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Bang-Bang Control Applied on an HIV-1 Model

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Dedication

I dedicate this thesis with all my love and deep gratitude to:

My beloved parents, **Saddik** and **Tazouta Wassila**, for their unconditional support, sacrifices, and prayers that have always uplifted me.

My dear sister **Imène**, for her sincere affection and constant presence.

To the memory of my beloved uncle,
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May Allah have mercy on his soul and grant him eternal peace. Your wisdom, kindness, and love will always remain in my heart. This work is dedicated to you, with prayers and remembrance.
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- DNA: Deoxy Ribonucleic Acid.
- AES: Accident involving exposure to blood and/or biological fluids.
- RNA: Ribonucleic acid.
- CD4: Differentiation cell.
- CRF : Circulating Recombinant Form.
- AIDS: Acquired immune deficiency syndrome.
- cDNA: Complementary DNA
- HIV: Human immunodeficiency virus.
- CXCL4: C-X-C Chemokine Ligand 4 (also known as PF4).
- CCR5: Is the major co receptor for human immunode ciency virus.
- STI: Sexualy transmissible infection.
- PET: Post exposene therapy.
- PMP: Pontryagin maximum principle.
- a.e: for almost every.
- $\arg\max$: Argument of the maximum value of the variable (often control) that maximizes a function, such as the Hamiltonian.
- e.g: Exempli gratia = for example.
- iff: If and only if.
- i.e, id: Which means.

General Introduction

Comprehensive research on the **Human Immunodeficiency Virus** (HIV) aims to promote a deeper understanding of the virus, the immunopathology associated with the infection it causes, and the mechanisms that contribute to its persistence. This study is at the forefront of novel therapeutic strategies that may limit the spread of the illness and its progression and ultimately lead to a new method of treating the virus that causes **AIDS**.

In collaboration with organizations and the pharmaceutical industry, clinical research seeks to create novel medicines by conducting studies that adhere to established methods. Notwithstanding the advancements in infection control, it is crucial to uphold the significance of prevention. Analysis of prevention-related behavior and evaluation of treatment availability depends on researchers in the human and social sciences as well as public health.

Furthermore, fundamental and clinical research on HIV vaccine prevention continues to be a top focus. To create a vaccination that is available to everyone, researchers must expand their knowledge of immunological systems. This involves the ongoing development of vaccination candidates as well as the thorough testing of their immunological response-inducing potential and acceptability. HIV is the most researched virus in the world since several research teams have been addressing these problems for several years.

There are several AIDS medicines available today. But in only a few years, science has advanced significantly. Preventing the virus from growing en-bloc during one of the phases of its propagation is the goal of HIV therapy. Currently, the virus cannot be eradicated by these compounds. Initially, they were administered as triple treatments. We are now discussing multi-therapies, and depending on the situation, the combinations can range from two to five (or more) physicians.

First off, patients have been shown to take these medications less often (compliance) due to their serious adverse effects. These include nausea, diarrhea, neuropathy (atrophy of nerve cells), lipodystrophy (alterations in the body's fat distribution, such as face hollowing, neck or abdominal fat deposits) and psychiatric problems (depression, mood swings, and disorientation). When

keeping an eye on the patient, it is crucial to consider these things.

The success of antiretroviral therapies for HIV depends on at least 95% adherence, which might be difficult because of social and lifestyle limitations. Easing adherence while guaranteeing efficient virus control requires optimizing medication doses in order to enhance patients quality of life, reduce adverse effects, and preserve treatment efficiency.

Our goal is to ensure treatment effectiveness while reducing administered amounts and/or associated costs. We thus made the decision to develop a simplified model of in vivo viral transmission by incorporating several treatments used in hospital or clinical settings as injectable controls into the model. Next, using controls injected into the model, we modeled the various treatments currently used in hospital settings or in clinical research.

This method makes it easier to investigate cost functions and makes it easier to analyze the control system numerically. It also draws attention to the controversy over how to balance boosting healthy immune cells with lowering the virus load. Some support boosting CD4 cell proliferation, while others place more emphasis on avoiding viral exhaustion. This emphasizes how crucial a balanced approach is to creating the best HIV therapies.

The first chapter summarises the biological aspect of the problem to help the non-biologist reader understand the situation. It discusses how the infection spreads and develops in the body, how it is monitored, and what treatments are currently available and being researched to combat it.

The next chapter begins with an overview of the state of the art in the field, followed by a qualitative mathematical analysis to identify key model features such as competitiveness, uniform persistence, and the local and global stability of equilibrium points. **MATLAB** is employed to numerically simulate the model for different R_0 values.

The final part, which is an essential component of this study, presents the control method applied to the model together with its biological interpretation.

After that the **bang-bang control** is obtained by applying a linear criterion. In every situation, we do a comparison analysis. Comparative evaluation of the decrease in blood-borne viruses and the increase in healthy cells for each control group in relation to the decrease in infected cells.

Before combining the simulations, we first run them separately for each control. Each scenario is subjected to numerical simulations, which are undertaken for each.

At the end of the paper, a conclusion is presented, together with an example illustrating the main results. The study focuses on understanding the behavior of the system, while emphasizing the key mathematical tools used throughout.

Chapter 1

Biological Context

1.1 HIV Infection Dynamics

1.1.1 History of HIV Virus

The first cases of what would later be known as AIDS were reported in 1981 in the United States, when the Centers for Disease Control and Prevention (CDC) described unusual infections and rare cancers among young homosexual men. The syndrome, characterized by lesions in the lymphatic system and severe immune deficiency, quickly became a major public health concern. Subsequent cases among homosexual communities and intravenous drug users helped define and recognize this new syndrome as AIDS.

In 1983, French researchers led by Luc Montagnier at the Pasteur Institute isolated the virus responsible, initially named LAV (Lymphadenopathy Associated Virus). Around the same time, in the United States, Robert Gallo's team identified a similar virus, named HTLV-III (Human T-Lymphotropic Virus Type III). A conflict then arose between France and the United States concerning the priority of the discovery and the patents for HIV diagnostic tests, a dispute that was eventually settled through a shared agreement.

In 1985, abnormal serological responses were observed in blood samples from Senegalese sex workers, suggesting the existence of a second, related virus, more closely linked to simian retroviruses. This second virus was isolated in 1986 and named HIV-2, later confirmed to be less transmissible and less aggressive than HIV-1. Following a taxonomic classification carried out the same year, HIV types 1 and 2 were officially recognized as the causative agents of AIDS [27].

Throughout the late 1980s and early 1990s, the number of people living with HIV/AIDS increased dramatically, marking the beginning of a global pandemic. Meanwhile, extensive research efforts were launched to develop treatments and a vaccine. Although early vaccine trials generated hope, the

high variability and rapid mutation rate of HIV have so far prevented the creation of an effective preventive vaccine.

Today, while no definitive cure exists, antiretroviral therapies (ART) have transformed HIV infection into a manageable chronic condition, especially in developed countries. However, global disparities remain. According to UNAIDS, approximately 39 million people were living with HIV in 2023.

In Algeria, the prevalence is relatively low compared to global figures, but sustained efforts in prevention, diagnosis, and treatment are still necessary to control the epidemic [23].

1.1.2 Introduction to HIV

HIV is the human immunodeficiency virus. It is classifiedas an STI, i.e. an infection that can be transmitted during sexual relations, it can be transmitted by blood too.
What makes HIV so special is that it attacks immune system cells, in particular CD4 T lymphocytes. These are the cells that protect the body against diseases and other infections [10].

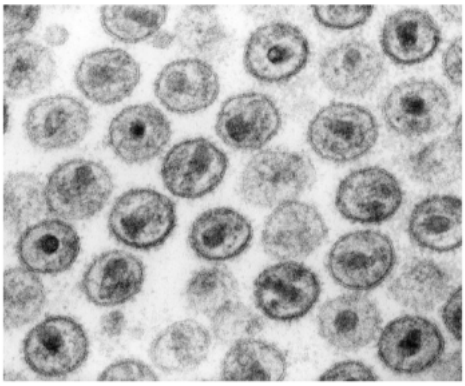

Figure 1.1: HIV under electron microscope [38].

Types of HIV:

There are two types of HIV: "**HIV-1**" and "**HIV-2**". These two viruses share about 42% of their genome. HIV-1 is the most common virus in the world, accounting for over 98% of infections, particularly in Europe and North America. In contrast, HIV-2 is mainly concentrated in West Africa, with a significant presence in countries such as Senegal, Côte d'Ivoire, Mali, Guinea-Bissau, Burkina Faso and Cape Verde. In Europe, HIV-2 is also present in France and Portugal, due to historical links with the region.

HIV-2 is less virulent and less transmissible than HIV-1, which explains its more limited prevalence.

1.1.3 Transmission of the virus

There are three ways of transmitting it [28].

- **Sexual transmission:** HIV is mainly transmitted through unprotected sex, accounting for $70 - 80\%$ of infections.
- **BTransmissionlood transmissiong:** During blood transfusions, syringe exchanges, or accidents, HIV can spread through the blood. The systematic screening of blood donors has significantly decreased this risk, which is estimated to be 1 in 500,000.
- **Transmission:** HIV can spread from mother to child during pregnancy or breastfeeding. HIV-1 rates are 15-45% without therapy, while HIV-2 rates are 4-8%. With preventative therapy, fewer than 1,000 babies are born infected.

1.2 Biological and immunological basics

1.2.1 The HIV Structure

The retrovirus HIV has a genotype made up of two identical **RNA** molecules. It does retrotranscription by integrating its **DNA** into the host cell's thanks to the **transcriptase inverse**. The virus has a diameter of 150 nm and is encased in a **lipidic envelope** of the infected cellule, which contains the glycoproteins **gp**120 and **gp**41. The **RNA** viral molecules and essential enzymes **integrase, protease, and inverse transcriptase** are found inside the **apside conique.**

- **Glycoproteins:** Are a type of conjugated proteins composed of proteins and carbohydrates [6].
- **RNA:** A molecule present in all living cells and certain viruses (ribonucleic acid) that allows for the creation of proteins.
- **DNA:** A molecule in all living cells (deoxyribonucleic acid) that carries the genetic information for an organism's development.
- **Inverse transcriptase:** An enzyme promoting the transcription of RNA to DNA, often of viral origin.

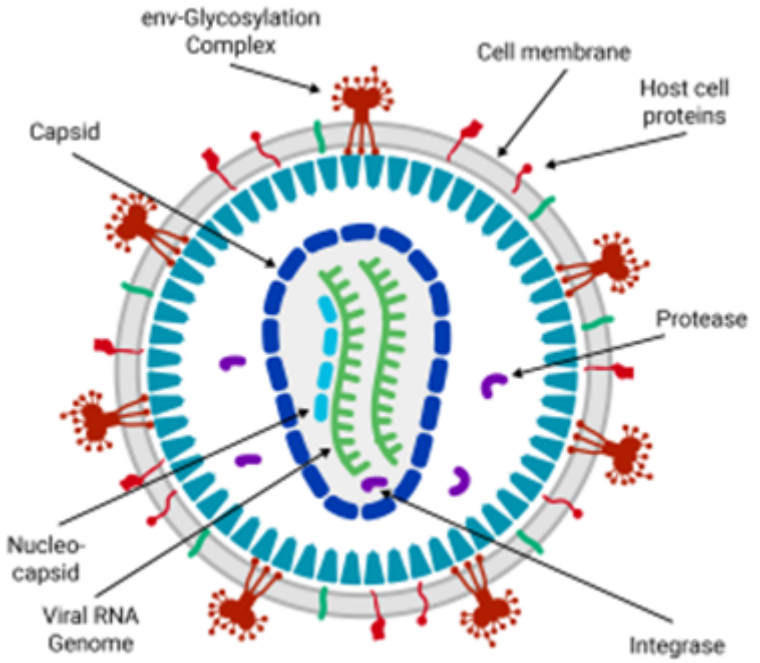

Figure 1.2: Structural representation of a virion HIV [29].

1.2.2 Replication Cycle

HIV primarily infects $CD4$ T lymphocytes, key cells of the immune system. It binds to these cells via the protein $gp120$, facilitated by co-receptors.

1. **Viral entry**: HIV fuses with the membrane of the target cell and releases its viral RNA.

2. **Retrotranscription**: The viral RNA is converted to cDNA by reverse transcriptase.

3. **Integration**: The cDNA is integrated into the host cell genome by integrase.

4. **Expression and replication**: The cell uses its own mechanism to produce new viral proteins.

5. **Assembly and release**: New virions form and bud out of the cell, ready to infect other cells.

The viral cycle relies entirely on the host's cellular machinery to replicate.

Once infected, the cell overwhelmed by the replication process performs a biological suicide called apoptosis, leading to the release of all presomal viruses inside the cell.

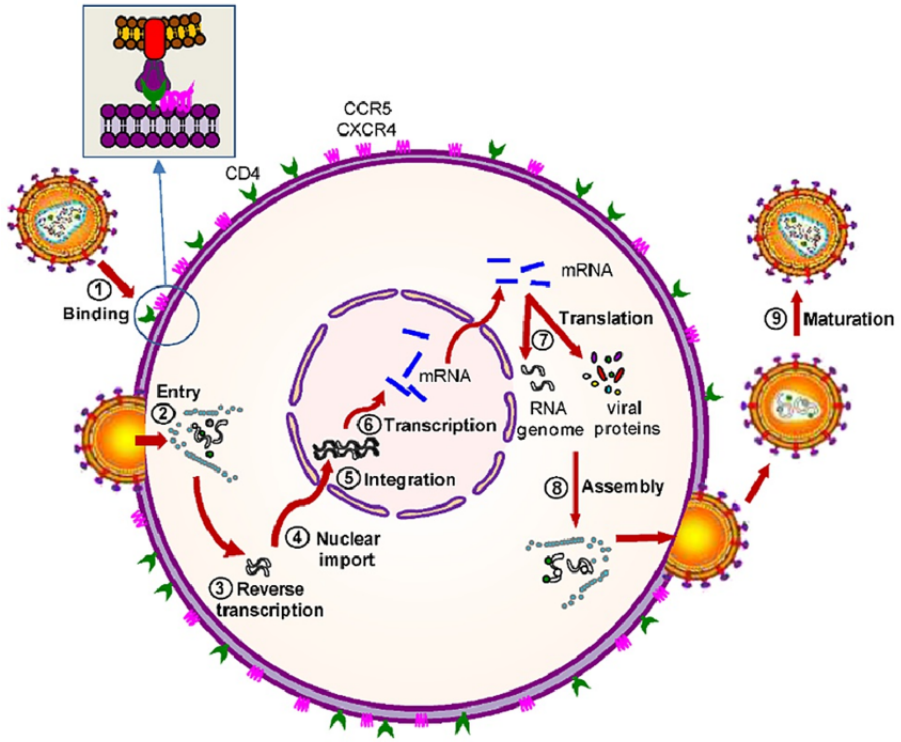

Figure 1.3: Simplified diagram of the HIV-1 replication cycle [13],[37].

1.2.3 Symptoms of HIV infection

The natural evolution of HIV infection can be broken down into three main phases.

- **Primary infection:** In the first days after the infection by the virus, the HIV rapidly grows and induces a drop in T-CD4$^+$ cells. A few weeks later, grippiness symptoms start to show up.
- **The asymptomatic phase:** The immune system controls HIV after stabilization, but it gradually kills T cells. The rate of CD4$^+$/CD8$^+$ and viral charge track the evolution.
- **The AIDS stage:** When viral charge exceeds 10,000 copies/mL and CD4$^+$ is less than 200 cell/mm^3, AIDS occurs. Each patient progresses differently; some develop in 8–10 years, while others remain asymptomatic for more than 20 years.

  Note: A very small percentage of people spontaneously suppress the HIV [38].

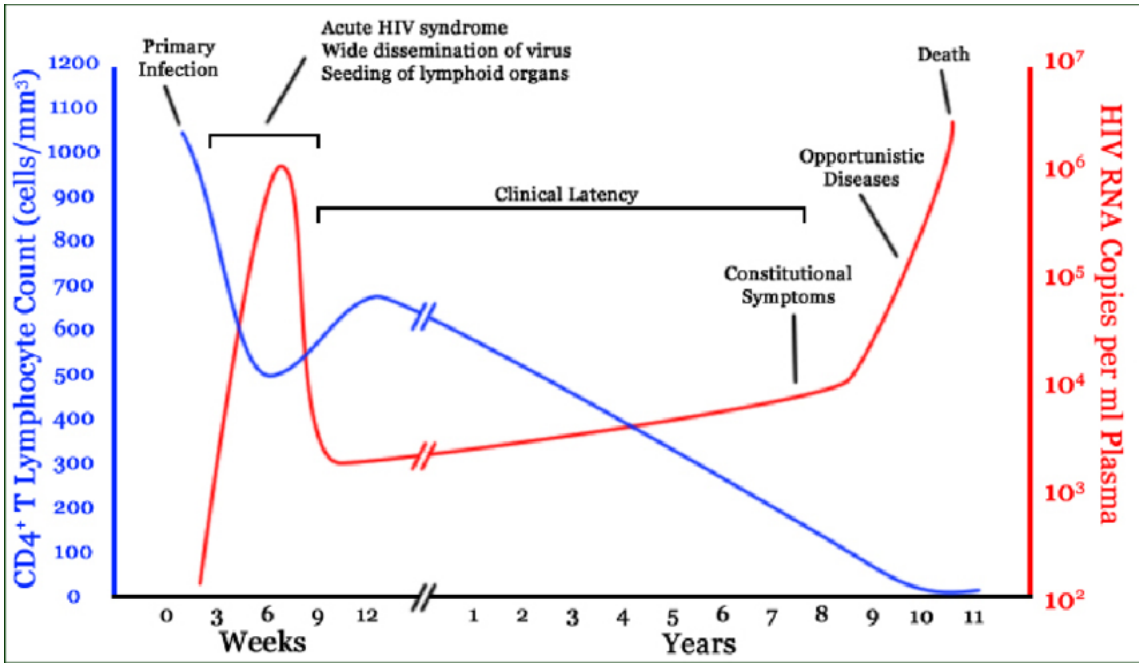

Figure 1.4: Evolution of HIV infection [33].

1.2.4 Epidemic

Today, it is known that a well-monitored HIV-positive individual has a very low risk of transmitting HIV after sexual activity under specific conditions:

- The treatment is administred regularly.
- The viral charge is undetectable, or below the threshold of 50 copies/ml in the plasma for over six months, according to most recent test.
- The viral charge is measured on a regular basis, at least every three or four months.

