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Etude et contrôle optimal de modèles de croissance de cellules gliales

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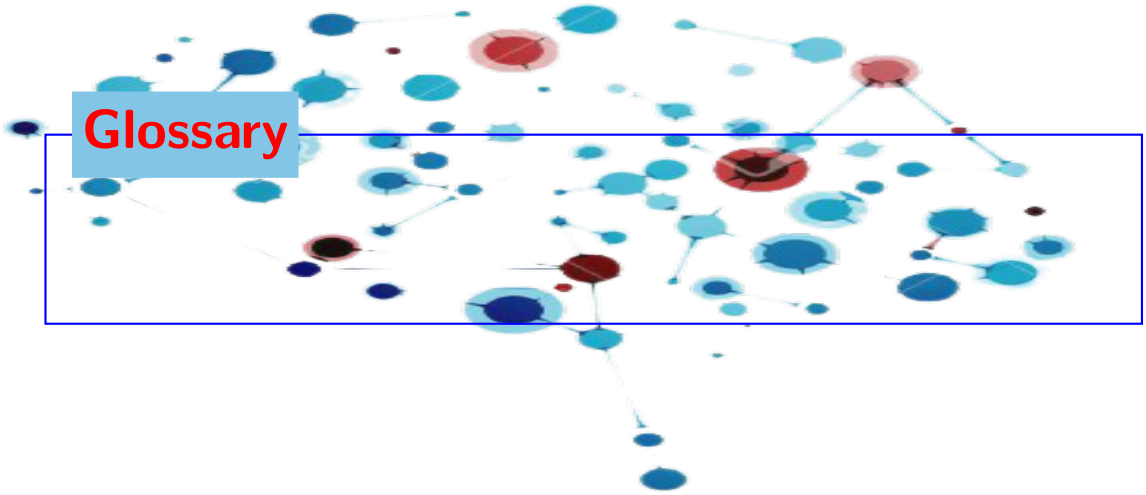


ATP Adenosine triphosphate. 5, 89

BBB Brain blood barier. 14, 15

CBF Cerebral blood flow. 14, 90
CNS Central nervous system. 2

DNA Deoxyribonucleic acid. 2, 3

LDH Lactate dehydrogenase enzyme. ix, 3–5, 14, 69, 70

MCT Monocarboxylate transporters. ix, xv, 5, 6, 12, 15, 30, 89, 90, 104, 120

NAD^+ Nicotinamide adenine. ix, 3, 4
NADH nicotinamide adenine dinucleotide (NAD) + hydrogen (H). ix, 3, 4

ODE Ordinary differential equation. xv, xvi, 14, 15, 44, 52, 63, 75, 89, 91, 110, 120
OXPHOS Oxidative phosphorylation. 5

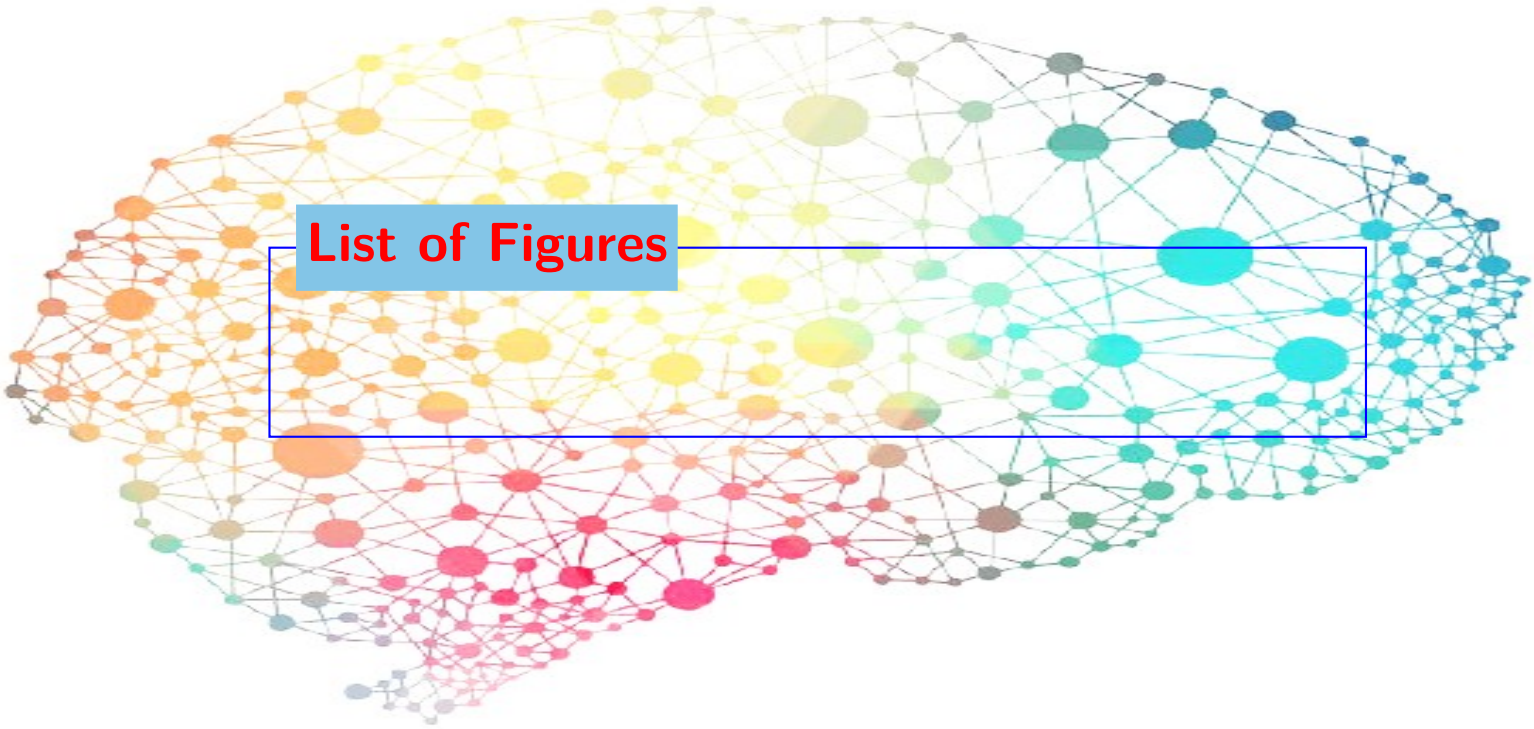
PDE Partial differential equation. 109
PSA Prostate Specific Antigen. 18

TCA Tricarboxylic acid. 5

WHO World health organization. 1

List of Symbols

- $\mathbb{R}$ The set of real numbers.
- L^p The lebesgue space.
- H^m The Sobolev Space.
- $((.,.))$ Usual inner product in $\mathbb{R}$.
- $||.||$ Usual norm in $\mathbb{R}$.
- C^0 Set of continuous functions.
- C^1 Set of continuously differentiable functions.
- $[E]$ The concentration of E.
- $\langle x \rangle = \dfrac{1}{\text{Vol}(\Omega)} \displaystyle\int_\Omega x\, dx$ the spatial average of x.
- $\chi_{[a,b]}$ The characteristic function on $[a, b]$.
- $||x||_{L^p(0,t;L^q(\Omega))} = \left(\displaystyle\int_0^t ||x(s)||^p_{L^q(\Omega)} ds \right)^{\frac{1}{p}}$.
- $||x||_{L^\infty(0,t;L^p(\Omega))} = \displaystyle\sup_{s\in[0,t]} ||x(s)||_{L^p(\Omega)}$.
- $A \lesssim B$, means that $A \leq CB$ where C is a positive constant independent of A and$B$.
- $\mathcal{U}_{ad}$: set of admissible controls.
- $min(a; b)$ minimum between a and b.
- $max(a; b)$ maximum between a and b.



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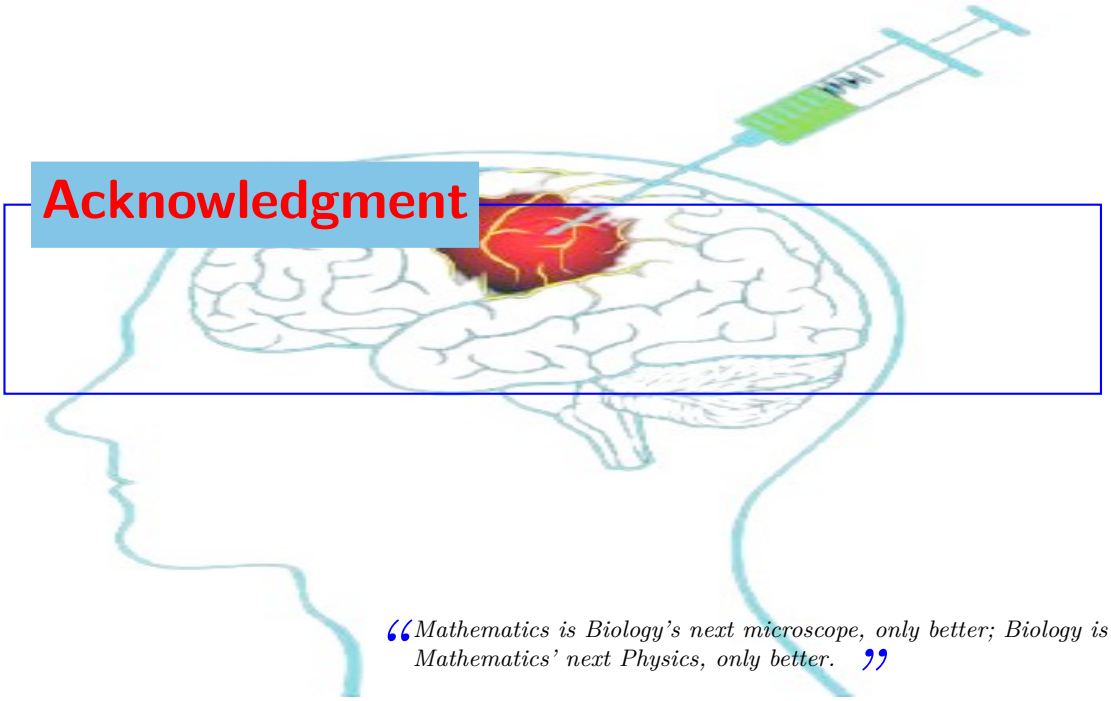

"Mathematics is Biology's next microscope, only better; Biology is Mathematics' next Physics, only better."

Cohen

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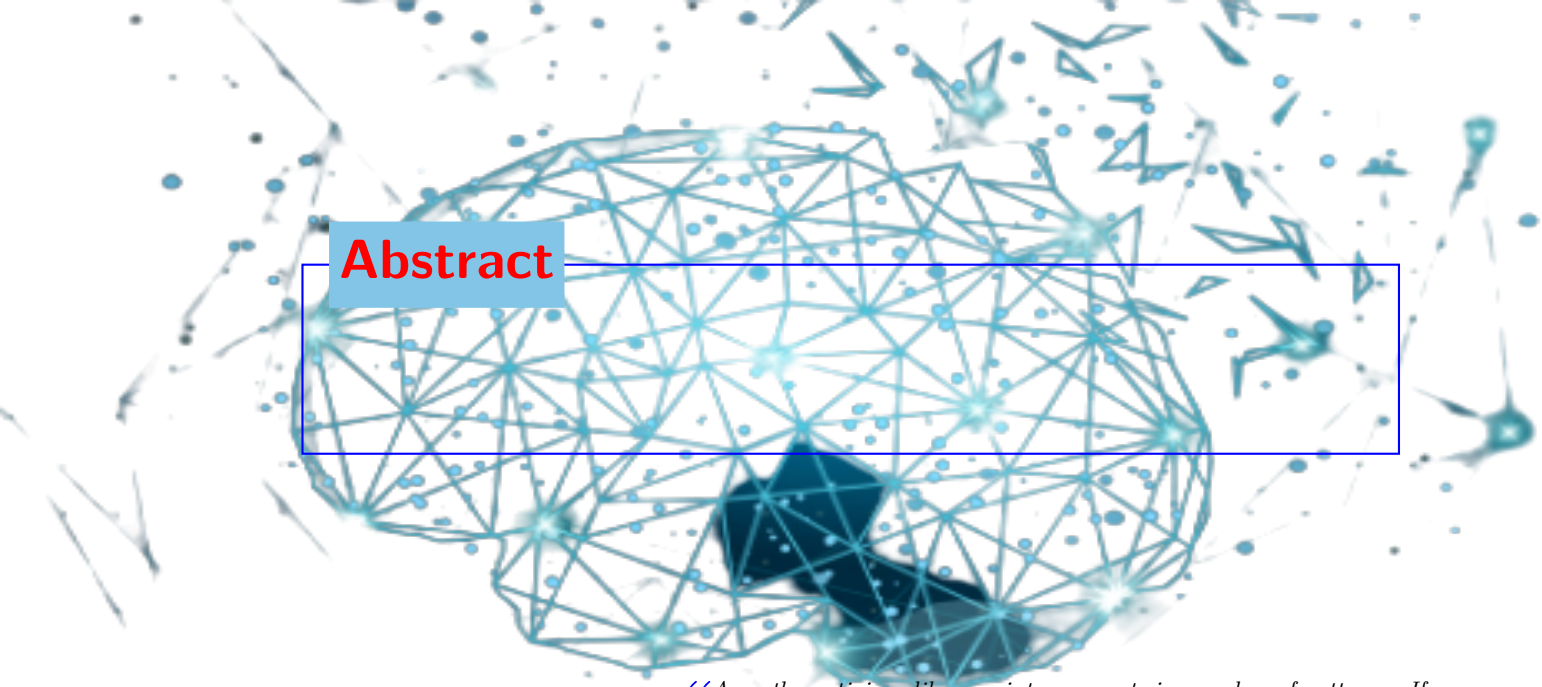


Abstract

“A mathematician, like a painter or poet, is a maker of patterns. If his patterns are more permanent than theirs, it is because they are made with ideas.”

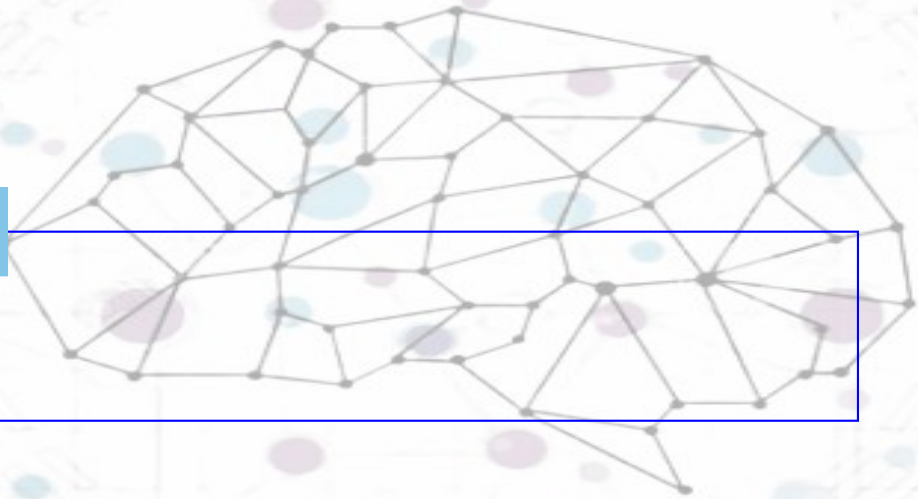
G. H. Hardy

This thesis addresses different therapeutic approaches for gliomas, either directly or at the level of metabolism using optimal control theory. Indeed, we first consider an Allen-Cahn equation modeling tumor growth, and since the structure of the model can change in the presence of nutrients, it is then coupled with an evolution equation for nutrient dynamics. In addition, the treatment of gliomas is considered in terms of control that represents the concentration of the cytotoxic drug at a given rate. Our goal in this part is to choose the control and the treatment time such that the corresponding tumor growth and its final distribution are the best possible approximation to the desired values. Our first step is thus devoted to the study of the well-posedness of our state system, which allows us to define the control-to-state operator that is continuous. Then, we show the existence of a minimizer of our cost functional, where our control-to-state operator is Fréchet differentiable. Next, our cost functional is also Fréchet differentiable with respect to time and control; finally, to simplify the first-order necessary optimality condition, we consider an adjoint system using Lagrange’s principle for which this system has a regular solution. On the other hand, we know that the progression and malignancy of gliomas are related to metabolism, in particular to the waste product of glycolysis, lactate. Thus, we first emphasize the fact that the more lactate the glioma produces, the more it transports the excess into the capillary to sustain proliferation, metastasis, and malignancy. Therefore, we consider the state equation as a parabolic problem modeling intracellular lactate dynamics. Our first challenge is to add a biologically relevant control that acts as a concentration of a certain drug to inhibit lactate production. Since the drug dose and time must not exceed or fall below a certain threshold in cancer treatment, we try to choose the best control at the most convenient time so that the corresponding intracellular lactate concentration is as close as possible to our desired evolution and final distribution of lactate. However, as aforesaid, the cell withdraws excess lactate by transporting it across the plasma cell membrane into the capillary to maintain its proliferation. This has inspired us to target lactate transport using an MCTs inhibitor that acts as a control term in a coupled ODE system that models lactate dynamics in both the intracellular and capillary domains. We address the question of how long a patient

needs to be treated and what is the optimal drug dose to achieve the desired capillary lactate concentration. To attain our goal, we consider a minimization problem with a conventional cost functional associated with the ODE system aforementioned. First, we show the existence of a unique regular non-negative solution of our ODE system, then we define the control-to-state operator and show that it is continuous on the corresponding topology. Next, we show the existence of a solution to our minimization problem under given constraints. Then we study the existence of a unique derivative of the control-to-state operator and its Fréchet differentiability. We then show the Fréchet differentiability of the cost functional with respect to time and control. Moreover, we define the adjoint system by Lagrange's principle, simplify the first-order necessary optimality condition, and finally, we emphasize the choice of the control term with numerical simulations.

Keywords. Tumor growth; Allen-Cahn model; Altered metabolism; glioma treatment; lactate dehydrogenase; reaction-diffusion equation; first-order necessary optimality conditions.

Résumé



“Science is facts; just as houses are made of stones, so is science made of facts; but a pile of stones is not a house and a collection of facts is not necessarily science. ”

Jules Henri Poincare

Cette thèse aborde différentes approches thérapeutiques pour les gliomes, soit directement, soit au niveau du métabolisme en utilisant la théorie du contrôle optimal. En effet, nous considérons tout d'abord un système couplant une équation d'Allen-Cahn modélisant la croissance tumorale, avec une équation d'évolution pour la dynamique des nutriments. Le traitement des gliomes est considéré en termes de contrôle qui représente la concentration du médicament cytotoxique à un taux donné. Notre objectif dans cette partie est de choisir le contrôle et le temps de traitement de telle sorte que la croissance tumorale correspondante et sa distribution finale soient la meilleure approximation possible des valeurs désirées. Notre première étape est donc consacrée à l'étude du caractère bien posé de notre système d'état, ce qui nous permet de définir l'opérateur contrôle-état qui est continu. Ensuite, nous montrons l'existence d'un minimiseur de notre fonction de coût, où notre opérateur contrôle-état est différentiable au sens de Fréchet. Ensuite, notre fonctionnelle de coût est également différentiable au sens de Fréchet par rapport au temps et au contrôle. Enfin, pour simplifier la condition d'optimalité nécessaire du premier ordre, nous considérons un système adjoint utilisant le principe de Lagrange pour lequel ce système a une solution régulière. D'autre part, nous savons que la progression et la malignité des gliomes sont liées au métabolisme, en particulier au déchet de glycolyse et de lactate. Ainsi, nous soulignons d'abord le fait que plus le gliome produit de lactate, plus il transporte l'excès dans le capillaire pour soutenir la prolifération, les métastases et la malignité. Par conséquent, nous considérons l'équation d'état comme un problème parabolique modélisant la dynamique du lactate intracellulaire. Notre premier défi consiste à ajouter un contrôle biologiquement pertinent qui agit comme une concentration d'un certain médicament pour inhiber la production de lactate. Puisque la dose de médicament et le temps ne doivent pas dépasser ou descendre en dessous d'un certain seuil dans le traitement du cancer, nous essayons de choisir le meilleur contrôle au moment le plus opportun afin que la concentration de lactate intracellulaire correspondante soit aussi proche que possible de notre évolution souhaitée et de la distribution finale du lactate. Cependant, comme nous l'avons dit plus haut, la cellule retire l'excès de lactate en le transportant à travers la membrane plasmique de la cellule dans le capillaire

pour maintenir sa prolifération. Ceci nous a inspiré à cibler le transport du lactate en utilisant un inhibiteur de MCTs qui agit comme un terme de contrôle dans un système couplé de type EDO qui modélise la dynamique du lactate dans les domaines intracellulaire et capillaire. Nous abordons la question de savoir combien de temps un patient doit être traité et quelle est la dose optimale de médicament pour atteindre la concentration de lactate capillaire souhaitée. Pour atteindre notre objectif, nous considérons un problème de minimisation avec une fonction de coût conventionnelle associée au système d'EDO susmentionné. Tout d'abord, nous montrons l'existence d'une solution régulière unique et non négative de notre système EDO, puis nous définissons l'opérateur contrôle-état et montrons qu'il est continu sur la topologie correspondante. Puis, nous montrons l'existence d'une solution à notre problème de minimisation sous des contraintes données. Nous étudions ensuite l'existence d'une dérivée unique de l'opérateur contrôle-état et sa différentiabilité de Fréchet. Nous montrons ensuite la différentiabilité de Fréchet de la fonctionnelle de coût par rapport au temps et au contrôle. De plus, nous définissons le système adjoint par le principe de Lagrange, nous simplifions la condition d'optimalité nécessaire au premier ordre, et enfin, nous mettons en évidence le choix du terme de contrôle par des simulations numériques.

