1) and cost functional (6.15) is given by

$$H(\mathbf{x}, \sigma, p) = \mathbf{q}^T \mathbf{x}(t) + p^T A_{\sigma(t)} \mathbf{x}(t) \tag{6.16}$$

Theorem 6.2. *Let $\sigma^o(t, \mathbf{x}_0) : [0, t_f] \times \mathbb{R}^n_+ \to \mathcal{I} = \{1, \ldots, M\}$ be an admissible switching signal relative to $\mathbf{x}_0$ and $\mathbf{x}^o(t)$ be the corresponding trajectory. Let $\pi^o(t)$ denote a positive vector solution of the system of differential equations*

$$\dot{\mathbf{x}}^o(t) = A_{\sigma^o(t, \mathbf{x}_o)} \mathbf{x}^o(t) \tag{6.17}$$

$$-\dot{\pi^o}(t) = A^T_{\sigma^o(t, \mathbf{x}_o)} \pi^o(t) + \mathbf{q} \tag{6.18}$$

$$\sigma^o(t, \mathbf{x}^o) = arg \min_{k \in \mathcal{I}} \left\{ \pi^{oT} A_k \mathbf{x}^o(t) \right\}, \tag{6.19}$$

with the boundary conditions $\mathbf{x}^o(0) = \mathbf{x}_0$ and $\pi^o(t_f) = \mathbf{c}$. Then $\sigma^o(t, \mathbf{x}_0)$ is an optimal switching signal relative to $\mathbf{x}_0$ and the value of the optimal cost functional is

$$J(\mathbf{x}_0, \mathbf{x}^o, \sigma^o) = \pi^{oT}(0) \mathbf{x}_o \tag{6.20}$$

Proof. The scalar function

$$\mathbf{v}(\mathbf{x}, t) = \pi^{oT}(t) \mathbf{x} \tag{6.21}$$

is the generalized solution of the Hamilton-Jacobi-Bellman (HJB) equation

$$0 = \frac{\partial \mathbf{v}}{\partial t} + H\left(\mathbf{x}(t), \sigma^o(t, \mathbf{x}_0), \frac{\partial \mathbf{v}}{\partial \mathbf{x}}(\mathbf{x}, t)^T \right), \tag{6.22}$$

where

$$H(\mathbf{x}, \sigma, p) = \mathbf{q}^T \mathbf{x}(t) + p^T(t) A_\sigma \mathbf{x}(t). \tag{6.23}$$

In fact

$$\frac{\partial \mathbf{v}}{\partial \mathbf{x}}(\mathbf{x}, t) = \pi^o(t)^T \tag{6.24}$$

$$\frac{\partial \mathbf{v}}{\partial t}(\mathbf{x}, t) = \dot{\pi}^o(t)^T \mathbf{x} \tag{6.25}$$

so that, for almost all $t \in [0, t_f]$

$$\dot{\pi^o}(t)^T \mathbf{x}^o(t) + \mathbf{q}^T \mathbf{x}^o(t) + \pi^o(t)^T A_{\sigma^o(t, \mathbf{x}_0)} \mathbf{x}^o(t) = 0. \tag{6.26}$$

Moreover, it satisfies the boundary condition

$$v(\mathbf{x}^o(t_f), t_f) = \pi^o(t_f)^T \mathbf{x}^o(t_f) = \mathbf{c}^T \mathbf{x}^o(t_f) \tag{6.27}$$

and so the proof is completed.

□

It is worth underlining that the values of optimal cost functionals (formula (6.6) and (6.20)) in Theorem 6.1 and Theorem 6.2, respectively, are coincident, and the optimal control laws of (6.5) and (6.19) are coincident too, upon assuming in (6.5) $\mathbf{q}_k = \mathbf{q}, \forall k$.

6.2 Guaranteed cost control

Due to the complexity of the exact solution of the general optimal control problem (see Theorem 6.1 and Theorem 6.2), in this section we introduce a suboptimal, guaranteed cost algorithm associated with the optimal control problem. To this end, we define the simplex

$$\Lambda \doteq \left\{ \lambda \in \mathbb{R}^M : \sum_{k=1}^{M} \lambda_k = 1,\ \lambda_k \geq 0 \right\}, \tag{6.28}$$

which allows us to introduce the following piecewise copositive Lyapunov function:

$$v(\mathbf{x}) \doteq \min_{k=1,\ldots,M} \alpha_k^T \mathbf{x} \doteq \min_{\lambda \in \Lambda} \left(\sum_{k=1}^{M} \lambda_k \alpha_k^T \mathbf{x} \right), \tag{6.29}$$

where $\alpha_k \in \mathbb{R}^n$, for $k = 1, \ldots, M$. The Lyapunov function in (6.29) is not differentiable everywhere. In fact, if we define $I(\mathbf{x}) = \left\{ k : v(\mathbf{x}) = \alpha_k^T \mathbf{x} \right\}$, then $v(\mathbf{x})$ fails to be differentiable for those $\mathbf{x} \in \mathbb{R}_+^n$ such that $I(\mathbf{x})$ is composed of more than one element. Now, we denote by $\mathcal{M}$ the subclass of Metzler matrices whose columns sum up to zero, that is all matrices $\Pi \doteq [\pi_{i,j}]$, with $i, j = 1, \ldots, M$, with elements $\pi_{ij} \in \mathbb{R}$ s.t.

$$\pi_{ji} \geq 0\ \forall j \neq i,\ \sum_{j=1}^{M} \pi_{ji} = 0,\ \forall i. \tag{6.30}$$

Thus, any $\Pi \in \mathcal{M}$ has an eigenvalue at zero, since $\mathbf{c}^T \Pi = 0$, where $\mathbf{c}^T = [1\ 1\ 1\ \ldots\ 1]$.

Theorem 6.3. *Consider the linear positive switched system (6.1). Take any $\Pi \in \mathcal{M}$ and $\{\alpha_1, \ldots, \alpha_M\}$, with $\alpha_k \in \mathbb{R}_+^n$, satisfying the coupled co-positive Lyapunov inequalities:*

$$A_k^T \alpha_k + \sum_{j=1}^{M} \pi_{jk} \alpha_j \prec 0,\ k = 1, \ldots, M. \tag{6.31}$$

Then, the switching control rule, given by

$$\sigma(t) \doteq arg \min_{k=1,\ldots,M} \alpha_k^T \mathbf{x}(t) \tag{6.32}$$

makes the equilibrium solution $\mathbf{x} = 0$ of system (6.1) globally asymptotically stable.

Proof. Since the Lyapunov function (6.29) is not differentiable for all $t \in \mathbb{R}_+$, we need to deal with the Dini derivative:

$$D^+v(\mathbf{x}(t)) = \underset{h\to 0^+}{lim\ sup} \frac{v(\mathbf{x}(t+h)) - v(\mathbf{x}(t))}{h}. \tag{6.33}$$

Assume, in accordance with (6.32), that at an arbitrary $t \in \mathbb{R}_+$, the state switching control is given by $\sigma(t) = k$ for some $k \in I(\mathbf{x}(t))$. Therefore, remembering also that (6.30) is valid for all $\Pi \in \mathcal{M}$ and that $\alpha_j^T\mathbf{x} \geq \alpha_k^T\mathbf{x}(t)$ for all $j = 1, \ldots, M$, we have

$$\begin{aligned} D^+v(\mathbf{x}(t)) = \lim_{h\to 0^+} \sup \frac{v(\mathbf{x}(t) + hA_k\mathbf{x}(t)) - v(\mathbf{x}(t))}{h} = \\ \min_{l\in I(\mathbf{x}(t))} \alpha_l^T A_k\mathbf{x}(t),\ \forall k \\ \leq \alpha_k^T A_k\mathbf{x}(t) < -\sum_{j=1}^{M} \pi_{jk}\alpha_j^T\mathbf{x}(t) \\ = -\pi_{kk}\alpha_k^T\mathbf{x}(t) - \sum_{j\neq k} \pi_{jk}\alpha_j^T\mathbf{x}(t) \\ \leq -\pi_{kk}\alpha_k^T\mathbf{x}(t) - \sum_{j\neq k} \pi_{jk}\alpha_k^T\mathbf{x}(t) \\ = -\sum_{j=1}^{M} \pi_{jk}\alpha_k^T\mathbf{x}(t) = -\alpha_k^T\mathbf{x}(t)\sum_{j=1}^{M} \pi_{jk} = 0, \end{aligned} \tag{6.34}$$

which proves the theorem, since the Lyapunov function $v(\mathbf{x}(t))$ defined in (6.29) is radially bounded.

□

Remark. *A necessary condition for the Lyapunov Metzler inequalities to be feasible w.r.t. $\{\alpha_1, \ldots, \alpha_M\}$ is that the matrices $A_k + \pi_{kk}I$ have to be asymptotically stable for all $k = 1, \ldots, M$. Hence $\rho(A_{kk}) < -\pi_{kk}$, where $\rho(A_{kk})$ is the spectral radius of the matrix A_{kk}.*

The following theorem gives a guaranteed cost associated with the switching law introduced in formula (6.32).