There is currently no cure for HIV or AIDS. Even if the virus becomes undetectable in tests, this doesn't mean the infection is gone from the body. A person who is HIV-positive can live a long life with proper treatment, and HIV is now considered a chronic illness. **As long as they are not properly treated, HIV-positive individuals are still at risk of transmitting the virus**. AIDS is caused by untreated HIV infection, which can ultimately lead to death. HIV infection is still spreading, and some vulnerable groups are abandoning their defenses.

1.3 Therapeutic strategies for HIV control

HIV infection requires appropriate therapeutic management to maintain patient health and limit the progression of the infection. Although many antiretroviral drugs are available today, in our work we focus only on certain

targeted strategies applied at different stages of the viral life cycle.
The therapeutic approaches studied in our model are as follows :

1. **Increasing the viral clearance rate:** This can be achieved using antiretroviral drugs that inhibit the HIV protease enzyme, thereby preventing the cleavage and proper assembly of viral polyproteins. As a result, only immature and non-infectious viral particles are produced. Furthermore, bee venom nanoparticles have shown the ability to directly disrupt the viral envelope and inhibit protease activity, providing an innovative approach to neutralize free virions without damaging host cells [1], [12].

2. **Preventing integration of the virus into the host cell:** This includes blocking the viral integrase enzyme to stop the insertion of viral cDNA into the host genome. Additionally, CCR5-modified cells are genetically engineered to lack the CCR5 receptor, making them resistant to HIV entry. Other promising approaches include antiviral gels (topical microbicides) and cannabis extracts, which have shown potential to reduce local viral replication at mucosal surfaces [2], [8].

3. **Reducing apoptosis of infected cells:** By inhibiting the reverse transcriptase enzyme of HIV which blocks the conversion of viral RNA into DNA the replication cycle is interrupted at an early stage [9]. As a result, the infected cells are kept alive longer, which helps reduce the occurrence of the apoptosis process.

1.4 Prevention and Future

Additionally, future research is focusing on the development of effective HIV vaccines using mRNA-based and viral vector platforms and on long-acting antiretroviral formulations to improve adherence and reduce dosing frequency. Cutting edge strategies such as therapeutic vaccines, broadly neutralizing antibodies, and gene editing techniques (e.g. CRISPR/Cas9) are under investigation with the aim of achieving sustained viral remission or a functional cure. If successful, these advances could transform HIV prevention and treatment in the coming decades.

Chapter 2

Mathematical model presentation and study

2.1 Introduction

Recent advances in the development of potent antiviral drugs have greatly improved our understanding of viral infections such as HIV. In addition to paving the way for more effective treatments, these advances have provided essential quantitative data on viral dynamics in vivo. However, interpreting and analyzing these data requires mathematical tools capable of modeling the complex interactions between viruses and host cells.

To this end, both deterministic and stochastic mathematical models have been developed to describe these dynamics. These models are based on ordinary differential equations, both linear and non-linear, and can incorporate various biological factors such as immune responses, resistance to antiviral treatments, and the evolution of viral populations. In-depth analysis of these models allows us not only to better understand the spread of the virus and the effect of treatments, but also to assess the conditions under which eradication of the infection could be envisaged. In this chapter, we will analyze a mathematical model in detail, highlighting its construction, its basic assumptions and their relevance to the study of viral infections.

2.1.1 The basic model

During an HIV infection, the virus attaches itself to T $CD4^+$ cells and travels through the bloodstream, converting its RNA into DNA and causing the inverted enzyme transcriptase to break down. With the help of the enzyme integrase, the viral DNA then identifies the DNA of the host cell, which facilitates the growth and assembly of new viral particles known as virions, which are then released, see first chapter, or [24].

T-cell proliferation in the HIV environment is still poorly understood. The mathematical models that describe how the HIV-1 virus interacts with the immune system include the use of a source constant, which indicates how many CD4$^+$T cells are present in the blood, decreased by the natural mortality rate that these cells have. Some models use a logistic approach [32] to limit the growth of healthy cells, which is represented by a kind of equation:

$$\dot{S} = \delta - \alpha S + bS\left(1 - \frac{S}{K}\right)$$

Other models [31] take into account the saturation of the immune system by both healthy and infected cells, giving, equation of the form:

$$\dot{S} = \delta - \alpha S + bS\left(1 - \frac{S+I}{K}\right)$$

In our research, we simulate the development of healthy cells, taking into account their regenerative capacity, rather than assuming a fixed number. To do so, we prefer a logistic expansion approach that shows the function of the thymus and the bone marrow in producing new cells based on the body's needs. This model offers a better illustration of the interaction between the HIV-1 virus and the immune system, integrating the biological processes that influence the course of the infection. We then consider the mathematical model that describes the interaction between the immune system and the HIV-1 virus, as described by:

$$\begin{cases} \dot{S}(t) = \alpha S(t)\left(1 - \frac{S(t)}{K}\right) - \beta S(t)V(t) \\ \dot{I}(t) = -\mu I(t) + \beta S(t)V(t) \\ \dot{V}(t) = -\sigma V(t) + \gamma\mu I(t) \end{cases} \tag{2.1}$$

With the positive initial condition:

$$S(0) = S_0, I(0) = I_0, \quad V(0) = V_0, \tag{2.2}$$

where: $t \in [0, T]$ and $T > 0$.

Interpreting the system :

* $S(t)$: is the quantity of non-infected T-CD4$^+$ cells at time t, by blood unit.
* $I(t)$: is the quantity of T-CD4$^+$ cells infected by the virus at time t, by blood unit.

* $V(t)$: is the quantity of free virus circulating in the blood at time t, by blood unit.

2.1.2 Identification of system parameters

The following parameters characterise the model (2.1):

* α : Growth rate of healthy cells.
* K : Capacity of the system (maximum number of immune cells that can be present in the blood at any time).
* β : Infection rate.
* μ : Mortality rate of infected cells.
* σ : Virus mortality rate.
* γ : The number of viruses produced by an infected cell during its lifetime.

The initial conditions are set assuming that $S_0 \leq K$, and that $\alpha < K$, while considering that $\gamma \gg 1$ for reasons of realism. All system parameters are positive and are summarised in the following table:

Parameters	Value	Unit	References
α	0.03	cells per day	[8]
K	10^3	cells per mm^3	Estimated
μ	0.24	cells per day	[8]
β	2.4×10^{-5}	mm^3 per day	[8]
σ	2.4	viruses per day	[16]
γ	3000	number of virions	[16]

Table 2.1: Identification of system (2.1) parameters.

The system (2.1) can be schematised as follows:

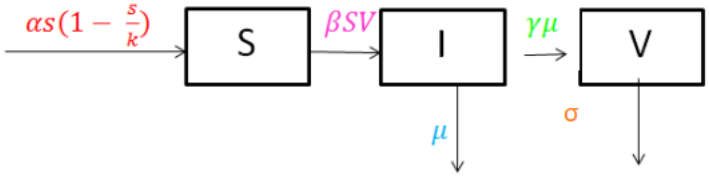

Figure 2.1: HIV model counting (diagram).

2.2 Mathematical tools

In this section we present the main mathematical tools to be used to perform the formal model study.

Definition 2.1 (Spectral Radius)

The spectral radius of a matrix $A \in M_n(\mathbb{R})$ is defined as the maximum absolute value of its eigenvalues, that is:

$$\rho(A) = \max_{\lambda \in \mathrm{Sp}(A)} |\lambda|$$

where $\mathrm{Sp}(A)$ *denotes the set of all eigenvalues of* A*.*

Dynamical System:

We consider an *autonomous dynamical system* in $\mathbb{R}^n$ of the form:

$$\dot{x}(t) = f\big(x(t)\big), \quad x(t) \in \mathbb{R}^n,$$

where

$$f : \mathbb{R}^n \longrightarrow \mathbb{R}^n$$

is continuously differentiable.

In this framework:

- $x(t)$ denotes the *state vector* at time t.
- $f(x)$ is the *vector field* that governs its evolution.
- Solution $x(t)$ exists and is unique by the Cauchy–Lipschitz theorem, see thoerem 2.2

Cauchy–Lipschitz Theorem [17]

Consider the following initial value problem:

$$\begin{cases} \dot{x}(t) = f(x(t)) \\ x(t_0) = x_0 \end{cases} \tag{$\star$}$$

Let $f : \mathbb{R}^n \to \mathbb{R}^n$ be a function that is continuous on $\mathbb{R}^n$ and locally Lipschitz with respect to the second variable.

Then, for any initial condition $(t_0, x_0) \in I \times \mathbb{R}^n$, the problem $(*)$ admits a unique local solution $x(t)$, defined on an interval $[t_0, T_{\max}] \subseteq I$.

Proposition 2.1 (Global existence of the solution)

Let $x(t)$ be the unique local solution to the Cauchy problem ($\star$), (2.2). If the solution remains bounded on its maximal interval of definition $[0, T_{\max}[$, then it can be extended beyond $T_{\max}$. In particular, if it stays in a compact subset of $\mathbb{R}^n$, then $T_{\max} = +\infty$ and the solution is global.

Definition 2.2 (Positively Invariant Set)

*A set $\Gamma \subset \mathbb{R}^n$ is said to be **positively invariant** for a dynamical system if every solution starting in Γ remains in Γ for all future times, that is, if $x(0) \in \Gamma$, then $x(t) \in \Gamma$ for all $t \geq 0$.*

Definition 2.3 (Dissipativity)

*A dynamical system is said to be **dissipative** if there exists a bounded subset $\Gamma \subset \mathbb{R}^n$ which is positively invariant and attracts all trajectories starting in $\mathbb{R}^n_+$. In other words, all solutions eventually enter and remain in a bounded region of the phase space.*

Equilibrium Point [36]

An **equilibrium point** x^* of a dynamical system is defined as a solution where the derivative of the state is zero:

$$f(x^*) = 0$$

Stability [36]

The equilibrium point x^* is said to be *stable* if, for every $\varepsilon > 0$, there exists $\delta > 0$ such that, if $\|x_0 - x^*\| < \delta$, then $\|x(t) - x^*\| < \varepsilon$ for all $t \geq 0$, where $x(t)$ is the solution of the system initialized at x_0.

Asymptotic Stability:[17]

The equilibrium point x^* is said to be *asymptotically stable* if:
1. It is stable (see the previous definition).
2. There exists $\delta' > 0$ such that, if $\|x_0 - x^*\| < \delta'$, then:

$$\lim_{t \to \infty} x(t) = x^*$$

Remark: Asymptotic stability means not only that the solutions stay close to x^* for large enough t, but that they actually converge to this equilibrium point.

Theorem 2.1 (Routh Hurwitz)

The Routh-Hurwitz criterion is an algebraic criterion used to assess the stability of linear dynamical systems. It based on the characteristic polynomial $P(\lambda)$ whose roots are all strictly real [11].
We consider the following polynominal of order n:

$$P(\lambda) = \lambda^n + a_1\lambda^{n-1} + a_2\lambda^{n-2} + \cdots + a_{n-1}\lambda + a_n$$

We say that P is Hurwitz iff all its roots are negative.
According to the Routh-Hurwitz criterion:
1- If n=2:

$$P(\lambda) = \lambda^2 + a_1\lambda + a_2$$

$$a_1 > 0, \quad a_2 > 0 \quad \Leftrightarrow \quad P \text{ is Hurwitz.}$$

2- If n=3:

$$P(\lambda) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3$$

We say that P is Hurwitz iff:

$$\begin{cases} a_1 > 0, a_2 > 0, a_3 > 0 \\ a_3.a_2 > a_1 \end{cases}$$

2- If n¿3: See [11]

Definition 2.4 (Positive Definite Function)

*A function $f : \mathbb{R}^n \to \mathbb{R}$ is said to be **positive definite** if:*

$$f(0) = 0 \quad \text{and} \quad f(x) > 0 \quad \text{for all } x \in \mathbb{R}^n \setminus \{0\}.$$

Definition 2.5 (Negative Definite Function)

*A function $f : \mathbb{R}^n \to \mathbb{R}$ is said to be **negative definite** if:*

$$f(0) = 0 \quad \text{and} \quad f(x) < 0 \quad \text{for all } x \in \mathbb{R}^n \setminus \{0\}.$$

Definition 2.6 *[21]*

Let $\Omega \subset \mathbb{R}^n$ be an open neighborhood of an equilibrium point $x^* \in \mathbb{R}^n$. A function $V : \Omega \to \mathbb{R}$ is called a Lyapunov function for the dynamical system

$$\dot{x} = f(x) \tag{2.3}$$

if:

- $V \in C^1(\Omega)$.

- *V is positive definite over Ω i.e: $V(x^*) = 0$ and $V(x) > 0$ for all $x \in \Omega \setminus \{x^*\}$,*

- *The derivative along trajectories, $\dot{V}(x) = \nabla V(x) \cdot f(x)$ is negative semi-definite definite over Ω i.e: satisfies $\dot{V}(x) \leq 0$ for all $x \in \Omega$.*

Theorem 2.2 (Lyapunov's Theorem) [14]

- *If the lyapunov function V is positive definite and $\dot{V}$ is negative semi-definite over Ω, then the equilibrium point x^* of the system (2.3) is stable.*

- *If the function V is positive definite and $\dot{V}$ is negative definite over Ω, then the equilibrium point x^* of the system (2.3) is asymptotically stable.*

LaSalle's Invariance Principle

Theorem 2.3 (LaSalle's Invariance Principle) [14]

Let $\Omega \subset \mathbb{R}^n$ be a compact, positively invariant set. Suppose $V : \Omega \to \mathbb{R}$ is continuously differentiable for the system (2.3) and satisfies

$$\dot{V}(x) \leq 0 \quad \text{for all } x \in \Omega.$$

with,

$$E = \{x \in \Omega \mid \dot{V}(x) = 0\},$$

and let M be the largest invariant set contained in E. Then every trajectory starting in Ω approaches M as $t \to +\infty$.

Corollary 2.1

If V is positive definite with respect to an equilibrium point $x^* \in \Omega$ and $\dot{V}$ is negative definite on Ω, then x^* is asymptotically stable.

Rung-Kutta of order 4:[15]

The Runge-Kutta algorithm is a numerical analysis method for approximating the solution of the Cauchy problem such that: $\begin{cases} \dot{y} = f(t, y) \\ y(t_0) = y_0 \end{cases}$

The Runge-Kutta algorithm of order 4, is given by [15] :

$$\boxed{y_{n+1} = y_n + \frac{h}{6}(k_1 + k_2 + k_3 + k_4)}$$

Where:

$$\begin{aligned} k_1 &= f(t_n, y_n) \\ k_2 &= f\left(t_n + \frac{h}{2}, y_n + \frac{h}{2}k_1\right) \\ k_3 &= f\left(t_n + \frac{h}{2}, y_n + \frac{h}{2}k_2\right) \\ k_4 &= f\left(t_n + h, y_n + hk_3\right) \end{aligned}$$

2.3 Qualitative study of the model

a/ Existence and Uniqueness

It is essential to use Theorem (⋆) to investigate the consistency and uniqueness of the solution to our model (2.1)

Theorem 2.4 *[36]*

For any initial conditions $S_0 > 0, I_0 > 0$ and $V_0 > 0$ the problem (2.1) admits a unique solution $(S(t), I(t), V(t))$ defined for any $t \geq 0$.

Proof.

Put

$$x(t) = \begin{pmatrix} S(t) \\ I(t) \\ V(t) \end{pmatrix}, \quad x(0) = \begin{pmatrix} S_0 \\ I_0 \\ V_0 \end{pmatrix}, \quad f(x(t)) = \begin{pmatrix} f_1(x(t)) \\ f_2(x(t)) \\ f_3(x(t)) \end{pmatrix}, \text{ with:}$$

$$\begin{cases} f_1(x(t)) = \alpha S(t)\left(1 - \frac{S(t)}{K}\right) - \beta S(t)V(t) \\ f_2(x(t)) = -\mu I(t) + \beta S(t)V(t) \\ f_3(x(t)) = -\sigma V(t) + \gamma\mu I(t) \end{cases}$$

Thus, the problem (2.1) takes the following form as a Cauchy problem:

$$\begin{cases} \dot{x}(t) = f(x(t)) \\ x(t_0) = x_0 \end{cases} \tag{2.4}$$

where $x \in \mathbb{R}^3_+$. Since f_1, f_2, f_3 belong to $C^1(\mathbb{R}^3_+)$, this implies that $f(x(\cdot))$ is of class $C^1(\mathbb{R}^3_+)$, and hence locally Lipschitz. According to the Cauchy–Lipschitz theorem, the problem (2.4) admits a unique local solution, i.e., there exists $T_{\max} > 0$ such that the solution exists and is unique on the interval $[0, T_{\max}[$.

To prove that the solution is globally defined for all $t \geq 0$, it is sufficient to show that the solution remains within a bounded and positively invariant region of $\mathbb{R}^3_+$.

This will be established in the following steps through the proofs of positivity and boundedness.

Therefore, the local solution provided by the theorem extends globally (2.1).

■

Positivity:

Proposition 2.2 *The positive cone is positively invariant by* (2.1).

PROOF.

Let's call the positive cone N, so: N is defined as follows:

$$N = \mathbb{R}^3_+ = \left\{(S, I, V) \in \mathbb{R}^3 \mid S \geq 0, I \geq 0, V \geq 0\right\}.$$

In which, the following inequalities are verified:

$$\begin{array}{ll} \dfrac{dS}{dt} & \Big|_{S=0} = 0 \\ \dfrac{dI}{dt} & \Big|_{I=0} = \beta SV \geq 0 \\ \dfrac{dV}{dt} & \Big|_{V=0} = \gamma\mu I \geq 0 \end{array}$$

This indicates that the vector field is directed towards the interieur of $\mathbb{R}^3_+$, $\forall t \geq 0$. As a result, any trajectory starting in $\mathbb{R}^3_+$ stays in N regardless of the initial positive value. ■

Boundedness:

Proposition 2.3 *Model* (2.1) *is dissipative.*

PROOF.