Mots Clès. Croissance tumorale; modèle d'Allen-Cahn; métabolisme altéré; traitement du gliome; lactate déshydrogénase; équation de réaction-diffusion; conditions d'optimalité nécessaires de premier ordre.

Chapter 1

Introduction

"When you chase a dream, you learn about yourself. You learn your capabilities and limitations, and the value of hard work and persistence."

Nicholas Sparks

After cardiovascular diseases, cancer ranks second in the list of deadly diseases, according to the WHO [40]. A fact that attracts scientists from different fields to study its aspects to develop the best therapies. So, in this work, we are interested in studying some optimal control problems that govern glioma therapy directly at the cellular level or indirectly at the metabolic level. The purpose of this chapter is to familiarize the reader with some of the concepts used in the rest of our work, to display some results on some problems concerning tumor growth and treatment, and finally to provide a summary of our main results.

1.1 Biological background

1.1.1 The origin and development of gliomas

Cancer occurs due to genetic mutations in cells. In turn, these mutations can change the number or activity of proteins involved in regulating cell life. Important clues about how mutated genes cause cancer come from studying the role of their counterparts in normal cells. A scientist described a molecular "bucket brigades" that transmits growth-stimulating signals from outside the cell to the depths of the cell (see [77]). When cells secrete proteins called growth factors, the growth signal between cells begins. These proteins pass through space between cells and bind to specific receptors. The signal is transmitted to a series of other proteins, and finally to the nucleus, which reminds the cell to complete its growth cycle. By overstimulating the growth-promoting mechanism and bypassing or ignoring the normal braking system (apoptosis, the programmed cell death), cells may become malignant. The braking system, like the growth signal system, works with the molecular "bucket brigades", in this case, it sends a signal that growth should stop. Another important discovery is the cell clock, which is a target in the nucleus that promotes or inhibits growth (see [71]).

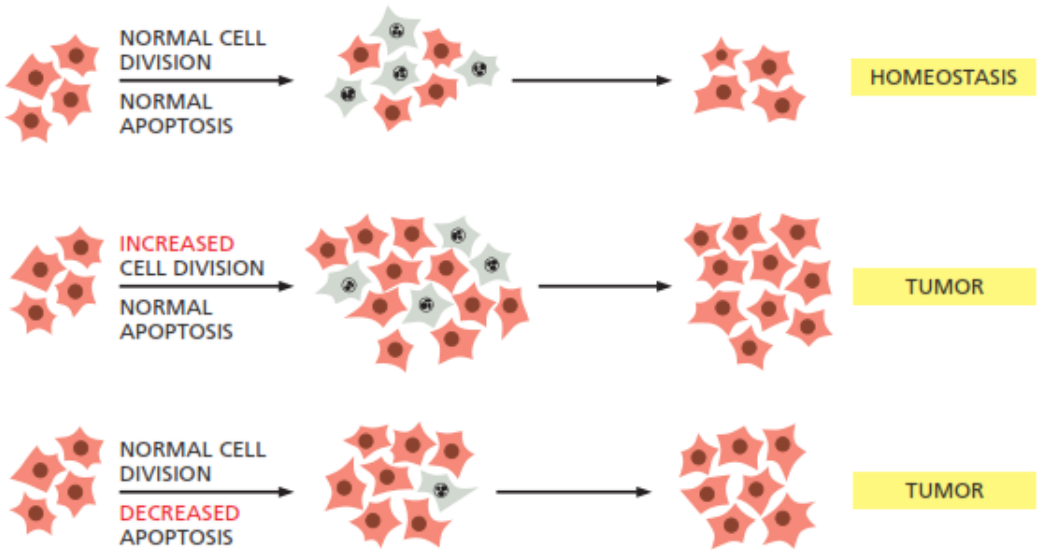


Figure 1.1 – Both increased cell division and decreased apoptosis can contribute to tumorigenesis (see [1])

Epigenetic continuous changes that result from the adjustment of chromatic structure without alteration of the cell's DNA sequence, also lead to cancer. But somatic mutations that change DNA sequence appear to be an essential and universal characteristic, and in this sense cancer is a genetic disease (see [1]).

Most cancers have characteristics that reflect their origin. For example, gliomas are cancers that originate from glial or neuroglial cells. Although they are not neurons, they play an important role in defining synaptic contacts and maintaining the signaling ability of neurons (see [66]). Gliomas are the most common tumors of the CNS, particularly the brain. There are numerous classification systems in use, Gliomas are classified on the basis of cell origin, grade, and location. According to cell type, they are divided into ependymomas, originating from ependymal cells, astrocytomas, originating from astrocytes, oligodendrogliomas, originating from oligodendrocytes, and mixed gliomas, originating from different glial cells. According to their grade, they are classified as low-grade and high-grade gliomas on the basis of increased cell density, nuclear atypias, mitosis, vascular proliferation, and necrosis. Gliomas classified by location are sorted based on whether they are located above or below a membrane in the brain called the tentorium, which separates the cerebrum (above) from the cerebellum (below) (see [51]).

In this thesis, we are interested in the study of cancer cells in particular, wherever cancer is mentioned is regarded as gliomas.

1.1.2 Modes of treatment of glioms

Current cancer treatments include surgery, targeted therapy, immunotherapy (boosting the immune system), radiotherapy (using radiation to kill cancer cells), and chemotherapy (using drugs to kill cancer cells). The latter three treatments are usually given in cycles. In this subsection, we present two types of treatment that we have used in our models.

– One of the most popular cancer treatments is chemotherapy. Tumor cells duplicate

more than normal cells, and most therapies target proliferating cell populations (and that's one reason why therapies also hit healthy tissue with rapid renewal rates). To accomplish this task, chemotherapies can target specific proteins that are present in a phase of the cell cycle, i.e., the various stages a cell must go through to duplicate. For example, they may target cyclins (proteins that control the transition between phases) to keep cells in the G1 phase so they stay quiescent; these drugs are called cytostatic drugs. It is more common to target the S or G2 (synthesis and repair) phases when DNA duplicates. This can lead to irreversible damage and subsequent apoptosis of the cells; these are cytotoxic drugs (see [65]).

Since chemotherapy may cause the damage of healthy cells, the treatment is applied in cycles where a cycle is a period of treatment followed by a longer period of rest to allow the patient's body to produce new healthy cells. The goal of these treatments is to shrink the tumor to a more manageable size so that surgery can be performed (see [42]).

So, usually for a final treatment time $T > 0$, $\tau \in [0, T]$ represents the treatment time of one cycle.

– Targeted drugs refer to drugs that specifically target, bind to, and act on cancer-causing sites at the cellular or molecular level. These targets may be molecules that play key roles in tumorigenesis and regulate signal transduction pathways. Drugs that target these molecules can specifically kill tumor cells without affecting the normal tissue cells around the tumor, thereby treating the tumor. Compared to chemotherapy, targeted drugs have the advantage that they can be selected based on the characteristics of different patients and do not target normal, proliferating cells, but they are less broadly applicable than chemotherapy(see [76]). Such therapies are used in Chapters 3 and 4, as inhibitors for lactate production and transport.

1.1.3 Lactate dehydrogenase enzyme

In this subsection we will introduce the enzyme LDH, which is crucial to the mechanism of lactate production and will be mentioned later in the context of this thesis as a therapeutic target of glioma.

Lactate dehydrogenase LDH is a tetrameric enzyme that belongs to the family of 2-hydroxy acid oxidoreductase, it increases the rate of the simultaneous inter-conversion of pyruvate to lactate and nicotinamide adenine dinucleotide NADH to NAD^+.

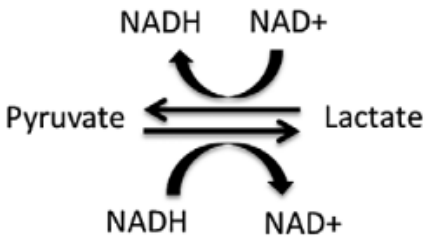


Figure 1.2 – The reversible reaction of the catalysis of pyruvate and NADH to lactate and NAD^+ by LDH enzyme (see [75]).

LDH is formed of four genes: LDHA, LDHB, LDHC, and LDHD. The first three genes use or produce lactate, mainly LDHA is also known as the M subunit as it is predominantly found in skeletal muscle, and LDHB is also known as the H subunit as it is predominantly found in the heart (see [75]). Five isoenzymes can be derived from M and H subunits: LDH-1, LDH-2, LDH-3, LDH-4, and LDH-5.

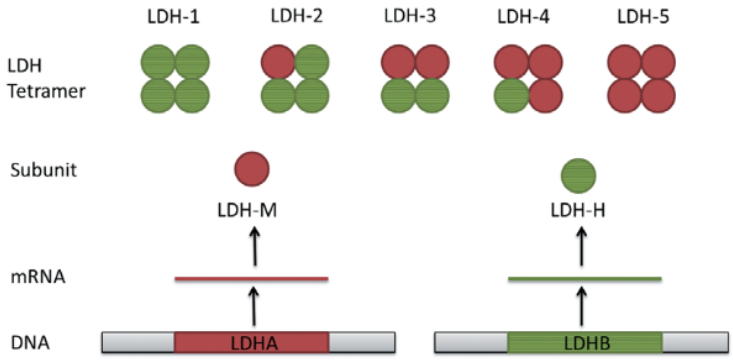


Figure 1.3 – The LDH isoenzymes are composed of different ratios of LDH-M and LDH-H subunits, transcribed from LDHA and LDHB, respectively, taken from [75].

LDHA has a higher affinity for pyruvate, and thus preferentially converting pyruvate to lactate and NADH to NAD^+, however, LDHB has a higher affinity to lactate and converts lactate to pyruvate and NAD^+ to NADH.

The inhibition of LDHA is a safe therapeutic approach for cancer, particularly, Gossypol, which is a natural product found in cottonseed, has been also used as an antimalarial, works on blocking the binding of NADH, it is now used in phase I and phase II clinical oncology trials (see [32]).

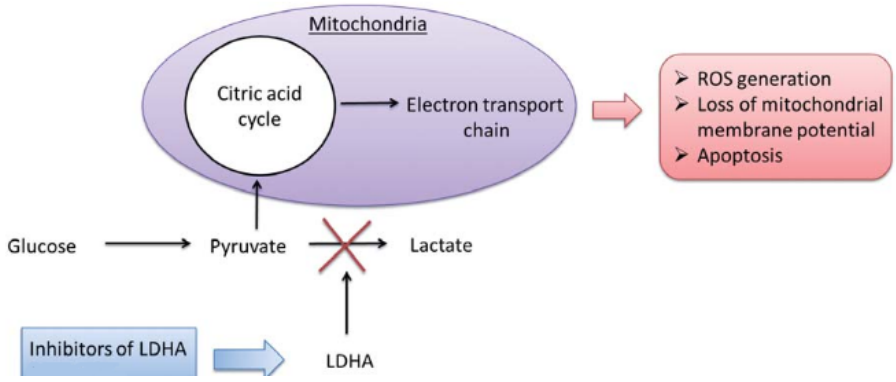


Figure 1.4 – LDHA inhibition forces cancer cells to use oxidative phosphorylation and thus pyruvate enters the mitochondria which leads to reactive oxygen species (ROS) generation and apoptosis (see [75]).

1.1.4 Metabolism of cancer cells

This subsection is devoted to distinguishing the metabolism of cancer cells from normal cells. We present the mechanism of this metabolism in the presence of some enzymes, in particular LDH, which contributes to lactate formation.

In normal cells, pyruvate is generated from glucose by glycolysis and enters the citric acid

cycle in mitochondria, where it is oxidatively decarboxylated to form acetyl-CoA, which is used to fuel oxidative phosphorylation, theoretically generating 36 net GLSATP per molecule of glucose. However, when the oxygen concentration is infrequent, cells become unable to undergo OXPHOS to produce ATP so glycolysis becomes the main generator of ATP, producing 2ATP per one molecule of glucose. Glyceraldehyde phosphate dehydrogenase (GAPDH) uses NAD^+ to convert glyceraldehyde 3-phosphate (GADP) to D-1,3bisphosphoglycerate (1,3BPG) so NAD^+ is needed to enable the sixth step of glycolysis. Usually, NAD^+ is regenerated through OXPHOS by electron transport chain, so when oxygen is scarce, NAD^+ is regenerated from NADH by LDHA to maintain glycolysis which in turn produce lactate from pyruvate, in a process called anaerobic glycolysis (see [75]).

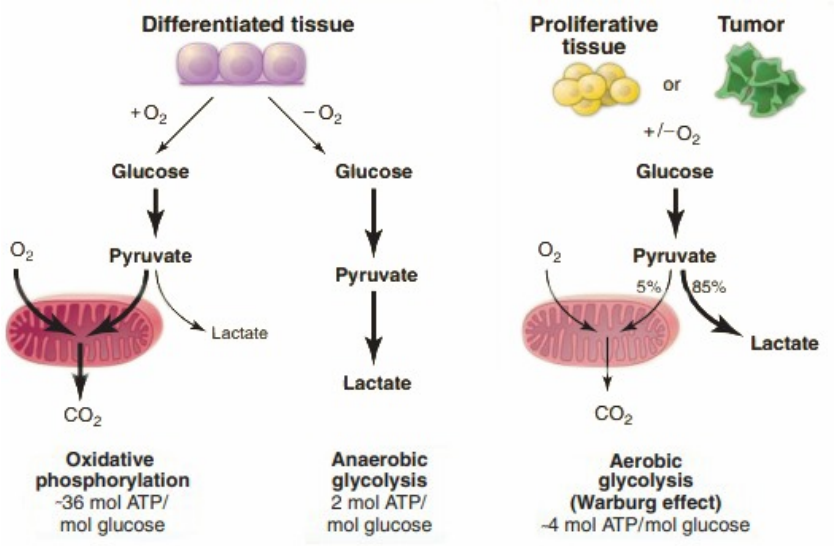


Figure 1.5 – Schematic representation of the differences between oxidative phosphorylation, anaerobic glycolysis, and aerobic glycolysis (see [52]).

In cancer cells, even in the presence of oxygen, cells undergo aerobic glycolysis or Warburg effect, which is observed by Otto Warburg in the 1920's. Cancer cells uptake large amounts of glucose to generate sufficient ATP to satisfy the metabolic needs, pyruvate is converted into lactate utilizing LDHA enzyme.

By contrast, LDHB converts lactate into pyruvate, which makes lactate an energy source for many cells. Also, aerobic cells may take lactate through MCT1, converts it to pyruvate which enters TCA cycle to fuel cells, so also the inhibition of MCT1 leads to the death of anaerobic cancer cells and is good for cancer therapy (see [70]).

1.1.5 Monocarboxylate transporters

This subsection presents the mechanism of monocarboxylate transporters as a means of transferring a substance across the cell membrane. In particular, these transporters play an important role in the transport of lactate from the cell to the capillary and vice versa.

Monocarboxylates such as pyruvate, lactate, and the ketone bodies (acetoacetate and β-hydroxybutyrate) play an essential role in carbohydrate, lipid, and amino acid metabolisms

and must be transported rapidly across the plasma membrane of cells. This transport is mediated by proton-linked monocarboxylate transporters (MCTs, 1-4) (see [49]).

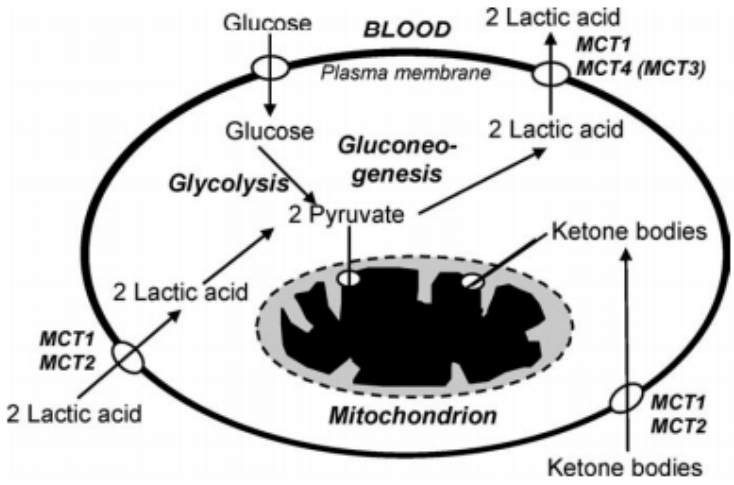


Figure 1.6 – The role of MCTs in metabolism (see [49]).

MCTs regulate efflux and influx of lactate across the plasma membrane, high concentrations of lactate resulting from increased glycolysis lead to acidification of the intracellular milieu which is lethal to the cell, so this is prevented by the cotransport of both protons and lactate out of cells by MCTs (see [70]). The transport mechanism of MCTs could be described as an electroneutral $1H^{+}$monocarboxylate^{-} cotransport, in other words, monocarboxylate transport via MCT4 is accompanied by the transport of H^{+} across the plasma membrane. In agreement with this mechanism, lactate transport was pH-dependent, increasing with decreasing pH.

Due to its role in regulating intracellular PH and thus avoiding the deleterious of the cell, MCT inhibition is a cancer therapeutic approach, lactate transport was blocked by several inhibitors such as p-chloromercuribenzoesulphonic acid and DIDS (see [31]).

Targeting MCTs leads to lactate accumulation in the intracellular domain which induces apoptosis or inhibit lactate uptake by aerobic cells which reduces tumor angiogenesis, metastasis, the deleterious effects of extracellular lactate on the immune cells and invasion (see [70]).

1.1.6 Michaelis-Menten Kinetics

Lactate cannot pass from the intracellular domain to capillary and vice versa by passive diffusion, a faster transport rate with facilitated diffusion is fulfilled through MCTs, a process that can be described employing Michaelis-Menten kinetics. More precisely, this expression describes what happens on the membrane of a cell, as an example (see [35]), knowing that water-soluble molecules, mostly, cannot pass through the hydrophobic environment of the cell membrane directly and must be carried by some means. Hence, molecular receptors embedded in the bacterial cell membrane are involved in "capturing" these polar molecules in a loose complex, carrying them across the membrane barrier, and releasing them to the cell's interior.

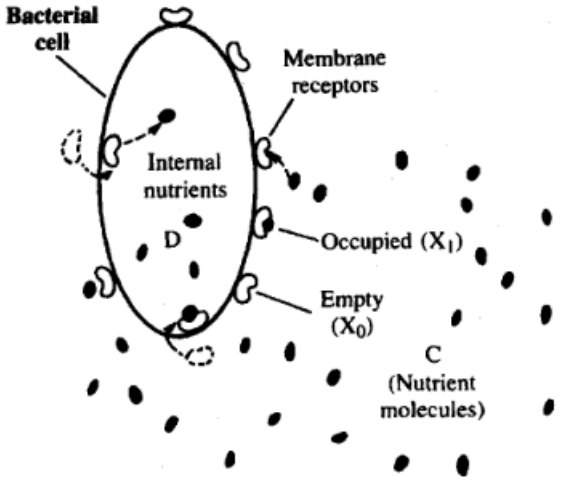


Figure 1.7 – Passage of nutrient molecules into the cell (see [35]).

The directions and rates of reactions are given by

$$C + X_0 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} X_1 \xrightarrow{k_2} P + X_0.$$

C denotes external nutrient molecule, X_0, an unoccupied receptor, X_1, a nutrient-receptor complex, P, a nutrient molecule successfully captured by cell. Moreover, k_1, k_{-1} and k_2 represent the rates of reactions.

The rate of formation of P, the rate at which nutrient-receptor complex, X_1, dissociates to form product is based upon the rate constant k_2 and the concentration of X_1, as follows

$$v_0 = \frac{d[P]}{dt} = k_2 \times [X_1].$$

But, we have

$$[X_1] = \frac{[E]_r[C]}{K_m + [C]},$$

where $[E]_r$ is equal to the sum of concentrations of unoccupied receptor and that of nutrient-receptor complex, in addition, we have

$$K_m = \frac{k_{-1} + k_2}{k_1}.$$

The term $k_2[E]_r$ represents the maximum velocity, so finally, we have

$$v_0 = \frac{V_{\max}[C]}{K_m + [C]}.$$

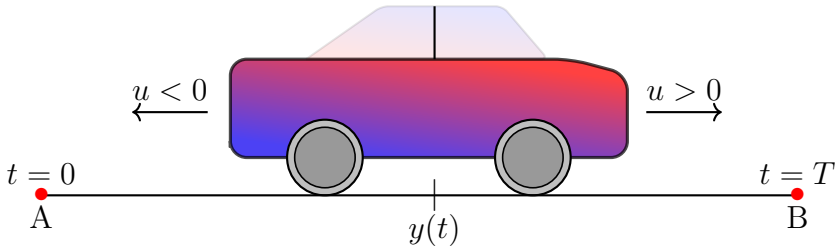
1.2 An overview on optimal control theory

This section is divided into two parts. The first part introduces the theory of optimal control through an example. The second part, however, is intended to remind the reader of some concepts used in the study of optimal control problems.

1.2.1 General concept of optimal control theory

In control theory, one is interested in controlling the state of a system by using controls. The dynamics of the system is the way in which the state changes under the influence of the controls. In addition to the system and the state, two other concepts are needed in control theory, namely the constraints on our controls and the objective or target state(s) of our system.

We consider the vehicle in the figure below, as an example of optimal control concept.



At time $t = 0$, the vehicle is at position A and moves along a straight line to reach point B at time $T > 0$. Suppose that the vehicle of mass m is accelerated in either direction by a variable force $u(t)$, so that it takes positive values when moving to the right and negative values when moving to the left, so that the maximum value it can reach in both directions is 1.