Theorem 6.4. *Consider the p.s.s. (6.1) and let the non-negative vectors $\mathbf{q}_k$ for $k = 1, \ldots, M$ be given. Moreover, take any $\Pi \in \mathcal{M}$ and let $\{\alpha_1, \ldots, \alpha_M\}$, with $\alpha_k \in \mathbb{R}_+^n$ that satisfy the coupled copositive Lyapunov inequalities:*

$$A_k^T\alpha_k + \sum_{k=1}^{M} \pi_{jk}\alpha_j + q_k \prec 0, \text{ for } k = 1, \ldots M. \tag{6.35}$$

The state-switching law control (6.32) makes the equilibrium solution $\mathbf{x} = 0$ of the system (6.1) globally asymptotically stable and

$$\int_0^\infty q_{\sigma(t)}^T\mathbf{x}(t)dt \leq \min_{k=1,\ldots,M} \alpha_k^T\mathbf{x}_0. \tag{6.36}$$

Proof. If (6.35) hods, then (6.31) holds too, so we can say that the equilibrium point $\mathbf{x} = 0$ for system (6.1) is globally asymptotically stable, under the control law

(6.32).
Moreover, if we assume

$$v(\mathbf{x}) = \min_{k=1,\dots,M} \alpha_k^T \mathbf{x}, \tag{6.37}$$

then

$$\begin{aligned} D^+(v(\mathbf{x})) &= \min_{l \in I(\mathbf{x}(t))} \alpha_l^T A_k \mathbf{x} \leq \alpha_k^T A_k \mathbf{x} \\ &\leq -\pi_{kk} \alpha_k^T \mathbf{x} - \sum_{j \neq k} \pi_{jk} \alpha_k^T \mathbf{x} - q_k^T \mathbf{x} = -q_k^T \mathbf{x}. \end{aligned} \tag{6.38}$$

Hence

$$D^+(v(\mathbf{x})) \leq -q_k^T \mathbf{x}(t), \tag{6.39}$$

which, after integration, gives

$$\begin{aligned} v(\mathbf{x}(t)) - v(0) &= \int_0^t D^+ v(\mathbf{x}(\tau)) d\tau \\ &\leq -\int_0^t q_{\sigma(\tau)}^T \mathbf{x}(\tau) d\tau. \end{aligned} \tag{6.40}$$

Due to the asymptotic stability $v(\mathbf{x}(t))$ goes to zero as t goes to infinity, therefore

$$\int_0^t q_{\sigma(\tau)}^T \mathbf{x}(\tau) d\tau \leq v(0) = \min_{k=1,\dots,M} \alpha_k^T \mathbf{x}_0. \tag{6.41}$$

This concludes the proof.

□

It is worth noticing that (6.35) is not linear in the unknown variables π_{jk} and α_k, for $k, j = 1, \dots, M$. Indeed, we need an alternative reformulation in order to have an efficient numerical search. In particular, the idea is to obtain a simpler, even if more conservative, stability condition that can be expressed by means of LMIs.
The next corollary shows that, working with a subclass of $\mathcal{M}$-matrices, characterized by having the same diagonal elements, this goal is accomplished.

Corollary 6.4.1. *Let $q_k \in \mathbb{R}_+^n,\ k = 1, \dots, M$, be given. Assume that there exists a set of positive vectors $\{\alpha_1, \dots, \alpha_M\}$, $\alpha_k \in \mathbb{R}_+^n$ and a scalar $\gamma > 0$ satisfying the modified coupled copositive Lyapunov inequalities:*

$$A_k^T \alpha_k + \gamma(\alpha_j - \alpha_k) + q_k \prec 0 \ k \neq j = 1, \dots, M. \tag{6.42}$$

The state switching control is (6.32) makes the equilibrium solution $\mathbf{x} = 0$ of the system (6.1) globally asymptotically stable and

$$\int_0^\infty q_{\sigma(t)}^T \mathbf{x}(t) dt \leq \min_{k=1,\dots,M} \alpha_k^T \mathbf{x}_0. \tag{6.43}$$

Proof. Take the matrix $\Pi \in \mathcal{M}$ such that $\pi_{kk} = -\gamma$, therefore

$$\gamma^{-1} \sum_{j \neq k} \pi_{jk},\ \forall k = 1, \dots, M. \tag{6.44}$$

Since $\pi_{jk} \geq 0, \forall j \neq k,\ j, k = 1, \dots, M$ we can multiply (6.42) by π_{jk}, summing up $\forall j \neq k,\ j, k = 1, \dots, M$ and finally multiplying the result by $\gamma^{-1} > 0$, so obtaining

$$A_k^T \alpha_k + q_k \prec -\sum_{j=1}^M \pi_{jk} \alpha_j,\ \forall k = 1, \dots, M. \tag{6.45}$$

Hence the upper bound (6.36) holds.

□

For this reason, we introduce a theorem which gives a switching law which ensures an upper bound to a cost functional defined over a finite time period.

Theorem 6.5. *Consider the linear positive switched system (6.1) and let the positive vectors* $\mathbf{q}_k$*, for* $k = 1, \dots, M$ *be given. Moreover, take any* $\Pi \in \mathcal{M}$ *and let* $\{\alpha_1(t), \dots, \alpha_M(t)\}$*, with* $\alpha_k \colon [0,\ t_f] \to \mathbb{R}^n_+$ *be any positive solution of the differential inequalities*

$$\dot{\alpha}_k + A_k^T \alpha_k + \sum_{k=1}^{M} \pi_{jk} \alpha_j + q_k \preccurlyeq 0,\ \ k = 1, \dots, M \tag{6.46}$$

with a final condition $\alpha_k(t_f) = \mathbf{c},\ \forall k$*. Then, the cost function associated with the switching rule*

$$\sigma(\mathbf{x}(t)) = arg \min_{k=1,\dots,M} \alpha_k^T(t)\mathbf{x}(t) \tag{6.47}$$

satisfied the following upper bound

$$\int_0^{t_f} \mathbf{q}_{\sigma(t)}^T \mathbf{x}(t)dt + \mathbf{c}^T \mathbf{x}(t_f) \leq \min_{k=1,\dots,M} \alpha_k^T(0)\mathbf{x}_0 \tag{6.48}$$

Proof. Consider the Lyapunov function

$$v(\mathbf{x}, t) = \min_{l=1,\dots,M} \alpha_l^T(t)\mathbf{x}(t) \tag{6.49}$$

and let $k(t) = arg\ min_l \alpha_l^T(t)\mathbf{x}(t)$. Then

$$\begin{aligned} D_+(v(\mathbf{x}, t)) &= \min_i(\dot{\alpha}_i(t) + \alpha_i^T(t)A_k\mathbf{x}) \leq \dot{\alpha}_k(t) + \alpha_k^T(t)A_k\mathbf{x} \leq \\ &\leq -\pi_{kk}\alpha^T(t)\mathbf{x} - \sum_{j\neq k} \pi_{jk}\alpha_j^T(t)\mathbf{x} - \mathbf{q}_k^T\mathbf{x} \leq \\ &\leq -\pi_{kk}\alpha^T(t)\mathbf{x} - \sum_{j\neq k} \pi_{jk}\alpha_k^T(t)\mathbf{x} - \mathbf{q}_k^T\mathbf{x} = -\mathbf{q}_k^T\mathbf{x}. \end{aligned}$$

Hence, for all $\sigma(t)$,

$$D^+(v(\mathbf{x}, t)) \leq -\mathbf{q}_{\sigma(t)}^T \mathbf{x}(t) \tag{6.50}$$

which, after integration, gives

$$v(\mathbf{x}(t_f)) - v(\mathbf{x}_0) = \int_0^{t_f} D^+ v(\mathbf{x}(\tau))d\tau \leq -\int_0^{t_f} \mathbf{q}_{\sigma(\tau)}^T \mathbf{x}(\tau)d\tau. \tag{6.51}$$

Therefore,

$$\int_0^{t_f} D^+ v(\mathbf{x}(\tau))d\tau + \mathbf{c}^T \mathbf{x}(t_f) \leq v(\mathbf{x}_0) = \min_{k=1,\dots,M} \alpha_k^T(0)\mathbf{x}_0 \tag{6.52}$$

and this concludes the proof.

□

Notice that the inequalities (6.46) require the preliminary choice of the parameters π_{jk}.
In particular, the search for π_{jk} and α_k, for $k = 1, \dots, M$, that satisfy the Theorem 6.5 involves the solution of a bilinear matrix inequality.

We can, at the cost of some conservatism in upper bound, reduce the number of parameters ($\pi_{i,j}$, for $i,j = 1,\dots,M$) to a single one, say γ, so allowing an easy search the best γ as far as the upper bound is concerned.

Corollary 6.5.1. *Let $\mathbf{q} \in \mathbb{R}^n_+$ and $\mathbf{c} \in \mathbb{R}^n_+$ be given, and let the vectors $\{\alpha_1(t),\dots,\alpha_M(t)\}$, $\alpha_k : [0,t_f] \to \mathbb{R}^n_+$ satisfy for some $\gamma > 0$ the modified coupled copositive differential Lyapunov inequalities:*

$$\dot{\alpha}_k + A_k^T\alpha_k + \gamma(\alpha_j - \alpha_k) + q_k \preccurlyeq 0,\ k \neq j = 1,\dots,M, \tag{6.53}$$

with final condition $\alpha_k(t_f) = \mathbf{c}$, $\forall k$. Then, the switching control given by (6.47) is such that

$$\int_0^{t_f} \mathbf{q}^T_{\sigma(t)}\mathbf{x}(t)dt + \mathbf{c}^T\mathbf{x}(t_f) \leq \min_{k=1,\dots,M} \alpha_k^T(0)\mathbf{x}_0. \tag{6.54}$$

The result of Corollary 6.5.1 is very important for the problem of mitigating the viral escape. In fact, it can provide a simpler way for computing the switching rule (6.47).