Since $\beta S(t)V(t) \geq 0,\ \forall t \geq 0$, then, according to the first equation of the system (2.1), we get:

$$\frac{dS(t)}{dt} \leq \alpha S(t)\left(1 - \frac{S(t)}{K}\right). \tag{2.5}$$

The solution to the equation $\dot{S} = \alpha S(t)\left(1 - \frac{S(t)}{K}\right)$ is given by:

$$S(t) = \frac{S_0 K}{S_0 + (K - S_0)\, e^{-\alpha t}}$$

This shows that the population density of this model tends towards K, when $t \longrightarrow +\infty$, and by comparison, we find:

$$\limsup_{t\to\infty} S(t) \leq K$$

Then, summing the first two equations of our model (2.1), we obtain:

$$\dot{S} + \dot{I} = \alpha S\left(1 - \frac{S}{K}\right) - \mu I$$

The logistic function has a maximum $M = \frac{\alpha K}{4}$, so :

$$\dot{S} + \dot{I} \leq M - \mu I \tag{2.6}$$

Or:

$$\left(\dot{S} + \dot{I}\right) + \mu(S + I) \leq M + \mu S$$

This implies:

$$\left(\dot{S} + \dot{I}\right) + \mu(S + I) \leq M + \mu K$$

We put: $m' = M + \mu K > 0$ and $W = S + I$, hence:

$$\dot{W} + \mu W \leq m'$$

After resolution, we find that:

$$\forall t \geq 0, \qquad W(t) \leq \frac{m'}{\mu} + \left(W_0 - \frac{m'}{\mu}\right) e^{-\mu t}$$

This means that:

$$\limsup_{t\to\infty} W(t) \leq \frac{m'}{\mu}$$

So ($S + I$) is bounded, which implies the boundedness of I. This gives:

$$\exists m_1 > 0 \ , \ \forall t \geq 0, I(t) \leq m_1.$$

In other words:

$$\limsup_{t\to\infty} I(t) \leq m_1$$

By replacing in the third equation of the system (2.1), we find:

$$\dot{V} + \sigma V \leq \gamma \mu m_1.$$

We obtain:

$$\forall t \geq 0, \qquad V(t) \leq \frac{\gamma\mu m_1}{\sigma} + \left(V_0 - \frac{\gamma\mu m_1}{\sigma}\right) e^{-\sigma t}$$

It follows that:

$$\limsup_{t\to\infty} V(t) \leq \frac{\gamma\mu m_1}{\sigma}$$

Let: $m_2 = \frac{\gamma\mu m_1}{\sigma}$, then:

$$\limsup_{t\to+\infty} S(t) \leq K, \quad \limsup_{t\to+\infty} I(t) \leq m_1 \ \ and \quad \limsup_{t\to+\infty} V(t) \leq m_2$$

Now we define the set:

$$\Gamma = \left\{(S, I, V) \in \mathbb{R}^3 : 0 \leq S \leq K, 0 \leq I \leq m_1, 0 \leq V \leq m_2\right\}.$$

All solutions of (2.1) which lie in $\mathbb{R}^3_+$ are confined in Γ. The set Γ is compact and positively invariant with respect to the system (2.1). So it is attractive, which implies that model (2.1) is dissipative. ■

Conclusion:

Problem (2.1) with the initial condition $S_0 > 0, \quad I_0 > 0 \quad and \quad V_0 > 0$ has a unique solution defined for $t \geq 0$.

b/ Determining Equilibrium Points

To determine the equilibrium points of (2.1), we need to solve the following system:

$$\begin{cases} \alpha S(1 - \frac{S}{K}) - \beta SV = 0 & (1) \\ -\mu I + \beta SV = 0 & (2) \\ -\sigma V + \gamma\mu I = 0 & (3) \end{cases}$$

According to the first equation (1), we have: $S = 0$ or $\alpha\left(1 - \dfrac{S}{K}\right) - \beta V = 0.$

- If $S = 0$, from (2), (3) we have $I = 0$ and $V = 0$,
  which gives the origin as an point equilibrium, $\boxed{E_0(0, 0, 0)}$.

- If $\alpha(1-\frac{S}{K})-\beta V=0$, then:

$$S=K\left(1-\frac{\beta}{\alpha}V\right). \tag{2.7}$$

Pulling I from (3), we find:

$$I=\frac{\sigma}{\gamma\mu}V. \tag{2.8}$$

By replacing S and I respectively by (2.7) and (2.8) in (2), we get :

$$V=0 \text{ or } \frac{-\sigma}{\gamma}+\beta K\left(1-\frac{\beta}{\alpha}V\right)=0$$

- If $V=0$, replacing in (2.7) and (2.8) , gives $I=0$, $S=K$. The second equilibrium point $\boxed{E_1(K,0,0)}$.

- If $V=\frac{\alpha}{\beta}\left(1-\frac{\sigma}{\gamma\beta K}\right)$, replace in (2.7) and (2.8), we find :

$$I=\frac{\sigma\alpha}{\mu\gamma\beta}\left(1-\frac{\sigma}{\mu\beta K}\right).$$

Then $S=\frac{\sigma}{\gamma\beta}$, which gives the third equilibrium point E^*:

$$\boxed{E^*\left(S^*,I^*,V^*\right)}$$

where:

$$\begin{aligned} S^* &= \frac{\sigma}{\gamma\beta} \\ I^* &= \frac{\sigma\alpha}{\mu\gamma\beta}\left(1-\frac{\sigma}{\gamma\beta K}\right) \\ V^* &= \frac{\alpha}{\beta}\left(1-\frac{\sigma}{\gamma\beta K}\right) \end{aligned}$$

In summary, (2.1) has three equilibria:

1. $E_0(0,0,0)$ the **trivial equilibrium**, it represents the extinction of all populations.

2. $E_1(K,0,0)$ the **healthy equilibrium** that represents a healthy, uninfected body.

3. $E^*(S^*,I^*,V^*)$ the **positive equilibria**, exists if and only if: $\boldsymbol{\frac{\gamma\beta K}{\sigma}>1}$ and it represents a cohabitation between the different populations cells in the body.

c/ Basic reproduction rate

The basic reproduction number, denoted by R_0, represents the average number of secondary infections produced by a single infected individual during their entire infectious period in a fully susceptible population. It is a key threshold parameter that determines whether an infectious disease can invade and persist in a population [4].
We compute the basic reproduction number R_0 via the next-generation matrix method, applied to system (2.1). First, we rewrite the model in the form

$$\dot{x} \;=\; F(x) \;-\; V(x)$$

where: $x = (S, I, V)^\top$, $F(x) = \begin{pmatrix} 0 \\ \beta SV \\ 0 \end{pmatrix}$ and $V(x) = \begin{pmatrix} \beta SV - \alpha S\left(1 - \frac{S}{K}\right) \\ \gamma I \\ \sigma V - \gamma\mu I \end{pmatrix}$

The jacobian of F, V:

$$\frac{\partial F}{\partial x} = \begin{pmatrix} 0 & 0 & 0 \\ \beta V & 0 & \beta S \\ 0 & 0 & 0 \end{pmatrix} \quad \text{and} \quad \frac{\partial V}{\partial x} = \begin{pmatrix} \beta V - \alpha(1 - \frac{2S}{K}) & 0 & \beta S \\ 0 & \mu & 0 \\ 0 & -\gamma\mu & \sigma \end{pmatrix}.$$

Evaluating the Jacobian matrices at the disease-free equilibrium $E_1 = (K, 0, 0)$ yields:

$$\frac{\partial F}{\partial x}\,|_{E_1} = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & \beta K \\ 0 & 0 & 0 \end{pmatrix}, \quad \frac{\partial V}{\partial x}\,|_{E_1} = \begin{pmatrix} \alpha & 0 & \beta K \\ 0 & \mu & 0 \\ 0 & -\gamma\mu & \sigma \end{pmatrix}$$

The inverse of V is:

$$\left(\frac{\partial V}{\partial x}\,|_{E_1}\right)^{-1} = \begin{pmatrix} \frac{1}{\alpha} & \frac{-\gamma\beta K}{\alpha\sigma} & \frac{-\beta K}{\alpha\sigma} \\ 0 & \frac{1}{\mu} & 0 \\ 0 & \frac{\gamma}{\sigma} & \frac{1}{\sigma} \end{pmatrix}$$

The next generation matrix K is then:

$$K = \frac{\partial F}{\partial x}\,|_{E_1} \times \left(\frac{\partial V}{\partial x}\,|_{E_1}\right)^{-1}$$

$$K = \begin{pmatrix} 0 & 0 & 0 \\ 0 & \frac{\gamma\beta K}{\sigma} & \frac{\beta K}{\sigma} \\ 0 & 0 & 0 \end{pmatrix}$$

Now, we calculate the eigenvalues of the matrix K, to do so, calculate the

characteristic polynome:

$$Q(\lambda) = -\lambda^2 \left(\lambda - \frac{\gamma\beta K}{\sigma}\right).$$

And the associates eigenvalues are:

$$\lambda_{1,2} = 0, \quad \lambda_3 = \frac{\gamma\beta K}{\sigma}$$

The spectral radius of the following generation matrix K, is given by $\frac{\gamma\beta K}{\sigma}$.

From this, we can deduce the basic reproduction number R_0 for the model (2.1)

$$\boxed{R_0 = \frac{\gamma\beta K}{\sigma}}$$

d/ Local stability of equilibrium points

We calculate the Jacobian matrix around the equilibrium points to investigate their local stability. System (2.1) Jacobian matrix may be found as follows:

$$J(x) = \begin{pmatrix} \alpha - \frac{2\alpha}{K}S - \beta V & 0 & -\beta S \\ \beta V & -\mu & \beta S \\ 0 & \gamma\mu & -\sigma \end{pmatrix}$$

Proposition 2.4

Consider system (2.1) and let:

$$R_0 = \frac{\gamma\beta K}{\sigma}.$$

1. *The disease–free equilibrium $E_0 = (0, 0, 0)$ is an unstable saddle: its Jacobian at E_0 has eigenvalues $\lambda_1 = \alpha > 0$, $\lambda_2 = -\mu < 0$, $\lambda_3 = -\sigma < 0$.*

2. *The "healthy" equilibrium $E_1 = (K, 0, 0)$ is*

   - *locally asymptotically stable if $R_0 < 1$.*
   - *a saddle (one positive, two negative eigenvalues) if $R_0 > 1$.*

Proof. At E_0, the Jacobian is:

$$J(E_0) = \begin{pmatrix} \alpha & 0 & 0 \\ 0 & -\mu & 0 \\ 0 & \gamma\mu & -\sigma \end{pmatrix}$$

a lower-triangular matrix whose diagonal entries are its eigenvalues $\alpha > 0$, $-\mu < 0$, $-\sigma < 0$, hence E_0 is an unstable saddle.

At E_1, the Jacobian is:

$$J(E_1) = \begin{pmatrix} -\alpha & 0 & -\beta K \\ 0 & -\mu & \beta K \\ 0 & \gamma\mu & -\sigma \end{pmatrix}$$

Its characteristic polynomial factors as:

$$-(\lambda+\alpha)\big[\lambda^2 + (\mu+\sigma)\lambda + (\mu\sigma - \gamma\mu\beta K)\big].$$

The root $\lambda = -\alpha < 0$ is always negative. The remaining quadratic:

$$\lambda^2 + (\mu+\sigma)\lambda + (\mu\sigma - \gamma\mu\beta K)$$

has all roots with negative real parts if and only if its coefficients:

$$a_1 = \mu + \sigma > 0, \qquad a_2 = \mu\sigma - \gamma\mu\beta K > 0,$$

which is equivalent to $\gamma\beta K < \sigma$, i.e. $\frac{\gamma\beta K}{\sigma} < 1$. When $R_0 > 1$, one of the roots becomes positive, so E_1 is a saddle. ■

Proposition 2.5

E^* ($R_0 > 1$), is a locally asymptotically stable if and only if $1 < R_0 < D$ where:

$$D = \frac{2\alpha(\mu+\sigma)}{-\left[(\mu+\sigma)^2 + \mu\sigma\right] + \sqrt{\left[(\mu+\sigma)^2 + \mu\sigma\right]^2 + 4\beta\mu\gamma(\mu+\gamma)}}. \tag{2.9}$$

Proof. The Jacobian matrix at E^* is given by:

$$J(E^*) = \begin{pmatrix} \frac{-\alpha\sigma}{\gamma\beta K} & 0 & -\frac{\sigma}{\gamma} \\ \alpha\left(1 - \frac{\sigma}{\gamma\beta K}\right) & -\mu & \frac{\sigma}{\gamma} \\ 0 & \gamma\mu & -\sigma \end{pmatrix}$$

Replacing $\frac{\sigma}{\gamma\beta K}$ by $\frac{1}{R_0}$, we find:

$$J(E^*) = \begin{pmatrix} \frac{-\alpha}{R_0} & 0 & -\frac{\sigma}{\gamma} \\ \alpha\left(1 - \frac{1}{R_0}\right) & -\mu & \frac{\sigma}{\gamma} \\ 0 & \gamma\mu & -\sigma \end{pmatrix}$$

The characteristic polynomial is given by:

$$P(\lambda) = -\left[\lambda^3 + \left(\mu + \sigma + \frac{\alpha}{R_0}\right)\lambda^2 + \frac{\alpha(\mu+\sigma)}{R_0}\lambda + \mu\sigma\alpha\left(1 - \frac{1}{R_0}\right)\right]$$

As $R_0 > 1$, all these coefficients are negative, so to conclude the local stability of E^* it is sufficient to apply the Routh-Hurwitz theorem(2.1).
According to this theorem the positive point is locally asymptotically stable if and only if the following inequality:

$$\left(\mu + \sigma + \frac{\alpha}{R_0}\right)\frac{\alpha(\mu+\sigma)}{R_0} > \mu\sigma\alpha\left(1 - \frac{1}{R_0}\right).$$

Since the real α is positive, consider:

$$\Delta = \left(\mu + \sigma + \frac{\alpha}{R_0}\right)\frac{(\mu+\sigma)}{R_0} - \mu\sigma\left(1 - \frac{1}{R_0}\right).$$

Let's study its sign as a function C of, such that: $C = \frac{1}{R_0}$.
Let's put : $A = \mu + \sigma$, $B = \mu\sigma$, we find:

$$\Delta = \alpha A C^2 + (A^2 + B)C - B \tag{2.10}$$

Δ is a polynomial of degree 2 in C, with a strictly positive discriminant :

$$\blacktriangle = (A^2 + B)^2 + 4\alpha(AB)$$

And the two roots of (2.10)

$$C_1 = \frac{-(A^2+B) - \sqrt{\blacktriangle}}{2\alpha A} \quad \text{and} \quad C_2 = \frac{-(A^2+B) + \sqrt{\blacktriangle}}{2\alpha A}$$

C_1 is strictly negative, on the other hand, C_2 is strictly positive.
Since: $\alpha A > 0$, the parabola opens upward, hence

$$\Delta(C) > 0 \iff C < C_1 \quad \text{or} \quad C > C_2.$$

But $C_1 < 0$, and biologically C lies in $(0, 1)$. Therefore the only relevant interval where $\Delta(C) > 0$ is:

$$C > C_2.$$

Finally, requiring $C < 1$ as well, we obtain the necessary and sufficient condition.

$$\boxed{C_2 < C < 1.}$$

This provides

$$\frac{1}{C_2} > R_0 > 1$$

Let's say:

$$D = \frac{1}{C_2}, \quad \text{then:}$$
$$D = \frac{2\alpha A}{-(A^2+B) - \sqrt{(A^2+B)^2 + 4\alpha(AB)}}$$
$$= \frac{2\alpha(\mu+\sigma)}{-((\mu+\sigma)^2+(\mu\sigma)) - \sqrt{((\mu+\sigma)^2+(\mu\sigma))^2 + 4\alpha((\mu+\sigma)(\mu\sigma))}}$$

■

Conclusion: If $D > R_0 > 1$, than E^* is a locally asymptotically stable, and if $D < R_0$, it is unstable.

e/ Global stability

In this section we will have a look at the global stability of the healthy equilibrim point E_1, which we will investigate by means of the following proposition.

Proposition 2.6

The healthy equilibrium point $E_1(K, 0, 0)$ is globally asymptotically stable in Γ if $R_0 < \frac{1}{\gamma} \leq 1$.

Proof.

For this demonstration we will use Lyapunov's theorem (2.2). Let's consider at the domain:

$$\Gamma = \left\{(S, I, V) \in \mathbb{R}^3 : 0 \leq S \leq K, 0 \leq I \leq m_1, 0 \leq V \leq m_2\right\}.$$

Before analyzing the stability of the endemic equilibrium E_1, we recall the notion of persistence.

Definition 2.7

*We say that the system is **uniformly persistent** in Γ if there exists a constant $\eta > 0$ such that for all solutions with initial conditions $S(0), I(0), V(0) > 0$, we have:*

$$\liminf_{t\to\infty} I(t) \geq \eta, \quad \liminf_{t\to\infty} V(t) \geq \eta.$$

A sufficient condition for persistence is $\mathcal{R}_0 > 1$, which guarantees the existence of a stable endemic equilibrium and the non-extinction of the disease.

Let υ be a function defined in Γ by:

$$\upsilon(S, I, V) = a(S - K) - aK \ln\left(\frac{S}{K}\right) + bI + cV,$$

with $a, b, c > 0$ are positive constants to be determined.
The Lyapunov function $\nu(S, I, V)$ is positive definite in a neighborhood of the equilibrium point E_1, that is:

$$\nu(S, I, V) > 0 \quad \text{for all } (S, I, V) \neq E_1,$$

and

$$\upsilon(E_1) = \upsilon(K, 0, 0) = 0.$$

In fact, since $S \leq K$, then the first terms of υ are written as follows:

$$a(S - K) - aK \ln\left(\frac{S}{K}\right) = aK\left(\frac{S}{K} - 1 - \ln\left(\frac{S}{K}\right)\right)$$

Let us study the sign of the function: $\phi(\tau) = \tau - 1 - \ln(\tau)$, where : $\tau \leq 1$.

1. **Domain of Definition:**

   The function $\phi(\tau)$ is well-defined when $\ln(\tau)$ exists, i.e., for $\tau > 0$. Since the study is restricted to $\tau \leq 1$, we consider the interval $0 < \tau \leq 1$.

2. **Derivative of ϕ:**

   We compute the derivative of $\phi(\tau) = \tau - 1 - \ln(\tau)$:

   $$\phi'(\tau) = 1 - \frac{1}{\tau}.$$

3. **Sign of the Derivative :** We analyze the sign of $\phi'(\tau) = 1 - \frac{1}{\tau}$.

   - **For $\tau = 1$:**
   $$\phi'(1) = 1 - 1 = 0$$
   - **For $0 < \tau < 1$:**
   $$\frac{1}{\tau} > 1 \quad \Rightarrow \quad 1 - \frac{1}{\tau} < 0$$
   Hence, $\phi'(\tau) < 0$ for all $0 < \tau < 1$.

   <u>Remark 1:</u>

   $\phi(\tau)$ is strictly decreasing on $(0, 1]$. The function is strictly **decreasing** and tends to $+\infty$ as $\tau \to 0^+$, then reaches the value 0 at $\tau = 1$.

τ	0		1		$+\infty$
$\Phi'(\tau)$		$-$	0	$+$	
$\Phi(\tau)$	$+\infty$	$\searrow$	0	$\nearrow$	$+\infty$

Thus, the function $\phi(\tau)$ is positive on $(0, 1]$ and decreases to 0.
Remark 2: υ is therefore a positive definite function on Γ.