Taking $y(t)$ as the position of the vehicle at time t, y_0 and y_T as the positions corresponding to points A and B, respectively, Newton's law demonstrates that.

$$my''(t) = u(t).$$

Thus, our control problem is: minimize $T > 0$, associated with the following constraints.

$$\begin{aligned} my''(t) &= u(t), \\ y(0) = y_0, &\quad y'(0) = 0, \\ y(T) = y_T, &\quad y'(T) = 0, \\ |u(t)| \leq 1, &\quad \forall\, t \in [0, T]. \end{aligned}$$

Here the cost functional to be minimized is the time $T > 0$ needed for the travel. An initial value problem to determine the state $y(t)$ of the system influenced by the control $u(t)$, under the constraints $y(T) = y_T$, $y'(T) = 0$, $|u(t)| \leq 1$, $\forall\, t \in [0, T]$ (see [60, 73]).

1.2.2 Some preliminaries

We consider in this subsection the following optimal control problem for nonstationary heat source

$$\begin{aligned} \min J(y, u) := &\frac{1}{2} \iint_{\Sigma} |y(x,t) - y_\Sigma|^2 dx\, dt + \frac{1}{2} \int_{\Gamma} |y(x,T) - y_d|^2 dx\, dt \\ &+ \frac{\lambda}{2} \iint_{Q} |u(x,t)|^2 dx\, dt, \end{aligned} \tag{1.1}$$

subject to

$$\begin{aligned} y_t - \Delta y &= \beta u \quad \text{in } Q := [0,T] \times \Omega, \\ \partial_\nu y &= 0 \qquad \text{on } \Sigma := [0,T] \times \Gamma, \\ y(0,x) &= 0 \qquad\qquad \text{in } \Omega, \end{aligned} \tag{1.2}$$

and

$$u_a(x,t) \leq u(x,t) \leq u_b(x,t) \quad \text{for a.e. } (x,t) \in Q.$$

And the set of admissible controls is defined by

$$\mathcal{U}_{ad} = \{u \in L^2(Q) : u_a(x,t) \leq u(x,t) \leq u_b(x,t) \quad \text{for a.e. } (x,t) \in Q\}.$$

The variable $y(x,t)$ represents the temperature at position $x \in \Omega$ at time $t \in [0,T]$, u represents a variable heat source that serves as a control. J is the objective functional to be minimized, i.e. the objective is to achieve the best possible approximation to the desired evolution boundary temperature y_Σ and a final boundary distribution temperature y_d, in addition to a minimum cost due to the effect of the control given by the term

$$\frac{\lambda}{2} \iint_Q |u(x,t)|^2 \, dx \, dt,$$

where $\lambda \geq 0$ can be viewed as a measure of the energy cost needed to implement the control u, and the factor $\frac{1}{2}$ that appears before the integrals does not affect the solution of the problem. It is introduced only for sake of convenience and it cancels out later when differentiating.

The study of such problems begins in showing that the state system given by the boundary value problem (1.2) admits a unique solution $y(x,t)$ for some control $u(x,t)$ in a suitable functional space.

Then, the existence of a solution for (1.1) is investigated, i.e. the existence of some optimal control u^* associated to optimal state y^*, which follows again from the continuity of the control- to- state operator $\mathcal{S}$, for which to any control there is a unique state.

First order necessary optimality condition. The first order necessary optimality condition satisfies

$$D_u J(y^*, u^*)(u - u^*) \geq 0, \tag{1.3}$$

but we already have that $\mathcal{S}(u) = y$, then (1.3) verifies

$$D_u J(\mathcal{S}(u^*), u^*)(u - u^*) \geq 0. \tag{1.4}$$

So, for (1.4) to be verified, we need to show that the control- to - state operator $\mathcal{S}$ is Fréchet differentiable. Then we show that the functional J is also Fréchet differentiable with respect to time and control, respectively.

One way to simplify the first order necessary optimality condition is by applying $\mathcal{L}$agrangian technique, which may also help in having an idea about the form of the optimality condition, so the $\mathcal{L}$agrangian function $\mathcal{L}$ associated with the optimal control problem (1.1)-(1.2) satisfies

$$\mathcal{L} = J(y,u) - \iint_Q (y_t - \Delta y - \beta u) p \, dx \, dt.$$

The adjoint system is given by

$$D_y\mathcal{L}(y^*, u^*, p)y = 0 \quad \text{for all } y \text{ with } y(0) = 0.$$

Simultaneously, one can expect the following necessary optimality condition

$$D_u\mathcal{L}(y^*, u^*, p)(u - u^*) \geq 0 \quad \text{for all } u \in \mathcal{U}_{ad}.$$

1.3 Modeling

In this part, we are concerned with some mathematical models that introduce our problems in Chapters 2, 3, and 4.

1.3.1 Optimal control of tumor growth in the presence of nutriennts

Starting with modeling the behavior of a cell or a living organism, first, we think of its birth and death, given by the Lotka-Voltera model (see [65])

$$\begin{cases} \dfrac{dN(t)}{dt} = N(t)\left(b(t) - d(t)\right), \\ N(0) = N_0, \end{cases}$$

where $N(t)$ denotes the total population density of cells, $b(t)$ and $d(t)$ represent the birth and death rates of the cell, respectively.

Since the birth and death rates depend on the availability of nutrients, then b and d are usually taken as a nonlinear function $R(N(t))$, leading to the equation

$$\frac{dN(t)}{dt} = N(t)R(N(t)),$$

many nonlinearities could be taken, such as logistic and Gompertz models.

The mathematical theory of diffusion is based on the hypothesis that the rate of transfer of diffusing substance through unit area of a section is proportional to the concentration gradient measured normal to the section, i.e.

$$F = -D\,\frac{\partial C}{\partial x},$$

where F is the rate of transfer per unit area of section, C the concentration of diffusing substance, x the space coordinate measured normal to the section, and D is called the diffusion coefficient. In some cases, D can reasonably be taken as constant such as in dilute solutions, however in other cases not (see [59]). As an example, tumor cells invade white matter faster than grey matter, so D changes depending on the position of the tumor x (see [44]).

We know that the change in time of the concentration of diffusing substance enclosed by the surface equals to the mass that traverses the surface, so we have,

$$\frac{\partial C}{\partial t} = divF.$$

Consequently,

$$\frac{\partial C}{\partial t} = D\,\frac{\partial^2 C}{\partial x^2}.$$

So, the reaction diffusion equation is given as follows

$$u_t - D\Delta u = f(u),$$

where $D\Delta u$ denotes the random motion with coefficient D, and $f(u)$ represents the reaction term which may count for the proliferation or death of the cells.

On the other hand, the Allen-Cahn equation (see [13])

$$\begin{aligned} \frac{\partial u}{\partial t} - \epsilon^2\Delta u + f(u) = 0, \qquad & \text{in } \Omega \times (0,T), \\ \partial_\nu u = 0, \qquad & \text{on } \partial\Omega \times (0,T), \end{aligned} \tag{1.5}$$

is important in materials science, where Ω represents the volume occupied by the material, u is an order parameter corresponding, for example, to the ordering of atoms per unit cell in a crystal lattice, and the function f is the derivative of a double-well potential F whose wells correspond to the phases of the material is given by

$$F(s) = \frac{1}{4}\left(s^2 - 1\right)^2. \tag{1.6}$$

Equation (1.5) is based on a free energy (see [48])

$$E(u) = \frac{\epsilon^2}{2}|\nabla u|^2 + f(u),$$

The standard derivation of the Ginzburg-Landau or Allen-Cahn equation is based on considering the total free energy of the region Ω occupied by the material

$$\Psi(u) = \int_\Omega E(u)dx.$$

The term $f(u)$ represents the uniform energy of the order parameter u, and the term $\frac{\epsilon^2}{2}|\nabla u|^2$ represent the energy of the interface. The formal variation of $\Psi(u)$ with respect to fields u that vanish on $\partial\Omega$ is given by

$$\delta\Psi(u) = \int_\Omega \left(f'(u)\delta u + \epsilon\nabla u\cdot\delta\nabla u\right)dx = \int_\Omega \left(f'(u) + \epsilon\Delta u\right)\delta u dx,$$

and give the following expression

$$\frac{\delta\Psi(u)}{\delta u} = f'(u) + \epsilon\Delta u,$$

and hence the Allen-Cahn equation. Such a model prohibits discontinuities of u and the interface is represented by a thin phase-to-phase transition layer possessing small thickness, hence the term diffuse interface model(as opposed to sharp interface models models, which is found by making ϵ tends to zero). If the potential is defined by (1.6), the typical width of an interface is ϵ.

In the view of tumor growth, modeling must take into account the proliferation of the cells that depends on the nutrient uptake and apoptosis, the programmed cell death. More importantly, what we are going to model is the cell density of two phases, a healthy phase, and a tumor phase.

As mentioned earlier, a cancer cell arises from a normal one due to some genetic mutations. Therefore, we will consider a phase-field model that replaces the boundary conditions at the interface with a partial differential equation for the evolution of an auxiliary field that takes the role of an order parameter. This phase-field takes two different values $+1$ and -1 in each of the phases, with a smooth change between the two values in the zone around the interface, which is then diffuse with finite width. A discrete location of the interface can be defined as the set of all points at which the phase-field takes a certain value (e.g. 0).

Moreover, like normal tissues, cancer cells require nutrients to stay alive and proliferate. When modeling tumor growth, it is therefore common to combine the tumor growth equation with an equation that models the dynamics of nutrients.

So, let $\varphi = \varphi_1 - \varphi_2$ be the phase field representing the difference between tumor and healthy phases, $\varphi = -1$ denotes healthy phase and $\varphi = 1$ denotes tumor phase, and let σ be the concentration of nutrients, we have

$$\partial_t \varphi - B\Delta\varphi + f(\varphi) = (\mathcal{P}\sigma - \mathcal{A} - \alpha u)h(\varphi), \quad \text{in } \Omega \times (0,T) =: Q, \tag{1.7}$$

where B the diffusion coefficient, depends on tumor mobility and interface width, h is an interpolation function where $h(-1) = 0$ and $h(1) = 1$, $\mathcal{P}\sigma h(\varphi)$ and $\mathcal{A}h(\varphi)$ model the proliferation and apoptosis, programmed cell death, of tumor cells at rates $\mathcal{P}$ and $\mathcal{A}$, respectively.

Many therapeutic concepts are used in cancer treatments, the direct ones may be done through cytostatic drugs which block proliferation or cytotoxic drugs, the one we are concerned about, which kills proliferative cells. So, here $\alpha u h(\varphi)$ models the elimination of proliferative tumor cells through a cytotoxic drug at rate α.

Note that when the right hand side of (1.7) is null, we have an Allen-Cahn equation of the form

$$\partial_t \varphi - B\Delta\varphi + f(\varphi) = 0 \qquad \text{in } \Omega \times (0,T),$$

$$\partial_\nu \varphi = 0 \qquad \text{on } \partial\Omega \times (0,T),$$

where

$$f(\varphi) = \varphi^3 - \varphi.$$

One of the main nutrients consumed by tumor cells is lactate (see subsection 1.1.3 for more details), when the concentration of lactate is high, it is transported to the capillaries by MCTs, however, when the cell lacks nutrient, it uptakes lactate from capillaries in a process called lactate shuttle, employing MCT1. Taking σ as the concentration of nutrients and σ_s the nutrient concentration in a pre-existing vasculature, then $\beta\,(\sigma_s - \sigma)$ refers to nutrient delivery from blood vessels at rate β, when $\sigma_s > \sigma$ and nutrient removal from domain when $\sigma_s < \sigma$. On the other hand, the nutrient dynamics is modeled by the following reaction diffusion equation

$$\partial_t \sigma = \Delta\sigma - \mathcal{C}\sigma h(\varphi) + \beta(\sigma_s - \sigma), \quad \text{in } Q,$$

where $\mathcal{C}h(\varphi)$ is the nutrient consumption by the proliferative cells.
Since both cells and nutrients are not supposed to flux through domain we consider Neumann boundary conditions so that

$$\partial_\nu \varphi = \partial_\nu \sigma = 0 \quad \text{on } \partial\Omega \times (0,T),$$

where ν is the outward normal on the boundary $\partial\Omega$.

Moreover, φ_0 and σ_0 are the initial phase difference and nutrient concentration at $x \in \Omega$.

Hence we have the following system coupling an Allen-Cahn equation and a reaction diffusion equation

$$\partial_t \varphi - B\Delta\varphi + f(\varphi) = (\mathcal{P}\sigma - \mathcal{A} - \alpha u)h(\varphi), \quad \text{in} \quad \Omega \times (0,T) =: Q, \tag{1.8}$$

$$\partial_t \sigma = \Delta\sigma - \mathcal{C}\sigma h(\varphi) + \beta(\sigma_s - \sigma), \quad \text{in} \quad Q, \tag{1.9}$$

$$\partial_\nu \varphi = \partial_\nu \sigma = 0, \quad \text{on} \quad \Gamma \times (0,T), \tag{1.10}$$

$$\varphi(0) = \varphi_0, \ \sigma(0) = \sigma_0, \quad \text{in} \quad \Omega. \tag{1.11}$$

We aim to control tumor growth through treatment with cytotoxic drugs administered to patients in several cycles, each followed by a long rest period during which the healthy cells can recover. In this way, we aim to minimize the growth of the tumor in Q and its final distribution in Ω. Considering that the duration of a cycle in which the patient undergoes treatment is rigorous for the patient's health, we consider minimizing the treatment time. Finally, a low dose of treatment does not affect the tumor and a high dose may cause the tumor to adapt to the therapy and destroy the healthy cells, so we also minimize the dosage of the drugs.

We consider for positive constants r, β_u, β_T, and nonnegative constants $\beta_Q, \beta_\Omega, \beta_S$ the functional to be minimized

$$\begin{aligned}\mathcal{J}_r(\varphi,u,\tau) =& \frac{\beta_Q}{2}\int_0^\tau \int_\Omega |\varphi - \varphi_Q|^2 dx\,dt + \frac{\beta_\Omega}{2}\frac{1}{r}\int_{\tau-r}^\tau \int_\Omega |\varphi - \varphi_\Omega|^2 dx\,dt \\ &+ \frac{\beta_S}{2}\frac{1}{r}\int_{\tau-r}^\tau \int_\Omega 1 + \varphi(x) dx\,dt + \frac{\beta_u}{2}\int_0^T \int_\Omega |u|^2 dx\,dt + \beta_T \tau.\end{aligned} \tag{1.12}$$

Where φ_Q represents a desired evolution for the tumor cells while φ_Ω represents a desired final distribution. The first two terms of $\mathcal{J}_r$ are of standard tracking type is often considered in the literature of parabolic optimal control (see [73]) and the third term of $\mathcal{J}_r$ measures the size of the tumor at the end of the treatment. The fourth term penalizes large concentrations of the cytotoxic drugs, and the fifth term of $\mathcal{J}_r$ penalizes long treatment times (see [43]). So, the main problem becomes

$$\text{minimize } \mathcal{J}_r(\varphi,u,\tau) \text{ subject to } (1.8)-(1.11),\ u \in \mathcal{U}_{ad},\ \tau \in [r,T].$$

1.3.2 Modeling the control on lactate transport

Even in the presence of ample oxygen, tumor cells predominantly rely on glycolysis to produce energy in a phenomenon called the Warburg effect or aerobic glycolysis.

Based on our interest in applying therapeutic strategies in the metabolic state that target

lactate production and transport, we will adopt a transport model (see [4] and [47]) that describes lactate flow between cell and blood capillary, so in this model, it is interesting to consider the elements that are important in lactate kinetics.

- The production of lactate by the cells due to glycolysis, denoted by J_1.
- Exchange through BBB denoted J_2.
- J_3 denotes the sum of lactate consumption by mitochondria after catalysis by LDH-B to pyruvate, and the diffusion to adjacent regions.
- Cerebral blood flow denoted by CBF.
- PH variations.

LAC_i and LAC_c denote intracellular and capillary lactate concentrations, respectively. LAC_a and LAC_v are the arterial and venous lactate concentrations as well. Furthermore, V_i and V_c are respectively the dimensionless capillary and intracellular volume fractions.

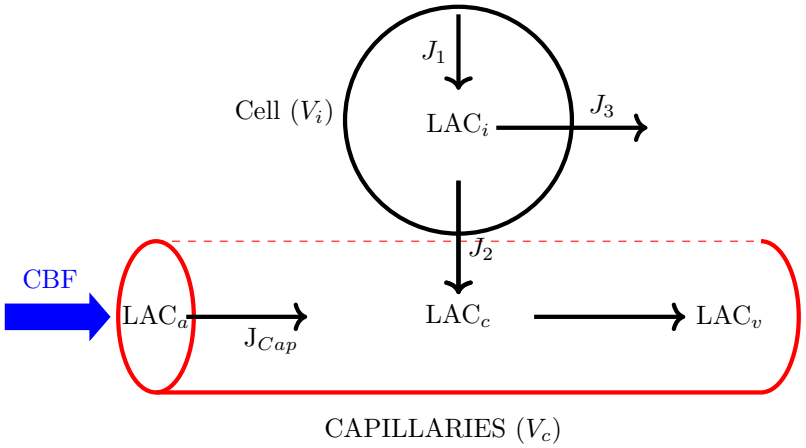


Figure 1.8 – A scheme that describes the lactate flow from cell towards capillary, taken from [47]

The intracellular and capillary metabolic balance equations lead to the following ODE system

$$\begin{cases} V_i \dfrac{dLAC_i}{dt} = J_1 - J_2 - J_3, \\ V_c \dfrac{dLAC_c}{dt} = J_{cap} + J_2. \end{cases} \tag{1.13}$$

The contribution of CBF to the variation of capillary lactate concentration (see [74]), is given by

$$J_{cap}(t) = CBF(t)\,(LAC_a(t) - LAC_v(t))\,,$$

but

$$LAC_v(t) = 2LAC_c(t) - LAC_a(t),$$

then

$$J_{cap}(t) = 2CBF(t)\,(LAC_a(t) - LAC_c(t))\,.$$

For simplicity, $F(t) = 2CBF(t)$, and the arterial lactate concentration is considered constant, so $LAC_a(t) = L$, then $\forall\, t \in \mathbb{R}^+$, we have

$$J_{cap}(t) = F(t)\,(L - Lac_c(t))\,.$$

Moreover, set $J(t, LAC_i(t)) = J_1 - J_2$, which can be viewed as a forcing function. J is non-negative since the cell is seen as it cannot export more lactate than it has.

Finally, the flux of lactate through BBB, J_2, which in turn is affected by intracellular and capillary H^+ concentrations, takes the following form, which is taken from a more general transport formula for cotransport, the Michaelis-Menten Kinetics, discussed in Subsection 1.1.6

$$J_2 = \kappa \left(\frac{Lac_i H_i^+}{K_H + Lac_i H_i^+} - \frac{Lac_c H_c^+}{K_H + Lac_c H_c^+} \right),$$

K_H, is a constant of type Michaelis-Menten, expressed in mM×M, κ is the maximum transport rate, depending on the total area of the capillary endothelium and the density of the MCTs. H_i^+ and H_c^+ are assumed constants.

Finally, set $k = \dfrac{K_H}{H_i^+}$ and $k' = \dfrac{K_H}{H_c^+}$ to obtain

$$J_2 = \kappa \left(\frac{Lac_i}{k + Lac_i} - \frac{Lac_c}{k' + Lac_c} \right),$$

and therefore

$$\begin{cases} V_i \dfrac{dLAC_i}{dt} = J(t, Lac_i) - \kappa \left(\dfrac{Lac_i}{k + Lac_i} - \dfrac{Lac_c}{k' + Lac_c} \right) \\ V_c \dfrac{dLAC_c}{dt} = F(t)\,(L - Lac_c) + \kappa \left(\dfrac{Lac_i}{k + Lac_i} - \dfrac{Lac_c}{k' + Lac_c} \right). \end{cases}$$

Setting u and v as the intracellular and capillary lactate concentrations, respectively, and $\epsilon = \dfrac{V_c}{V_i}$ as the volume separating the cell and capillary compartments, we obtain the following system of ODEs

$$\begin{cases} u'(t) = J(t,u) - \kappa \left(\dfrac{u}{k+u} - \dfrac{v}{k'+v} \right), & \text{in} \quad [0,T], \\ \epsilon v'(t) = F(t)\,(L - v) + \kappa \left(\dfrac{u}{k+u} - \dfrac{v}{k'+v} \right), & \text{in} \quad [0,T], \\ (u(0), v(0)) = (u_0, v_0)\,, & \text{in} \quad \mathbb{R}^+ \times \mathbb{R}^+. \end{cases} \tag{1.14}$$

To maintain proliferation, highly glycolytic cancer cells prevent intracellular acidification by exporting lactate to the extracellular space via monocarboxylate transporters (MCT1 and MCT4). This, in turn, leads to acidification of the extracellular PH in the tumor microenvironment, which indeed promotes metastasis, angiogenesis, and, most importantly, immunosuppression (see [28] and [7]).

A potential therapeutic target in cancer is therefore MCT1/4 inhibition, as it has been shown in [7] that cell proliferation is reduced both in vitro and in vivo by pharmacological or genetic MCT1/4 inhibition. Syronsingopine, an antihypertensive drug, is a dual MCT1/4 inhibitor that can be used to treat cancer.

Our main goal is to add a control term w at a rate γ representing the desired treatment with syrosingopine, where $w = 0$ represents no dosing and $w = 1$ represents full dosing.