6.3 Applications to the 4 variant, 2 drug combination model

6.3.1 Using Optimal Control

We use a final time cost, since the typical course of HIV infection under therapies has a long period of suppression of the strains, followed by an exponential growth of the HRG. If the rate of the final exponential growth is almost independent of the particular treatment, then the total viral load at the final time is a surrogate for the duration of viral suppression to low levels. The duration of the time in which we are able to maintain the total viral load at low levels is an important clinical parameter. Moreover, [9] shows that in absence of ongoing viral replication, the generation of new variants is also stopped.
In Section 6.1, Theorem 6.1 gives the general solution of the optimal control problem, which is quite demanding, because to find out the optimal switching signal $\sigma(\cdot)$ it is necessary to solve a two boundary integration problem.
We hypothesise to use the small system given by formulas (3.9), (3.10) and (3.11). Moreover, we suppose to have time intervals of thirty days, thus we name $\tau = 30$ $[days]$.
In the sequel, we present the simplest procedure to compute the switching signal in Theorem 6.1. Furthermore, we suppose that all the state weight vectors $\mathbf{q}_k$, for $k = 1,\dots,M$ are all zero. In this manner, we consider a cost functional which is given only by one term:

$$J_{t_f} = \mathbf{c}^T\mathbf{x}(t_f), \tag{6.55}$$

where $c = [1\ 1\ 1\ 1]^T$.
Clearly, the cost functional (6.55) is the total viral load at the end of the therapy. Termed $\tilde{t_f} = \frac{t_f}{\tau}$, with for simplicity τ an integer divisor of t_f ($t_f \in \mathbb{N}$, given in $[days]$). Thus, $\tilde{t_f}$ is given in $[months]$, for we use $\tau = 30$ $[days]$.

6.3.2 Brute Force Algorithm

The first approach we might think to obtain the optimal solution is through a "brute force algorithm", which analyses all possible values at each time instant of the state trajectory, in order to choose at each decision time instant (which we term with t_k, for $k = 1, \dots, \tilde{t_f}$) the state which minimizes the cost functional (6.55).
Now, we hypothesize that the considered time instants t_k are coincident with the decision time instants. In this way, we are considering the possibility to switch the therapy every months.
Assuming the initial state to be given, $\mathbf{x}_0$, and considering the decision time equal to τ, during which the treatment is fixed, we can do the following steps:

1. We compute the sets of all states that can be reached by the system at each decision time t_k, for $k = 1, \dots, \tilde{t_f}$;

2. We evaluate all possible state trajectories, obtained with all possible switching trajectories (of number $M^{\tilde{t_f}}$), and we choose the one which minimises the cost functional (6.55).

Clearly, this approach becomes really demanding with the increasing of t_f.

6.3.3 Dynamic Programming Approach

An alternative approach to compute the optimal switching law $\sigma^o(t)$, and thus the optimal trajectory $\mathbf{x}^o(t)$ is the so called *dynamic programming approach*[1]. This approach is based on the Bellman's principle of optimality, which is:

Proposition 6.1. *Let $\sigma^o(\cdot)$ and $\mathbf{x}^o(\cdot)$ be respectively the optimal switching law and the optimal state trajectory corresponding to the initial state $\mathbf{x}(0) = \mathbf{x}_0$ and the time interval $[0, \tilde{t_f}]$. Then, for an arbitrary instant $t_l \in [\tilde{t_0}, \dots, \tilde{t_k}, \dots, \tilde{t_f}]$ the switching strategy $\sigma^o(t_l)$, $\sigma^o(t_{l+1})$, $\sigma^o(t_{l+2}), \dots,$ $\sigma(\tilde{t_f})$ represents the optimal switching law corresponding to the initial state $\mathbf{x}(t_l)$ in $[0, \tilde{t_f}]$, considering the decision instants in the sequence $[\tilde{t_0}, \dots, \tilde{t_k}, \dots, \tilde{t_f}]$.*

Proof. Starting from the state $\mathbf{x}^o(t_l)$, we assume that the optimal strategy is $\tilde{\sigma}(t_l)$, $\tilde{\sigma}(t_{l+1})$, $\tilde{\sigma}(t_{l+2}), \dots,$ $\tilde{\sigma}(\tilde{t_f})$. Apply the switching law $\sigma^o(\tilde{t_0}), \dots, \sigma^o(t_{l-1}), \tilde{\sigma}(t_l)$, $\tilde{\sigma}(t_{l+1})$, $\tilde{\sigma}(t_{l+2}), \dots,$ $\tilde{\sigma}(\tilde{t_f})$, then the cost function $J_{\tilde{t_f}}$ would assume a smaller value w.r.t. its minimum value $J^o_{\tilde{t_f}}$. It is opposite to the hypothesis of optimality on $\sigma^o(\cdot)$. □

[1]Dynamic programming approach is a method for solving a complex problem by breaking it down into a set of simpler sub-problems, solving each of those ones just once, and storing their solutions. Thus, the next time the same problem occurs, instead of recomputing the solution, one looks up to the previous result obtained.
This type of programming is often used in optimization problems: a dynamic programming algorithm will examine the previously solved sub-problems and will combine their solutions to give the best solution for the given problem.

The dynamic programming approach has the main feature which is to solve the problems backward. Intuitively, the idea of this kind of programming is:

1. Assume we have find the value $\mathbf{x}^o(t_f)$, the remaining decision of the switching law which minimizes the cost functional over the time interval $[t_f - \tau, t_f]$ is $\sigma^o(t_f - \tau)$;

2. Now, we can go a step backward: supposing to have the state $\mathbf{x}^o(t_f - 2\tau)$, the remaining decision of the switching law which minimizes the cost functional over the time interval $[t_f - 2\tau, t_f]$ is $\sigma^o(t_f - 2\tau)$;

3. We can go on by computing the whole switching law until we find $\mathbf{x}(0)$ and the corresponding $\sigma^o(0)$, having taken $t_0 = 0$. We have seen in Theorem 6.1 that the optimal trajectory $\mathbf{x}^o(\cdot)$ and the optimal switching signal $\sigma^o(\cdot)$ satisfy the HJB equation (6.8) and together with the state differential equations (6.3) and the two boundary conditions we obtain the optimal solution $\mathbf{x}^o(\cdot)$, by finding the optimal switching law $\sigma^o(\cdot)$. As said, the optimal control problem, in Theorem 6.1, cannot be solved with the normal integration techniques. A number of algorithms have been proposed to solve the introduced optimal control problem, but we present only the simplest solution, considering the cost functional made by only the term depending on the final state $\mathbf{x}(t_f)$ (6.55).

We define recursively the sequence of matrices:

$$
\begin{aligned}
\tilde{\Omega}_0 &= \mathbf{c}, \\
\tilde{\Omega}_1 &= \left[e^{A_1^T \tau} \cdot \tilde{\Omega}_0,\ e^{A_2^T \tau} \cdot \tilde{\Omega}_0,\ e^{A_3^T \tau} \cdot \tilde{\Omega}_0,\ \ldots\ e^{A_M^T \tau} \cdot \tilde{\Omega}_0 \right], \\
&\vdots \\
\tilde{\Omega}_k &= \left[e^{A_1^T \tau} \cdot \tilde{\Omega}_{k-1},\ e^{A_2^T \tau} \cdot \tilde{\Omega}_{k-1},\ e^{A_3^T \tau} \cdot \tilde{\Omega}_{k-1},\ \ldots\ e^{A_M^T \tau} \cdot \tilde{\Omega}_{k-1} \right], \\
&\vdots \\
\tilde{\Omega}_{\tilde{t_f}} &= \left[e^{A_1^T \tau} \cdot \tilde{\Omega}_{\tilde{t_f}-1},\ e^{A_2^T \tau} \cdot \tilde{\Omega}_{\tilde{t_f}-1},\ e^{A_3^T \tau} \cdot \tilde{\Omega}_{\tilde{t_f}-1},\ \ldots\ e^{A_M^T \tau} \cdot \tilde{\Omega}_{\tilde{t_f}-1} \right].
\end{aligned}
$$

Then, we can compute the optimal switching law and the optimal switching trajec-

tory, as follows:

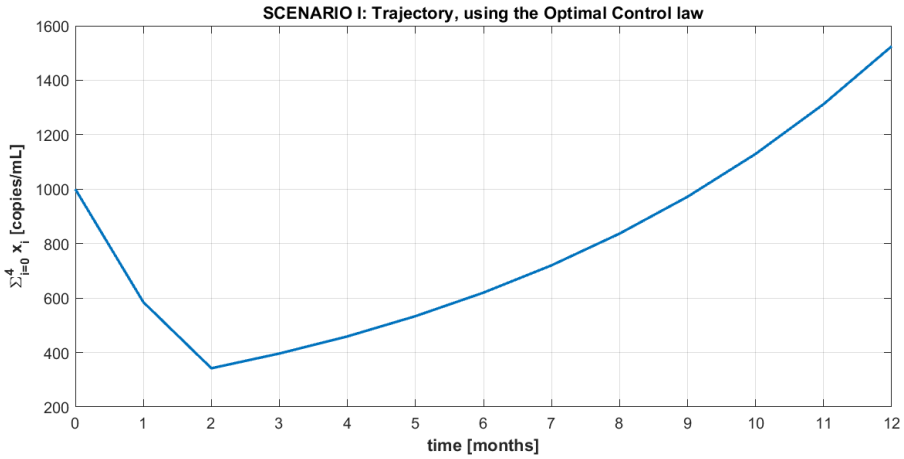
$$\begin{aligned}
\sigma^o(0) &= arg\,\min_j \left(\tilde{\Omega}^T_{\tilde{t_f}}\right)^{(j)} \mathbf{x}(0) \\
\mathbf{x}(1) &= A_{\sigma^o(0)}\mathbf{x}(0) \\
\sigma^o(\tau) &= arg\,\min_j \left(\tilde{\Omega}^T_{\tilde{t_f}-1}\right)^{(j)} \mathbf{x}(\tau) \\
&\vdots \\
\sigma^o(k\tau) &= arg\,\min_j \left(\tilde{\Omega}^T_{\tilde{t_f}-k}\right)^{(j)} \mathbf{x}(k\tau) \\
\mathbf{x}((k+1)\tau) &= A_{\sigma^o(k\tau)}\mathbf{x}(k\tau) \\
&\vdots \\
\sigma^o(t_f-\tau) &= arg\,\min_j \left(\tilde{\Omega}^T_{1}\right)^{(j)} \mathbf{x}(t_f-\tau) \\
\mathbf{x}(t_f) &= A_{\sigma^o(t_f-\tau)}\mathbf{x}(t_f-\tau).
\end{aligned}$$

The implementation of the previous strategy requires storing the columns of matrices $\tilde{\Omega}^T_{t_k}$, for $k = 1, \ldots, \tilde{t_f}$, with $\tilde{t_f} = 12$. Thus, this number of columns increases with an exponential growth, in fact the total number of stored columns is $1 + M + M^2 + \cdots + M^{\tilde{t_f}}$.
Clearly, this kind of algorithm is for obtaining the solution of the Optimal Control problem, by taking specific switching time instants from 0 days to 360 days with time step τ, which is equal to 30 days.
It is worth highlighting that, even if we build up the optimal control law onwards, we are resorting, in a certain manner, to the Bellman's principle of optimality. In fact, at each step $t_k \in [0, \tilde{t_f}]$, the optimal value $\sigma^o(\bar{t})$ is obtained as the optimal strategy corresponding to the initial state $\mathbf{x}^o(t_k)$ and time interval $[t_k, \tilde{t_f}]$.

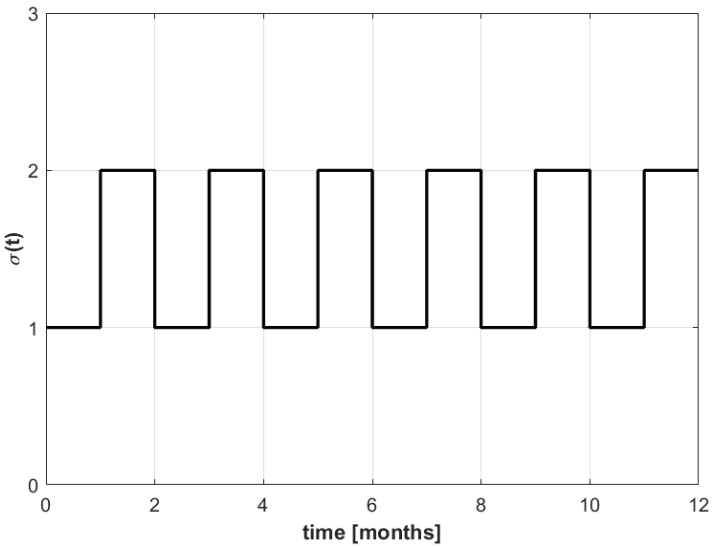
We compute the optimal control law with the previous algorithm only for the symmetric case of the 4 variant, 2 drug combination model (see Subsection 3.2.2).
Looking at the simulation results we notice that:

1. In Figure 6.1b the optimal switching rule is plotted and it is visible that it is periodic with period τ (i.e. the therapy changes every month);

2. The viral load at the end of the year is equal to 1525 $[copies/mL]$, a viral concentration smaller than the one obtained after one year of monotherapy, which is equal to 3139 $[copies/mL]$ (see Table 3.5). The trajectory of the total viral load using the optimal switching law is shown in Figure 6.1a.



(a) Scenario I: optimal trajectory of $\sum_{i=1}^{4} V_i$.



(b) Scenario I: optimal switching law $\sigma(\cdot)$.

Figure 6.1: Optimal control for the small model.

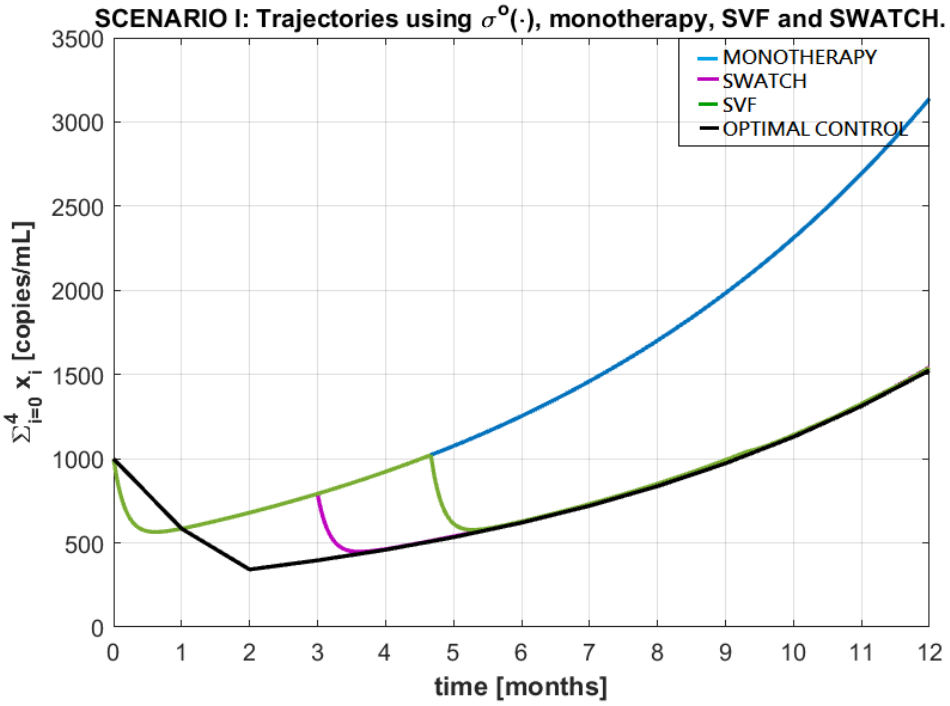


Figure 6.2: Trajectories for the small model of HIV, using different control laws.

In Figure 6.2 are plotted the trajectories for the 4 variant, 2 drug combination model in the case of using only one therapy, using the Optimal Control law, the SWATCH rule and the SVF one.
It is worth noticing that, even if we are using a continuous time model, we are computing the optimal switching law under the assumption that the decision instants t_k, for $k = 1, \ldots, \tilde{t_f}$ are equally spaced of $\tau = 30$ $[days]$ from 0 to 360 [days].

6.3.4 Using Guaranteed Cost Control over infinite horizon

From the Remark in Subsection 6.2, we know that if we hypothesize that the matrix Π iszero it is necessary for the feasibility of the LMIs that all the subsystems dynamic matrices have to be Hurwitz. In this manner, we ensure subsystems' stability, we introduce a weighting factor $\gamma > 0$ as follows:

$$\dot{\hat{\mathbf{x}}}(t) = \left(A_{\sigma(t)} - \gamma I_4\right) \hat{\mathbf{x}}(t), \tag{6.56}$$

the solution of (6.56) is given by:

$$\hat{\mathbf{x}}(t) = e^{\left(A_{\sigma(t)} - \gamma I_4\right)(t - t_0)} \hat{\mathbf{x}}_0, \tag{6.57}$$

and, $t_0 = 0$ tanking as initial time instant, we obtain:

$$\hat{\mathbf{x}}(t) = e^{\left(A_{\sigma(t)} - \gamma I_4\right)t} \hat{\mathbf{x}}_0. \tag{6.58}$$

As it can be seen from equation (6.58), we have introduced in this way an exponential weight. And we have ensured the necessary condition for the feasibility of the LMIs (6.35).
We denote the modified state matrices $\hat{A}_k = A_k - \gamma I_4$, $k = 1, \ldots, M$.
Consider the vectors α_k given by:

$$\alpha_k = -\left(\hat{A}_k^T\right)^{-1} \mathbf{c}. \tag{6.59}$$

As $\hat{A}_k$ for $k = 1, 2, \ldots, M$ are Metzler and Hurwitz, their transpose are Metzler and Hurwitz too. Moreover, in (6.59) we compute the inverse of a Metzler and Hurwitz matrix, that is a negative matrix [4]. So, the vectors α_k, for $k = 1, \ldots, M$ are all positive and we have obtained the solution of the LMIs (6.35), upon choosing a zero Metzler matrix $\Pi \in \mathcal{M}$.
In the end, we consider the switching signal (6.32), using the modified state equations (6.56):

$$\sigma\left(\hat{\mathbf{x}}(t_k)\right) \doteq arg \min_{k=1,\ldots,M} \alpha_k^T \hat{\mathbf{x}}(t_k). \tag{6.60}$$

We know that this switching rule ensures an upper bound to the infinite horizon cost function.
Taking $\gamma = 0.01$ to ensure the necessary condition for feasibility of the LMIs, with the help of MATLAB® we obtain a switching rule equal to the Optimal Control. In fact, $\sigma(\cdot)$ is periodic with period τ and $\sigma(0) = 1$. This fact is quite surprising, because the switching rule is derived from the application of Theorem 6.4, which guarantees an upper bound to the cost functional over an infinite horizon and doesn't ensure the minimum value of the cost functional (which instead we ensure using the Optimal Control). Furthermore, to assure the feasibility of the LMIs, we modify the state matrices as shown in (6.56).
Clearly, when the switching law $\sigma(\cdot)$ is applied to the original system (i.e. with

unmodified state matrices) we obtain at the end of one year of simulations the same total viral load value of the Optimal Control case, which is 1525[*copies*/*mL*].