Then, calculate the derivative of υ with respect to t:

$$\frac{d\upsilon}{dt} = \dot{\upsilon} = a\dot{S} - aK\frac{\dot{S}}{S} + b\dot{I} + c\dot{V}$$

$$= a\frac{\dot{S}}{S}(S - K) + b\dot{I} + c\dot{V}$$

$$= a\left[\alpha\left(1 - \frac{S}{K}\right) - \beta V\right](S - K) + b\left[-\mu I + \beta SV\right] + c\left[-\sigma V + \gamma\mu I\right]$$

$$= a\left[-\frac{\alpha}{K}(S - K)^2\right] - a\beta V(S - K) + b\beta SV - b\mu I + c\gamma\mu I - c\sigma V$$

$$= -\frac{\alpha}{K}a(S - K)^2 - a\beta VS + a\beta VK + b\beta SV - b\mu I + c\gamma\mu I - c\sigma V$$

$$= -\frac{\alpha}{K}a(S - K)^2 - (a - b)\beta VS - (c\sigma - a\beta K)V - \mu(b - c\gamma)I$$

We have:

$$\dot{\upsilon} < 0 \text{ iff } : \begin{cases} (a - b) \geq 0 \\ (c\sigma - a\beta K) \geq 0 \\ (b - c\gamma) \geq 0 \end{cases} \Rightarrow \begin{cases} a \geq b \\ a \leq \frac{\sigma}{\beta K}c \\ b \geq c\gamma \end{cases}$$

Or:

$$0 \leq c\gamma \leq b \leq a \leq \frac{\sigma}{\beta K}c. \quad \text{This inequality is only true if } : \gamma \leq \frac{\sigma}{\beta K}$$

$$\boxed{1 \leq \frac{1}{R_0}, \quad \Longleftrightarrow \quad R_0 \leq 1}.$$

So, $\dot{\nu}$ is negative definite if and only if: $\mathbf{R_0 \leq \frac{1}{\gamma}}$
Now, by applying Lyapunov's theorem (2.2), we conclude that
$E_1 = (K, 0, 0)$ **is globally asymptotically stable (GAS)** when $R_0 < 1$. Indeed, since the Lyapunov function V is positive definite and its time derivative along the trajectories of the system is negative definite, the largest invariant set in $\{\dot{V} = 0\}$ is reduced to the equilibrium $\{E_1\}$. Consequently, all trajectories converge to E_1, establishing its global asymptotic stability. ■

In this section, rely on [26], to demonstrate the overall stability of positive equilibrium E^* see [25]. The result is that:

Proposition 2.7

- *For $1 \leq R_0 \leq D$, the endemic equilibrium point E^* from model (2.1) is globally asymptotically stable with respect to the solutions that do not lie*

in the set:

$$L = \{(S, I, V) \mid S = 0 \text{ or } (I = 0 \text{ and } V = 0)\}$$

- *When $R_0 > D$, the endemic equilibrium point E^* becomes unstable. However, there exists at least one trajectory that is orbitally asymptotically stable.*

2.4 Numerical simulations

Using the Matlab software, model (2.1) is simulated thanks to the Runge Kutta algorithm (2.2). As demonstrated in the theoretical analysis of stability in the previous section, three scenarios are identified based on R_0 values.

According to our theoretical analysis of stability, we consider three cases depending on the value of R_0, taking into account the chosen initial conditions: $S_0 = 1000/mm^3, I_0 = 10/mm^3, V_0 = 100/mm^3$. [26]

- **1st case :** Figure 2.2 shows the behaviour of healthy cells in red, infected cells in blue, and the virus in green.
  The parameters are chosen so that $R_0 = 0.96 : \sigma = 5, \gamma = 200, \mu = 0.24, \beta = 0.000024, \alpha = 0.03$ and $K = 1000$. Figure 2.3 shows the corresponding phase portrait.

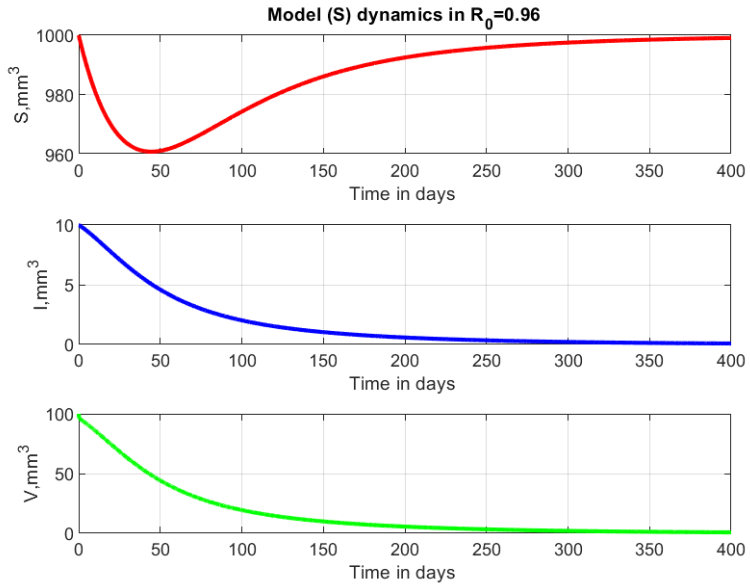

Figure 2.2: The dynamics of model (2.1) when $R_0 = 0.96$.

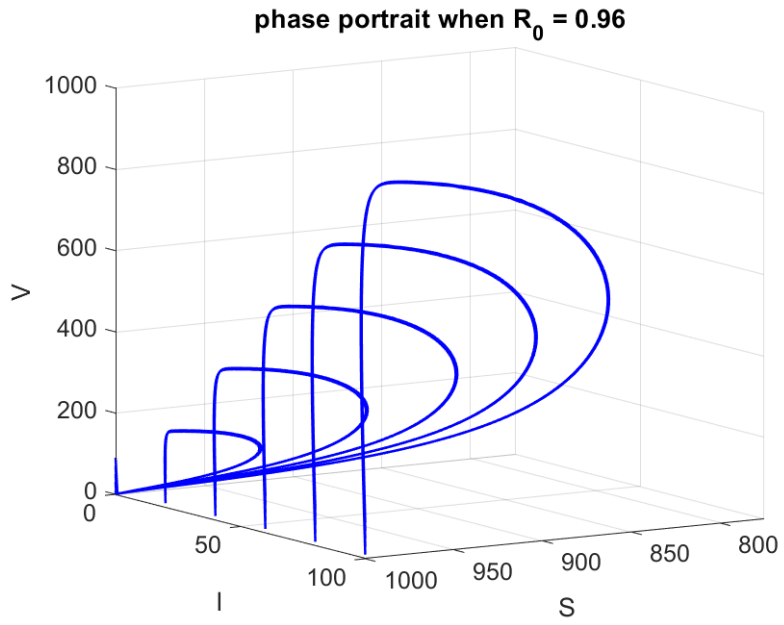

Figure 2.3: The corresponding phase portrait when $R_0 = 0.96$.

- **2nd case :** In figure 2.4, the parameters are chosen so that:
  $1 < R_0 = 6 < D = 15.90$:
  $\sigma = 2.4, \gamma = 600, \mu = 0.24, \beta = 0.000024, \alpha = 0.3$ and $K = 1000$.
  Figure 2.5 shows the corresponding phase portrait.

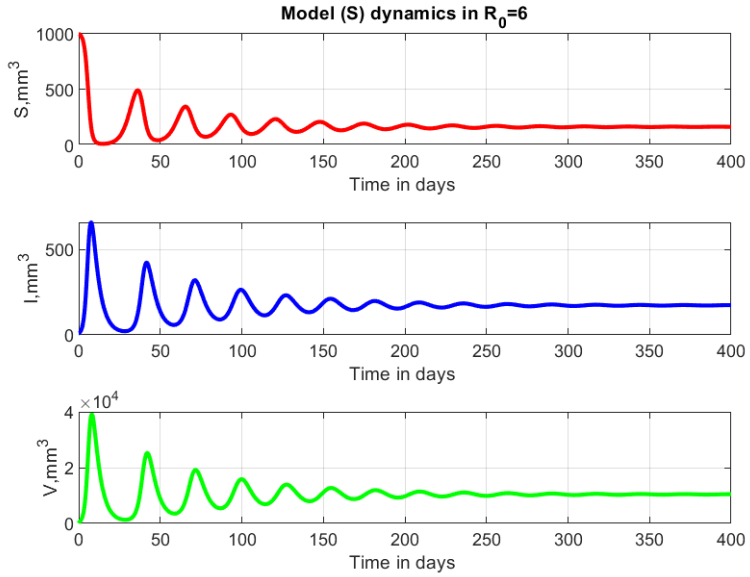

Figure 2.4: The dynamics of the model (2.1) when $R_0 = 6$.

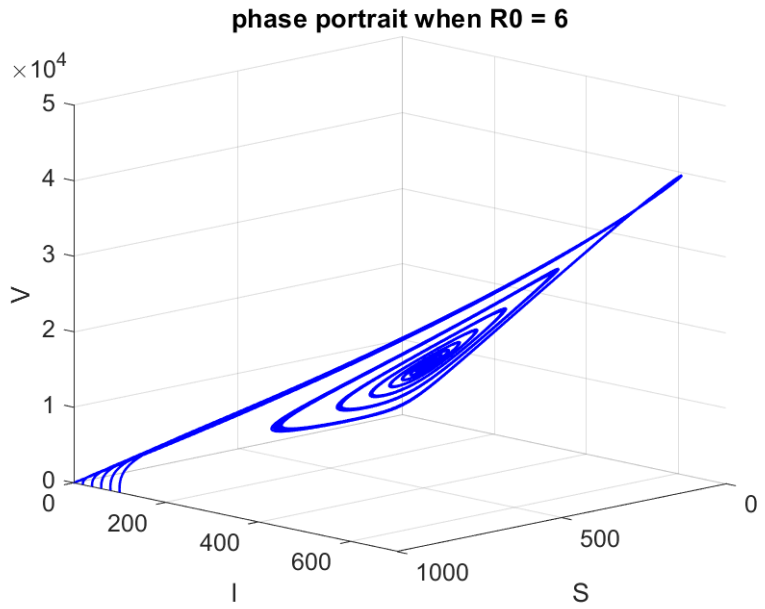

Figure 2.5: The corresponding phase portrait when $R_0 = 6$.

- **3rd case :** Figure 2.6 shows the dynamics when the parameters are chosen so that: $1 < D = 15.90 < R_0 = 22 : \sigma = 2.4, \gamma = 2200, \mu = 0.24, \beta = 0.000024, \alpha = 1.3$ and $K = 1000$. Figure 2.7 shows the corresponding phase portrait.

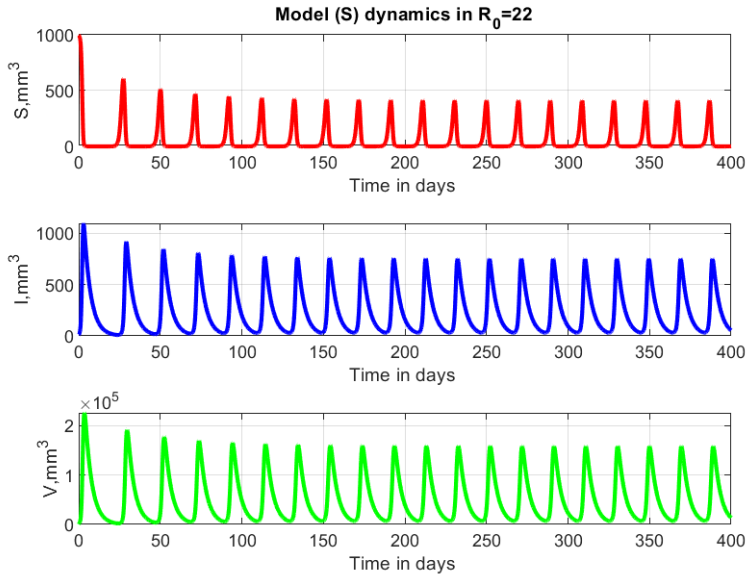

Figure 2.6: The dynamics of the model (2.1) when $R_0 = 22$.

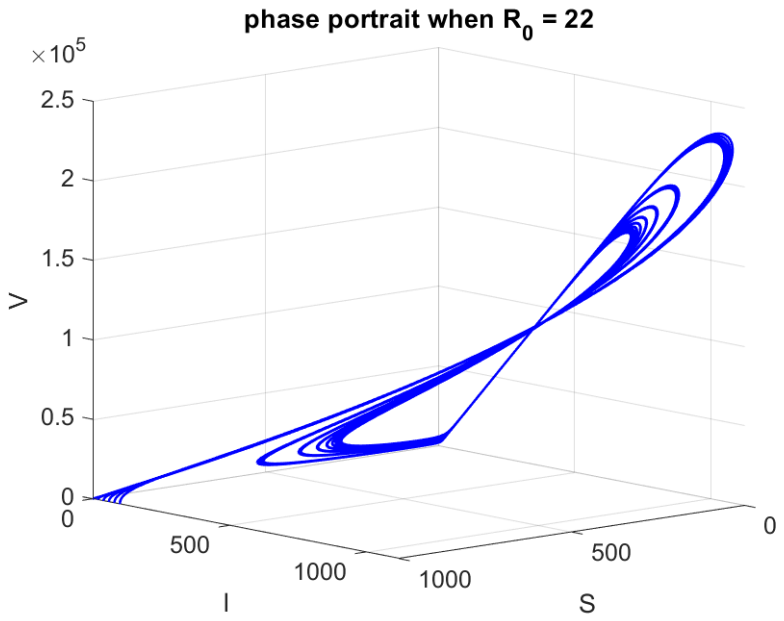

Figure 2.7: The phase portrait corresponding to $R_0 = 22$.

2.5 Conclusion

In this chapter, we have explored a mathematical model describing HIV transmission. We analyzed the model by identifying its equilibrium points, computing the basic reproduction number R_0, and investigating the stability of the equilibria. Finally, we performed numerical simulations, which provided the following results:

- If $0 < R_0 < 1$, we have two equilibria, the origin (E_0) unstable and the second (E_1) locally asymptotically stable.
- If $R_0 > 1$ the first equilibrium point (E_0) is unstable, the second equilibrium point (E_1) is unstable and we have the existence of a locally asymptotically stable third equilibrium point (E^*), which is locally asymptotically stable as long as $1 < R_0 < D$.
- If $R_0 > D$, the third equilibrium point (E^*) is unstable.

Chapter 3

Study of the controlled model

3.1 Introduction

Optimal control is a method that aims to define a control law to optimize a given criterion, such as minimizing a cost or enhancing the effectiveness of a treatment. In the context of infectious diseases, particularly HIV, optimal control plays a crucial role in designing therapeutic strategies that balance treatment efficacy with its associated constraints.

Among the various optimal control approaches, **bang-bang control** stands out due to its extreme nature: the treatment is either applied at full intensity or completely halted. This method, grounded in **Pontryagin's maximum principle**, optimizes the administration of antiretroviral therapies by alternating between periods of treatment activation and interruption.

The objective of this chapter is to apply the bang-bang control method to the dynamic model of HIV studied in chapter 2. We begin by reviewing the key concepts of **controllability** and optimal control, followed by a detailed exploration of how bang-bang control can be applied on our model. Finally, we present **numerical simulation**s to illustrate the results and analyze the impact of optimal control on the viral dynamics.

3.2 Controllability Notion

Controllability refers to the ability of a system to reach a final state $x_1 \in \mathbb{R}^n$ from an initial state x_0, within a finite time T, using an admissible control $u(t) \in \mathbb{R}^m$.

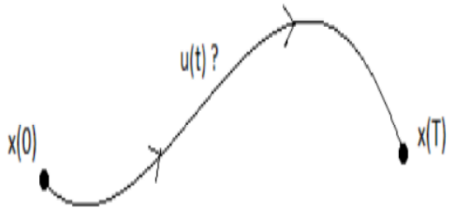

Figure 3.1: Controllability problem.

3.2.1 Accessible Set

The accessible set represents the set of points that can be reached from an initial state x_0 within a finite time $T > 0$, using admissible controls. It is defined as:

$$\mathrm{Acc}(x_0, T) := \{x_u(T) \mid u \in L^\infty([0, T], \Omega)\},$$

where $\Omega \subset \mathbb{R}^m$ is the set of admissible controls and $x_u(t)$ is the trajectory (solution) of the system associated with the control u. In other words, the accessible set gathers all possible end-points of the system's trajectories at time T, as the control u varies.

3.2.2 Controllability

A system is said to be controllable over a time horizon $T > 0$ if it is possible to drive it from any initial state $x_0 \in \mathbb{R}^n$ to any desired final state $x_1 \in \mathbb{R}^n$ within the time interval $[0, T]$, using an admissible control $u(t)$.

Formally, this means that the reachable set satisfies:

$$\mathrm{Acc}(x_0, T) = \mathbb{R}^n.$$

That is, for any pair of states x_0 and x_1, there exists a control u such that the solution to the following Cauchy problem meets the final condition $x(T) = x_1$:

$$\begin{cases} \dot{x}(t) = f(x(t), u(t)), \\ x(0) = x_0, \\ x(T) = x_1. \end{cases}$$

We now define the notion of local controllability around an equilibrium point.

3.2.3 Linearized System

Nonlinear systems are more complex than linear systems, which makes studying their controllability more difficult. A common approach is to linearise the system around its equilibrium points, which makes it easier to analyse the controllability of the linearised system. In this way, the controllability of nonlinear systems is generally studied locally around these points.[35]
The nonlinear system is written in the following form:

$$\begin{cases} \dot{x}(t) = f(x(t), u(t)), \forall t \in [t_0, T] \\ x(t_0) = x_0 \end{cases} \tag{M}$$

$x(t) \in \mathbb{R}^n$ is the state, $u \in L^2([0,T], \mathbb{R}^m)$ is the control, and $f : \mathbb{R}^n \times \mathbb{R}^m \longmapsto \mathbb{R}^n$ a map of class C^1. Suppose that for any $x_0 \in \mathbb{R}^n$ and any measurable control $u(t) \in L^2([0,T], \mathbb{R}^m)$, there is a unique solution of (M), defined for all $\forall t \in [t_0, T]$ by:

$$x(t, x_0, u) = x_0 + \int_{t_0}^{t} f(x(\nu), u(\nu))\, d\nu.$$

It is assumed that the system (M) has an equilibrium point (x_e, u_e), i.e.: $f(x_e, u_e) = 0$.
To linearise the system (M) around this equilibrium point.
It is sufficient to take:

$$A = \frac{\partial f}{\partial x}(x_e, u_e) \quad \text{and} \quad B = \frac{\partial f}{\partial u}(x_e, u_e)$$

As a result, the system (M) is locally controllable in time $[t_0, T]$ if and only if the linearized system around the equilibrium point is controllable in the same time interval:

$$\begin{cases} \dot{x}(t) = Ax(t) + Bu(t), \quad \forall t \in [t_0, T] \\ x(t_0) = x_0 \end{cases} \tag{M'}$$

Theorem 3.1 *(Kalman criterion for local controllability) [35]*

The autonomous linear system (M') is controllable if and only if the controllability matrix C(A,B) is of maximum rank, hence :

$$\text{rang } C(A, B) = n.$$

This is called the Kalman criterion, and:

$$C(A, B) = \begin{bmatrix} B & AB & A^2B & \cdots & A^{n-1}B \end{bmatrix}$$

is called the Kalman matrix.
In this case, system (M') is said to be locally controllable in (x_e, u_e).