Here, we apply the control to the term representing the transport of lactate out of the cell into the capillary employing MCT inhibitor.

So, our new system becomes

$$u'(t) = J(t, u(t)) - \kappa \left((1 - \gamma w) \frac{u(t)}{k + u(t)} - \frac{v(t)}{k' + v(t)} \right), \quad \text{in } (0, T), \tag{1.15}$$

$$\epsilon v'(t) = F(t)(L - v(t)) + \kappa \left((1 - \gamma w) \frac{u(t)}{k + u(t)} - \frac{v(t)}{k' + v(t)} \right) \quad \text{in } (0, T), \tag{1.16}$$

$$(u(0), v(0)) = (u_0, v_0) \in \mathbb{R}_+ \times \mathbb{R}_+. \tag{1.17}$$

Accompanied with the following objective functional to be minimized

$$\mathcal{J}(v, w, \tau) = \frac{1}{2} \int_0^\tau \|(v - v_Q)(t)\|^2 \, dt + \frac{1}{2r} \int_{\tau - r}^\tau \|(v - v_d)(t)\|^2 \, dt + \frac{1}{2} \int_0^\tau \|w(t)\|^2 \, dt. \tag{1.18}$$

Here r is a positive constant, the function v_Q corresponds to the desired evolution capillary lactate concentration and v_d to the desired final capillary lactate concentration. Moreover, a patient undergoes several cycles of treatment, so that each cycle is followed by a resting period during which the healthy cells can recover, so that τ is the treatment time of each cycle and T is the final treatment time.

A large value of $|v - v_Q|^2$ means that the patient has high levels of capillary lactate concentration, likewise a large value of $|w|^2$ would mean that the patient is suffering from a high dose of the drug.

Achieving the desired goal is accomplished by the following problem.

$$\text{minimize } \mathcal{J} \text{ associated to } \quad (1.15) - (1.17),\ w \in \mathcal{W}_{ad},\ \tau \in [r, T]. \tag{1.19}$$

1.3.3 Modeling the control on lactate production

A common feature of tumor cells is the abnormal glycolytic metabolism known as the Warburg effect, in which cancer cells preferentially use glycolysis even in the presence of abundant oxygen, in contrast to healthy cells, which generally use oxidative phosphorylation for energy. The shift from oxidative phosphorylation to glycolysis, which is associated with high glucose uptake due to the lower energetic efficiency of glycolysis compared to oxidative phosphorylation, is one of the hallmarks of tumors. As a result, increased lactate production is observed, contributing to malignancy progression, lowering PH for invasion, and triggering immune escape.

The enzyme LDH occupies a central position in the metabolic reprogramming of tumor cells. It plays a key role in maintaining altered glycolytic metabolism and enables tumor cell survival when glycolysis is the sole source of energy. Structurally, LDH enzyme is a tetrameric enzyme consisting of two different types of subunits LDH-A and LDH-B. LDH-A has high activity in converting pyruvate to lactate, whereas LDH-B is more efficient in catalyzing the reverse reaction of lactate to pyruvate (see Subsection 1.1.3).

An isoform of LDHA, hLDH-5 (see Subsection 1.1.3), was overexpressed in a variety of tumors, revealing a link between its increase and the aggressive phenotype of the tumor.

In addition, hLDH-5 has been found to play an important role in the development and maintenance of metastatic tumors, and serum hLDH-5 levels have been associated with resistance to chemotherapy and radiotherapy. For these reasons, hLDH-5 is now considered a promising therapeutic target for the treatment of cancer(see [17, 25, 30, 32, 39, 54, 57, 58, 72, 78]).

Several LDHA inhibitors are mentioned in the literature for either type of tumors (see [45, 56, 67, 68]). In this thesis, we are interested in gliomas, so we consider treatment with gossypol, which showed dose-dependent cytotoxic activity in various cancer cells and in gliomas in particular

We leverage from system (1.13), but if we consider spatial diffusion, we have the following system (see [62]).

$$\begin{aligned} &\partial_t u - \alpha\Delta u = \beta u + f(x,t) + \frac{ku}{k'+u} \quad \beta \geq 0,\ k > 0 \quad \text{in } \Omega \times (0,T), \\ &\frac{\partial u}{\partial \nu} = 0 \qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \text{on } \partial\Omega \times (0,T), \\ &u|_{t=0} = u_0(x) \qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \text{in } \Omega. \end{aligned}$$

Here u represents the intracellular lactate concentration. Furthermore, the non-linear term $\dfrac{ku}{k'+u}$ stands for lactate transport from capillary, where k is the maximum transport rate and k' is the Michaelis-Menten constant. The function f represents the creation and consumption of lactate and βu stands for the loss of lactate due to the convert of lactate to pyruvate by the LDHB enzyme and due to migration to neighboring tissues (note that the above equation can also model the extra-cellular (capillary) lactate concentration, in which case βu corresponds to the blood flow). One can see that

$$\frac{ku}{k'+u} = k - \frac{kk'}{k'+u}.$$

Based on the previous model, we consider the following problem, for $T > 0$ in a bounded domain $\Omega \subset \mathbb{R}^3$ with C^3-boundary Γ,

$$\partial_t u - \alpha\Delta u + \beta u - \frac{k}{k'+u} = J(x,t)(1-\gamma v), \quad \text{in} \quad \Omega \times (0,T) =: Q, \tag{1.20}$$

$$\partial_\nu u = 0, \quad \text{on} \quad \Gamma \times (0,T), \tag{1.21}$$

$$u(0,x) = u_0(x), \quad \text{in} \quad \Omega. \tag{1.22}$$

Here, we introduce a control v which represents the concentration of gossypol inhibitor, where $v = 0$ stands for no dose and $v = 1$ stands for full dose. We further write $\dfrac{kk'}{k'+u}$ as $\dfrac{k}{k'+u}$ and note that $J = f - k$. Finally, $\gamma J(x,t)v$ is the inhibition of lactate production at rate γ. The cost functional to be minimized is given by

$$\mathcal{J}(u,v,\tau) = \frac{\beta_Q}{2}\int_0^\tau \int_\Omega |u-u_Q|^2 dx\,dt + \frac{\beta_\Omega}{2r}\int_{\tau-r}^\tau \int_\Omega |u-u_\Omega|^2 dx\,dt + \frac{\beta_v}{2}\int_0^T \int_\Omega |v|^2 dx\,dt, \tag{1.23}$$

where u_Q, u_Ω represent the desired evolution and distributional lactate concentrations both in $L^2(Q)$. A cancer patient is treated in cycles; each treatment cycle is followed

by a rest period to allow the healthy cells to recover. Here $\tau \in (0, T]$ represents the treatment time of one cycle and $T > 0$ is a fixed maximal time in which the patient is allowed to undergo treatment. The first two terms of (1.23) are of standard tracking type as often considered in the literature of parabolic optimal control (see [73]) and the third one penalizes large concentrations of the applied inhibitor. Our problem becomes

$$\text{minimize } \mathcal{J} \text{ associated to (1.20)} - \text{(1.22)}. \tag{1.24}$$

1.4 Problematic

This section is devoted to the presentation of some results that are close to our work, so we divide it into three subsections. In the first subsection, we consider two optimal control problems that study tumor growth models (see [23] and [43]). In the second subsection, we consider a problem that studies a system modeling lactate kinetics in one compartment (either intracellular or extracellular) (see [62]), for which we constructed our control problem. Finally, the third subsection deals with an ODE model studied in (see [46]), which we used later in our work to apply an appropriate control.

1.4.1 Some optimal control problems on tumor growth models

In [23], the target was prostate cancer through two controls as a combination of two treatments a cytotixic drug along with a targeted therapy presented by an antiangiogenic drug. A system of an Allen-Cahn equation and two reaction diffusion equations was considered. The first equation models the spatial location of the tumor denoted as the phase-field in the presence of nutrient, the second models the dynamics of nutrient and the last equation models the dynamics of tissue PSA concentration. They consider the following system

$$\begin{cases} \partial_t \phi - \lambda \Delta \phi + F'(\phi) - m(\sigma) h'(\psi) = -U h'(\phi), & \text{in } \Omega \times (0,T), \\ \partial_t \sigma - \eta \Delta \sigma + \gamma_h \sigma + \gamma_{ch} \sigma \phi = S_h(1-\phi) + (S_c - S)\phi, & \text{in } \Omega \times (0,T), \\ \partial_t p - D \Delta p + \gamma_p P = \alpha_h + \alpha_{ch} \phi, & \text{in } \Omega \times (0,T), \\ \phi = 0, \partial_\nu \sigma = \partial_\nu p = 0, & \text{on } \Gamma \times (0,T), \\ \phi(0,x) = \varphi_0(x),\ \sigma(0,x) = \sigma_0(x),\ p(0,x) = p_0(x), & \text{in } \Omega, \end{cases} \tag{1.25}$$

where ϕ is a phase-field that identifies the spatial location of the tumor; σ is the concentration of a vital nutrient; and p is the tissue PSA concentration. The serum PSA is commonly used in clinical practice can be obtained as $P_s = \int_\Omega p\, dx$. F' denotes the derivative of F, so that $F(\phi) = M\phi^2(1-\phi)^2$ and $h(\phi) = M\phi^2(3-2\phi)$, where M is a positive constant.

$$\gamma_{ch} := \gamma_c - \gamma_h,\ \ \alpha_{ch} := \alpha_c - \alpha_h,\ \ S_{ch} := S_c - S_h.$$

The model parameters $\lambda, \eta, D, \gamma_p, \gamma_c, \gamma_h, \alpha_c, \alpha_h, S_c$ and S_h are positive constants with biological significance. For the solution of the initial boundary value problem (1.25), the

functions $U(t,x)$ and $S(t,x)$ are considered to be given, so that $U(t,x)$ models the inhibiting effect of a cytotoxic drug on tumor dynamics, while $S(t,x)$ represents the reduction of nutrient supply produced by an antiangiogenic drug. The function $m(\sigma)$ is given by

$$m(\sigma) = m_{ref}\left(\frac{\rho + A}{2} + \frac{\rho - A}{\pi}\arctan\left(\frac{\sigma - \sigma_l}{\sigma_r}\right)\right),$$

where m_{ref} is a positive constant, while rho and A are constants that determine the rate of cell proliferation and apoptosis. Here $\rho = K_\rho/\overline{K}_\rho$ and $A = -K_A/\overline{K}_A$. Where, K_ρ and K_A are, respectively, the proliferation and apoptosis rates of tumor cells while $\overline{K}_\rho$ and $\overline{K}_A$ are scaling positive constants. The positive constants σ_l and σ_r are, respectively, a reference and a threshold value for the nutrient concentration.

The optimal control problem in this work was to find the functions $U(t,x)$ and $S(t,x)$ that provide the optimal cytotoxic and antiangiogenic effects to treat a certain PCa case. Therefore, the optimal control problem stated was

$$\text{minimize}\{J(U,S);\ (U,S) \in \mathcal{U}_{ad}\},$$

subject to (1.25), where the objective functional was given as

$$\begin{aligned} J(U,S) \ &= \frac{k_1}{2}\int_0^T\int_\Omega (\phi(t,x) - \phi_Q)^2\,dx\,dt + \frac{k_2}{2}\int_\Omega (\phi(T,x) - \phi_\Omega)^2\,dx \\ &\quad + k_3\int_\Omega \phi(T,x)\,dx + \frac{k_4}{2}\int_0^T\left[\left(\int_\Omega p(t,x)\,dx - p_\Omega(t)\right)^+\right]dt \\ &\quad + k_5\int_\Omega p(T,x)\,dx \\ &= \frac{k_6}{2}\int_0^T\int_\Omega U^2(t,x)dx\,dt + \frac{k_7}{2}\int_0^T\int_\Omega S^2(t,x)dx\,dt, \end{aligned} \tag{1.26}$$

and

$$\mathcal{U}_{ad} = \{(U,S) \in (L^\infty(Q_T))^2\,;\, 0 \le U \le U_{max},\ 0 \le S \le S_{max},\ \text{a.e. in } Q_T\}.$$

And S_{max}, U_{max} are positive threshold values and $Q_T := (0,T)\times\Omega$, r^+ represents a positive part of r; the functions ϕ_Q, ϕ_Ω are prescribed targets fro tumor phase in Q_T and in Ω at the final time, respectively, while p_Ω represents an upper target function for the spatial mean value of the tissue PSA, so that

$$\phi_Q \in L^2(Q_T),\ \phi_{\Omega\in L(\Omega)},\ p_\Omega \in L^2(0,T).$$

The constants k_i, $i = 1,\ldots,7$ in equation (1.26) are nonnegative such that there exists at least one i so that $k_i > 0$.

The authors has studied the optimal control problem, and illustrated some numerical computations using isogeometric analysis, a recent generalization of finite element method with superior approximation properties granted by the use of splines as basis functions. These simulations suggest that antiangiogenic therapies may not be optimal for treating PCa, because the used drugs docetaxel and bevacizumab are reference drugs in therapeutic investigations of advanced optimal control. however, the optimal control problem used in this work is drug-independent, i.e, it provides optimal cytotoxic and antiangiogenic drug

effects without accounting for any specific drug delivery plan.

On the other hand, the authors in [43] considered an optimal control problem involving a cancer treatment with cytotoxic drugs. It is well known that while cytotoxic drugs primarily target and damage rapidly dividing cells such as tumor cells, the drugs can also accumulate in the body and have negative side effects on the immune system and various vital organs such as the kidneys and liver. In the worst case, too high a dose of cytotoxic drugs can cause tumor cells to mutate and become resistant to treatment. Thus, from the patient's perspective, the shortest treatment time in which the goals of chemotherapy are achieved is most ideal. Thus, the optimal control problem that have been studying involves finding the optimal distribution of the drug and the optimal treatment time.

For $T > 0$, in a bounded domain $\Omega \subset \mathbb{R}^3$ with C^3- boundary Γ, the following Cahn–Hilliard model for tumor growth was considered (see [43]),

$$\begin{cases} \partial_t \varphi = \Delta \mu + (\mathcal{P}\sigma - \mathcal{A} - \alpha u)\, h(\varphi), & \text{in } \Omega \times (0,T), \\ \mu = A\Psi'(\varphi) - B\Delta\varphi, & \text{in } \Omega \times (0,T), \\ \partial_t \sigma = \Delta\sigma - \mathcal{C}\sigma h(\varphi) + \beta\,(\sigma_s - \sigma)\,, & \text{in } \Omega \times (0,T), \\ \partial_\nu \varphi = \partial_\nu \sigma = 0,\ \partial_\nu \mu = 0 & \text{on } \Gamma \times (0,T), \\ \varphi(0) = \varphi_0,\ \sigma(0) = \sigma_0, & \text{in } \Omega. \end{cases} \tag{1.27}$$

Where α is a positive constant, φ denotes the dierence in volume fraction, where $\varphi = 1$ represents the tumor phase and $\varphi = 1$ represents the healthy tissue phase. The function μ is a chemical potential associated to φ, $\Psi'(\varphi)$ is the derivative of a potential $\Psi(\varphi)$ with equal minima at $\varphi = \pm 1$, σ is the concentration of an unspecied chemical species acting as nutrient for the tumor cells, while u denotes the concentration of cytotoxic drugs. The function $h(\varphi)$ is an interpolation function such that $h(-1) = 0$ and $h(1) = 1$, the parameters $\mathcal{P}, \mathcal{A}, \mathcal{C}$, and $\mathcal{B}$ denote the constant proliferation rate, apoptosis rate, nutrient consumption rate, and nutrient supply rate, respectively. The positive constants A and B are related to the thickness of the interfacial layer and the surface tension, while $_\nu$ is the unit outward normal of Γ. The term $h(\varphi)\mathcal{P}\sigma$ models the proliferation of tumor cells which is proportional to the concentration of the nutrient, the term $h(\varphi)\mathcal{A}$ models the apoptosis of tumor cells, and $\mathcal{C}h(\varphi)\sigma$ models the consumption of the nutrient only by the tumor cells. The term $\alpha u h(\varphi)$ models the elimination of the tumor cells by the cytotoxic drugs at a constant rate α. Meanwhile, σ denotes the nutrient concentration in a pre-existing vasculature, and $\beta(\sigma_s - \sigma)$ models the supply of nutrient from the blood vessels if $\sigma_s > \sigma$ and the transport of nutrient away from the domain Ω if $\sigma_s < \sigma$.

For positive constants r, β_u, β_T, and nonnegative constants β_Q, β_Ω and β_S, the objective functional considered is as follows

$$\begin{aligned} \mathcal{J}_r(\varphi, u, \tau) = \frac{\beta_Q}{2}\int_0^\tau \int_\Omega |\varphi - \varphi_Q|^2 dx\, dt + \frac{\beta_\Omega}{2}\frac{1}{r}\int_{\tau-r}^\tau \int_\Omega |\varphi - \varphi_\Omega|^2 dx\, dt \\ + \frac{\beta_S}{2}\frac{1}{r}\int_{\tau-r}^\tau \int_\Omega (1+\varphi)\, dx\, dt + \frac{\beta_u}{2}\int_0^T \int_\Omega |u|^2 dx\, dt + \beta_T \tau. \end{aligned}$$

Where, $\tau \in (0, T]$ represents the treatment time, φ_Q represents a desired evolution for the tumor cells while φ_Ω represents a desired final distribution. The first two terms of $\mathcal{J}_r$ are of standard tracking type as often considered in the literature of parabolic optimal control, and the third term of $\mathcal{J}_r$ measures the size of the tumor at the end of the treatment. The fourth term penalizes large concentrations of the cytotoxic drugs, and the fifth term of $\mathcal{J}_r$ penalizes long treatment times.

The optimal control problem studied is $\min \mathcal{J}_r(\varphi, u, \tau)$ associated to (1.27), where the set of admissible controls verifies,

$$\mathcal{U}_{ad} = \{u \in L^\infty(0, T; L^\infty(\Omega)) : 0 \leq u \leq 1 \text{ a.e. in } Q\}.$$

1.4.2 A reaction-diffusion equation associated with brain lactate kinetics

We have introduced earlier in Subsection 1.3.3 the mathematical model presented in [62], which describes brain lactate kinetics in one compartment (either intracellular or extracellular), when spatial diffusion is taken into account. Recall the considered system

$$\begin{cases} \partial_t u - \alpha \Delta u + \beta u + \dfrac{ku}{k' + u} = f(x,t), & \text{in } \Omega \times (0, T), \\ \partial_\nu u = 0, & \text{on } \Gamma, \\ u|_{t=0} = u_0, & \text{in } \Omega. \end{cases} \tag{1.28}$$

The main objective of this work was to show the well-posedness of this system. First, the author has established some apriori estimates, then considering the assumption $\dfrac{k}{k+u} \geq 1$, he obtained that the solution u is nonnegative. Moreover the solution has uniform (with respect to time) and dissipative (in the sense that it is independent of time and bounded sets of initial data, at least for large times) upper bound, since

$$0 \leq u(x,t) \leq e^{-Ft} \|u_0\|_{L^\infty(\Omega)} + \frac{1}{F}\left(\|f\|_{L^\infty(\Omega)} + 1\right) \text{ a.e. } (x,t).$$

Assuming that

$$\begin{cases} u_0 \in H^2_N(\Omega) = \{v \in H^2(\Omega),\ \partial_\nu v = 0 \text{ on } \Gamma\},\ u \geq 0 \text{ a.e. } x, \\ f \in L^1(0,T; L^\infty(\Omega)) \cap L^\infty(0,T; L^2(\Omega)) \cap L^2(0,T; H^1(\Omega)) \cap H^1(0,T; L^2(\Omega)),\ \forall\ T > 0, \\ f \geq -1 \text{ a.e. } (x,t). \end{cases}$$

Then (1.28) possesses a unique strong solution u such that, $\forall\, T > 0$,

$$u \in L^\infty(0,T; H^2_N(\Omega)) \cap L^2(0,T; H^3(\Omega)) \quad \text{and} \quad \partial_t u \in L^\infty(0,T; L^2(\Omega)) \cap L^2(0,T; H^1(\Omega)).$$

Moreover, the solution u satisfies

$$0 \leq u(x,t) \leq \|u_0\|_{L^\infty(\Omega)} + \int_0^t \|f\|_{L^\infty(\Omega)}\, ds + t \text{ a.e. } (x,t).$$

In addition, if $u_0 >$ a.e. x and $f \geq 0$ a.e. (x,t), then

$$u(x,t) \geq \frac{e^{-Ft}}{\left\| \frac{1}{u_0} \right\|_{L^\infty(\Omega)}} \quad \text{a.e. } (x,t).$$

1.4.3 Analysis of a mathematical model for brain lactate kinetics

Lactate kinetics has been an interest of study for many researchers, in particular, the model (1.14) with initial conditions $(u(0), v(0)) = (\overline{u}_0, \overline{v}_0)$, was considered in [46], the authors have considered two cases $\epsilon > 0$ and $\epsilon = 0$.