6.3.5 Using Guaranteed Cost Control over finite horizon

Differently from the infinite horizon case, it is not necessary to modify the state matrices.
Considering Theorem 6.5, we can solve backward in time the differential equations (6.46) with vectors $\mathbf{q}_k = \mathbf{c}$, for $k = 1, \ldots, M$. As in the previous case, we choose the Metzler matrix $\Pi \in \mathcal{M}$ equal to zero, and we start from the final condition[2] $\alpha_k(t_f) = \mathbf{c}$, $\forall k$. In the end we consider the switching law:

$$\sigma\left(\mathbf{x}(t_k)\right) = arg \min_{k=1,\ldots,M} \alpha_k^T(t_k)\mathbf{x}(t_k). \tag{6.61}$$

The switching signal comes out to be both periodic of period τ, and it starts from $\sigma(0) = 1$. Then, the resultant trajectory which gives the sum of the total viral load is exactly equal to the one obtained using either the Optimal Control strategy, or the guaranteed cost control over infinite horizon.

Remark. *When we have to solve a differential equation imposing an initial condition, instead of a final condition we have to do the following steps:*

1. *We define a new function $v(t)$, s.t. $v(0) = \alpha(t_f)$[3] and so $v(t) = \alpha(t_f - t)$,*
2. *We compute its derivative $\dot{v}(t) = -\dot{\alpha}(t_f - t)$.*

Thus, supposing to solve (6.46) for the case of differential equations, and having in mind the hypotheses previously done, we obtain that the differential equation

$$\dot{\alpha}_k(t) = -A_k^T \alpha_k(t) - \mathbf{c},\ k = 1, 2. \tag{6.62}$$

Doing the changes of functions s.t. we have to solve a Cauchy's problem, we obtain

$$\dot{v}_k(t) = -\dot{\alpha}_k(t_f - t),\ k = 1, 2. \tag{6.63}$$

Clearly, the time derivative of $v_k(t)$ is a positive vector. We have as initial condition a positive vector, $v(0) = \mathbf{c}$, then we have that the evolution of the vectorial functions $v_k(t)$, for $k = 1, 2$ is at each time a positive vector, and so the same holds for $\alpha_k(t)$, for $k = 1, 2$.

6.3.6 Comparisons

A good parameter to evaluate the efficiency of a specific treatment is the total viral load at the end of the treatment. In Table 6.1 there are all the values of the total viral load at the end of one year of monotherapy, SVF therapy, SWATCH one, treatment obtained by solving Optimal Control problem, the Guaranteed Cost Control over finite horizon and over infinite horizon. In Table **??**, we recall the meanings of SVF and SWATCH.
Looking at the Table 6.1, it is visible that

[2] To solve with MATLAB® a differential equation with final condition, it is sufficient to reverse the time span.

[3] We drop off the subscript k for simplicity.

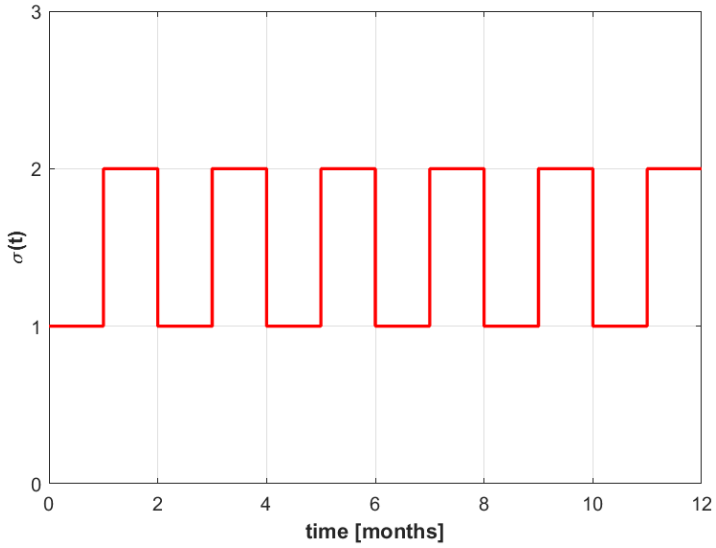


Figure 6.3: Switching law for the guaranteed cost approach over finite horizon.

1. Using Optimal Control and Suboptimal ones give lower values of the total viral load at the end of the treatment than using SWATCH and SVF controls,

2. Using the Optimal Control, the Guaranteed Cost Control over infinite and finite horizon is equivalent, indeed the total viral load at the end of the treatment is the same.

In all cases, it is clear that switching between therapies is effective to fight against the viral rebound.

Strategy:	$\Sigma_{i=1}^{n} V_i$:
Monotherapy	3139 $[copies/mL]$
SVF	1547 $[copies/mL]$
SWATCH	1543 $[copies/mL]$
Optimal Control	1525 $[copies/mL]$
Guaranteed cost control over infinite horizon	1525 $[copies/mL]$
Guaranteed cost control over finite horizon	1525 $[copies/mL]$

Table 6.1: Total viral load at the end of one year of treatment.

Switch on Virologic Failure (SVF):
if $\mathbf{x}(t+\tau) > 1000[copies/mL]$
if $\sigma(t) = 1$
$\sigma(t+\tau) = 2$
elseif $\sigma(t) = 2$
$\sigma(t+\tau) = 1$
endif
endif

SWitch Antiretroviral Therapy Combinations against HIV (SWATCH):
switch every three months

Table 6.2: SVF and SWATCH rule.

6.4 Applications to the 16 variant, 2 drug combination model

6.4.1 Using the Luenberger observer

Laboratory tests performed during patient visits can be used to assist in the selection of drug regimens. These are genotypic resistance testing, $CD4+T$ counts and viral load. It is worth noticing that genotypic resistance testing has helped to treat in the best manner the patients infected with drug-resistant HIV. Thus, the output of the nonlinear p.s.s. can be written in the following vector form:

$$y(t) = \begin{bmatrix} y_1(t) \\ y_2(t) \end{bmatrix} = \begin{bmatrix} \frac{T(t)}{V_1(t)} \\ \vdots \\ V_n(t) \end{bmatrix}, \tag{6.64}$$

where $T(t)$ is the $CD4+T$ cell counts at time t and $V_i(t)$, $i = 1, \dots n$ are the viral concentrations of n genotypes, at time t. We consider $n = 16$ different genotypes.
Drug treatments are introduced after four years of infection and are used for six years. We assume frequent patient's visits to the hospital, once a month, but we assume that treatment regimens can be switched only every three months [28]. As macrophage counts are assumed constant (700 $[cells/mm^3]$), only CD4+T cell counts are necessary to update the switched linear model (3.3) in Subsection 3.2.2.
The control strategies which we saw previously can be un-practical, due to common implementation issues in biomedical problems: such as irregularity of measurements or incomplete state measurements. So, we cannot compute the control strategy, because we do not have the value of the state variables.
For these reasons, we use a Luenberger observer, based on the linear positive switched system (3.3) to estimate the infected cells variables (T_i^*, M_i^*) from the nonlinear model (3.2).

It is worth noticing that many procedures for control design are based on the assumption that full state vector is available for measurement. These procedures specify the actual input value as a function of the actual value of the state vector. Clearly, the system evolves according to its state vector equations, and so it is a natural consequence to design the input control based on the state vector.
In many systems, however the state vector is not completely available at each time

t, and thus in order to design a control based on the current state, it is necessary to estimate it. When faced with this rather common difficulty, there are two approaches.

The first is to find out new procedures that require fewer measurements, either by restricting the choice of static feedback functions, or by developing more complex dynamic feedback processing procedures. The second, and simpler, approach is to construct an approximation of the full state vector on the basis of the available measurements. In this manner, we can use control procedures based on the approximated state, in place of the current state and we overcome the problem of inaccessible state variables.

We hypothesise that the values that we can access are the concentrations of viral populations $V_1(t)$, $V_2(t)$, ... $V_n(t)$, because we assume that during the patient's visits at the hospital are measured only the different viral concentrations and the number of healthy CD4+T cells T(t).