3.3 Some principles of non linear optimal control systems

A control problem consists in finding a control $u(t)$ and the associated trajectory that minimises or maximises a given objective $C(u)$. In general, an optimal control problem can be formulated as follows, let the control system:

$$\begin{cases} \dot{x}(t) = f(t, x(t), u(t)), \forall t \in [t_0, T] \\ x(t_0) = x_0 \end{cases} \tag{3.1}$$

where :
$f : [t_0, T] \times \mathbb{R}^n \times U \longmapsto \mathbb{R}^n$. The set of admissible controls is defined as:
$U_{\text{adm}} = L^1([t_0, T], U)$, and:

$$U = \{u : [t_0, T] \to \mathbb{R}^m \,|\, u \text{ is measurable, } u(t) \in U_{adm} \text{ a.e. on } [t_0, T]\}$$

The objective is to find an optimal control u^* that satisfies the following assertion:

$$\min_{u \in U} C(u), \quad \text{with} \quad C(u) = \psi(T, x(T)) + \int_{t_0}^{T} g(t, x(t), u(t))\, dt.$$

where:

$$\left.\begin{array}{l} g : [t_0, T] \times \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}, \\ \psi :]t_0, +\infty[\times \mathbb{R}^n \to \mathbb{R} \end{array}\right\} \text{ are two given functions.} \tag{3.2}$$

The fundamental assumptions that ensure the existence and uniqueness of optimal controls are as follows: to guarantee the existence and uniqueness of a solution to system (3.1), we first consider the hypothesis regarding the function f.

- **H1)** $f \in C^1([t_0, T] \times \mathbb{R}^n \times U, \mathbb{R}^n)$.
- **H2)** $\exists c > 0$, $\forall t \in [t_0, T]$, $\forall y \in \mathbb{R}^n$, and $v \in U$, we have :

$$|f(t, y, v)|_{\mathbb{R}^n} \leq c(1 + |y|_{\mathbb{R}^n} + |v|_{\mathbb{R}^m}).$$

- **H3)** $\forall r > 0, \exists C_r > 0, \forall t \in [t_0, T], \forall y \in \overline{B}(0, r), \forall v \in U$,

$$|\frac{\partial f}{\partial x}(t, y, v)|_{\mathbb{R}^n} \leq C_r(1 + |v|_{\mathbb{R}^m}).$$

We assume that the hypotheses (H1, H2, H3) are satisfied. Then $\forall u \in U_{\text{adm}}$, there exists a unique solution of the problem (3.1) [35].

- **H4)** $\forall R > 0, \exists C_R > 0, \forall t \in [t_0, T], \forall y \in \overline{B}(0, R), \forall v \in U,$

$$|g(t, y, u)| \leq C_R(1 + |v|_{\mathbb{R}^m}).$$

- **H5)** The functions g and ψ are bounded below on $[t_0, T] \times \mathbb{R}^n \times \mathbb{R}^m$ and on $[t_0, +\infty[\times\mathbb{R}^n$, respectively.
  The assumption (H4) ensures that the cost $C(u)$ is well-defined, and the assumption (H5) guarantees that the infimum of $C(u)$ over U_{adm} is finite.

3.3.1 Pontryagin maximum principle (PMP)

Let's recall the formulation of the control system:

$$\begin{cases} \dot{x}(t) = f(t, x(t), u(t)), \quad \forall t \in [t_0, T], \\ x(t_0) = x_0, \\ C(u^*) = \max_{u \in U_{adm}} C(u). \end{cases} \tag{3.3}$$

with:

$$C(u) = \psi(T, x(T)) + \int_{t_0}^{T} g(t, x(t), u(t))\, dt.$$

and $x(T)$ free (i.e. non-specific) and T free or fixed,

Definition 3.1 *(**Hamiltonian**) [35]*

To facilitate the formulation of the maximum principle, we define the Hamiltonian:

$$H : [t_0, T] \times \mathbb{R}^n \times \mathbb{R}^n \times U_{adm} \to \mathbb{R} \quad \textit{such that:}$$

$$H(t, x, \lambda, u) = \langle \lambda, f(t, x, u) \rangle + g(t, x, u)$$

We assume that the functions f and g satisfy the following additional assumptions:

- ***H6)** The function g satisfies: $g \in C^1([t_0, T] \times \mathbb{R}^n \times U_{adm}; \mathbb{R})$ i.e. g is of class C^1 with respect to x and u, and the function ψ satisfies:*
  $\psi \in C^1([t_0, +\infty[\times\mathbb{R}^n; \mathbb{R})$.

- ***H7)** For all $R > 0$, there exists a constant $\tilde{C}_R > 0$ such that:*

$$\forall t \in [t_0, T], \forall y \in \bar{B}(0, R), \forall v \in U_{adm}, \quad \left|\frac{\partial g}{\partial x}(t, y, v)\right| \leq \tilde{C}_R(1 + |v|_{\mathbb{R}^m}).$$

Theorem 3.2 *(**Pontryagin maximum principle**) [35]*

We consider the optimal control problem defined by equations,(3.3) assuming that the hypotheses H_i (for $i = 1, \ldots, 7$) are satisfied.

Sufficient Conditions:

If u^* is an optimal control and x^* is the corresponding state trajectory, then there exists an absolutely continuous function $\lambda : [t_0, T] \to \mathbb{R}^n$, called the ***adjoint vector****, such that:*

- ***(a)***

$$\begin{cases} \dot{x}^*(t) = \dfrac{\partial H}{\partial \lambda}(t, x^*(t), \lambda(t), u^*(t)), \\ \qquad = f(t, x^*(t), u^*(t)), \textit{for a.e. } t \in [t_0, T], x^*(t_0) = x_0. \\ \dot{\lambda}(t) = -\dfrac{\partial H}{\partial x}(t, x^*(t), \lambda(t), u^*(t)), \\ \qquad = -\dfrac{\partial f}{\partial x}(t, x^*(t), u^*(t))^\top \lambda(t) - \dfrac{\partial g}{\partial x}(t, x^*(t), u^*(t)), \quad \textit{for a.e. } t \in [t_0, T] \\ \lambda(T) = \dfrac{\partial \psi}{\partial x}(T, x^*(T)) \quad \textit{(Transversality condition)} \end{cases}$$

- ***(b)***

$$u^*(t) \in \arg\max_{v \in U_{adm}} H(t, x^*(t), \lambda(t), v), \quad \textit{for a.e. } t \in [t_0, T],$$

that is,

$$H(t, x^*(t), \lambda(t), u^*(t)) = \max_{v \in U_{adm}} H(t, x^*(t), \lambda(t), v), \quad \textit{for a.e. } t \in [t_0, T].$$

- ***(c)*** *If the final time T is free, we have:*

$$H(T, x^*(T), \lambda(T), u^*(T)) = -\frac{\partial \psi}{\partial t}(T, x^*(T)).$$

A triplet (x^*, u^*, λ) that satisfies the above conditions is called an extremal or a candidate for optimality.

Necessary condition:

On the other hand, if $x^*(t)$ and $u^*(t)$ are optimal state and control variables, then they satisfy the following conditions:

$$\begin{cases} \dot{\lambda}(t) = -\frac{\partial H}{\partial x}(t, x^*(t), \lambda(t), u^*(t)) \\ \lambda(T) = \nabla \psi(T, x(T)) \\ \frac{\partial H}{\partial u} = (t, x^*(t), \lambda(t), u^*(t)) = H_u(t, x^*(t), \lambda(t), u^*(t)) = 0. \end{cases}$$

3.3.2 Bang-bang control

In problems where the control appears linearly in the system dynamics or in the cost functional, the optimal solution often exhibits discontinuities in the control variable. This behavior naturally leads to the appearance of the so-called *bang-bang* controls [7].
Consider the following problem:

$$\begin{cases} \dot{x}(t) = f(t, x(t), u(t)) = f_1(t, x(t), u(t)) + u f_2(t, x(t), u(t)), \quad \forall t \in [t_0, T], \\ x(t_0) = x_0, \\ u(t) \in [a, b], \end{cases}$$

$$\begin{aligned} &\max_u \quad \int_{t_0}^{T} g(t, x(t), u(t))\, dt + \psi(T, x(T)) \\ &= \max_u \quad \int_{t_0}^{T} [g_1(t, x(t), u(t)) + u(t) \cdot g_2(t, x(t), u(t))]\, dt + \psi(T, x(T)) \end{aligned}$$

Definition 3.2 *[19]*

A bang-bang control is a type of optimal strategy in which the control $u^*(t)$ takes values only at the extrema of its admissible domain $U_{adm} = [a, b]$, with no intermediate values.

Theorem 3.3 ***(bang-bang control [19])***

According to the Pontryagin Maximum Principle (PMP (3.2)), the optimal control $u^*(t)$ maximizes the Hamiltonian H :

$$\begin{aligned} H(t, x, u, \lambda) &= \langle \lambda, f(t, x, u) \rangle + g(t, x, u) \\ &= \lambda^\top f(t, x, u) + g(t, x, u). \\ &= \lambda[f_1(t, x, u) + u f_2(t, x, u)] + g_1(t, x, u) + u g_2(t, x, u) \\ &= u[\lambda f_2(t, x, u) + g_2(t, x, u)] + \lambda f_1(t, x, u) + g_1(t, x, u). \end{aligned}$$

We put : $\phi(t, x, \lambda) = [\lambda f_2(t, x, u) + g_2(t, x, u)]$, then we have:

$$H(t, x, u, \lambda) = u\phi(t, x, \lambda) + \lambda f_1(t, x, u) + g_1(t, x, u)$$

where ϕ is the switching function, and the objective is to maximize H with respect to u, at the optimal control u^*.

$$u^*(t) = \begin{cases} a & \text{if } \phi(t, x, \lambda) < 0 \\ b & \text{if } \phi(t, x, \lambda) > 0 \end{cases}, \forall t \in [0, T].$$

• *If* $\phi(t,x,\lambda) \neq 0$ *the control is of* ***bang-bang*** *type for a given period of time.*
• *If* $\phi(t,x,\lambda) = 0$ *over an interval of time, the value of* u^* *is* ***singular****, It is also called a* ***singular arc****.*

Example 3.1 *Consider the following problem:*

$$\begin{cases} \dot{x}(t) = x(t)u(t), \quad t \in [0,T], \\ x(0) = x_0, \\ 0 \leq u(t) \leq 1 \\ \max_u \int_0^T (1-u(t))x(t)\,dt \end{cases}$$

with: $f(t,x,u) = x(t)u(t)$ *and* $\quad g(t,x,u) = (1-u(t))x(t)$.
The Hamiltonian for this problem is defined by:

$$H(t,x,u,\lambda) = \lambda f(t,x,u) + g(t,x,u),$$

Thus, the Hamiltonian is written as:

$$H(t,x,u,\lambda) = \lambda xu + (1-u)x$$

According to Pontryagin's maximum principle, if there exists an optimal control u^* *and an optimal trajectory* x^**, then:*

$$\begin{cases} \dot{x}^*(t) = \dfrac{\partial H}{\partial \lambda} = xu \\ \dot{\lambda}(t) = -\dfrac{\partial H}{\partial x} = -\lambda u - (1-u) \\ x^*(0) = x_0, \\ \lambda(T) = \dfrac{\partial \psi}{\partial x} = 0 \quad \textit{(Transversality condition)} \end{cases} \tag{3.4}$$

The solution to the adjoint equation: $\dot{\lambda} = -\lambda u - (1-u)$ *with,* $\lambda(T) = 0$.
Case 1: $u(t) = 0$
When $u(t) = 0$*, the equation becomes:*

$$\dot{\lambda}(t) = -(1) = -1$$

The solution to this equation is:

$$\lambda(t) = -(t-T)$$

Thus, $\lambda(t)$ *is decreasing for* $u(t) = 0$.
Case 2: $u(t) = 1$
When $u(t) = 1$*, the equation becomes:*

$$\dot{\lambda}(t) = -(\lambda(t) + 0) = -\lambda(t)$$

The solution to this equation is:

$$\lambda(t) = Ce^{-t}$$

using $\lambda(T) = 0 \Rightarrow \lambda(t) \equiv 0,\ \forall t \in [t_0, T]$.
The first equation in (3.4) $\dot{x}(t) = ux, \quad \forall t \in [0, T]$*:*

$$x^*(t) = \begin{cases} x_0 & \text{if } u(t) = 0 \\ x_0 e^t & \text{if } u(t)=1 \end{cases}$$

3.4 Study of the controlled model

We want to control the evolution of HIV by introducing **three control** inputs, denoted by $u_i(t)$, for $i = 1, 2, 3$ at different stages of the process, and applying them simultaneously.

- In the context of the HIV model, the objective of the first control u_1 is to increase the virus clearance rate. This may include therapies such as protease inhibitors, nanoparticles containing bee venom, targeted antibodies, or a combination of these methods [12].
  Model (2.1) is written as follows when the effect of the first control therapy is taken into account:

$$\begin{cases} \dot{S}(t) = \alpha S(t)\left(1 - \frac{S(t)}{K}\right) - \beta S(t)V(t) \\ \dot{I}(t) = -\mu I(t) + \beta S(t)V(t) \\ \dot{V}(t) = -\sigma V(t)(\mathbf{1} + \mathbf{u_1(t)}) + \gamma\mu I(t) \\ S(0) = S_0, \quad I(0) = I_0, \quad V(0) = V_0 \end{cases} \tag{3.5}$$

- The second control u_2 aims to prevent viral entry into host cells, a crucial step in the infection process. It involves the SV term in the model and may include integrase inhibitors, therapies such as modified $CD4^+T$ cells with dysfunctional CCR5, microbicide gels, the CXCL4 protein, or cannabis-derived substances to slow HIV progression.(see [5] ,[2], [3], [34])
  The controlled model associated with (2.1) is then written as:

$$\begin{cases} \dot{S}(t) = \alpha S(t)(1 - \frac{S(t)}{K}) - \beta S(t)V(t)(\mathbf{1} - \mathbf{u_2(t)}) \\ \dot{I}(t) = -\mu I(t) + \beta S(t)V(t)(\mathbf{1} - \mathbf{u_2(t)}) \\ \dot{V}(t) = -\gamma V(t) + \sigma\mu I(t) \\ S(0) = S_0, I(0) = I_0, V(0) = V_0 \end{cases} \tag{3.6}$$

- The third control u_3 aims to reduce the apoptosis of infected cells to limit the release of new viruses. It may include reverse transcriptase inhibitors and is applied to the term μ_I in the model (2.1).
  Our third controlled model:

$$\begin{cases} \dot{S}(t) = \alpha S(t)(1 - \frac{S(t)}{K}) - \beta S(t)V(t) \\ \dot{I}(t) = -\mu I(t)(\mathbf{1} - \mathbf{u_3(t)}) + \beta S(t)V(t) \\ \dot{V}(t) = -\sigma V(t) + \gamma\mu I(t)(\mathbf{1} - \mathbf{u_3(t)}) \\ S(0) = S_0, I(0) = I_0, V(0) = V_0 \end{cases} \tag{3.7}$$

- In general, when all the controls are used at the same time, we get:

$$\begin{cases} \dot{S}(t) = \alpha S(t)(1 - \frac{S(t)}{K}) - \beta S(t)V(t)(\mathbf{1} - \mathbf{u_2(t)}) \\ \dot{I}(t) = -\mu I(t)(\mathbf{1} - \mathbf{u_3(t)}) + \beta S(t)V(t)(\mathbf{1} - \mathbf{u_2(t)}) \\ \dot{V}(t) = -\sigma V(t)(\mathbf{1} + \mathbf{u_1(t)}) + \gamma\mu I(t)(\mathbf{1} - \mathbf{u_3(t)}) \\ S(0) = S_0, I(0) = I_0, V(0) = V_0 \end{cases} \tag{3.8}$$

The objective is to analyze the model's response to each control individually and then observe the effects when all controls are applied together. Time-dependent treatments are incorporated through controls $u_i(t)$, where $i = 1, 2, 3$. Values of $u_i = 0$ or $u_i = 1$ represent models with no control or full treatment, while $u_i > 1$ (for $i = 2, 3$) corresponds to cytotoxic treatments. u_1 affects only viral particles and is bounded by a constant $L > 1$. Taking this into account, consider the following set:

$$U = \left\{ \begin{array}{c} u_i(.) \text{ Lebesgue measurable for: } i = \overline{1,3};\ \ a \leq u_1(t) \leq L\ ,\ (L > 1)\ \ , \\ \text{and} \quad 0 < a \leq u_i(t) \leq \mathrm{b} < 1\ \ , \text{ for } \ i = 2, 3, \quad t \in [0, T] \end{array} \right\}$$

3.4.1 Local controllability

In this section we focus on studying the local controllability of our new system (3.8) around all equilibrium points of system (2.1).

Proposition 3.1

The system (3.8) is uncontrollable around the trivial and healthy E_0, E_1 equilibrium points, regardless of the control applied $u_i \in U$, where $i = 1, 2, 3$.