When $\epsilon > 0$, the problem is well posed, moreover

$$v(t) \leq max\left(v_0, \frac{T + F_2 L}{F_1}\right) := B_v.$$

On the other hand, setting

$$J(t,x) \leq B_J \ \forall (t,x) \in \mathbb{R} \quad \text{and} \quad B_J\,(k' + B_v) < \kappa k'.$$

And setting

$$z = \frac{B_v}{k' + B_v} + \frac{B_J}{\kappa},$$

then $\forall t \in \mathbb{R}^+$:

$$u(t) \leq max\left(\frac{kz}{1-z}, u_0\right) := B_u.$$

Moreover, lower bounds are derived

$$v(t) \geq min\left(v_0, max\left(\frac{F_1 L - \kappa \dfrac{B_v}{k' + B_v}}{F_2}, 0\right)\right) := M_v$$

and

$$u(t) \geq min\left(u_0, M_v \frac{k}{k'}\right) := M_u.$$

And the following unique stationary point is a node

$$u_l := \frac{k\left(\dfrac{J}{\kappa} + \dfrac{v_l}{k' + v_l}\right)}{1 - \left(\dfrac{J}{T} + \dfrac{v_l}{k' + v_l}\right)}$$

and

$$v_l := L + \frac{J}{F}.$$

The equilibrium does not always exist, and the parameters need to satisfy

$$J^2 + JF(L + k') - TFk' < 0.$$

When $\epsilon = 0$, and given that $F(t) = F$ and $J(t,x) = J$ are constants, then the limit system is as follows

$$\begin{cases} u_0'(t) = J - \kappa\left(\dfrac{u_0(t)}{k+u_0(t)} - \dfrac{v_0(t)}{k'+v_0(t)}\right), \\ F\left(L - v_0(t)\right) + \kappa\left(\dfrac{u_0(t)}{k+u_0(t)} - \dfrac{v_0(t)}{k'+v_0(t)}\right) = 0, \\ u_0(0) = \overline{u}_0 \ \in \mathbb{R}^+. \end{cases} \tag{1.29}$$

This system is well-posed, moreover the stationary point is locally stable. Moreover, taking u and v to be the difference of the solution of System (1.14) and (1.29), respectively, they get

$$u(t)^2 + \epsilon v(t)^2 \leq$$

$$exp\left(\frac{T^2 t}{F}\left(\frac{8}{k^2} + \frac{4}{k'^2}\right)\right)\left(\epsilon\left(\overline{v}_0 - \Psi\left(\overline{u}_0\right)\right)^2 + \frac{k^2(J+T)^2}{\left(F + \dfrac{k'T}{(k'+L+\frac{T}{F})^2}\right)^2}\frac{2\epsilon^2}{\left(\frac{2}{k^2}+\frac{1}{k'^2}\right)}\right)$$

$$-\frac{k^2\left(J+T\right)^2}{\left(F + \dfrac{k'T}{\left(k'+L+\frac{T}{F}\right)^2}\right)^2}\frac{2\epsilon^2}{\left(\frac{2}{k^2}+\frac{1}{k'^2}\right)},$$

where $\Psi(\overline{u}_0) = \overline{v}_0$.

Finally, numerical simulations were established for both cases, the functions F and J are constants and when

$$J\begin{cases} \mathbb{R}^+ & \longrightarrow & \mathbb{R}^+ \\ x & \longmapsto & G_J - L_J + \dfrac{C_J}{x+\epsilon_J}, \end{cases}$$

and

$$F\begin{cases} \mathbb{R}^+ & \longrightarrow & \mathbb{R}^+ \\ t & \longrightarrow & \begin{cases} F_0\left(1+\alpha_f\right) & \text{if} \quad \exists\, N \in \mathbb{N}/\left(N-1\right)t_f + t_i < t < Nt_f, \\ F_0 & \text{if not.} \end{cases} \end{cases}$$

The simulations for this case are given in Figure 1.9

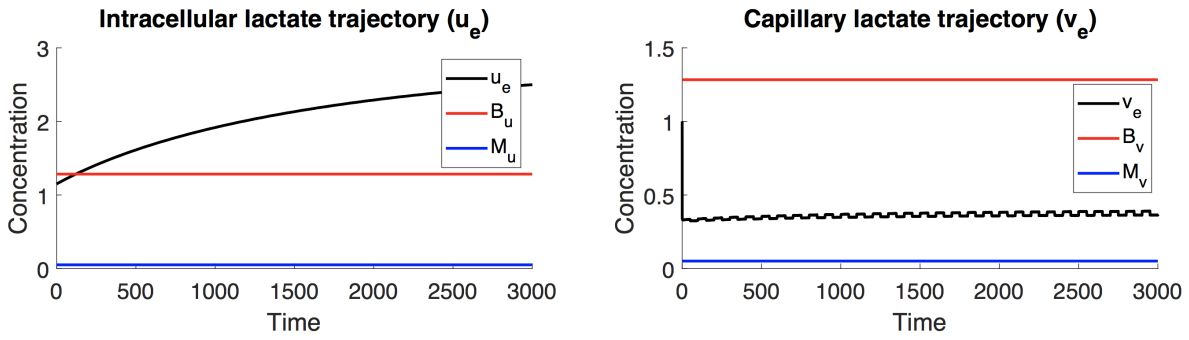


Figure 1.9 – Intracellular and capillary lactate concentrations

1.5 Contributions

This section is concerned with a brief summary of our main results, so it is divided into three subsections.

1.5.1 Optimal control problem of tumor growth model

The results presented in Chapter 2 is a paper accepted in the journal of Discrete and Continuous Dynamical Systems Series S.

We consider for $T > 0$, which is the maximum treatment time, in a bounded domain $\Omega \subset \mathbb{R}^n, n = 1, 2, 3$, with C^2- boundary Γ the system (1.8)-(1.11) described in Section 1.3.1.

Moreover, for positive constants r, β_u, β_T, and nonnegative constants $\beta_Q, \beta_\Omega, \beta_S$, we consider the functional

$$\mathcal{J}_r(\varphi, u, \tau) = \frac{\beta_Q}{2}\int_0^\tau\int_\Omega |\varphi - \varphi_Q|^2 dx\, dt + \frac{\beta_\Omega}{2}\frac{1}{r}\int_{\tau-r}^\tau\int_\Omega |\varphi - \varphi_\Omega|^2 dx\, dt$$
$$+\frac{\beta_S}{2}\frac{1}{r}\int_{\tau-r}^\tau\int_\Omega (1+\varphi)\, dx\, dt + \frac{\beta_u}{2}\int_0^T\int_\Omega |u|^2 dx\, dt + \beta_T\tau.$$

The first two terms of $\mathcal{J}_r$ are of standard tracking type is often considered in the literature of parabolic optimal control (see [73]) and the third term of $\mathcal{J}_r$ measures the size of the tumor at the end of the treatment. The fourth term penalizes high concentrations of the cytotoxic drug, and the fifth term of $\mathcal{J}_r$ penalizes long treatment times (see [43]).

A cancer patient undergoes treatment for several cycles, the duration of each of which is given as τ, followed by a rest period during which the healthy cells are allowed to recover. The total treatment time is denoted by T. We tend to optimize the treatment time of each cycle at a given drug dose such that we achieve the desired evolution of tumor cells φ_Q in Q and their desired final distribution target φ_Ω in Ω, so that φ can be a stable conguration of the system such that the tumor does not grow again after the treatment is completed. One can also choose φ_Ω as a conguration which is suitable for surgery.

The main objective of this chapter is to study the problem

$$\text{minimize } \mathcal{J}_r \text{ associated to } (1.8) - (1.11) \text{ and } u \in \mathcal{U}_{ad},\ \tau \in [r, T], \tag{1.30}$$

where the set of admissible controls satisfy

$$\mathcal{U}_{ad} := \{u \in L^\infty(Q) : 0 \leq u \leq 1, \text{a.e. in } Q\}.$$

For this purpose, we consider first the following assumptions

(A) The initial conditions satisfy, $\varphi_0, \sigma_0 \in H^1(\Omega)$, with $0 \leq \sigma_0 \leq 1$ a.e. $x \in \Omega$. The target functions $\varphi_\Omega, \varphi_Q \in L^2(Q)$, and the vasculature nutrient concentration σ_s satisfies $0 \leq \sigma_s \leq 1$, a.e. in Q.

(B) The interpolation function $h : \mathbb{R} \to [0, 1]$ is continuously differentiable and Lipschitz with Lipschitz constant M. In addition, the parameters $\mathcal{P}, \mathcal{A}, \mathcal{C}, \beta$ are non negative constants, and α is a positive constant.

We start by showing that the state system is well-posed, by proving the following theorem:

Theorem 1.1 (Existence and uniqueness of weak solution)

Assume that Assumptions (A) and (B) hold. Then, Problem (1.8)-(1.11) admits a unique weak solution (φ, σ) such that $0 \leq \sigma \leq 1$ and

$$(\varphi, \sigma) \in \mathcal{Y} := \Big(L^2(0, T; H^2(\Omega)) \cap L^\infty(0, T; H^1(\Omega)) \cap H^1(0, T; L^2(\Omega))\Big)^2.$$

Moreover, the control-to-state operator

$$\begin{array}{rccc} S: & L^2(Q) & \longrightarrow & \mathcal{Y} \\ & u & \longmapsto & (\varphi, \sigma) \end{array}$$

is continuous for the corresponding topology.

Where $\mathcal{Y} := (L^2(0, T; H^2(\Omega)) \cap L^\infty(0, T; H^1(\Omega)) \cap H^1(0, T; L^2(\Omega)))^2$.

Moreover, we prove that S is continuous, so that the solution of (1.8)-(1.11) is unique for either value of u.

Now, since the solution (φ, σ) of (1.8)-(1.11) exists and starting from Assumption (A) which states that $0 \leq \sigma_0 \leq 1$, we show that $0 \leq \sigma \leq 1$.

On the other hand, we show the existence of a solution for (1.30), this is done by proving the following theorem:

Theorem 1.2

Assume that Assumptions (A) and (B) hold and let $\mathcal{J}_r$ be defined by (1.12). Then there exist $(u^*, \tau^*) \in \mathcal{U}_{ad} \times [r, T]$ such that

$$\mathcal{J}_r(u^*, \tau^*) \leq \mathcal{J}_r(u, \tau), \quad \text{for every } (u, \tau) \in \mathcal{U}_{ad} \times [r, T].$$

To show the Fréchet differentiability of the control-to-state operator with respect to the control, we first demonstrate the existence of the Fréchet derivative by considering a

linearized System of (1.8)-(1.11) at (u_*, τ_*) for $w \in L^2(Q)$ as follows

$$\begin{cases} \partial_t \Phi - B\Delta\Phi + \Phi f'(\varphi^*) = (\mathcal{P}\Sigma - \alpha w)h(\varphi^*) + (\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*)\Phi h'(\varphi^*), & \text{in } Q, \\ \partial_t \Sigma = \Delta\Sigma - \mathcal{C}\Sigma h(\varphi^*) - \mathcal{C}\sigma^*\Phi h'(\varphi^*) - \beta\Sigma, & \text{in } Q, \\ \partial_\nu \Sigma = \partial_\nu \Phi = 0, & \text{on } \Gamma \times (0,T), \\ \Sigma(0) = \Phi(0) = 0, & \text{in } \Omega. \end{cases} \tag{1.31}$$

We establish the existence of a unique regular solution of (1.31) by proving the next theorem, and hence the unique Fréchet derivative of S at (u_*, τ_*) exists.

Theorem 1.3

Let $u^* \in \mathcal{U}_{ad}$. Then, System (1.31) admits a unique solution

$$(\Phi, \Sigma) \text{ in } \left(L^2(0,T;H^2(\Omega)) \cap H^1(0,T;L^2(\Omega)) \cap C([0,T];L^2(\Omega))\right)^2.$$

Now, we set $(\varphi^w, \sigma^w) := S(u^* + w)$, $(\varphi^*, \sigma^*) := S(u^*)$, and $u^w := u^* + w$, after that, we show that the remainders

$$\theta = \varphi^w - \varphi^* - \Phi \quad \text{and} \quad \rho = \sigma^w - \sigma^* - \Sigma,$$

satisfy

$$\|(\theta, \rho)\|_{\mathcal{Y}}^2 \leq c \|w\|_{L^2(Q)}^4 .$$

For this aim we prove the following theorem:

Theorem 1.4

Let (Φ, Σ) be the solution of the linearized system (1.31) at u^*, then the remainders θ and ρ satisfy

$$\|(\theta, \rho)\|_{\mathcal{Y}}^2 \leq c \|w\|_{L^2(Q)}^4 ,$$

with

$$\mathcal{Y} := L^2(0,s;H^2(\Omega)) \cap H^1(0,s;L^2(\Omega)) \cap L^\infty(0,s;H^1(\Omega)), \ \ s \in (0,T).$$

Furthermore, the Fréchet differentiability of the cost functional with respect to time is established as in [43], however, the Fréchet derivative of the cost functional with respect to the control at (u^*, τ^*) is given by

$$D_u \mathcal{J}_r(u^*, \tau^*)w = \beta_Q \int_0^{\tau^*} \int_\Omega |\varphi^* - \varphi_Q| \Phi^w \, dx \, dt + \beta_\Omega \int_{\tau^* - r}^{\tau^*} \int_\Omega |\varphi^* - \varphi_\Omega| \Phi^w \, dx \, dt$$
$$+ \frac{\beta_s}{r} \int_{\tau^* - r}^{\tau^*} \int_\Omega \Phi^w \, dx \, dt + \beta_u \int_0^T \int_\Omega u \, w \, dx \, dt.$$

Since this problem is constrained, and we want to eliminate the term Φ from $D_u \mathcal{J}_r$, we considered an adjoint system by means of Lagrangian principle, then established the

existence of regular multipliers of the following system

$$\begin{cases} -\partial_t p - B\Delta p = (\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*)\, h'(\varphi^*)p + \beta_Q\,(\varphi^* - \varphi_Q) \\ \qquad\qquad + \dfrac{1}{2r}\chi_{[\tau^*-r,\tau^*]}(t)\,(2\beta_\Omega\,(\varphi^* - \varphi_\Omega) + \beta_s) - f'(\varphi^*)p - \mathcal{C}\sigma^* h'(\varphi^*)q, & \text{in } [0,T]\times\Omega, \\ -\partial_t q - \Delta q = \mathcal{P}h(\varphi^*)p - (\mathcal{C}h(\varphi^*) + \beta)\, q, & \text{in } [0,T]\times\Omega, \\ \partial_\nu p = \partial_\nu q = 0, & \text{on } [0,T]\times\Gamma, \\ p(\tau^*) = q(\tau^*) = 0, & \text{in } \Omega. \end{cases} \tag{1.32}$$

For this purpose we prove this theorem:

Theorem 1.5

Let u^* be an optimal control, and $(\varphi^*, \sigma^*) = \mathcal{S}(u^*)$ be the corresponding state. Then the adjoint Problem (1.32) has a unique solution

$$(p,q) \in \Big(H^1(0,\tau^*;L^2(\Omega)) \cap L^\infty(0,\tau^*;H^1(\Omega)) \cap L^2(0,\tau^*;H^2(\Omega)) \cap C([0,\tau^*];H^1(\Omega))\Big)^2.$$

Finally, we demonstrate that the optimal control u^* satisfies the following simplified first-order necessary optimality condition

$$(D_u\mathcal{J}_r(u^*,\tau^*))(u-u^*) = \beta_u \int_0^T \int_\Omega u^*(u-u^*)\,dx\,dt + \alpha \int_0^{\tau^*} \int_\Omega h(\varphi^*)(u-u^*)p\,dx\,dt \geq 0.$$

1.5.2 An Optimal Control Problem Describing Lactate Production Inhibition

The results presented in Chapter 3 is a paper published in the journal of Applicable Analysis with doi:10.1080/00036811.2021.1999418

We leverage from the model that we presented in Subsection 1.3.3. So, we consider for $T > 0$ in a bounded domain $\Omega \subset \mathbb{R}^3$ with C^3- boundary Γ, the following problem detailed in Subsection 1.3.3 and in Chapter 3.

$$\begin{cases} \partial_t u - \alpha\Delta u + \beta u - \dfrac{k}{k'+u} &= J(x,t)(1-\gamma v), & \text{in} \quad \Omega\times(0,T) =: Q, \\ \partial_\nu u &= 0, & \text{on} \quad \Gamma\times(0,T), \\ u(0,x) &= u_0(x), & \text{in} \quad \Omega. \end{cases} \tag{1.33}$$

In addition to the following cost functional

$$\mathcal{J}(u,v,\tau) = \frac{\beta_Q}{2}\int_0^\tau\int_\Omega |u-u_Q|^2 dx\,dt + \frac{\beta_\Omega}{2r}\int_{\tau-r}^\tau\int_\Omega |u-u_\Omega|^2 dx\,dt + \frac{\beta_v}{2}\int_0^T\int_\Omega |v|^2 dx\,dt, \tag{1.34}$$

this is a conventional functional used in optimal control theory (see [73]).

Our problem is

$$\text{minimize } \mathcal{J} \text{ associated to (1.33).} \tag{1.35}$$

We start with the following assumptions

(C) The constants $k, \alpha \geq 0$, $\beta > 0$, $\gamma > 0$, and the function $J \in L^\infty(Q)$ are such that $J \geq -\dfrac{k}{k'}$ and $u_0 \geq 0$.

(D) The control $v \in \mathcal{V}_{ad} := \{v \in L^\infty(Q) : \ 0 \leq v \leq 1\}$

First, we establish that the solution u is nonnegative (thanks to Assumption (C)).

Then the existence of solution of the state System (1.33) is demonstrated by proving the following theorem:

Theorem 1.6 (Existence and uniqueness of weak solutions)

Assume that Assumptions (C) and (D) hold and that $u_0 \in H^1(\Omega)$. Then, Problem (1.33) admits a unique weak solution u such that $u \geq 0$ and

$$u \in \mathcal{Y} := L^2(0,T;H^2(\Omega)) \cap L^\infty(0,T;H^1(\Omega)) \cap H^1(0,T;L^2(\Omega)).$$

Moreover, the control-to-state operator

$$\begin{array}{rccc} S: & L^2(Q) & \longrightarrow & \mathcal{Y} \\ & v & \longmapsto & u \end{array}$$

is continuous on the corresponding topology.

Now, we establish the existence of a solution for our problem (1.35) through the following theorem:

Theorem 1.7

Assume that Assumptions (C) and (D) hold and let $\mathcal{J}$ be defined by (1.34). Then, there exist $(v^*, \tau^*) \in \mathcal{V}_{ad} \times (0,T)$ such that

$$\mathcal{J}(v^*, \tau^*) \leq \mathcal{J}(v, \tau), \quad \text{for every } (v, \tau) \in \mathcal{V}_{ad} \times (0,T).$$

To establish the existence of the Frećhet derivative of the control-to-state operator with respect to the control, we consider the linearized system at u^* associated to the control v^*, for $w \in L^2(Q)$.

$$\begin{cases} \partial_t U - \alpha \Delta U + \beta U = -\dfrac{k}{(k' + u^*)^2} U - \gamma J w, & \text{in} \quad Q, \\ \partial_\nu U = 0, & \text{on} \quad \Gamma \times (0,T), \\ U(0,x) = 0, & \text{in} \quad \Omega. \end{cases} \tag{1.36}$$

Satisfying the following variational formulation, for $\xi \in H^1(\Omega)$,

$$\int_\Omega \partial_t U\, dx + \alpha \int_\Omega \nabla U \cdot \nabla \xi\, dx + \beta \int_\Omega U\, \xi\, dx = -\int_\Omega \frac{k}{(k' + u^*)^2} U\, \xi\, dx - \gamma \int_\Omega J(x,t) w\, \xi\, dx.$$

We prove the existence of a unique solution of (1.36) by proving the following theorem:

Theorem 1.8

Let $v^* \in \mathcal{V}_{ad}$. Then the System (1.36) admits a unique solution

$$U \in L^2(0,T;H^2(\Omega)) \cap H^1(0,T;L^2(\Omega)) \cap C([0,T];H^1(\Omega)).$$

Moreover, for $w \in L^2(Q)$, we set $u^w := S(v^* + w)$ and $u^* := S(v^*)$ and U as the solution of the linearized System (1.36) at v^*. Then the remainder ρ satisfy

$$\|\rho\|_{\mathcal{Y}}^2 \leq c\, \|w\|_{L^2(Q)}^4 .$$

The Fréchet derivative of the functional $\mathcal{J}$ with respect to time is given by

$$D_\tau \mathcal{J}(v^*, \tau^*) = \frac{\beta_\Omega}{2} \left(\|u(\tau^*) - u_\Omega(\tau^*)\|_{L^2(\Omega)}^2 - \frac{1}{r} \|u(\tau^* - r) - u_\Omega(\tau^* - r)\|_{L^2(\Omega)}^2 \right) + \frac{\beta_Q}{2} \|u(\tau^*) - u_Q(\tau^*)\|_{L^2(\Omega)}^2 .$$

For $u_Q \in H^1(0,T;L^2(\Omega))$, $u_\Omega, u^* \in H^1(-r,T;L^2(\Omega))$, we deduce the following first-order necessary optimality condition with respect to time

$$D_\tau \mathcal{J}(v^*, \tau^*)(s - \tau^*) \geq 0 \quad \forall\ s \in [0,T].$$

Furthermore, the Fréchet derivative of the cost functional with respect to the control is given by

$$D_v \mathcal{J}(v^*, \tau^*) w = \beta_Q \int_0^{\tau^*} \int_\Omega |u^* - u_Q| U\, dx\, dt + \beta_\Omega \int_{\tau^* - r}^{\tau^*} \int_\Omega |u^* - u_\Omega| U\, dx\, dt + \beta_v \int_0^T \int_\Omega v\, w\, dx\, dt.$$

To eliminate U from the above equation, we consider the following adjoint system by means of Lagrangian principle

$$\begin{cases} \partial_t p + \alpha \Delta p = \beta p + \dfrac{k\, p}{(k' + u^*)^2} - \beta_Q (u^* - u_Q) + \dfrac{\beta_\Omega}{r} \chi_{[\tau^* - r, \tau^*]}(t)(u^* - u_\Omega), & \text{in } [0,T] \times \Omega, \\ \partial_\nu p = 0, & \text{on } [0,T] \times \Gamma, \\ p(\tau^*) = 0, & \text{in } \Omega. \end{cases} \tag{1.37}$$

We have the following theorem by which we prove the existence of a regular multiplier p.