It is worth noticing that the concentration T(t) is not part of the state vector of the used Luenberger observer. The CD4+T cell count is used to update the observers' dynamic matrices $A_{\sigma(t)}$, for $\sigma(\cdot) = 1, 2$.

The switched observer (made by two observers) we use has equations:

$$\dot{\hat{\mathbf{x}}}(t) = A_{\sigma(t)}\hat{\mathbf{x}}(t) + L_{\sigma(t)}\left(y_2(t) - \hat{y}_2(t)\right), \tag{6.65}$$

$$\hat{y}_2(t) = C\hat{\mathbf{x}}(t), \tag{6.66}$$

where $\hat{\mathbf{x}}(\cdot)$ is the state estimated vector, the matrices $L_{\sigma(\cdot)}$ (for $\sigma(\cdot) = 1, 2$) are the observer gains, and $\hat{y}_2(\cdot)$ is the estimated output vector of the genotype distribution. CD4+T cells counts are necessary for updating the linear positive switched system (6.65). $A_{\sigma(\cdot)}$, for $\sigma(\cdot) = 1, 2$ are the state matrices of the p.s.s., given by (3.4), (3.5) and (3.6) (see Section 3.2.2).

In order to have $\hat{y}_2(t)$ equal to the vector containing all the different genotypes, we choose

$$C = \begin{bmatrix} 0 & 0 & 1 & 0 & & \dots & & & \dots & & & \dots & & & & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & & \dots & & & \dots & & & & 0 \\ 0 & & \dots & & & \dots & 0 & 0 & 1 & 0 & & \dots & & & & 0 \\ \vdots & & \dots & & & \dots & & & \dots & 0 & 1 & 0 & & & & 0 \\ \vdots & & & & & \dots & & & \dots & & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & & & & & \dots & & & \dots & & & & \dots & 0 & 0 & 1 \end{bmatrix} = \begin{bmatrix} \mathbf{e}_3^T \\ \mathbf{e}_6^T \\ \mathbf{e}_9^T \\ \mathbf{e}_{12}^T \\ \mathbf{e}_{15}^T \\ \mathbf{e}_{18}^T \\ \mathbf{e}_{21}^T \\ \mathbf{e}_{24}^T \\ \mathbf{e}_{27}^T \\ \mathbf{e}_{30}^T \\ \mathbf{e}_{33}^T \\ \mathbf{e}_{36}^T \\ \mathbf{e}_{39}^T \\ \mathbf{e}_{42}^T \\ \mathbf{e}_{45}^T \\ \mathbf{e}_{48}^T \end{bmatrix},$$

where the vectors $\mathbf{e}_i^T$, for $i = 1, \dots, 48$ are vectors of the canonical base of the space $\mathbb{R}^{48}$.

The first thing to evaluate is if we can observe the state through the hypothesised

observer (6.66). We recall that a system is completely observable if by observation of the system outputs the value of the initial state can be deduced within a finite time period (see Appendix A for more information).
To find out if a system is observable, we compute the rank of the observation matrices of the pairs $(A_{\sigma(t)=1}, C)$ and $(A_{\sigma(t)=2}, C)$, which effectively are of full rank. Thus, it is possible to estimate the state with (6.66).
As well known, if the pair (A_σ, C) is observable, the eigenvalues of $A_\sigma - L_\sigma C$ can be placed arbitrary. As the dynamic matrix of the estimation error is $A_\sigma - L_\sigma C$, we select its eigenvalues such that the estimation error goes to zero quickly. 'Quickly' means that the eigenvalues of the dynamic matrix of the estimation error $A_\sigma - L_\sigma C$ have to be placed with real parts more negative than the Frobenius eigenvalue of A_σ. For, we are considering continuous systems, it means that we have to choose eigenvalues with real parts strictly negative, i.e. the error dynamic matrix $A_\sigma - L_\sigma C$ has to be Hurwitz.
In this manner, we implement a full-order observer to apply a Guaranteed Cost Control over finite horizon. The simulation results are explained in Subsection 6.4.3.

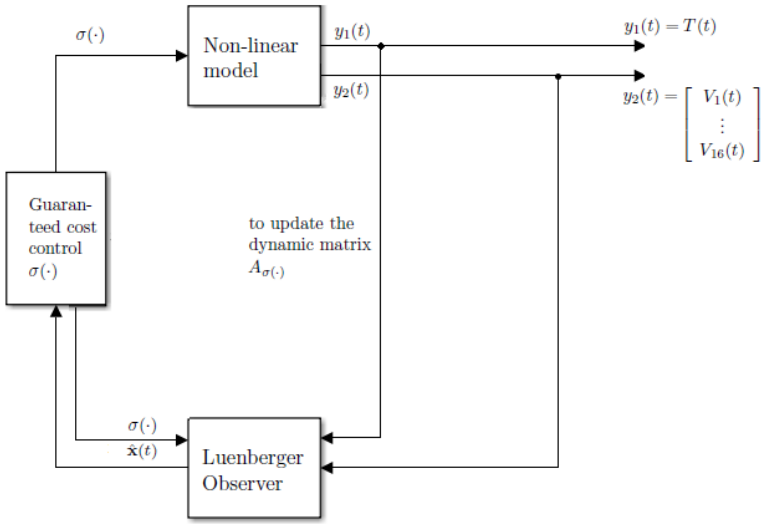


Figure 6.4: Scheme of the project, using the Luenberger Observer.

6.4.2 Model Predictive Control

An approach for determining near optimal switching drug schedules is Model Predictive Control (MPC). MPC appears to be suitable for applications to the biomedical area, owning to its robustness to model uncertainties, disturbances and the possibility of handling constraints.
In what follows, we will present the basic idea of MPC, and then, we will present results derived by Hernandez-Vargas and coauthors [22], using the 16 variant, 2 drug combination model introduced in Section 3.2.2.
The main feature of MPC approach is that the optimization procedure resorts to

predictions based on a model, hence the name of Model Predictive Control.

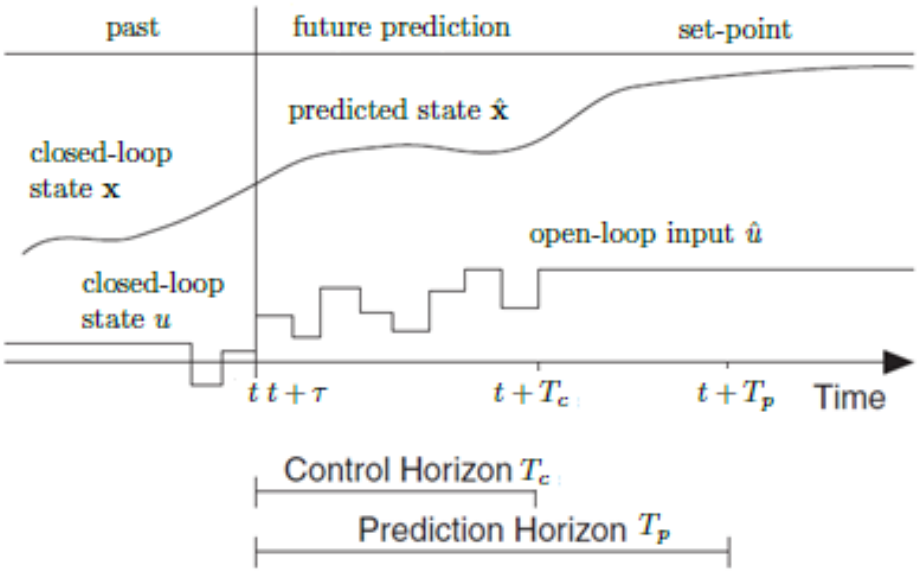


Figure 6.5: Model Predictive Control approach.

To be more precise, the basic steps of the procedure are (see Figure **??**):

1. At time istant t the controller, using measurements just collected, predicts the future dynamics behaviour of the system over a prediction horizon T_p and computes the optimal control rule over a control horizon T_c;

2. Only the first step of the optimal control sequence is implemented (the remaining inputs are not taken in account any more);

3. At time $t + \tau$ new measurements are available and this procedure, namely prediction and optimization, is reiterated at each sample time. We can think of the prediction and control horizon as two sliding windows moving forward: the former predicts how far into the future the controller predicts the state evolution, while the latter defines how far into the future it plans the control action.
   Due to disturbances, measurement noise and model-plant mismatch the true system behavior is different from the predicted one. Taking into account only the first step of the optimal control sequence is a useful of feedback mechanism.