Proof. [25]

For the study of local controllability, we use Kalman's criterion (3.1) .
We put:

$$F(t, S, I, V, u_1(t), u_2(t), u_3(t)) = \begin{pmatrix} \alpha S\left(1 - \frac{S}{K}\right) - \beta SV\left(1 - u_2(t)\right) \\ -\mu I\left(1 - u_3(t)\right) + \beta SV\left(1 - u_2(t)\right) \\ -\sigma V\left(1 + u_1(t)\right) + \gamma\mu I\left(1 - u_3(t)\right) \end{pmatrix}$$

Let's calculate :

$$A_c = \frac{\partial F}{\partial x} = \begin{pmatrix} \alpha(1-\frac{2S}{K}) - \beta V(1-u_2) & 0 & -\beta S(1-u_2) \\ \beta V(1-u_2) & -\mu(1-u_3) & \beta S(1-u_2) \\ 0 & \gamma\mu(1-u_3) & -\sigma(1+u_1) \end{pmatrix},$$

$$B_c = \frac{\partial F}{\partial u_i} = \begin{pmatrix} 0 & \beta SV & 0 \\ 0 & -\beta SV & -\mu I \\ -\sigma V & 0 & -\gamma\mu I \end{pmatrix}, \ i = 1, 2, 3$$

It is sufficient to note that $B_c\,|_{E_0} = B_c\,|_{E_1} = 0$, which, according to Kalman's criterion (see theorem (3.1)), leads to the result.
This result is easy to understand, since around the origin and the healthy equilibrium point, there is no infection, and therefore **nothing** to control ! ■

Proposition 3.2

If $R_0 > 1$, the four models (3.5), (3.6), (3.7), and (3.8) are locally controllable around the equilibrium point E^* if and only if R_0 does not belong to the set of critical values:

$$\left\{ \frac{2\sigma}{\sigma+\mu}, \ \frac{2\alpha}{\alpha+\mu} \right\}.$$

Proof. [25]

The function F is written:

$$F(t, S, I, V, u(t)) = \begin{pmatrix} f_1(S, I, V, u(t)) \\ f_2(S, I, V, u(t)) \\ f_3(S, I, V, u(t)) \end{pmatrix}$$

For the study of the local controllability around the 3rd equilibrium point E^* we have 4 cases:

i) For model (3.5) : We compute the matrices A_1 and B_1:

$$A_1 = \frac{\partial f_1}{\partial x} \begin{pmatrix} \alpha\left(1-\frac{2S}{K}\right) - \beta V & 0 & -\beta S \\ \beta V & -\mu & \beta S \\ 0 & \gamma\mu & -\sigma(1+u_1) \end{pmatrix}, B_1 = \frac{\partial f_1}{\partial u_1} \begin{pmatrix} 0 \\ 0 \\ -\sigma V \end{pmatrix}$$

Put: $X = \alpha\left(1-\frac{2S}{K}\right), \quad Y = \beta V, \quad Z = \beta S, \quad W = \sigma(1+u_1)$

So:

$$A_1 = \begin{pmatrix} X-Y & 0 & -Z \\ Y & -\mu & Z \\ 0 & \gamma\mu & -W \end{pmatrix}$$

From Kalman's criterion we calculate the Kalman's matrix associated to that case : $\Lambda_1 = (B_1 \quad A_1B_1 \quad A_1^2B_1)$ is given by:

$$\Lambda_1 = -\sigma V \begin{pmatrix} 0 & -Z & -Z(X-Y)+ZW \\ 0 & Z & -YZ-\mu Z-WZ \\ 1 & -W & \gamma\mu Z+W^2 \end{pmatrix}$$

Then, calculate the derminant of the matrix Λ_1:

$$det(\Lambda_1) = -\sigma V Z^2 \begin{vmatrix} -1 & -(X-Y)+W \\ 1 & -Y-\mu-W \end{vmatrix} = -\sigma V Z^2[X+\mu]$$

$\det \Lambda_1 = 0 \Longleftrightarrow X = -\mu$.

By replacing $X = \alpha\left(1-\frac{2S}{K}\right)$ using the first coordinate of the chronic equilibrium S^*, we obtain:

$R_0 \neq \frac{2\alpha}{\alpha+\mu}$, then: $\det(\Lambda_1) \neq 0$ and $\text{rank}(\Lambda_1) = 3$.

Therefore, the system is **locally controllable** around the chronic equilibrium for any measurable bounded control $u_1 \in U$.

ii) For model (3.6) : We campute the A_2 and B_2:

$$A_2 = \frac{\partial f_2}{\partial x}\begin{pmatrix} \alpha\left(1-\frac{2S}{K}\right)-\beta V(1-u_2) & 0 & -\beta S(1-u_2) \\ \beta V(1-u_2) & -\mu & \beta S(1-u_2) \\ 0 & \gamma\mu & -\sigma \end{pmatrix}, B_2 = \frac{\partial f_2}{\partial u_2}\begin{pmatrix} \beta SV \\ -\beta SV \\ 0 \end{pmatrix}$$

We put: $X = \alpha\left(1-\frac{2S}{K}\right), \quad Y = \beta V(1-u_2), \quad Z = \beta S(1-u_2)$

So:

$$A_2 = \begin{pmatrix} X-Y & 0 & -Z \\ Y & -\mu & Z \\ 0 & \gamma\mu & -\sigma \end{pmatrix}$$

From Kalman's criterion we calculate Kalman's matrix: $\Lambda_2 = (B_2 \quad A_2B_2 \quad A_2^2B_2)$ is given by:

$$\Lambda_2 = -\beta SV \begin{pmatrix} 1 & X-Y & (X-Y)^2+\gamma\mu Z \\ -1 & Y+\mu & Y(X-Y-\mu)-\mu(\mu+\gamma Z) \\ 0 & -\gamma\mu & \gamma\mu(Y+\mu\sigma) \end{pmatrix}$$

We calculate the derminant of the matrix Λ_2:

$$\det(\Lambda_2) = \gamma\mu SV\big[(Y+\mu)(Y+\mu+\sigma) + Y(X-Y-\mu) \\ -\mu(\mu+\gamma Z) + (X-Y)(Y+\mu+\gamma) + (X-Y)^2 + \gamma\mu Z\big]$$

$$\begin{aligned}\det(\Lambda_2) &= \gamma\mu SV\left[(Y+\mu+\sigma) + Y(X-Y-\mu) - \mu^2(X-Y)^2\right] \\ &= \gamma\mu SV\left[X^2 + (\mu+\sigma)X + \sigma\mu\right]\end{aligned}$$

$\det \Lambda_2 = 0 \Longleftrightarrow X = -\mu$ or $X = -\sigma$.

By replacing $X = \alpha\left(1 - \dfrac{2S}{K}\right)$ and using the first coordinate of the chronic equilibrium, we obtain two values of R_0 : $R_0 = \dfrac{2\alpha}{\alpha+\mu}$ and $R_0 = \dfrac{2\sigma}{\sigma+\mu}$.
So, $\det(\Lambda_1) \neq 0$, iff $R_0 \neq \dfrac{2\alpha}{\alpha+\mu}$ and $R_0 \neq \dfrac{2\sigma}{\sigma+\mu}$.

In that case: $\operatorname{rank}(\Lambda_2) = 3$.

Therefore, the system is **locally controllable** around the chronic equilibrium for any measurable bounded control u_2.

iii) For model (3.7):

We compute the matrices A_3 and B_3:

$$A_3 = \frac{\partial f_3}{\partial x} = \begin{pmatrix} \alpha\left(1 - \dfrac{2S}{K}\right) - \beta V & 0 & -\beta S \\ \beta V & -\mu(1-u_3) & \beta S \\ 0 & \gamma\mu(1-u_3) & -\sigma \end{pmatrix}, \quad B_3 = \frac{\partial f_3}{\partial u_3} = \begin{pmatrix} 0 \\ \mu I \\ -\gamma\mu I \end{pmatrix}$$

We set:

$$X = \alpha\left(1 - \frac{2S}{K}\right), \quad Y = \beta V, \quad Z = \beta S, \quad \nu = \mu(1-u_3)$$

So:

$$A_3 = \begin{pmatrix} X-Y & 0 & -Z \\ Y & -\nu & Z \\ 0 & \gamma\nu & -\sigma \end{pmatrix}$$

According to Kalman's criterion, we define the Kalman matrix:

$$\Lambda_3 = \begin{pmatrix} B_3 & A_3B_3 & A_3^2B_3 \end{pmatrix}$$

$$\Lambda_3 = \mu I \begin{pmatrix} 0 & \gamma Z & \gamma Z(-\nu + X - Y - \sigma) \\ 1 & -\nu - \gamma Z & \nu^2 + \gamma\nu Z + \gamma Z(Y + \nu + \sigma) \\ -\gamma & \gamma(\nu + \sigma) & -\gamma(\nu^2 + \nu\sigma + (\gamma Z\nu + \sigma^2)) \end{pmatrix}$$

We calculate the derminant of the matrix Λ_3:

$$\det(\Lambda_3) = \mu\gamma^2 IZ \begin{vmatrix} 0 & 1 & -\nu + X - Y - \sigma \\ 1 & -\nu - \gamma Z & \nu^2 + \gamma\nu Z + \gamma Z(Y + \nu + \sigma) \\ -1 & \nu + \sigma & -[\nu^2 - \sigma\nu + (\gamma Z\nu + \sigma^2)] \end{vmatrix}$$

$$\det(\Lambda_3) = \mu\gamma^2 IZ\,[X(\sigma - \gamma Z) - Y\sigma]$$

By replacing with the chronic equilibrium coordinates, it is obtained that: $(\sigma - \gamma Z) = 0$, so : $det(\Lambda_3) = \frac{-\alpha^2}{\beta}\sigma^3(1 - \frac{1}{R_0})^2$.

In this case, the system (3.7) is **locally controllable** around the chronic equilibrium for any measurable bounded control u_3.

iv) For model (3.8) : We have already calculated :

$$B_c = \begin{pmatrix} 0 & \beta SV & 0 \\ 0 & -\beta SV & \mu I \\ -\sigma V & 0 & -\gamma\mu I \end{pmatrix}$$

thus: $detB_c = -\sigma V(\mu\beta SVI) \neq 0$
Since B_c is of $rank(\Lambda) = 3$, then the Kalman matrix associated to that case, given by $\Lambda = (B_c, A_cB_c, A_c^2B_c^2)$ is of rank 3 too.

Based on these findings, all of our model (3.5) (3.6) (3.7) (3.8), are locally controllable around E^* if and only if R_0 does not belong to the set containing the two specific values:$\left\{\frac{2\sigma}{\sigma+\mu},\ \frac{2\alpha}{\alpha+\mu}\right\}$. ■

3.4.2 Optimal control calculation

We consider four controlled versions of the HIV model, each with its own cost functional. Since the optimal control procedure is similar for all cases, we present in detail the derivation only for system (2.1) with its three controls u_1, u_2, and u_3, and associated costs.

1. Minimize the number of infected cells in the body for the system :

$$J_I\,(u_i^*) = \min_{u_i \in U} \int_0^T I(t)dt\ , \qquad i = 1, 2, 3.$$

2. Minimize the number of free viruses circulating in the blood for the system:

$$J_V\left(u_i^*\right) = \min_{u_i \in U} \int_0^T V(t)dt \ , \qquad i = 1, 2, 3.$$

3. Maximize the number of healthy cells for the system:

$$J_S\left(u_i^*\right) = \max_{u_i \in U} \int_0^T S(t)dt \ , \qquad i = 1, 2, 3$$

3.4.3 Determining the control

We assume that:

1.

$$\begin{cases} \dot{x}(t) = f_1(t, x(t), u_1(t)) = A_1(t)x(t) + B_1(t)u_1(t), \\ \dot{x}(t) = f_2(t, x(t), u_2(t)) = A_2(t)x(t) + B_2(t)u_2(t), \\ \dot{x}(t) = f_3(t, x(t), u_3(t)) = A_3(t)x(t) + B_3(t)u_3(t). \end{cases}$$

Where: $x = (S, I, V)$, so the initial condition is: $x_0 = (S_0, I_0, V_0)$.

2. And the objective function is:

$$g(t, u_i(t)) = \begin{pmatrix} J_I\left(u_i^*\right) \\ J_V\left(u_i^*\right) \\ J_S\left(u_i^*\right) \end{pmatrix} \qquad \text{i=1,2,3}$$

- Case (3.5) :

$$J_I\left(u_1^*\right) = \min_{u_1 \in U} \int_0^T I(t)dt$$

The Hamiltonian H associated with the system (1) is:

$$H(t, x(t), \lambda(t), u_1(t)) = \lambda f_1(t, x(t), u_1(t)) + g(t, x(t), u_1(t))$$

$$\begin{aligned} H(t, x(t), \lambda(t), u_1(t)) \ = \ & -I(t) + \lambda_1(t)\left[\alpha S(t)\left(1 - \frac{S(t)}{K}\right) - \beta S(t)V(t)\right] \\ & + \lambda_2(t)\left[-\mu I(t) + \beta S(t)V(t)\right] + \lambda_3(t) \\ & \left[\gamma\mu I(t) - \sigma V(t)(\mathbf{1} + \mathbf{u_1(t)})\right] \end{aligned}$$

Proposition 3.3

If there exists an optimal control u^* and an associated optimal trajectory x^*, then the pair (x^*, u^*) satisfies the sufficient conditions of Pontryagin's Maximum Principle. In particular, x^* is an optimal trajectory under this principle.

PROOF. There exists an adjoint vector :

$$\lambda_i : [0, T] \to \mathbb{R}, \quad i = 1, 2, 3$$

So that:
(a)

$$\begin{cases} \dot{\lambda_1}(t) = -\frac{\partial H}{\partial S} = -\lambda_1(t)\left[\alpha\left(1 - \frac{2S(t)}{K}\right) - \beta V(t)\right] - \lambda_2(t)\beta V(t) \\ \dot{\lambda_2}(t) = -\frac{\partial H}{\partial I} = 1 + \mu\lambda_2(t) - \gamma\mu\lambda_3(t) \\ \dot{\lambda_3}(t) = -\frac{\partial H}{\partial V} = \beta S(t)\lambda_1(t) - \beta S(t)\lambda_2(t) + \sigma(1 + u_1(t))\lambda_3(t) \\ \lambda_1(T) = \lambda_2(T) = \lambda_3(T) = 0 \text{ (transversal conditions)} \end{cases}$$

(b)

$$H(t, x^*(t), \lambda(t), u_1^*(t)) = \max_{u_1 \in U} H(t, x^*(t), \lambda(t), u_1).$$

$$\sigma V(t)\lambda_3(t)u_1^*(t) = \max_{u_1 \in U} \sigma V(t)\lambda_3(t)u_1(t).$$

Switching Function and Bang-Bang Control for $u_1(t)$:

We define the switching function:

$$\phi(t) = \sigma V(t)\lambda_3(t)$$

We compute its time derivative:

$$\frac{\partial \phi}{\partial t} = \sigma \dot{V}(t)\lambda_3(t) + \sigma V(t)\dot{\lambda}_3(t)$$

Using the system dynamics:

$$\dot{V}(t) = -\sigma V(t)(1 + u_1(t)) + \gamma\mu I(t)$$

$$\dot{\lambda}_3(t) = \beta S(t)(\lambda_1(t) - \lambda_2(t)) + \sigma(1 + u_1(t))\lambda_3(t)$$

Substituting:

$$\begin{aligned}\dot{\phi}(t) = \sigma\left[-\sigma V(t)(1+u_1(t)) + \gamma\mu I(t)\right]\lambda_3(t) \\ + \sigma V(t)\left[\beta S(t)(\lambda_1(t)-\lambda_2(t)) + \sigma(1+u_1(t))\lambda_3(t)\right]\end{aligned}$$

Simplifying:

$$\boxed{\dot{\phi}(t) = \sigma\gamma\mu I(t)\lambda_3(t) + \sigma\beta S(t)V(t)(\lambda_1(t)-\lambda_2(t))}$$

By analyzing $\dot{\phi}(t)$, and considering by the transversality that $\phi(T) = \dot{\phi}(T) = 0$, it follows that $\dot{\phi}(t)$ vanishes at least once on the interval $[0, T]$. Thus, $\phi(t)$ changes sign at least once, which excludes the existence of a singular arc. This confirms that the optimal control is of **bang-bang type**.

We now determine the form of the optimal **bang-bang control**:

$$u_1^*(t) = \begin{cases} u_{\min} & \text{if } \phi(t) < 0 \\ \text{undefined} & \text{if } \phi(t) = 0 \\ u_{\max} & \text{if } \phi(t) > 0 \end{cases}$$

Since $\sigma > 0$ and $V(t) > 0$, the sign of $\phi(t)$ depends solely on $\lambda_3(t)$. Therefore:

$$u_1^*(t) = \begin{cases} a & \text{if } \lambda_3(t) < 0 \\ \text{undefined} & \text{if } \lambda_3(t) = 0 \\ L & \text{if } \lambda_3(t) > 0 \end{cases}$$

Remark 1:

To reduce the concentration of free viruses in the blood, the cost functional,

$$J_V(u_2) = \min_{u_2 \in \mathcal{U}} \int_0^T V(t)\, dt$$

is used. Similarly, to increase the number of healthy cells,

$$J_S(u_1) = \max_{u_1 \in \mathcal{U}} \int_0^T S(t)\, dt$$

a corresponding cost functional is considered. In both cases, the expression of the optimal control for system (3.5) remains unchanged. Only the forms of the associated Hamiltonians and the corresponding adjoint systems are modified, and are therefore not detailed here for brevity. ■

- Cases (3.6) and (3.7):

$$J_I(u_1^*) = \min_{u_1 \in U} \int_0^T I(t)dt$$

Proposition 3.4

If an optimal control u^* exists, then the associated trajectory x^* necessarily satisfies the conditions of Pontryagin's Maximum Principle.

PROOF.

Using the same principle of maximum Pontryaguin, we calculate the al control for the systems (3.6) and (3.7), summarized in what follows:

$$u_2^*(t) = \begin{cases} a & \text{if } \lambda_2(t) - \lambda_1(t) < 0 \\ \text{undefined} & \text{if } \lambda_2(t) - \lambda_1(t) = 0 \\ b & \text{if } \lambda_2(t) - \lambda_1(t) > 0 \end{cases}$$

Since the Hamiltonian is linear with respect to the control variable u_2^*, we have $\frac{\partial^2 H(t)}{\partial u_2^2} = 0$. This implies that no singular control arises in this case:

$$u_3^*(t) = \begin{cases} a & \text{if } \gamma\lambda_3(t) - \lambda_2(t) < 0 \\ \text{undefined} & \text{if } \gamma\lambda_3(t) - \lambda_2(t) = 0 \\ b & \text{if } \gamma\lambda_3(t) - \lambda_2(t) > 0 \end{cases}$$

Remark 2 :

The optimal controls u_2^* and u_3^* are consistent across the cases of minimizing free virus levels and maximizing healthy cells, though the corresponding Hamiltonians and adjoint systems change with each case. ■

- Case (3.8) :

In this part we will study the optimal $u = (u_1^*, u_2^*, u_3^*)$ control model (3.8) for the 3 controls simultaneously .

Put :

$$F(t, x(t), u_i(t)) \begin{cases} f_1(t, x(t), u(t)) \\ f_2(t, x(t), u(t)) \\ f_3(t, x(t), u(t)) \end{cases} \text{, i=1,2,3}$$

We also have : $\psi(x(T)) = \psi(S(T), I(T), V(T)) = 0$, or : $x = (S, I, V)$.