Theorem 1.9

Let v^* be an optimal control, and $u^* = \mathcal{S}(v^*)$ be the corresponding state. Then the adjoint Problem (1.37) has a unique solution

$$p \in H^1(0,\tau^*;L^2(\Omega)) \cap L^\infty(0,\tau^*;H^1(\Omega)) \cap L^2(0,\tau^*;H^2(\Omega)) \cap C([0,\tau^*];H^1(\Omega)).$$

Finally, we simplified the first-order necessary optimality condition with respect to control by using the variational formulations of (1.31) and (1.32) to get

$$(D_v\mathcal{J}(v^*,\tau^*))(v-v^*) = \beta_v \int_0^T \int_\Omega v^*(v-v^*)\,dx\,dt \geq 0.$$

1.5.3 An Optimal Control Problem Describing Lactate Transport Inhibition

The results presented in Chapter 4 is a paper to appear.

As demonstrated in Subection 1.1.5, targeting MCTs is a good therapeutic approach for cancer, for this aim, we consider in Chapter 4 the model (1.15)-(1.17) described in details in Subsection 1.3.2.

$$\begin{cases} u'(t) &= J(t,u(t)) - \kappa\left((1-\gamma w)\dfrac{u(t)}{k+u(t)} - \dfrac{v(t)}{k'+v(t)}\right), & \text{in } (0,T), \\ \epsilon v'(t) &= F(t)(L-v(t)) + \kappa\left((1-\gamma w)\dfrac{u(t)}{k+u(t)} - \dfrac{v(t)}{k'+v(t)}\right), & \text{in } (0,T), \\ (u(0),v(0)) &= (u_0,v_0) \in \mathbb{R}_+ \times \mathbb{R}_+. \end{cases} \tag{1.38}$$

Moreover, the cost functional to be minimized is given by

$$\mathcal{J}(v,w,\tau) = \frac{1}{2}\int_0^\tau \|(v-v_Q)(t)\|^2\,dt + \frac{1}{2r}\int_{\tau-r}^\tau \|(v-v_d)(t)\|^2\,dt + \frac{1}{2}\int_0^\tau \|w(t)\|^2\,dt. \tag{1.39}$$

Where (1.39) corresponds to the conventional functional in optimal theory when r tends to 0 (see [73]). Similarly as in Chapters 2 and 3, we set $\tau \in [r,T]$ to be treatment time of each cycle, however, T is the final treatment time.

So our main problem is

$$\text{minimize } \mathcal{J} \text{ associated to } (1.38). \tag{1.40}$$

First, we start with the following assumptions

(E) The constants $\kappa, L > 0$, $k, k' \geq 0$, $0 \leq \gamma \leq 1$, and the function F is positive bounded continuous function; i.e., there exist two positive constants F_1 and F_2, such that $F_1 < F < F_2$. The function J is Lipschitz with respect to u such that the derivative of J with respect to u is bounded.

(F) The control $w \in \mathcal{W}_{ad} := \{w \in L^2(0,T;\mathbb{R}_+) :\ 0 \leq w \leq 1\}$.

Recall the following definition:

Definition 1.1

An ODE system $x'(t) = f(t, x(t))$ on $\mathbb{R}^n$, $x = (x_1, \dots, x_n)^\top$, $f = (f_1, \dots, f_n)^\top$ is called quasipositive, if the condition

$$x \geq 0,\ x_k = 0 \implies f_k(t, x(t)) \geq 0,$$

is verified for all $k = 1, \dots, n$.

So, starting from nonnegative initial values $(u_0, v_0) \in (\mathbb{R}_+)^2$, and since our system (1.38) is quasipositive, then the solution is nonnegative, moreover, the existence is demonstrated by Cauchy Lipschitz, thanks to Assumption (F), we have the following theorem:

Theorem 1.10 (Existence and uniqueness of solution)

Assume that Assumptions (E) and (F) hold and that $(u_0, v_0) \in \mathbb{R}_+ \times \mathbb{R}_+$. Then, System (1.38) admits a unique solution (u, v), satisfying

$$(u, v) \in (C^1([0, T], \mathbb{R}_+)^2.$$

Moreover, the control-to-state operator

$$\begin{array}{rccc} S: & \mathcal{W}_{ad} & \longrightarrow & C^1([0,T],\mathbb{R}_+)^2 \\ & w & \longmapsto & (u, v), \end{array}$$

is continuous with respect to a suitable topology.

Moreover, the existence of a solution of (1.40) is demonstrated in the proposition below.

Proposition 1.1

Let $w \in \mathcal{W}_{ad}$ and $\tau \in [r, T]$, and let (u, v) be the solution of System (1.38) corresponding to w. Then there exist $w_* \in \mathcal{W}_{ad}$ and $\tau_* \in [r, T]$, such that

$$\inf_{(w,\tau)\in\mathcal{W}_{ad}\times[r,T]} \mathcal{J}(v, w, \tau) = \mathcal{J}(v_*, w_*, \tau_*),$$

where (u_*, v_*) is the solution of (1.38) corresponding to w_*.

The natural approach consists in proving that the control-to-state operator S is Fréchet differentiable at w_* and applying the chain rule to $\mathcal{J}(v, w) = \mathcal{J}(S(v), v)$. So, let $w_* \in \mathcal{W}_{ad}$ be a solution of (1.40), with corresponding state (u^*, v^*), and let $h \in \mathcal{W}_{ad}$. In order to establish the existence of the Fréchet derivative of S at w_*, we consider the following

linearized system.

$$\begin{cases} U' = J_u(t,u^*)U - \kappa\left(-\gamma h\dfrac{u^*}{k+u^*} + (1-\gamma w_*)\dfrac{k\,U}{(k+u^*)^2} - \dfrac{k'\,V}{(k'+v^*)^2}\right), & \text{on } [0,T], \\ \epsilon V' = -FV + \kappa\left(-\gamma h\dfrac{u^*}{k+u^*} + (1-\gamma w_*)\dfrac{k\,U}{(k+u^*)^2} - \dfrac{k'\,V}{(k'+v^*)^2}\right), & \text{on } [0,T], \\ U(0) = V(0) = 0. \end{cases} \tag{1.41}$$

We demonstrate the following theorem:

Theorem 1.11

Let $w^* \in \mathcal{W}_{ad}$. Then, System (1.41) admits a unique solution

$$(U,V) \in C^1([0,T],\mathbb{R}_+)^2.$$

Now, to show that the control-to-state operator is Fréchet differentiable we take $h \in \mathcal{W}_{ad}$, set $(u_h, v_h) := S(w^* + h)$ and $(u_*, v_*) := S(w^*)$ and $(U,V) = D_w S(w^*)h$, so that we have the theorem below.

Theorem 1.12

Let (U,V) be the solution of the linearized system (1.41) corresponding to w^*. Then the remainders ρ and θ defined by

$$\rho = u_h - u_* - U \quad \text{and} \quad \theta = v_h - v_* - V,$$

satisfy

$$\|(\rho,\theta)\|^2_{L^\infty(0,T;\mathbb{R}_+)\cap H^1(0,T;\mathbb{R}_+)} \le c\,\|h\|^4_{L^2(0,T;\mathbb{R}_+)}.$$

Concerning the Fréchet differentiability of the cost functional with respect to time, we have the following proposition:

Proposition 1.2

Let $v_Q \in H^1(0,T;\mathbb{R}_+)$ and $v_d, v_* \in H^1(-r,T;\mathbb{R}_+)$. Then the mapping $\mathcal{J} : \mathcal{W}_{ad} \times [r,T] \longrightarrow \mathbb{R}_+$ is continuously Fréchet differentiable with respect to τ and

$$D_\tau \mathcal{J}(w_*,\tau_*) = \frac{1}{2}\|v(\tau_*) - v_Q(\tau_*)\|^2 + \frac{1}{2}\left(\|v(\tau_*) - v_d(\tau_*)\|^2 - \frac{1}{r}\|v(\tau_* - r) - v_d(\tau_* - r)\|^2\right).$$

In addition, we have that

$$D_\tau \mathcal{J}(w_*,\tau_*)(s - \tau_*) \ge 0 \quad \forall\ s \in [r,T].$$

The following proposition presents the result concerning the Fréchet differentiability of the cost functional with respect to the control.

Proposition 1.3

Let (w_*, τ_*) be a minimizer of $\mathcal{J}$, $h \in \mathcal{W}_{ad}$ so that $h = w - w_*$, and let (U, V) be a solution of the linearized System (1.41). Then the Fréchet derivative of the cost functional at (w_*, τ_*) with respect to the control w is given by

$$D_w\mathcal{J}(w_*, \tau_*)h = \int_0^{\tau_*} (v - v_Q)V dt + \frac{1}{r}\int_{\tau_*-r}^{\tau_*} (v - v_d)V dt + \int_0^T w_*\, h\, dt. \tag{1.42}$$

To eliminate the term V from Equation (1.42), we apply the Lagrangian principle. Using the Lagrangian function, we can formally eliminate the equality constraints given by the state System (1.38), for which we define the Lagrangian function with respective Lagrangian multipliers p and q by

$$\mathcal{L}(u, v, w, p, q) = \mathcal{J}(v, w) - \int_0^T p\left(u' - J(t, u) + \kappa\left((1 - \gamma w)\frac{u}{k + u} - \frac{v}{k' + v}\right)\right) dt$$

$$- \int_0^T q\left(\epsilon v' - F(L - v) - \kappa\left((1 - \gamma w)\frac{u}{k + u} - \frac{v}{k' + v}\right)\right) dt.$$

Proposition 1.4

Let (w_*, τ_*) be a solution of Problem (1.40), (u_*, v_*) be the solution of System (1.38) associated to w_*, and let (p, q) be two multipliers of $\mathcal{L}$. Then the adjoint system is given by

$$-p' = J_u(u_*, t)p - \kappa(1 - \gamma w)\frac{k}{(k + u_*)^2}p + \kappa(1 - \gamma w)\frac{k}{(k + u_*)^2}q, \quad \text{in } [0, T], \tag{1.43}$$

$$-\epsilon q' = (v_* - v_Q) + \frac{1}{r}\chi_{[\tau^*-r,\tau^*]}(t)(v_* - v_d) + \kappa\frac{k'}{k' + v_*}(p - q) - Fq, \quad \text{in } [0, T], \tag{1.44}$$

$$p(\tau_*) = q(\tau_*) = 0. \tag{1.45}$$

The existence of unique regular multipliers is established through the following theorem:

Theorem 1.13

Let w_* be an optimal control, and $(u_*, v_*) = S(w_*)$ be the corresponding states. Then the adjoint Problem (1.43)-(1.45) has a unique solution

$$(p, q) \in C^1([0, \tau^*]; \mathbb{R}_+)^2.$$

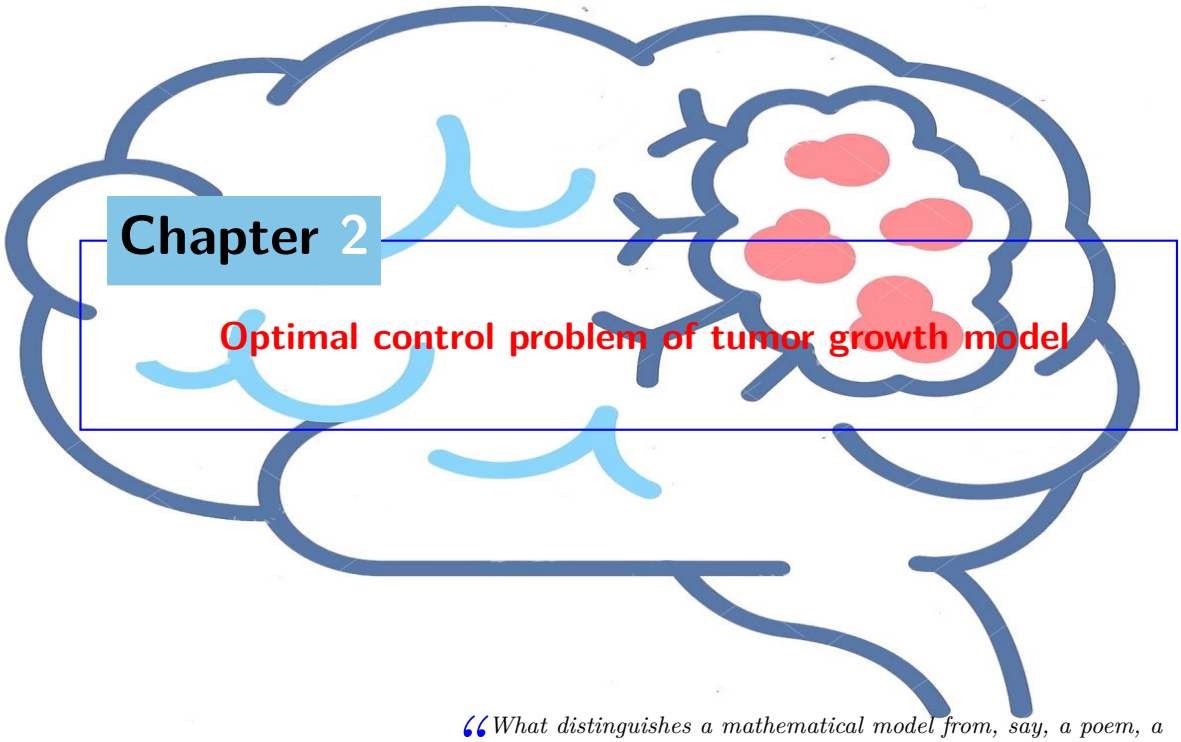
We end the theoretical part by letting (w_*, τ_*) to be a solution of Problem (1.40) with corresponding state variables $(u_*, v_*) = S(w_*)$, and adjoint variables p and q related to u_* and v_* respectively. And taking $h := w - w_* \in \mathcal{W}_{ad}$ for any $w \in \mathcal{W}_{ad}$, and (U, V) to be the linearized state variables associated to h, then we establish the following proposition:

Proposition 1.5

The optimal control w_* satisfies the following simplified first-order necessary optimality condition

$$D_w\mathcal{J}(w_*,\tau_*)h = \int_0^{\tau_*} w_*\, h\, dt + \kappa \int_0^{\tau_*} \gamma h \frac{u_*}{k+u_*}(p-q)\, dt \geq 0.$$

To demonstrate the choice of the control, we end this chapter with numerical simulations which verify in both considered cases; i.e., when J and F are constants and when they are functions so that F is chosen as a periodic function. We can see in both Figures 4.2b and 4.3d that the extracellular lactate concentration drops with time when we increase the dose of the inhibitor. However, in Figures 4.2a and 4.3c, we observe that as we increase the dose of the inhibitor the intracellular lactate concentration increases so leading to acidosis of the intracellular domain which inhibits tumor progression.



Chapter 2

Optimal control problem of tumor growth model

"What distinguishes a mathematical model from, say, a poem, a song, a portrait or any kind of "model", is that the mathematical model is an image or picture of reality painted with logical symbols instead of with words, sounds or watercolors."

John L. Casti

Our aim in this chapter is to study an optimal control problem for a tumor growth model. The state system couples an Allen-Cahn equation and a reaction diffusion equation that model the evolution of tumor in the presence of nutrient supply. Elimination of cancer cells via cytotoxic drug is considered and the concentration of the cytotoxic drug is represented as a control variable. To achieve the desired tumor density with an optimal drug dosage, we consider a cost functional that depends on a free time variable representing the treatment time to be optimized.

2.1 Introduction

2.1.1 Literature

Nowadays, various strategies are being developed in the fight against cancer, including experimental and theoretical techniques.

From the first decades of the twentieth century to the present day, and in light of the illustration of experimental results from different areas of cancer research, scientists have to resort to mathematical modeling. Thus, the power of mathematical modeling is used by scientists to distinguish between different mechanisms underlying important aspects of tumor development. Applied mathematics has the potential to reduce experimentation and provide scientists with information that can help control tumors by developing mathematical models that describe tumor growth (see [3, 6, 19, 29]).

The integration of mathematical investigations and experimental work, have together modeled our understanding of tumor development and helped to achieve some cancer treatments, so far, it may also be possible to optimize treatment for each individual, through collaboration between biologists, clinicians, and the development of mathematical models of tumor growth (see [9–12, 15]).

The Allen-Cahn equation (see [13])

$$\frac{\partial u}{\partial t} - \Delta u + f(u) = 0, \quad \text{in } \Omega \times (0,T), \tag{2.1}$$

is important in materials science, where Ω represents the volume occupied by the material, u is an order parameter corresponding, for example, to the ordering of atoms per unit cell in a crystal lattice, and the function f is the derivative of a double-well potential F whose wells correspond to the phases of the material is given by

$$F(s) = \frac{1}{4}\left(s^2 - 1\right)^2.$$

Furthermore, this equation is important in modeling tumor growth (see [23]).

The Cahn-Hilliard equation

$$\frac{\partial u}{\partial t} = -\Delta\left(\Delta u - f(u)\right),$$

was first introduced by Cahn and Hilliard (see [14]) to explain the phenomenon of spinodal decomposition observed in binary metal alloys.

The phase-field theory is used to derive models for problems with moving interfaces, specifically, they have been considered in the studies of tumor growth (see [16,37,38,63]).

The complexity of oncology has attracted the interest of mathematicians to guide the experimental research necessary for therapy development. Mathematical models, especially those involving phase separation models, have been used to help develop therapeutic strategies for cancer (see [23]), in particular, the authors in [43] considered the following Cahn-Hilliard model for tumor growth

$$\begin{cases} \partial_t \varphi = \Delta \mu + (\mathcal{P}\sigma - \mathcal{A} - \alpha u)\, h(\varphi), & \text{in } \Omega \times (0,T), \\ \mu = A\Psi'(\varphi) - B\Delta\varphi, & \text{in } \Omega \times (0,T), \\ \partial_t \sigma = \Delta\sigma - \mathcal{C}\sigma h(\varphi) + \beta\left(\sigma_s - \sigma\right), & \text{in } \Omega \times (0,T), \\ \partial_\nu \varphi = \partial_\nu \sigma = \partial_\nu \mu = 0, & \text{on } \Gamma \times (0,T), \\ \varphi(0) = \varphi_0,\ \sigma(0) = \sigma_0, & \text{in } \Omega, \end{cases} \tag{2.2}$$

along with the relaxed cost functional

$$\begin{aligned} \mathcal{J}_r(\varphi, u, \tau) = {} & \frac{\beta_Q}{2}\int_0^\tau \int_\Omega |\varphi - \varphi_Q|^2 dx\, dt + \frac{\beta_\Omega}{2}\frac{1}{r}\int_{\tau-r}^\tau \int_\Omega |\varphi - \varphi_\Omega|^2 dx\, dt \\ & + \frac{\beta_S}{2}\frac{1}{r}\int_{\tau-r}^\tau \int_\Omega (1+\varphi)\, dx\, dt + \frac{\beta_u}{2}\int_0^T \int_\Omega |u|^2 dx\, dt + \beta_T \tau. \end{aligned}$$

The authors have shown the existence of a solution for the problem $min\mathcal{J}_r(\varphi, u, \tau)$ associated to (2.2), in addition, they derived a simplified first-order necessary optimality condition.

Many mathematical models involving optimal control for tumor models have been studied. A distributed optimal control problem for a nonlocal convective Cahn-Hilliard equation with degenerate mobility and singular potential in three spatial dimensions is studied in [69]. A distributed optimal control of the Cahn-Hilliard system including the case of a double homogeneous energy density, where a first-order optimality condition for the original problem was derived by a boundary value process, was also studied in [53]. A distributed optimal control problem for a diffuse interface model of tumor growth was studied in [21]. We can also refer the reader to many problems dealing with tumor growth models [2, 20, 22, 24, 33, 34, 41–43, 55, 64] and the references therein.

We are interested in studying tumor growth based on a phase-field model, for this purpose, we proceed in this work and leverage the mathematical model presented in [43].

2.1.2 Position of our problem

Cancer treatments include surgery, immunotherapy (boosting the immune system), radiation therapy (using radiation to kill cancer cells), and chemotherapy (using drugs to kill cancer cells). The latter three treatments are used in cycles, where a cycle is a period of treatment followed by an extended period of rest to allow the patient's body to produce new healthy cells. The goal of these treatments is to reduce the size of the tumor until surgery can be performed. Further treatments may be necessary to eliminate any cancer cells that remain after surgery.