6.4.3 Comparisons

The two schemes introduced in Figure 6.4 and iin Figure 6.6 model two manners of computing the switching law to change the therapy. In fact, we use the two following control strategies:

- *Guaranteed Cost Control*: we compute the switching trajectory with for interval $[0, t_f]$. Then, using the trajectory of $\alpha(t)$ and the estimations of observer (6.65) and (6.66), we compute the switching law $\sigma(\cdot)$,

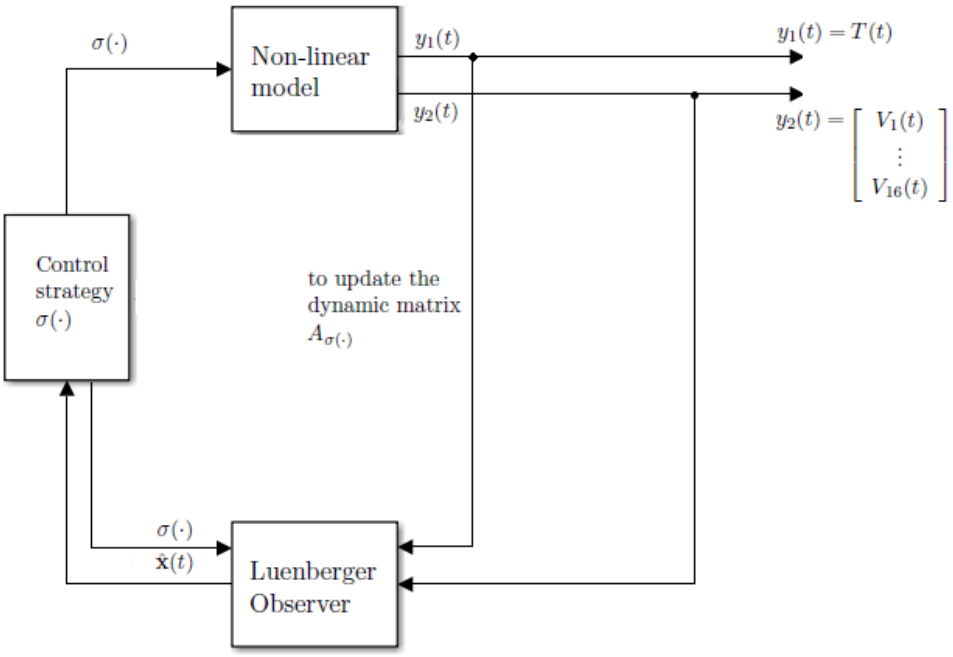


Figure 6.6: Scheme of the project, using the MPC approach.

- *MPC*: compute the switching trajectory using the great linear system, and update with the estimation of the observer (6.65) and (6.66). We take $T_p = 1$ $[year]$.

Strategy:	$\Sigma_{i=1}^{n} V_i$:	CD4+T cells:
SWATCH	258 $[copies/mL]$	602 $[copies/mm^3]$
SVF	231 $[copies/mL]$	682 $[copies/mm^3]$
Guaranteed Cost	241 $[copies/mL]$	736 $[copies/mm^3]$
MPC	7.5 $[copies/mL]$	857 $[copies/mm^3]$

Table 6.3: Simulation results after six years of HAARTs.

Simulations results in Table 6.3 reveal that the MPC strategy outperforms the other strategies.
MPC suggests that therapy 1 should be maintained for one year, then alternations between treatments will promote undetectable levels in the viral load.
Observer estimation during MPC strategy are shown in Figure 6.7. It is visible that it is a good estimation of infected cells, even if we hypothesise a constant number of macrophages and measurements once a month. Moreover, Figure 6.7 shows that MPC switching inhibits quickly those cells infected with WTG (g_1), whereas the other genotypes are kept under very low levels ($\leq 0.1[cells/mm^3]$). During the first year of monotherapy 1, we can see that g_4, the genotype resistant to this therapy, promotes infection of $CD4 + T$ cells and macrophages. However, MPC controls g_4 alternating between therapies.

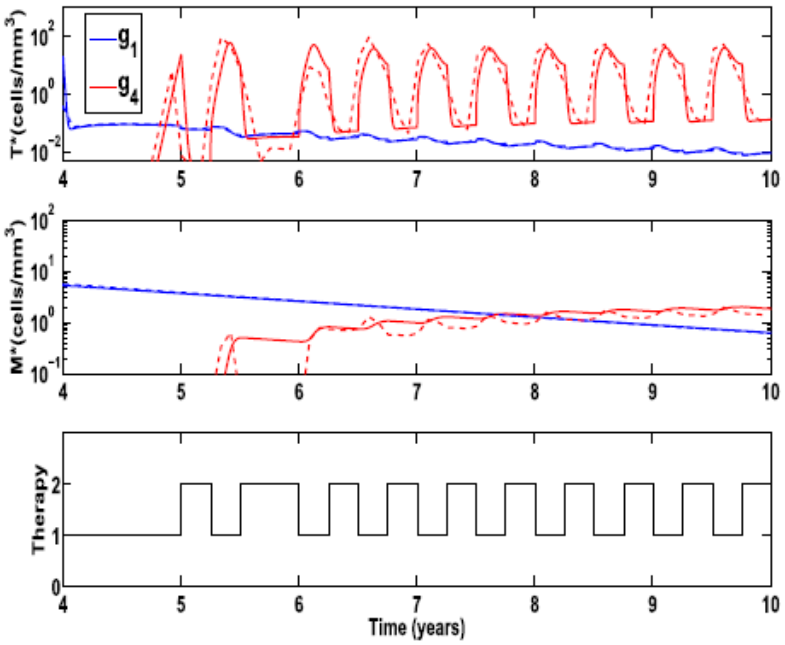


Figure 6.7: Treatment scheduling based on MPC, using a Luenberger observer. Solid lines: the dynamics of the nonlinear model, under therapy. Dashed lines: the respective estimations.

These results suggest that to use model-based strategies may provide good results with undetectable levels of viral load and high $CD4 + T$ cell counts.

Chapter 7

Conclusions

Simulation studies presented throughout the thesis show the importance of alternating HAART regimens: using different drugs at the right moment is of great importance in patient's treatment, as it allows to maintain HIV RNA at low levels and prevent the future appearance of resistant mutants.
However, finding the optimal control rule is a computationally demanding problem, as it is a two boundary integration problem. For this reason, it is only computed for the small model.
An alternative, suboptimal solution is represented by the guaranteed cost controls, which achieve good results, when compared to the optimal control.
However, when dealing with a real cases study, knowing the values of all genotypes and the number of infected $CD4+T$ cells and macrophages is often not possible. Thus, we built an observer in order to obtain an estimate of the full state. By using this estimate, we compute a guaranteed cost control which we apply to the nonlinear model of HIV under therapy.
The final strategy consists in using the Model Predictive Control. This strategy includes the same observer of the previous case. This approach has the advantage of being quite robust to model-mismatches. Additionally, its performance is similar to the optimal control.
It is very likely that these simulation studies could help to optimally schedule HIV treatment, a problem which has not been fully answered to present time.
Nevertheless, we are far from a full characterization of switching strategies able to halt virological failures of treatments.
In order to provide a more extensive description of HIV dynamics, we should consider more complicated mutation graphs and other immune cells involved in HIV infection. Moreover, we should introduce random variations in the model.
All these considerations make the the problem of HIV treatment scheduling an open and active field of research.

Appendices

Appendix A

Observability of linear continuous systems

The concept of observability refers to the possibility to find the state of a system from the measurable variables which are the inputs and the outputs. This concept is really important in control problems in which it is necessary to know the value of the state at each instant. In real problems, the state is not always available and observability is strictly connected to the possibility of realize algorithms which are able to estimate in real time the state value. When we have data that refer to time instants following the current time, we talk about observability.
Consider a linear, continuous, system of dimension n

$$\begin{aligned} \dot{\mathbf{x}}(t) &= A\mathbf{x}(t) + B\mathbf{u}(t) \\ \mathbf{y}(t) &= C\mathbf{x}(t). \end{aligned} \tag{A.1}$$

A state $\mathbf{x}$ is not observable in $[0,t]$, with $t>0$, if for every input function $\mathbf{u}(\cdot)$, the output function $\mathbf{y}(\cdot)$, which corresponds to the initial state $\mathbf{x}$ on $[0,t]$, is coincident with the output function which corresponds to the initial state $\mathbf{0}$.
In both cases the forced components of the output function $\mathbf{y}(\cdot)$ are the same, thus the state $\mathbf{x}$ is not observable on $[0,t]$ if and only if

$$Ce^{A\tau}\mathbf{x},\ 0 \leq \tau \leq t. \tag{A.2}$$

If we define with ω_t the linear map

$$\omega_t : X \to C[0,t]^p : \mathbf{x} \mapsto Ce^{A\tau},\ 0 \leq \tau \leq t \tag{A.3}$$

which links the initial state $\mathbf{x}$ to the free output function $\mathbf{y}_l(\cdot)$ which the initial state $\mathbf{x}$ induces in the time interval $[0,t]$. Clearly, $\mathbf{x}$ is not observable in $[0,t]$ if and only if $\mathbf{x} \in ker\omega_t$. The set of non-observable states in $[0,t]$ is a subspace

$$X_t^{no} \doteq ker\omega_t \tag{A.4}$$

of the state space X and which we name non-observable subspace in $[0,t]$. The following proposition is necessary to express the non-observable subspace X_t^{no} of a continuous system as a kernel of a matrix. For the matrix doesn't depend on t, clearly, X_t^{no} is independent of the length of the time interval $[0,t]$ in which we know the input and output data.