And the objective function is :

$$g(t,u_i(t)) = \begin{pmatrix} J_I\left(u_i^*\right) \\ J_V\left(u_i^*\right) \\ J_S\left(u_i^*\right) \end{pmatrix} \qquad \text{i=1,2,3}$$

The Hamiltonian associated with system (3.8) is:

$$\begin{aligned} H(t,x,\lambda,u) = g(t,u(t)) \\ &+ \lambda_1(t)\Big[\alpha S(t)\Big(1-\frac{S(t)}{K}\Big) - \beta S(t)V(t)(1-u_2(t))\Big] \\ &+ \lambda_2(t)\Big[-\mu I(t)(1-u_3(t)) + \beta S(t)V(t)(1-u_2(t))\Big] \\ &+ \lambda_3(t)\Big[\gamma\mu I(t)(1-u_3(t)) - \sigma V(t)(1+u_1(t))\Big] \end{aligned}$$

Proposition 3.5

For each case, there exists a unique optimal control u_i^* , $i = 1,2,3$ and an associated adjoint function $\lambda_i, i = 1,2,3$, satisfying the conditions of Pontryagin's Maximum Principle, and verifiyin:

$$\begin{cases} \dot{\lambda}_i(t) = -\dfrac{\partial H}{\partial x}, \quad x = (S,I,V) \\ \lambda_i(T) = 0, \quad i = 1,2,3. \quad \textit{transversality conditions .} \end{cases}$$

Proof.

• The adjoint system corresponding to the minimization of the infected cell population (1) is given by:

$$\begin{cases} \dot{\lambda}_1(t) = -\dfrac{\partial H}{\partial S} = \left[\beta V(t)(1-u_2(t)) - \alpha\left(1-\dfrac{2S(t)}{K}\right)\right]\lambda_1(t) \\ \qquad\qquad - \left[\beta V(t)(1-u_2(t))\lambda_2(t)\right] \\ \dot{\lambda}_2(t) = -\dfrac{\partial H}{\partial I} = \left[\mu(1-u_3(t))\right]\lambda_2(t) - \left[\gamma\mu(1-u_3(t))\right]\lambda_3(t) + 1, \\ \dot{\lambda}_3(t) = -\dfrac{\partial H}{\partial V} = \left[\beta S(t)(1-u_2(t))\right]\lambda_1(t) - \left[\beta S(t)(1-u_2(t))\right]\lambda_2(t) \\ \qquad\qquad + \left[\sigma(1+u_1(t))\right]\lambda_3(t), \\ \lambda_1(T) = \lambda_2(T) = \lambda_3(T) = 0. \end{cases}$$

• The adjoint system associated with the objective of minimizing the

viral load is (2) expressed as:

$$\begin{cases} \dot{\lambda}_1(t) = -\dfrac{\partial H}{\partial S} = \left[\beta V(t)(1-u_2(t)) - \alpha\left(1-\dfrac{2S}{K}\right)\right]\lambda_1(t) \\ \qquad\qquad - \left[\beta V(t)(1-u_2(t))\right]\lambda_2(t), \\ \dot{\lambda}_2(t) = -\dfrac{\partial H}{\partial I} = \left[\mu(1-u_3(t))\right]\lambda_2(t) - \left[\gamma\mu(1-u_3(t))\right]\lambda_3(t), \\ \dot{\lambda}_3(t) = -\dfrac{\partial H}{\partial V} = \left[\beta S(t)(1-u_2(t))\right]\lambda_1(t) - \left[\beta S(t)(1-u_2(t))\right]\lambda_2(t) \\ \qquad\qquad + \left[\sigma(1+u_1(t))\right]\lambda_3(t) + 1 \\ \lambda_1(T) = \lambda_2(T) = \lambda_3(T) = 0. \end{cases}$$

• And , when maximizing the healthy cells populations, one gets:

$$\begin{cases} \dot{\lambda}_1(t) = \left[\beta V(t)(1-u_2(t)) - \alpha\left(1-\dfrac{2S}{K}\right)\right]\lambda_1(t) - \left[\beta V(t)(1-u_2(t))\lambda_2(t)\right] - 1, \\ \dot{\lambda}_2(t) = \left[\mu(1-u_3(t))\right]\lambda_2(t) - \left[\gamma\mu(1-u_3(t))\right]\lambda_3(t), \\ \dot{\lambda}_3(t) = \left[\beta S(t)(1-u_2(t))\right]\lambda_1(t) - \left[\beta S(t)(1-u_2(t))\right]\lambda_2(t) + \left[\sigma(1+u_1(t))\right]\lambda_3(t), \\ \lambda_1(T) = \lambda_2(T) = \lambda_3(T) = 0. \end{cases}$$

Using Pontryagin's maximum principle (3.3) to determine the optimal control.

We obtain:

$$u_1^*(t) = \begin{cases} a & \text{if} \quad \lambda_3(t) > 0, \\ \text{undefined} & \text{if} \quad \lambda_3(t) = 0, \\ L & \text{if} \quad \lambda_3(t) < 0. \end{cases}$$

$$u_2^*(t) = \begin{cases} a & \text{if} \quad \lambda_2(t) - \lambda_1(t) < 0, \\ \text{undefined} & \text{if} \quad \lambda_2(t) - \lambda_1(t) = 0. \\ b & \text{if} \quad \lambda_2(t) - \lambda_1(t) > 0, \end{cases}$$

$$u_3^*(t) = \begin{cases} a & \text{if } \gamma\lambda_3(t) - \lambda_2(t) < 0, \\ \text{undefined} & \text{if } \gamma\lambda_3(t) - \lambda_2(t) = 0. \\ b & \text{if } \gamma\lambda_3(t) - \lambda_2(t) > 0, \end{cases}$$

■

3.5 Numerical simulations

This section is dedicated to the numerical analysis of the optimality system, highlighting the optimal controls obtained. The results, illustrated by curves, are obtained by solving a system of **6 ODEs** representing both the state dynamics and the corresponding adjoint equations.

The solution is obtained by an iterative method: the state equations are integrated with an initial control using a **Runge-Kutta 4 forward schema**, and then the adjoint equations are solved backwards using an **implicit Euler schema**, taking into account the final boundary conditions.

The controls are updated on the basis of their analytical characterisation. This process is repeated at each iteration and stops when the solutions are sufficiently close to those of the previous iteration, thus ensuring the convergence of the system.

The initial conditions for this are as follows: $S_0 = 1000$, $I_0 = 10$ and $V_0 = 100$. In all situations the adjoint state variables are zero, with $a = 0.01$, $b = 0.9$ and $L = 5$ (estimated value)[25].

1) Minimization of infected cells

i) **Minimization of infected cells under first control (1):**

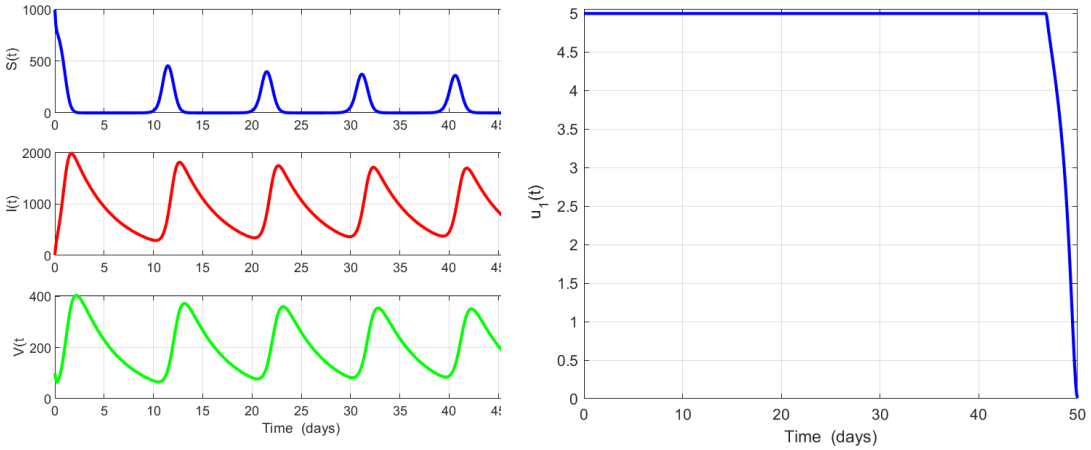

Figure 3.2: Minimizing I, system (3.5) with control u_1 , $R_0 = 22$.

Interpretation of results:

The optimal control $u_1(t)$ shows limited effectiveness: it helps reduce the number of infected cells I and the viral load V, but it does not fully eradicate the virus. The healthy cell population S increases slightly, but does not recover to its initial level.

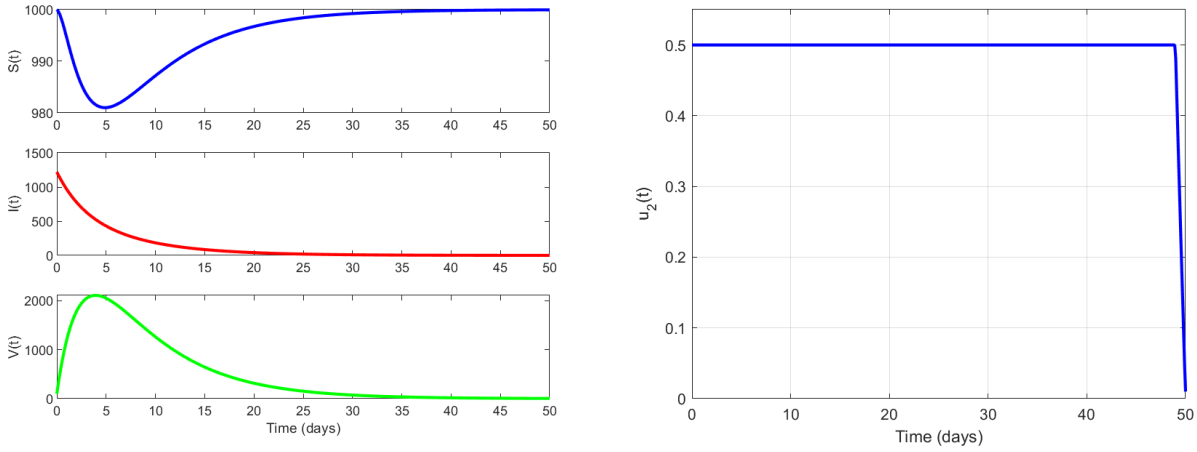

Figure 3.3: Minimizing I, system (3.6) with control u_2 , $R_0 = 22$.

Interpretation of results:

The control $u_2(t)$, which targets the prevention of new infections, proves to be highly effective when applied alone. It significantly reduces the viral load and the number of infected cells while promoting the recovery of healthy cells. These results highlight the crucial role of this mechanism in interrupting the infection cycle and demonstrate that targeting virus entry into cells is a powerful therapeutic strategy.

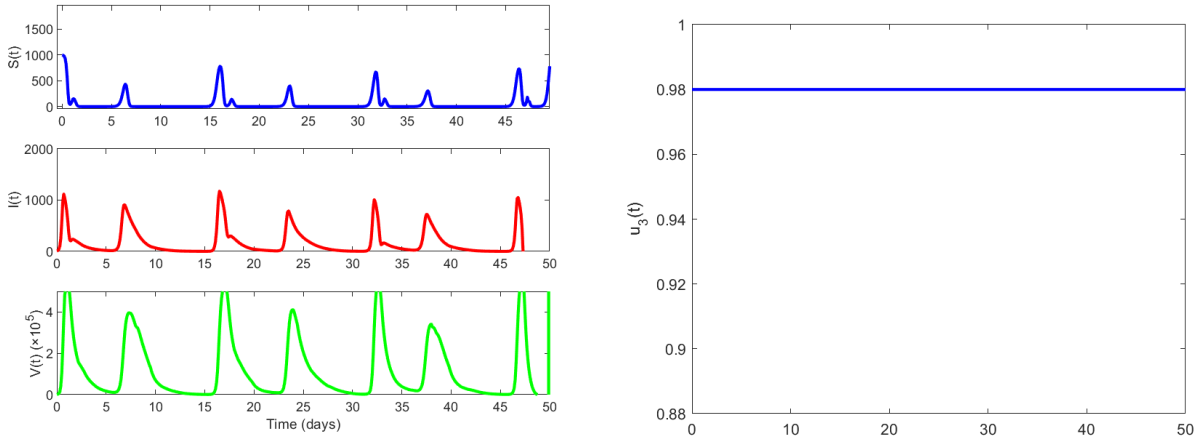

Figure 3.4: Minimizing I, system (3.7) with control u_3 , $R_0 = 22$.

Interpretation of results:

The optimal control $u_3(t)$ reaches its maximum almost immediately and remains constant, effectively reducing the population of infected cells. However, healthy cells stabilize at a low level, and the viral load remains relatively high. This suggests that while $u_3(t)$ is effective in targeting infection, it does not achieve full recovery. Its limited efficacy in a high R_0 context highlights the importance of early treatment and the implementation of combined therapeutic strategies, particularly for chronic infections such as HIV.

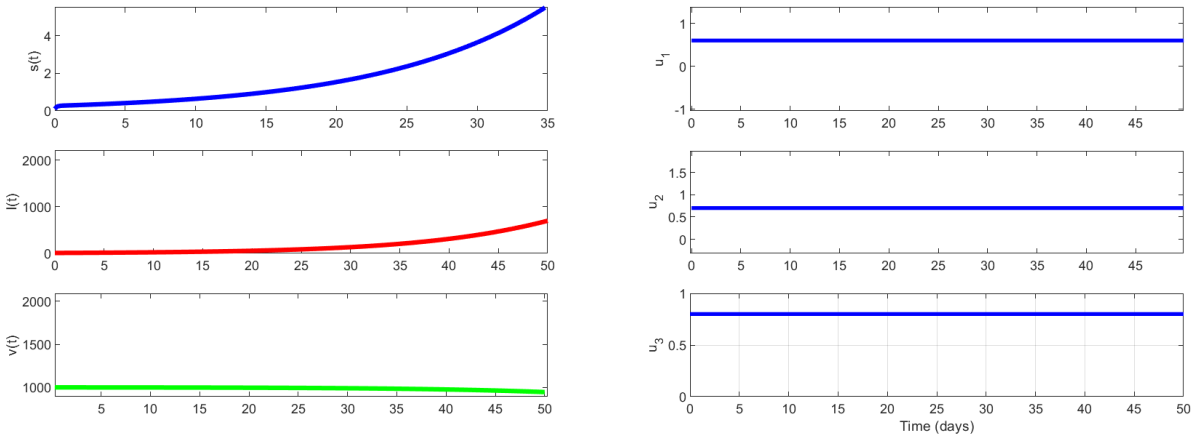

Figure 3.5: Minimizing I, system (3.8) with all controls, $R_0 = 22$.

Interpretation of results:

The applied controls manage to stabilize the infection without completely eliminating the virus. The viral load decreases and healthy cells are preserved to a certain extent. This highlights the limits of single or partially applied controls and supports the need for optimized combined strategies.

ii) **Minimizing viruses (2):**

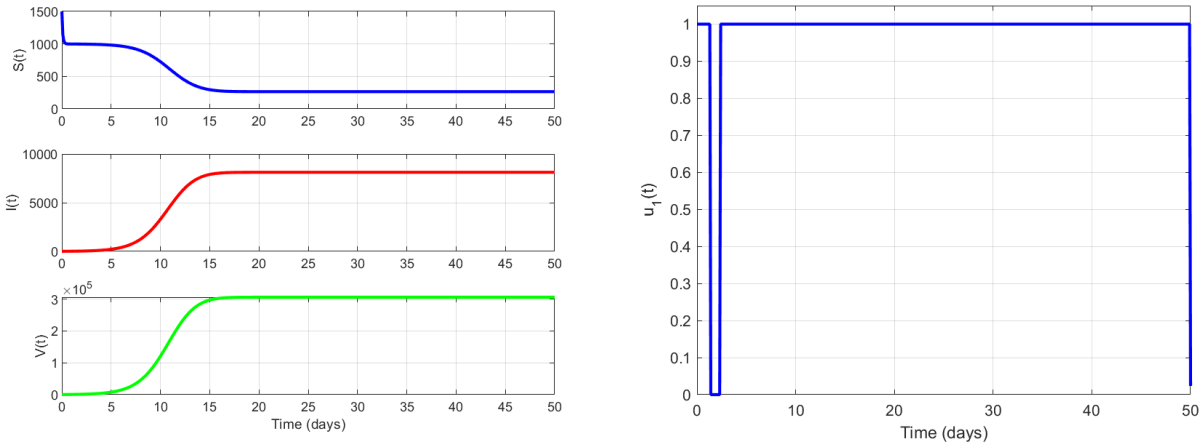

Figure 3.6: Minimizing V, system(3.5) with control u_1, $R_0 = 22$.

Interpretation of results:

Although the control limits the progression of the infection, the interplay between healthy cell growth, viral transmission, and high viral production ($\gamma = 2200$) prevents the complete elimination of the virus.

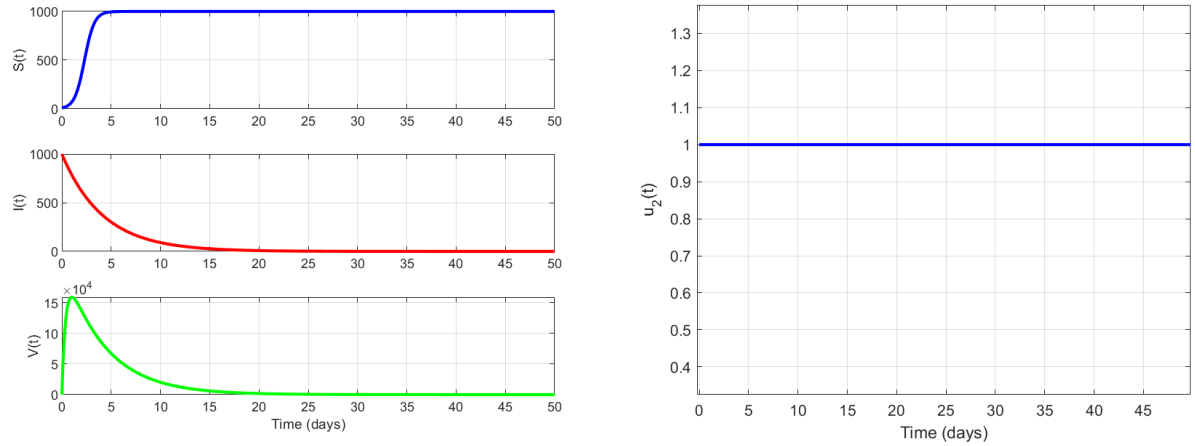

Figure 3.7: Minimizing V, system (3.6) with control u_2, $R_0 = 22$.