Cancer drugs are known to cause the death of rapidly dividing normal cells, such as in bone marrow, hair follicles, which impairs the immune system and is fatal for the patient. In addition, a high dose of these drugs may cause resistance to treatment, so the shortest treatment time along with the optimal drug dose must be found. Thus, to optimize the growth of the tumor, the final distribution of cancer cells, the number of drugs administered to the patient, and the treatment time of a cycle, we consider a system that couples the variation of tumor density with the concentration of nutrient delivery to the tumor cells in the presence of cytotoxic drug (control). For $T > 0$, which is the maximum treatment time, in a bounded domain $\Omega \subset \mathbb{R}^n, n = 1, 2, 3$ with C^2- boundary Γ, we have

$$\partial_t \varphi - B\Delta\varphi + f(\varphi) = (\mathcal{P}\sigma - \mathcal{A} - \alpha u)h(\varphi), \quad \text{in} \quad \Omega \times (0,T) =: Q, \tag{2.3}$$

$$\partial_t \sigma = \Delta\sigma - \mathcal{C}\sigma h(\varphi) + \beta(\sigma_s - \sigma), \quad \text{in} \quad Q, \tag{2.4}$$

$$\partial_\nu \varphi = \partial_\nu \sigma = 0, \quad \text{on} \quad \Gamma \times (0,T), \tag{2.5}$$

$$\varphi(0) = \varphi_0, \ \sigma(0) = \sigma_0, \quad \text{in} \quad \Omega. \tag{2.6}$$

Here, $\varphi = \varphi_C - \varphi_D$, where φ_C and φ_D are the concentrations of phases C and D, respectively. The double-well potential $F(s) = 4^{-1}(s^2-1)^2$ of derivative f allows the coexistence of tumor and healthy cells, so that $f(s) = s^3 - s$. The constant α is positive, $B = \lambda l^2$ is the diffusion coefficient of tumor cells, where λ and l denote tumor mobility and interface width, respectively. σ is the concentration of an unspecified chemical species that serves as a nutrient for tumor cells, while u denotes the concentration of cytotoxic drugs. The function $h(\varphi)$ verifying $h(-1) = 0$ and $h(1) = 1$ is an interpolation function, and the parameters $\mathcal{P}, \mathcal{A}, \mathcal{C}, \beta$ denote the constant proliferation rate, apoptosis rate, nutrient consumption rate and nutrient supply rate, respectively. The term $h(\varphi)\mathcal{P}\sigma$ models the

proliferation of tumor cells which is proportional to the concentration of nutrient, the term $h(\varphi)A$ models the apoptosis of tumor cells, and $\mathcal{C}h(\varphi)\sigma$ models the consumption of nutrient by tumor cells only. The term $\alpha u h(\varphi)$ models the elimination of tumor cells by the cytotoxic drug at a constant rate α. On the other hand, σ_s denotes the nutrient concentration in a pre-existing vasculature, and $\beta(\sigma_s - \sigma)$ models the delivery of nutrients from blood vessels when $\sigma_s > \sigma$ and the removal of nutrients from the domain Ω when $\sigma_s < \sigma$. In this work, the function u will act as our control. For realistic applications, the control $u : [0, T] \longrightarrow [0, 1]$, should be spatially constant, where $u = 1$ represents full dosage and $u = 0$ represents no dosage.

In Equation (2.3), the function h is defined over $\mathbb{R}$, but we are only interested here in the physical domain, which is $[-1, 1]$, and since the choice of h is not unique, we can take it, for example, as in Figure 2.1 illustrating the phase transition.

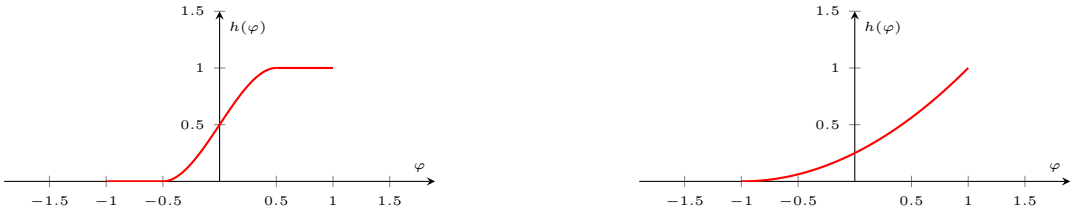


Figure 2.1 – Some examples for the interpolation function h

Remark 2.1

1. When the right hand side of (2.3) vanishes, we obtain the Allen-Cahn Equation (2.1).
2. Note that, in [43], the authors considered a Cahn-Hilliard equation coupled with a diffusion equation for tumor growth. However, in our work, we consider coupled Allen-Cahn and diffusion equations which can also be applied to tumor growth. Compared to the Cahn-Hilliard model studied in [43], this allows to simplify the mathematical analysis, while still keeping important aspects of phase separation. The numerical analysis of the model and simulations will be addressed in future works.

Now, we consider the objective functional $\mathcal{J}_r$ as in [43]. For positive constants r, β_u, β_T, and nonnegative constants $\beta_Q, \beta_\Omega, \beta_S$

$$\begin{aligned}\mathcal{J}_r(\varphi, u, \tau) =& \frac{\beta_Q}{2}\int_0^\tau\int_\Omega |\varphi - \varphi_Q|^2 dx\,dt + \frac{\beta_\Omega}{2}\frac{1}{r}\int_{\tau-r}^\tau\int_\Omega |\varphi - \varphi_\Omega|^2 dx\,dt \\ &+ \frac{\beta_S}{2}\frac{1}{r}\int_{\tau-r}^\tau\int_\Omega 1 + \varphi(x) dx\,dt + \frac{\beta_u}{2}\int_0^T\int_\Omega |u|^2 dx\,dt + \beta_T\tau.\end{aligned} \tag{2.7}$$

Here, $\tau \in [r, T]$ represents treatment time, φ_Q represents a desired evolution for the tumor cells while φ_Ω represents a desired final distribution. The first two terms of $\mathcal{J}_r$ are of standard tracking type often considered in the parabolic optimal control literature (see [73]) and the third term of $\mathcal{J}_r$ measures the size of the tumor at the end of treatment. The fourth term penalizes high concentrations of the cytotoxic drug, and the fifth term of $\mathcal{J}_r$ penalizes long treatment times (see [43]).

In this chapter, we study the optimal control problem

$$\text{minimize } \mathcal{J}_r(\varphi, u, \tau) \text{ subject to } (2.3) - (2.6),\ u \in \mathcal{U}_{ad},\ \tau \in [r, T],$$

where the space of admissible controls $\mathcal{U}_{ad}$ is defined by:

$$\mathcal{U}_{ad} := \{u \in L^\infty(Q) : 0 \leq u \leq 1, \text{ a.e. in } Q\}.$$

Assumptions

(A) The initial conditions satisfy, $\varphi_0, \sigma_0 \in H^1(\Omega)$, with $0 \leq \sigma_0 \leq 1$ a.e. $x \in \Omega$. The target functions $\varphi_\Omega, \varphi_Q \in L^2(Q)$, and the vasculature nutrient concentration σ_s satisfies $0 \leq \sigma_s \leq 1$, a.e. in Q.

(B) The interpolation function $h : \mathbb{R} \to [0, 1]$ is continuously differentiable and Lipschitz with Lipschitz constant M. In addition, the parameters $\mathcal{P}, \mathcal{A}, \mathcal{C}, \beta$ are non negative constants, and α is a positive constant.

Throughout this work, the same letter c (and, sometimes, $c', c'', c_1, c_2, c_{p,q}$) denotes a constant that may vary in the same line.

We denote by $\langle\phi\rangle$ the spatial average of a function ϕ in $L^1(\Omega)$,

$$\langle\phi\rangle = \frac{1}{\text{Vol}(\Omega)} \int_\Omega \phi \, dx.$$

2.2 Existence of solution

In this section, we study the existence of a unique weak solution of System (2.3)-(2.6). More precisely, we will prove the following theorem:

Theorem 2.1 (Existence and uniqueness of weak solution)

Assume that Assumptions (A) and (B) hold. Then, Problem (2.3)-(2.6) admits a unique weak solution (φ, σ) such that $0 \leq \sigma \leq 1$ and

$$(\varphi, \sigma) \in \mathcal{Y} := \left(L^2(0, T; H^2(\Omega)) \cap L^\infty(0, T; H^1(\Omega)) \cap H^1(0, T; L^2(\Omega))\right)^2.$$

Moreover, the control-to-state operator

$$\begin{array}{rccc} S: & L^2(Q) & \longrightarrow & \mathcal{Y} \\ & u & \longmapsto & (\varphi, \sigma) \end{array}$$

is continuous for the corresponding topology.

Proof. We employ the Faedo-Galerkin method (see [26]) to show the existence of solution of the parabolic System (2.3)-(2.6).

Existence of weak solution of (2.3)-(2.6).

The variational problems associated with (2.4) and (2.3), are given by:

$$\int_\Omega (\partial_t \sigma)\xi dx + \int_\Omega \nabla\sigma \cdot \nabla\xi dx + \beta \int_\Omega \sigma\xi dx = -\mathcal{C}\int_\Omega h(\varphi)\sigma\xi dx + \beta\int_\Omega \sigma_s \xi dx \tag{2.8}$$

and

$$\int_\Omega (\partial_t \varphi)\xi dx + B\int_\Omega \nabla\varphi\cdot\nabla\xi dx + \int_\Omega f(\varphi)\xi dx = \int_\Omega \left(\mathcal{P}\sigma h(\varphi) - \mathcal{A}h(\varphi) - \alpha u h(\varphi)\right)\xi dx, \tag{2.9}$$

for almost every $t \in (0,T)$ and for all $\xi \in H^1(\Omega)$.

A priori Estimates:

Estimate 1. Formally putting $\xi = 2\sigma$ in (2.8) and using Assumption (B), we get

$$\frac{d}{dt}\|\sigma\|^2_{L^2(\Omega)} + 2\|\nabla\sigma\|^2_{L^2(\Omega)} + 2\beta\|\sigma\|^2_{L^2(\Omega)} \le \mathcal{C}\|h(\varphi)\|_{L^\infty}\|\sigma\|^2_{L^2(\Omega)} + \beta^2\|\sigma_s\|^2_{L^2(\Omega)} + \|\sigma\|^2_{L^2(\Omega)}.$$

Setting $c_0 = min(2, 2\beta)$ and integrating over $[0,t]$, we find

$$\|\sigma(t)\|^2_{L^2(\Omega)} + c_0\left(\|\nabla\sigma\|^2_{L^2(0,t;L^2(\Omega))} + \|\sigma\|^2_{L^2(0,t;L^2(\Omega))}\right) \le c\|\sigma\|^2_{L^2(\Omega)} + \beta^2\|\sigma_s\|^2_{L^2(0,t;L^2(\Omega))} + \|\sigma_0\|^2_{L^2(\Omega)}.$$

Using Gronwall's lemma, we have

$$\|\sigma(t)\|^2_{L^2(\Omega)} + c_0\|\sigma\|^2_{L^2(0,t;H^1(\Omega))} \le \left(\beta^2\|\sigma_s\|^2_{L^2(0,t;L^2(\Omega))} + \|\sigma_0\|^2_{L^2(\Omega)}\right)e^{ct}. \tag{2.10}$$

Putting $\xi = 2\varphi$ in (2.9), we find

$$\frac{d}{dt}\|\varphi\|^2_{L^2(\Omega)} + 2B\|\nabla\varphi\|^2_{L^2(\Omega)} \le \|h(\varphi)\|_\infty\left(\mathcal{P}^2\|\sigma\|^2_{L^2(\Omega)} + \alpha^2\|u\|^2_{L^2(\Omega)} + \|\varphi\|^2_{L^2(\Omega)}\right)$$
$$+\mathcal{A}^2\|h(\varphi)\|^2_{L^2(\Omega)} + \|\varphi\|^2_{L^2(\Omega)}.$$

From (2.10), we know that

$$\|\sigma\|^2_{L^2(0,t;L^2(\Omega))} = \int_0^t \|\sigma(s)\|^2_{L^2(\Omega)}\,ds \le \frac{c'}{c}(e^{ct}-1).$$

Now, integrating over $[0,t]$ and since h is C^1, $u \in \mathcal{U}_{ad}$, we have

$$\|\varphi(t)\|^2_{L^2(\Omega)} + 2B\|\nabla\varphi\|^2_{L^2(0,t;L^2(\Omega))} \le \mathcal{A}^2\|h(\varphi)\|^2_{L^2(0,t;L^2(\Omega))} + \|\varphi_0\|^2_{L^2(\Omega)}$$
$$+\|h(\varphi)\|_\infty\left(\mathcal{P}^2\|\sigma\|^2_{L^2(0,t;L^2(\Omega))} + \alpha^2\|u\|^2_{L^2(0,t;L^2(\Omega))}\right) + \|\varphi\|^2_{L^2(0,t;L^2(\Omega))}\left(1 + \|h(\varphi)\|_\infty\right).$$

Thanks to Gronwall's inequality, we infer

$$\|\varphi(t)\|^2_{L^2(\Omega)} + 2B\|\nabla\varphi\|^2_{L^2(0,t;L^2(\Omega))} \le c + ce^{ct}.$$

Estimate 2. Putting $\xi = 2\partial_t\sigma$ in (2.8), using Young's inequality, and Assumption (B), we find

$$2\|\partial_t\sigma\|^2_{L^2(\Omega)} + \frac{d}{dt}\|\nabla\sigma\|^2_{L^2(\Omega)} + \beta\frac{d}{dt}\|\sigma\|^2_{L^2(\Omega)} \le \mathcal{C}\|h(\varphi)\|_\infty\frac{d}{dt}\|\sigma\|^2_{L^2(\Omega)} + \beta^2\|\sigma_s\|^2_{L^2(\Omega)} + \|\partial_t\sigma\|^2_{L^2(\Omega)}.$$

Setting $c_1 = min(1, \beta)$, integrating over $[0, t]$ and using (2.10), we find

$$\|\partial_t \sigma\|^2_{L^2(0,t;L^2(\Omega))} + c_1 \|\sigma\|^2_{L^2(0,t;H^1(\Omega))} \leq c_0 \|\sigma_0\|^2_{H^1(\Omega)} + \beta^2 \|\sigma_s\|^2_{L^2(0,t;L^2(\Omega))} + e^{ct}.$$

Putting $\xi = 2\partial_t \varphi$ in (2.9), we obtain

$$\begin{aligned} 2\|\partial_t\varphi\|^2_{L^2(\Omega)} + B\frac{d}{dt}\|\nabla\varphi\|^2_{L^2(\Omega)} \leq \|h(\varphi)\|_\infty \left(\mathcal{P}^2\|\sigma\|^2_{L^2(\Omega)} + \alpha^2\|u\|^2_{L^2(\Omega)} + \|\partial_t\varphi\|^2_{L^2(\Omega)}\right) \\ + \mathcal{A}^2\|h(\varphi)\|^2_{L^2(\Omega)} + \frac{d}{dt}\|\varphi\|^2_{L^2(\Omega)}. \end{aligned} \tag{2.11}$$

Equivalently

$$\|\partial_t\varphi\|^2_{L^2(\Omega)} + B\frac{d}{dt}\|\nabla\varphi\|^2_{L^2(\Omega)} \leq \|h(\varphi)\|_\infty \left(\mathcal{P}^2\|\sigma\|^2_{L^2(\Omega)} + \alpha^2\|u\|^2_{L^2(\Omega)}\right) + \mathcal{A}^2\|h(\varphi)\|^2_{L^2(\Omega)} + \frac{d}{dt}\|\varphi\|^2_{L^2(\Omega)}.$$

Multiplying Equation (2.3) by $\dfrac{1}{\text{Vol}(\Omega)}$ and integrating over Ω yield

$$\frac{d}{dt}\langle\varphi\rangle = -\langle f(\varphi)\rangle + \langle(\mathcal{P}\sigma - \mathcal{A} - \alpha u)\, h(\varphi)\rangle.$$

We already know that

$$\frac{d}{dt}\langle\varphi\rangle^2 = 2\langle\varphi\rangle\frac{d}{dt}\langle\varphi\rangle \leq \langle\varphi\rangle^2 + \left(\frac{d}{dt}\langle\varphi\rangle\right)^2 \leq \langle\varphi\rangle^2 + \langle f(\varphi)\rangle^2 + \langle(\mathcal{P}\sigma - \mathcal{A} - \alpha u)\, h(\varphi)\rangle^2.$$

Using the facts that

$$\langle\varphi\rangle^2 \leq \|\varphi\|^2_{L^2(\Omega)}$$

and

$$\langle f(\varphi)\rangle^2 \leq \|\varphi\|^2_{H^1(\Omega)},$$

we write

$$\frac{d}{dt}\langle\varphi\rangle^2 \leq \|\varphi\|^2_{L^2(\Omega)} + \|\varphi\|^2_{H^1(\Omega)} + \frac{\|h(\varphi)\|^2_{L^2(\Omega)}}{\text{Vol}(\Omega)^2}\left(\mathcal{P}^2\|\sigma\|^2_{L^2(\Omega)} + \mathcal{A}^2\text{Vol}(\Omega)^2 + \alpha^2\|u\|^2_{L^2(\Omega)}\right).$$

Setting $c' = min(B, 1)$ in (2.11), we have

$$\begin{aligned} &2\|\partial_t\varphi\|^2_{L^2(\Omega)} + c'\frac{d}{dt}\left(\|\nabla\varphi\|^2_{L^2(\Omega)} + \langle\varphi\rangle^2\right) \leq \mathcal{P}^2\|\sigma\|^2_{L^2(\Omega)} + \alpha^2\|u\|^2_{L^2(\Omega)} + \frac{d}{dt}\|\varphi\|^2_{L^2(\Omega)} \\ &+ \|\varphi\|^2_{L^2(\Omega)} + \|\varphi\|^2_{H^1(\Omega)} + \frac{\|h(\varphi)\|^2_{L^2(\Omega)}}{\text{Vol}(\Omega)^2}\left(\mathcal{P}^2\|\sigma\|^2_{L^2(\Omega)} + \mathcal{A}^2\text{Vol}(\Omega)^2 + \alpha^2\|u\|^2_{L^2(\Omega)}\right) \\ &\leq c\|\sigma\|^2_{L^2(\Omega)} + c\|u\|^2_{L^2(\Omega)} + \mathcal{A}^2\|h(\varphi)\|^2_{L^2(\Omega)} + \|\varphi\|^2_{L^2(\Omega)} + \|\varphi\|^2_{H^1(\Omega)} + \frac{d}{dt}\|\varphi\|^2_{L^2(\Omega)}. \end{aligned}$$

Finally, integrate over $[0, t]$, and since φ is bounded in $L^2(0,t;L^2(\Omega)) \cap L^\infty(0,t;L^2(\Omega))$ and σ is bounded in $L^2(0,t;L^2(\Omega))$ in addition to Assumption (B), we find

$$2\|\partial_t\varphi\|^2_{L^2(\Omega)} + c'\|\varphi(t)\|^2_{H^1(\Omega)} \leq e^{ct}.$$

The last inequality yields that $\varphi \in L^\infty(0,t;H^1(\Omega))$ and $\partial_t\varphi \in L^2(0,t;L^2(\Omega))$.

Estimate 3. Equations (2.3) and (2.4) can be written in the following forms:

$$\begin{cases} -\Delta\sigma &= -\partial_t\sigma - \mathcal{C}\sigma h(\varphi) + \beta\,(\sigma_s - \sigma)\,, & \text{in } Q, \\ -B\Delta\varphi &= \partial_t\varphi + \varphi - \varphi^3 + (\mathcal{P}\sigma - \mathcal{A} - \alpha u)\,h(\varphi), & \text{in } Q. \end{cases}$$

Since the right hand sides are in $L^2(\Omega)$ for a.e. $t \in (0,T)$ and $\partial_\nu\sigma = \partial_\nu\varphi = 0$ on Γ, then the elliptic regularity (see [61]) yields, $(\sigma,\varphi) \in H^2(\Omega)^2$ for a.e. $t \in (0,T)$, and there exists $K > 0$ such that

$$\|\sigma\|^2_{H^2(\Omega)} \leq K\left(\|\partial_t\sigma\|^2_{L^2(\Omega)} + \|\sigma\|^2_{L^2(\Omega)} + \|\sigma_s\|^2_{L^2(\Omega)}\right)$$

and

$$\|\varphi\|^2_{H^2(\Omega)} \leq K\left(\|\partial_t\varphi\|^2_{L^2(\Omega)} + \|\sigma\|^2_{L^2(\Omega)} + \|h(\varphi)\|^2_{L^2(\Omega)} + \|u\|^2_{L^2(\Omega)} + \|f(\varphi)\|^2_{L^2(\Omega)}\right).$$

It follows, from Estimates 1 and 2, that $(\sigma,\varphi) \in L^2(0,T;H^2(\Omega))^2$. In particular, since $(\partial_t\sigma, \partial_t\varphi) \in L^2(0,T;L^2(\Omega))^2$, then, using interpolation result, we deduce that $(\sigma,\varphi) \in C^0([0,T];H^1(\Omega))^2$ (see [36]). Therefore, we get

$$(\sigma,\varphi) \in \left(L^2(0,T;H^2(\Omega)) \cap H^1(0,T;L^2(\Omega)) \cap C^0([0,T];H^1(\Omega))\right)^2.$$

We will use Faedo-Galerkin method (see [26]) to show the existence of weak solution of the parabolic System (2.3)-(2.6). First, the variational formulations associated with (2.3) and (2.4) are given by

$$\int_\Omega \partial_t\varphi\,\xi dx + B\int_\Omega \nabla\varphi\cdot\nabla\xi dx + \int_\Omega f(\varphi)\xi dx = \mathcal{P}\int_\Omega \sigma h(\varphi)\xi dx - \mathcal{A}\int_\Omega h(\varphi)\xi dx - \alpha\int_\Omega uh(\varphi)\xi dx$$

and

$$\int_\Omega \partial_t\sigma\xi dx + \int_\Omega \nabla\sigma\cdot\nabla\xi dx = -\int_\Omega (\mathcal{C}h(\varphi) + \beta)\,\sigma\xi dx + \beta\int_\Omega \sigma_s\xi dx \tag{2.12}$$

for almost every $t \in (0,T)$ and for all $\xi \in H^1(\Omega)$.

The variational approximate problem.