Proposition A.1. *The non-observable space X_t^{no} of the system (A.1) is for each*

$t > 0$, the kernel of the observability matrix

$$\mathcal{O} = \begin{bmatrix} C \\ CA \\ \vdots \\ CA^{n-1} \end{bmatrix} \tag{A.5}$$

Proof. $\mathbf{x}$ is not observable in $[0, t]$ if and only if $\mathbf{y}_l(\tau) = Ce^{A\tau}\mathbf{x} = 0$, $\forall \tau \in [0, t]$, which means that

$$\sum_{k=0}^{\infty} \frac{CA^k \mathbf{x} \tau^k}{k!} = 0, \forall \tau \in [0, t]. \tag{A.6}$$

□

For, the subspace $X_t^{no} = ker\mathcal{O}$ doesn't depend on the time t, we name it as non-observable subspace and its symbol is X^{no}.
If $X^{no} = \{\mathbf{0}\}$, which means that $\mathcal{O}$ has full rank and so the system (A.1) is *observable.*

A.1 Trivial Observer

The most obvious approach to estimate the state of a known system which we hypothesise linear, continuous system of dimension n

$$\begin{aligned} \dot{\mathbf{x}}(t) &= A\mathbf{x}(t) + B\mathbf{u}(t) \\ \mathbf{y}(t) &= C\mathbf{x}(t), \end{aligned} \tag{A.7}$$

where the output vector is of dimension p, is to create a copy

$$\begin{aligned} \dot{\hat{\mathbf{x}}}(t) &= A\hat{\mathbf{x}}(t) + B\mathbf{u}(t) \\ \hat{\mathbf{y}}(t) &= C\hat{\mathbf{x}}(t), \end{aligned} \tag{A.8}$$

whose state $\hat{\mathbf{x}}(t)$ provides an estimate of the original system's state $\mathbf{x}(t)$. We know the input $\mathbf{u}(t)$, in fact it is the control function which we impose to the system. The simplicity of this method has a downside. If the initial state of the copy matches that of the original system, i.e. $\hat{\mathbf{x}}(0) = \mathbf{x}(0)$, the copy provides the exact value of the state of the original system. However, if the initial state doesn't match exactly, the error of the estimate evolves according to

$$\dot{\mathbf{e}}(t) = \dot{\hat{\mathbf{x}}}(t) - \dot{\mathbf{x}}(t) = A\left(\hat{\mathbf{x}}(t) - \mathbf{x}(t)\right) = A\mathbf{e}(t). \tag{A.9}$$

If the dynamic matrix A is Hurwitz, then the error of the estimate goes asymptotically to zero. On the other hand, if the dynamic matrix A is not Hurwitz, then the error of the estimate doesn't go to zero, but diverges during time.

A.2 Identity Observer

Clearly, it is necessary to find out an observer which is more sophisticate. We consider the same state space model introduced in the previous section (A.7).
It is visible by the system equations that the output vector gives, even if somewhat indirectly, information about the state of the system. W.r.t. the Trivial Observer

in the previous section, we add a term that takes into consideration the error of the estimate of the output vector, pre-multiplied by a arbitrary matrix $L \in \mathbb{R}^{n\times p}$. Thus, the state estimate dynamic equation is

$$\dot{\hat{\mathbf{x}}}(t) = A\hat{\mathbf{x}}(t) + L\left(\mathbf{y}(t) - C\hat{\mathbf{x}}(t)\right) + B\mathbf{u}(t). \tag{A.10}$$

The matrix $L \in \mathbb{R}^{n\times p}$ is the *observer gain*. The choice of the observer gain matrix affects the dynamic behaviour of the state estimate and thus the error of the state estimate.

By substituting $\mathbf{y}(t) = C\mathbf{x}(t)$ in (A.10), we can find the estimate error dynamic:

$$\dot{\mathbf{e}}(t) = \dot{\hat{\mathbf{x}}}(t) - \dot{\mathbf{x}}(t) = [A - LC]\left(\hat{\mathbf{x}}(t) - \mathbf{x}(t)\right) = [A - LC]\,\mathbf{e}(t). \tag{A.11}$$

A.3 Reduced-Order Observer

Suppose that the length n of our state vector is large, and $n-p$ is small. The computational load required to provide estimates of all n variables may be larger than acceptable, in fact the dynamic matrix A is $n \times n$, so the number of computations increases with n^2.

We again consider the system given by equations (A.7), but we use the measurements to obtain a certain number of $p' \leq p$ of elements of the state vector, and thus construct an estimator of order $n-p$ instead of n.

For simplicity, we assume that the matrix C is full (row) rank, and so the number of state variables which we obtain from the output function $\mathbf{y}(t)$ are exactly $p' = p$, and, as previously, we assume that the system is fully observable.

We compute a base change of the space state applying a transformation matrix P to the state $\mathbf{x}(t)$ to reorder and transform the state such that

$$\begin{bmatrix} \mathbf{w}(t) \\ \mathbf{y}(t) \end{bmatrix} = \tilde{\mathbf{x}}(t) = P\mathbf{x}(t) = \begin{bmatrix} T \\ C \end{bmatrix} \mathbf{x}(t). \tag{A.12}$$

A T such that the matrix P is non-singular surely exists, for we hypothesise that C is full rank. We derive the dynamic equations of the state estimate and the error of the estimate.

We start by considering the state equation of $\tilde{\mathbf{x}}(t)$, which is:

$$\dot{\tilde{\mathbf{x}}}(t) = \tilde{A}\tilde{\mathbf{x}}(t) + \tilde{B}\mathbf{u}(t), \tag{A.13}$$

where $\tilde{A} = P^{-1}AP$ and $\tilde{B} = P^{-1}B$.

Now, by substituting the definition (A.12) of the state $\tilde{\mathbf{x}}(t)$ divide the matrices $\tilde{A}$ and $\tilde{B}$ as follows:

$$\begin{bmatrix} \dot{\mathbf{w}}(t) \\ \dot{\mathbf{y}}(t) \end{bmatrix} = \begin{bmatrix} A_{11} & A_{12} \\ A_{21} & A_{22} \end{bmatrix} \begin{bmatrix} \mathbf{w}(t) \\ \mathbf{y}(t) \end{bmatrix} + \begin{bmatrix} B_1 \\ B_2 \end{bmatrix} \mathbf{u}(t). \tag{A.14}$$

As in the construction of the Identity Observer given in the previous section, we select the matrix L which multiplies t output vector $\mathbf{y}(t)$. So, considering separately $\dot{\mathbf{w}}(t)$ and $\dot{\mathbf{y}}(t)$, we define

$$\dot{\mathbf{w}}(t) - L\dot{\mathbf{y}}(t) = (A_{11} - LA_{21})\,\mathbf{w}(t) + (A_{12} - LA_{22})\,\mathbf{y}(t) + (B_1 - LB_2)\,\mathbf{u}(t), \tag{A.15}$$

then rearranging to obtain

$$\dot{\mathbf{w}}(t) - L\dot{\mathbf{y}}(t) = (A_{11} - LA_{21})\,[\mathbf{w}(t) - L\mathbf{y}(t)] + (A_{11}L - LA_{21}L + A_{12} - LA_{22})\,\mathbf{y}(t) + \\ + (B_1 - LB_2)\,\mathbf{u}(t). \tag{A.16}$$

Then, defining $\mathbf{v}(t) \doteq \mathbf{w} - L\mathbf{y}(t)$, we obtaion

$$\dot{\mathbf{v}}(t) = (A_{11} - LA_{21})\,\mathbf{v}(t) + (A_{11}L - LA_{21}L + A_{12} - LA_{22})\,\mathbf{y}(t) + (B_1 - LB_2)\,\mathbf{u}(t). \tag{A.17}$$

The vector $\mathbf{v}(t)$, of length $n - p$, represents the unknown part of the state, which evolves according to the dynamics defined by $A_{11} - LA_{21}$, and the inputs $\mathbf{u}(t)$ and $\mathbf{y}(t)$.
To estimate $\mathbf{v}(t)$, we construpt an observer of order $n - p$:

$$\dot{\mathbf{z}}(t) = (A_{11} - LA_{21})\,\mathbf{z}(t) + (A_{11}L - LA_{21}L + A_{12} - LA_{22})\,\mathbf{y}(t) + (B_1 - LB_2)\,\mathbf{u}(t). \tag{A.18}$$

The reduced-order estimator error is

$$\begin{aligned} \dot{\mathbf{e}}(t) &= \dot{\mathbf{z}}(t) - \dot{\mathbf{v}}(t) = \\ &= (A_{11} - LA_{21})\,[\mathbf{z}(t) - \mathbf{v}(t)] = \\ &= (A_{11} - LA_{21})\,\mathbf{e}(t), \end{aligned} \tag{A.19}$$

and it is visible that the error dynamic is also determined by the matrix $A_{11} - LA_{21}$.
Recalling the definition of $\mathbf{v}(t) = \mathbf{w}(t) - L\mathbf{y}(t)$, it is reasonable to hypothesise that its estimate is $\mathbf{z}(t) = \hat{\mathbf{w}}(t) - L\mathbf{y}(t)$, thus

$$\tilde{\mathbf{x}}(t) = \begin{bmatrix} \hat{\mathbf{w}}(t) \\ \mathbf{y}(t) \end{bmatrix} = \begin{bmatrix} \mathbf{z}(t) + L\mathbf{y}(t) \\ \mathbf{y}(t) \end{bmatrix}. \tag{A.20}$$

In the end, we can obtain the estimate of the original state by pre-multiplying (A.20) by P^{-1}, which is a transformation matrix and so it is full rank for construction.
Then, we obtain

$$\hat{\mathbf{x}}(t) = P^{-1}\tilde{\mathbf{x}}(t). \tag{A.21}$$

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