Interpretation of results:

The figures show the effectiveness of optimal u_2 control, which aims to maintain the healthy cell population over time while significantly reducing the viral load and the number of contaminated cells.
The intensity of control indicates the therapeutic effort required to achieve these goals.

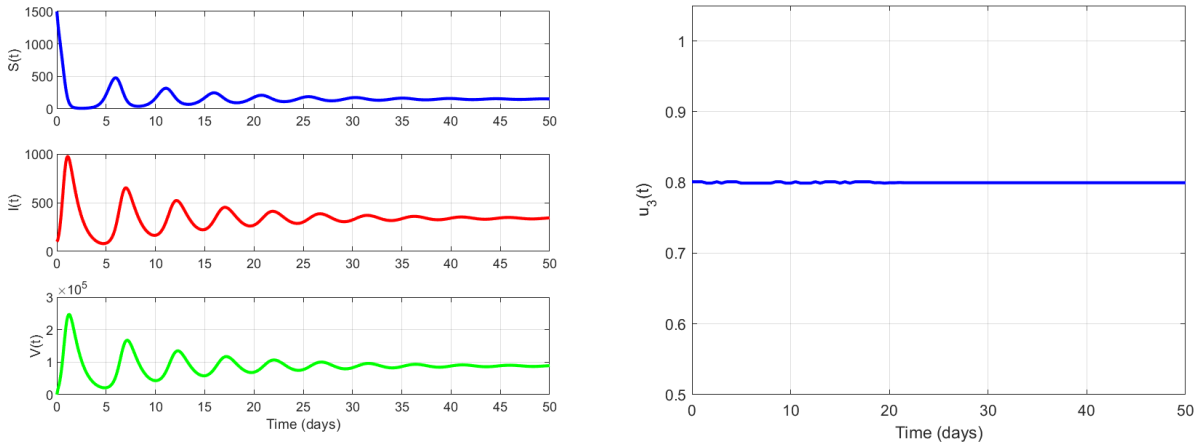

Figure 3.8: Minimizing V, system (3.7) with control u_3, $R_0 = 22$.

Interpretation of results:

The effectiveness of u_3 control is very limited. In fact, the oscillations observed and the maintenance of high viral levels indicate that it does not provide adequate infection control.

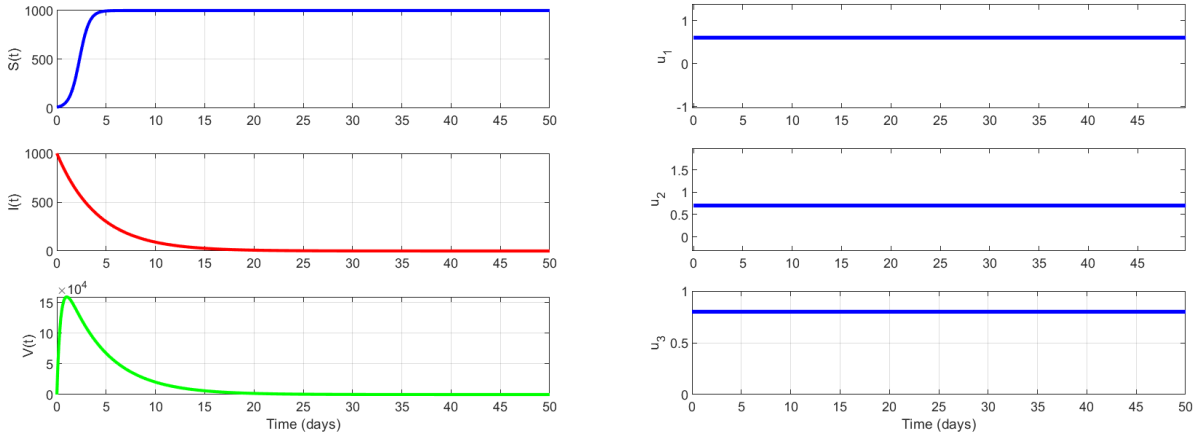

Figure 3.9: Minimizing V, system (3.8) with all controls, $R_0 = 22$.

Interpretation of results:

The combined use of the three controls u_1, u_2, u_3 effectively manages the infection by reducing both the viral load and the number of infected cells, while preserving healthy cells. This multimodal approach proves to be particularly effective within the model.

iii) **Maximization of healthy cells (3):**

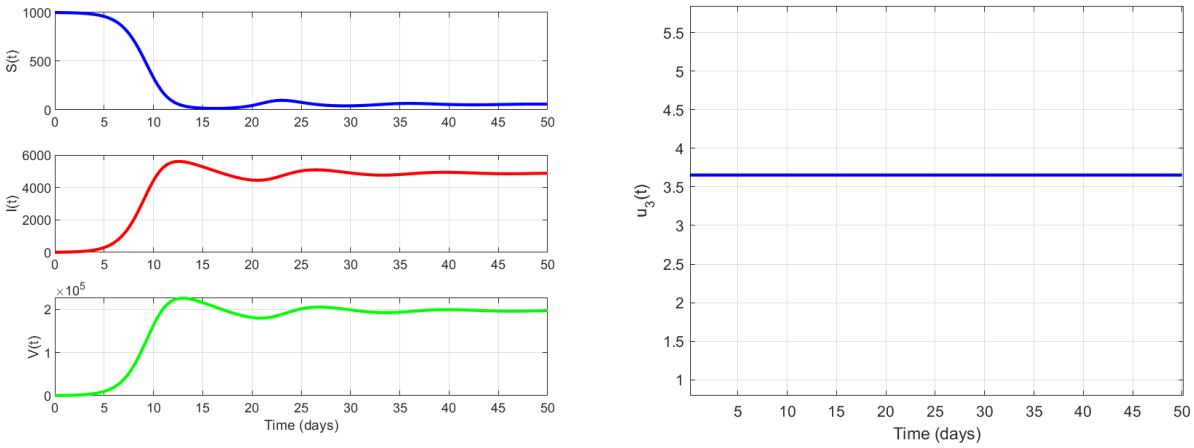

Figure 3.10: Maximizing S, system (3.5) with control u_1, $R_0 = 22$.

Interpretation of results:

Control u_1 control (enhanced viral clearance) initially suppresses infection and protects healthy cells. However, subsequent recrudescence suggests limited long-term efficacy or an optimisation strategy that tolerates brief viral reactivation to maximise overall healthy cells. Combined strategies may be needed.

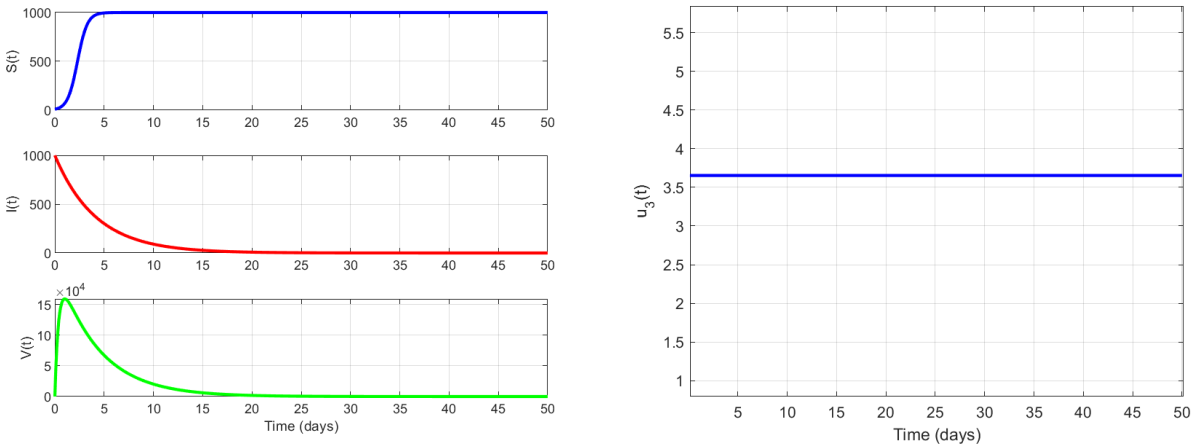

Figure 3.11: Maximizing S, system (3.6) with control u_2, $R_0 = 22$.

Interpretation of results:

As in the previous cases, the control u_2 is very effective.

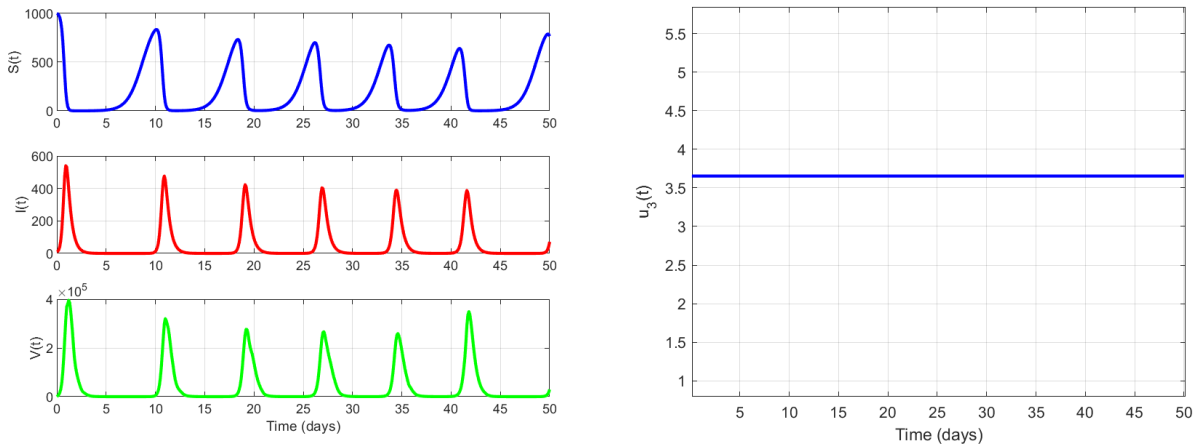

Figure 3.12: Maximizing S, system (3.7) with control u_3, $R_0 = 22$.

Interpretation of results:

Although some control over infected cells and virus production is observed, this single control strategy remains insufficient and unstable. It fails to sustainably reduce infection and does not effectively preserve healthy cells. A combined control approach appears to be essential for optimal results.

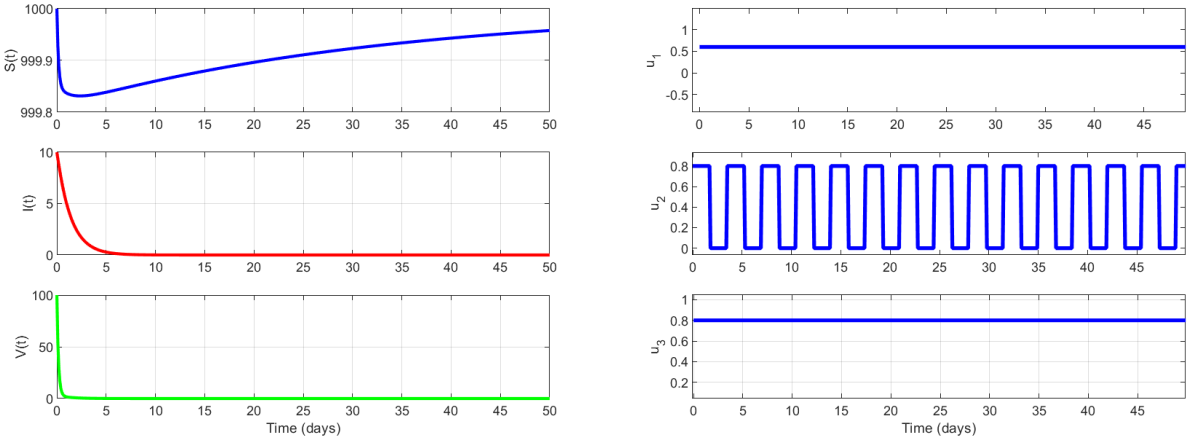

Figure 3.13: Maximizing S, system (3.8) with all controls , $R_0 = 22$.

Interpretation of results:

The combined use of the three controls proved highly effective in stabilising healthy cells and suppressing infection. However, the instability of the u_2 control makes its practical application difficult. Although promising, this optimal strategy will require solutions to overcome the challenges of u_2 implementation.

Conclusion

Numerical simulations carried out on all scenarios have demonstrated a strong superiority of the control $u_2(t)$, which aims to block the infection of healthy cells. This control not only reduced the number of infected cells significantly but also preserved the population of healthy $CD4^+$ T-cells and lowered the viral load in the bloodstream. Its biological effectiveness lies in its ability to prevent the virus from entering host cells, thereby halting the infection process at its source.

On the other hand, the isolated application of the controls $u_1(t)$ and $u_3(t)$ proved inefficient, and even counterproductive in some cases. The control $u_1(t)$, acting on viral clearance, was quickly overwhelmed by the high rate of viral production, rendering it insufficient on its own. The control $u_3(t)$, targeting the infected cells, led to unintended consequences: by eliminating infected cells without preventing new infections, it indirectly promoted a depletion of all immune cells, including healthy ones, thereby reinforcing the infection rather than suppressing it.

These findings are consistent with several studies on Highly Active Antiretroviral Therapy (HAART), where treatment success strongly depends on patient adherence and the balance between efficacy and side effects. A treatment strategy that could reduce the number of drugs or dosing intensity while maintaining viral suppression would not only enhance patient adherence but also limit drug resistance and toxicity.

The comparative analysis suggests that the best approach is to combine all three controls u_1, u_2, and u_3, each acting on a distinct stage of the infection cycle. This coordinated strategy ensures better long-term management of the disease by acting simultaneously on virus entry, replication, and infected cells.

In conclusion, the bang-bang control approach, especially when combining all controls, appears to be a powerful mathematical strategy to optimize HIV-1 treatment. It provides a promising direction for designing therapeutic protocols that are both biologically effective and clinically viable.
In the following, we provide a summary table comparing the effectiveness of the different control strategies studied in this work:

Criterion / Control	u_1	u_2	u_3	**All controls**
min I	maximum	maximum	moderate	maximum
min V	minimum	maximum	minimum	maximum
max S	moderate	maximum	minimum	maximum

Table 3.1: Control efficiency by criterion

General Conclusion

This work has focused on the within-host dynamics of HIV infection through the mathematical modeling of viral propagation and the implementation of optimal control strategies particularly of the bang-bang type. The main objective was to better understand the impact of targeted therapeutic interventions on viral load suppression and immune cell preservation, within a deterministic SIV (Susceptible–Infected–Virus) framework.

In the first part of our study, we began by revisiting the biological foundations of HIV infection, its transmission modes, and the mechanisms involved in viral replication. This overview allowed us to define and justify the structure of the mathematical model used, built on differential equations describing the interactions between healthy cells, infected cells, and viral particles. We analyzed the system's equilibrium points, calculated the basic reproduction number R_0, and studied the local and global stability of the infection-free and endemic equilibria. These theoretical results laid the foundation for the numerical simulations that followed.

The second part of the study was devoted to the application of control theory, using the Pontryagin Maximum Principle (PMP) and the bang-bang control principle to identify optimal treatment strategies. Three types of controls were considered:

- u_1 targeting viral clearance.
- u_2 acting on the healthy cells infection prevention.
- u_3 acting on the mortality of infected cells.

Summary of findings: Numerical simulations confirmed that the combined application of the three controls yields the best outcome in terms of viral suppression and healthy cell preservation. Among individual strategies, the control u_2 which blocks new infections was the most effective, while the isolated use of u_1 or u_3 showed limited or even counterproductive results.

Future perspectives: Several research directions could be explored to build upon this work:

- Introduce **time delays** in the model to account for biological lags in immune response or drug effects.
- Extend the framework to a **stochastic model**, better capturing variability in patient response or viral mutation.
- Couple the system with **pharmacokinetic and pharmacodynamic** models (PK/PD) to simulate more realistic drug action and resistance.

- Investigate **adaptive or feedback controls**, where treatment depends dynamically on the current viral load or cell count.
- Incorporate a **cost benefit analysis** (e.g., economic or toxicological cost functions) to evaluate therapeutic strategies more comprehensively.

These extensions would allow for a more faithful representation of clinical reality and could contribute to designing robust, patient-specific HIV treatment protocols grounded in both biological insight and mathematical rigor.

Another natural extension of this work would be to analyze the system's behavior at the critical threshold $R_0 = 1$. This case is mathematically delicate, as classical linear stability analysis fails to conclude. In such situations, the application of the **center manifold theorem** becomes relevant. It allows for a reduction of the system's dimensionality near the bifurcation point and enables a deeper understanding of the local dynamics. Studying this critical regime could offer new insights into the transition between eradication and persistence of infection.

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Abstract :

This work focuses on the study of a mathematical model describing the within-host dynamics of HIV infection while incorporating a Bang-Bang type control strategy. We first analyzed the qualitative properties of the system, including positivity, boundedness, and stability. Then, Pontryagin's Maximum Principle was applied to derive the optimal control, and numerical simulations were performed to demonstrate the effectiveness of the proposed strategy. The results show that the Bang-Bang control effectively reduces the number of infected cells and the viral load.

Keywords: HIV, mathematical model, optimal control, Bang-Bang control, stability.

Résumé :

Ce travail porte sur l'étude d'un modèle mathématique décrivant la dynamique de l'infection par le virus VIH à l'intérieur de l'hôte, en intégrant une stratégie de contrôle de type Bang-Bang. Nous avons d'abord analysé les propriétés qualitatives du système, notamment la positivité, la bornitude et la stabilité. Ensuite, le principe du maximum de Pontryagin a été appliqué pour dériver le contrôle optimal, et des simulations numériques ont été réalisées afin d'illustrer l'efficacité de la stratégie proposée. Les résultats obtenus montrent que le contrôle Bang-Bang permet de réduire efficacement le nombre de cellules infectées ainsi que la charge virale.

Mots clés : VIH, modèle mathématique, contrôle optimal, contrôle Bang-Bang, stabilité.

الملخص:

يهدف هذا العمل إلى دراسة نموذج رياضي يصف ديناميكية انتشار فيروس نقص المناعة البشرية (VIH) داخل جسم الإنسان مع الأخذ بعين الاعتبار تأثير استراتيجية تحكم من نوع Bang-Bang. قمنا بتحليل الخصائص النوعية للنظام مثل الاستقرارية والإيجابية وحدود الحلول. ثم تم تطبيق مبدأ بونترياغين للحصول على الشكل الأمثل للتحكم، وتم إجراء محاكاة عددية لتوضيح فعالية الاستراتيجية المقترحة. تظهر النتائج أن استراتيجية التحكم من نوع Bang-Bang تساهم في تقليل عدد الخلايا المصابة والحمل الفيروسي بفعالية.

كلمات مفتاحية : فيروس نقص المناعة البشرية، النموذج الرياضي، التحكم الأمثل، تحكم ، الاستقرار