Let ω_j be an eigenfunction of the following problem

$$\begin{cases} -\Delta\omega_j = \lambda_j^2\omega_j, & \text{in} \quad \Omega, \\ \partial_\nu\omega_j = 0, & \text{on} \quad \Gamma, \end{cases}$$

such that

$$\|\omega_j\|^2_{L^2(\Omega)} = \int_\Omega |\omega_j|^2 dx = 1.$$

The operator $L_N := -\Delta$ with Neumann boundary condition is self adjoint with compact resolvent from $L^2_0(\Omega) = \{u \in L^2(\Omega) : \langle u\rangle = 0\}$ into itself, then its eigenfunctions $\{\omega_j\}_{j=1}^\infty$ corresponding to the eigenvalues $\{\lambda_j\}_{j=1}^\infty$ form an orthonormal basis in $L^2(\Omega)$ and an orthogonal basis in

$$D(L_N^{1/2}) = H^1_N(\Omega) = \{\varphi \in H^1(\Omega) : \langle\varphi\rangle = 0 \text{ and } \partial_\nu\varphi = 0 \text{ on } \Gamma\}.$$

Consider the finite dimensional eigenspaces $V_n := \text{span}\ \{\omega_j,\ j = 1, \dots, n\}$ and the projection P_n, then $V_n \subset V_{n+1}$ and $\overline{\bigcup_n V_n} = H^1_N(\Omega)$ (see [26]). Set $\varphi_0^n = P_n\varphi_0$, $\sigma_0^n = P_n\sigma_0$, $\sigma_s^n = P_n\sigma_s$ and $u_n = P_nu$, such that $u_n \to u$ strongly in $L^2(0,T;L^2(\Omega))$, $\sigma_s^n \to \sigma_s$ in $L^2(0,T;L^2(\Omega))$, $\sigma_0^n \to \sigma_0$ in $L^2(\Omega)$ and $\varphi_0^n \to \varphi_0$ in $L^2(\Omega)$.

The approximated variational problem is given by

$$\begin{aligned}&\int_\Omega \partial_t\varphi_n\,\omega_j dx + B\int_\Omega \nabla\varphi_n\cdot\nabla\omega_j dx + \int_\Omega f(\varphi_n)\omega_j dx\\ &= \mathcal{P}\int_\Omega \sigma_n h(\varphi_n)\omega_j dx - \mathcal{A}\int_\Omega h(\varphi_n)\omega_j dx - \alpha\int_\Omega u_n h(\varphi_n)\omega_j dx\end{aligned} \tag{2.13}$$

and

$$\int_\Omega \partial_t\sigma_n\omega_j dx + \int_\Omega \nabla\sigma_n\cdot\nabla\omega_j dx = -\int_\Omega \left(\mathcal{C}h(\varphi_n)+\beta\right)\sigma_n\omega_j dx + \beta\int_\Omega \sigma_s^n\omega_j dx, \tag{2.14}$$

where $\varphi_n = \sum_{i=1}^n a_{n,i}(t)\omega_i$, $\sigma = \sum_{i=1}^n b_{n,i}(t)\omega_i \in V_n$, $a_{n,i} = (\varphi_n,\omega_i)$ and $b_{n,i} = (\sigma_n,\omega_i)\ \forall\, i = 1,\dots,n$. We also have $\|P\varphi_0\|_{H^1(\Omega)} \le \|\varphi_0\|_{H^1(\Omega)}$ according to Bessel's inequality. Equations (2.13) and (2.14) are equivalent to find $a_n(t)$ and $b_n(t)$ satisfying

$$\begin{aligned}&\frac{d}{dt}\sum_{i=1}^n a_{n,i}\int_\Omega \omega_i\omega_j dx + B\sum_{i=1}^n a_{n,i}\int_\Omega \nabla\omega_i\cdot\nabla\omega_j dx + \sum_{i=1}^n a_{n,i}\int_\Omega\left(\sum_{i=1}^n a_{n,i}\omega_i - 1\right)^2\omega_i\omega_j dx\\ &= \mathcal{P}\sum_{i=1}^n b_{n,i}\int_\Omega h(\sum_{i=1}^n a_{n,i}\omega_i)\omega_i\omega_j dx - \mathcal{A}\int_\Omega h(\sum_{i=1}^n a_{n,i}\omega_i)\omega_j dx\\ &-\alpha\int_\Omega u_n h(\sum_{i=1}^n a_{n,i}\omega_i)\omega_j dx + \sum_{i=1}^n a_{n,i}\int_\Omega \omega_i\omega_j dx\end{aligned} \tag{2.15}$$

and

$$\begin{aligned}&\frac{d}{dt}\sum_{i=1}^n b_{n,i}\int_\Omega \omega_i\omega_j dx + \sum_{i=1}^n b_{n,i}\int_\Omega \nabla\omega_i\cdot\nabla\omega_j dx\\ &= -\sum_{i=1}^n b_{n,i}\int_\Omega\left(\mathcal{C}h(\sum_{i=1}^n a_{n,i}\omega_i)+\beta\right)\omega_i\omega_j dx + \beta\int_\Omega \sigma_s^n\omega_j dx, \quad \omega_j,\omega_i \in V_n.\end{aligned} \tag{2.16}$$

(2.15) and (2.16) can be written in vector form as follows

$$\frac{da_n(t)}{dt}I_n = -Ba_n(t)W_n + \mathcal{P}b_n(t)M_n - \mathcal{A}H_n - \alpha U_n + a_n(t)fI_n$$

and

$$\frac{db_n(t)}{dt}I_n = -b_n(t)W_n - b_n(t)J_n + \beta S_n,$$

where

$$\begin{cases} (I_n)_{i,j} = \int_\Omega \omega_i\omega_j dx, \quad (W_n)_{i,j} = \int_\Omega \nabla\omega_i \cdot \nabla\omega_j dx, \\ (M_n)_{i,j} = \int_\Omega h\left(\sum_{i=1}^n a_{n,i}\omega_i\right)\omega_i\omega_j dx, \quad (H_n)_j = \int_\Omega h\left(\sum_{i=1}^n a_{n,i}\omega_i\right)\omega_j dx, \\ (J_n)_{i,j} = \int_\Omega \left(\mathcal{C}h(\sum_{i=1}^n a_{n,i}\omega_i) + \beta\right)\omega_i\omega_j dx, \quad (S_n)_j = \int_\Omega \sigma_s^n\omega_j dx, \\ (U_n)_j = \int_\Omega u_n h\left(\sum_{i=1}^n a_{n,i}\omega_i\right)\omega_j dx. \end{cases}$$

Recall that $0 \le \sigma_n \le 1$ and $0 \le u_n \le 1$, a.e. in Q and h is continuously differentiable with values between 0 and 1, so we have a system of ODEs in the following form

$$\begin{cases} a_n'(t) &= f(t, a_n(t), b_n(t)) \\ b_n'(t) &= g(t, a_n(t), b_n(t)). \end{cases}$$

It is obvious that $F = (f, g)$ is locally Lipschitz with respect to the second variable, and the system of ODEs has a unique local solution $(a_n, b_n) \in [0, T^*]^2$ for all $T^* \in [0, T]$. Multiplying Equation (2.16) by $b_{n,j}$ and summing over j from 1 to n, we find

$$\|\sigma_n(t)\|^2_{L^2(\Omega)} + c\,\|\sigma_n\|^2_{L^2(0,t;H^1(\Omega))} \le \left(\beta^2\,\|\sigma_s^n\|^2_{L^2(0,t;L^2(\Omega))} + \|\sigma_n(0)\|^2_{L^2(\Omega)}\right)e^t. \tag{2.17}$$

We find that σ_n is bounded in $L^\infty(0,T;L^2(\Omega)) \cap L^2(0,T;H^1(\Omega))$. Similarly, multiply Equation (2.15) by $a_{n,j}$ and sum over j from 1 to n, we get

$$\begin{aligned} &\|\varphi_n(t)\|^2_{L^2(\Omega)} + \|\nabla\varphi\|^2_{L^2(0,t;L^2(\Omega))} \le \|\varphi_n(0)\|^2_{L^2(\Omega)} + \mathcal{P}^2\,\|\sigma_n\|^2_{L^2(0,t;L^2(\Omega))} \\ &+\mathcal{A}^2\,\|h(\varphi_n)\|^2_{L^2(0,t;L^2(\Omega))} + \alpha^2\,\|u_n\|^2_{L^2(0,t;L^2(\Omega))} + c'\,\|\varphi_n\|^2_{L^2(0,t;L^2(\Omega))} \le ce^{c't}. \end{aligned} \tag{2.18}$$

It follows, that φ_n is bounded in $L^\infty(0,t;L^2(\Omega)) \cap L^2(0,t;H^1(\Omega))$. Therefore the solution $(a_n(t), b_n(t))$ is global in $[0,T]$. Multiply Equation (2.16) by $\dfrac{db_{n,j}(t)}{dt}$ and sum over j from 1 to n, we get

$$\|\partial_t\sigma_n\|^2_{L^2(0,t;L^2(\Omega))} + \|\nabla\sigma_n(t)\|^2_{L^2(\Omega)} \le (\mathcal{C}+\beta)\,\|\sigma_n\|^2_{L^2(0,t;L^2(\Omega))} + \beta^2\,\|\sigma_s^n\|^2_{L^2(0,t;L^2(\Omega))}.$$

We deduce that $\partial_t\sigma_n$ is bounded in $L^2(0,T;L^2(\Omega))$. It follows from (2.17) that there exists a relabeled subsequence $\{\sigma_n\}_n$ such that $\sigma_n \rightharpoonup \sigma$ weakly in $L^2(0,T;H^1(\Omega))$. Multiply Equation (2.15) by $\dfrac{da_{n,j}(t)}{dt}$ and sum over j from 1 to n, we have

$$\begin{aligned} &\|\partial_t\varphi_n\|^2_{L^2(0,t;L^2(\Omega))} + 2B\,\|\nabla\varphi_n(t)\|^2_{L^2(\Omega)} \le \mathcal{P}^2\,\|\sigma_n\|^2_{L^2(0,t;L^2(\Omega))} \\ &+ \|\nabla\varphi_n(0)\|^2_{L^2(\Omega)} + \mathcal{A}^2\,\|h(\varphi_n)\|^2_{L^2(0,t;L^2(\Omega))} + \alpha^2\,\|u_n\|^2_{L^2(0,t;L^2(\Omega))}. \end{aligned}$$

Consequently, $\partial_t \varphi_n$ is bounded in $L^2(0,T;L^2(\Omega))$, so there exists a relabeled subsequence $\left\{\frac{d\varphi_n}{dt}\right\}$, such that $\frac{d\varphi_n}{dt} \rightharpoonup y$ weakly in $L^2(0,T;L^2(\Omega))$. It also follows from (2.18) that there exists a relabeled subsequence $\{\varphi_n\}_n$ such that $\varphi_n \rightharpoonup \varphi$ weakly in $L^2(0,T;H^1(\Omega))$.

Passing to the limit.

Assume that $\psi \in C_c^\infty(0,T;H^1(\Omega))$, we have

$$\int_0^T \int_\Omega \frac{d\varphi_n}{dt}\psi(t)dx\,dt = -\int_0^T \int_\Omega \varphi_n(t)\psi'(t)dx\,dt$$

$$\text{as } n \to \infty, \quad -\int_0^T \int_\Omega \varphi(t)\psi'(t)dx\,dt = \int_0^T \int_\Omega \frac{d\varphi}{dt}\psi(t)dx\,dt.$$

So, we deduce that $y = \frac{d\varphi}{dt}$. On the other hand

$$\int_0^T \int_\Omega \nabla\varphi_n \cdot \psi dx\,dt = -\int_0^T \int_\Omega \varphi_n \nabla\psi dx\,dt$$

$$\text{as } n \to \infty, \quad -\int_0^T \int_\Omega \varphi\nabla\psi dx\,dt = \int_0^T \int_\Omega \nabla\varphi \cdot \psi dx\,dt.$$

Furthermore, we have that φ_n is bounded in $L^2(0,T;H^1(\Omega))$ compactly embedded in $L^2(0,T;L^2(\Omega))$, then

$$\varphi_n \longrightarrow \varphi \quad \text{strongly in } L^2(0,T;L^2(\Omega)),$$

and as h is Lipschitz, we infer

$$h(\varphi_n) \longrightarrow h(\varphi) \quad \text{strongly in } L^2(0,T;L^2(\Omega))$$

and

$$f(\varphi_n) \longrightarrow f(\varphi) \quad \text{strongly in } L^2(0,T;L^2(\Omega)).$$

Therefore, (2.13) converges weakly to

$$\int_0^T \int_\Omega \frac{d\varphi}{dt}\psi(t)dx\,dt + B\int_0^T \int_\Omega \nabla\varphi \cdot \nabla\psi dx\,dt + \int_0^T \int_\Omega f(\varphi)\psi dx\,dt$$
$$= \int_0^T \int_\Omega (\mathcal{P}\sigma - \mathcal{A} - \alpha u)h(\varphi)\psi dx\,dt.$$

Since $\varphi \in L^2(0,T;H^1(\Omega)) \cap H^1(0,T;L^2(\Omega))$, then $\varphi \in C([0,T];L^2(\Omega))$. Now choose a function $\psi \in C^1([0,T];H^1(\Omega))$ with $\psi(T) = 0$ in the above equation, we get

$$\int_0^T \int_\Omega \varphi'\psi dx\,dt + B\int_0^T \int_\Omega \nabla\varphi \cdot \nabla\psi dx\,dt + \int_0^T \int_\Omega f(\varphi)\psi dx\,dt$$
$$= \int_0^T \int_\Omega (\mathcal{P}\sigma - \mathcal{A} - \alpha u)h(\varphi)\psi dx\,dt.$$

Thus, we have

$$\begin{aligned} &-\int_0^T \int_\Omega \varphi\psi' dx\,dt + B\int_0^T \int_\Omega \nabla\varphi \cdot \nabla\psi dx\,dt + \int_0^T \int_\Omega f(\varphi)\psi dx\,dt \\ &= \int_0^T \int_\Omega (\mathcal{P}\sigma - \mathcal{A} - \alpha u)h(\varphi)\psi dx\,dt + \int_\Omega \varphi(0)\psi(0)dx. \end{aligned} \tag{2.19}$$

Similarly, we have in (2.13) that

$$-\int_0^T\int_\Omega \varphi_n\psi' dx\,dt + B\int_0^T\int_\Omega \nabla\varphi_n\cdot\nabla\psi dx\,dt + \int_0^T\int_\Omega f(\varphi_n)\psi dx\,dt$$
$$= \int_0^T\int_\Omega (\mathcal{P}\sigma_n - \mathcal{A} - \alpha u_n)h(\varphi_n)\psi dx\,dt + \int_\Omega \varphi_n(0)\psi(0)dx,$$

so that by passing to the limit in this equation, we obtain

$$-\int_0^T\int_\Omega \varphi\psi' dx\,dt + B\int_0^T\int_\Omega \nabla\varphi\cdot\nabla\psi dx\,dt + \int_0^T\int_\Omega f(\varphi)\psi dx\,dt$$
$$= \int_0^T\int_\Omega (\mathcal{P}\sigma - \mathcal{A} - \alpha u)h(\varphi)\psi dx\,dt + \int_\Omega \varphi_0\psi(0)dx.$$

Note that after subtracting (2.19) and the above equation, we obtain $\int_\Omega(\varphi(0)-\varphi_0)\psi(0)dx = 0$. Then, we deduce that $\varphi(0) = \varphi_0$ a.e. in $L^2(\Omega)$. Similarly (2.14) converges weakly to

$$\int_0^T\int_\Omega \sigma'\psi dx\,dt + \int_0^T\int_\Omega \nabla\sigma\cdot\nabla\psi dx\,dt = \mathcal{P}\int_0^T\int_\Omega \sigma h(\varphi)\psi dx\,dt$$
$$-\mathcal{A}\int_0^T\int_\Omega h(\varphi)\psi dx\,dt - \alpha\int_0^T\int_\Omega uh(\varphi)\psi dx\,dt.$$

Which is equivalent to

$$\begin{aligned}-\int_0^T\int_\Omega \sigma\psi' dx\,dt + \int_0^T\int_\Omega \nabla\sigma\cdot\nabla\psi dx\,dt &= \mathcal{P}\int_0^T\int_\Omega \sigma h(\varphi)\psi dx\,dt\\ -\mathcal{A}\int_0^T\int_\Omega h(\varphi)\psi dx\,dt - \alpha\int_0^T\int_\Omega uh(\varphi)\psi dx\,dt + \int_\Omega \sigma(0)\psi(0)dx.&\end{aligned} \tag{2.20}$$

Back to (2.14), we have

$$-\int_0^T\int_\Omega \sigma_n\psi' dx\,dt + \int_0^T\int_\Omega \nabla\sigma_n\cdot\nabla\psi dx\,dt = \mathcal{P}\int_0^T\int_\Omega \sigma_n h(\varphi_n)\psi dx\,dt$$
$$-\mathcal{A}\int_0^T\int_\Omega h(\varphi_n)\psi dx\,dt - \alpha\int_0^T\int_\Omega u_n h(\varphi_n)\psi dx\,dt + \int_\Omega \sigma_n(0)\psi(0)dx.$$

Finally, by passing to the limit in this equation, we obtain

$$-\int_0^T\int_\Omega \sigma\psi' dx\,dt + \int_0^T\int_\Omega \nabla\sigma\cdot\nabla\psi dx\,dt = \mathcal{P}\int_0^T\int_\Omega \sigma h(\varphi)\psi dx\,dt$$
$$-\mathcal{A}\int_0^T\int_\Omega h(\varphi)\psi dx\,dt - \alpha\int_0^T\int_\Omega uh(\varphi)\psi dx\,dt + \int_\Omega \sigma_0\psi(0)dx.$$

Hence, by subtracting (2.20) and the above equation, we find that $\sigma(0) = \sigma_0$ a.e. in $L^2(\Omega)$.

Boundedness property of σ.

Recall that, $0 \le \sigma_0 \le 1$. Let $\sigma^- = \min(0, -\sigma)$ and substitute ξ in Equation (2.12) by $-\sigma^- \in H^1(\Omega)$, we obtain

$$\frac{1}{2}\frac{d}{dt}\left\|\sigma^-\right\|^2_{L^2(\Omega)} = -\left\|\nabla\sigma^-\right\|^2_{L^2(\Omega)} - \mathcal{C}\int_\Omega h(\varphi)|\sigma^-|^2dx - \beta\int_\Omega \sigma_s\sigma^- dx - \beta\int_\Omega |\sigma^-|^2dx \le 0.$$

It follows from the positivity property of $\mathcal{C}$, h, σ_s and β, that

$$\sup_{t\in(0,T]} \left\|\sigma^-(t)\right\|^2_{L^2(\Omega)} \leq \left\|\sigma_0^-\right\|^2_{L^2(\Omega)}.$$

On the other hand, since $\sigma_0 \geq 0$ a.e. in Ω, then, we get $\sigma^-(0) = 0$ a.e. in Ω which leads to $\sigma^- = 0$ a.e. in Q. Hence $\sigma \geq 0$ a.e. in Q.

Similarly, let $(\sigma-1)^+ = \max(0, \sigma-1)$, and substitute ξ in (2.12) by $(\sigma-1)^+$, we obtain

$$\frac{1}{2}\frac{d}{dt}\left\|(\sigma-1)^+\right\|^2 + \left\|\nabla(\sigma-1)^+\right\|^2_{L^2(\Omega)} + \int_\Omega (Ch(\varphi)+\beta)\left|(\sigma-1)^+\right|^2 dx$$
$$+C\int_\Omega h(\varphi)(\sigma-1)^+dx + \beta\int_\Omega(1-\sigma_s)(\sigma-1)^+dx = 0.$$

It follows that

$$\sup_{t\in(0,T]} \left\|(\sigma-1)^+(t)\right\|^2 \leq \left\|(\sigma-1)^+(0)\right\|^2_{L^2(\Omega)}.$$

However, $\sigma_0 \leq 1$ a.e. in Ω, so that $\sigma_0 - 1 \leq 0$ a.e. in Ω, and $(\sigma_0-1)^+ = 0$ a.e. in Ω.

We infer that $(\sigma-1)^+ = 0$ a.e. in Q, and $\sigma \leq 1$ a.e. in Q.

Continuous dependence on the control.

This section is devoted to study the continuous dependence of the control-to-state operator on the control u, for this purpose, let $u_1, u_2 \in \mathcal{U}_{ad}$ be given, along with the corresponding solutions (φ_1, σ_1) and (φ_2, σ_2) of (2.3)-(2.6) with same initial data φ_0 and σ_0. Let $u = u_1 - u_2$, $\varphi = \varphi_1 - \varphi_2$, and $\sigma = \sigma_1 - \sigma_2$ satisfying for all $\xi \in H^1(\Omega)$

$$\int_\Omega \partial_t\sigma\xi dx + \int_\Omega \nabla\sigma\cdot\nabla\xi dx = -\int_\Omega (\mathcal{C}h(\varphi_1)+\beta)\,\sigma\xi dx - \mathcal{C}\int_\Omega \sigma_2\,(h(\varphi_1)-h(\varphi_2))\,\xi dx$$

and

$$\begin{aligned}&\int_\Omega \partial_t\varphi\xi dx + B\int_\Omega \nabla\varphi\cdot\nabla\xi dx + \int_\Omega (f(\varphi_1)-f(\varphi_2))\,\xi dx = \mathcal{P}\int_\Omega h(\varphi_1)\sigma\xi dx\\ &+\int_\Omega (\mathcal{P}\sigma_2 - \mathcal{A} - \alpha u_1)\,(h(\varphi_1)-h(\varphi_2))\,\xi dx - \alpha\int_\Omega h(\varphi_2)u\xi dx.\end{aligned} \tag{2.21}$$

Some calculations yield

$$\frac{d}{dt}\|\varphi\|^2_{L^2(\Omega)} + 2B\|\nabla\varphi\|^2_{L^2(\Omega)} \leq \mathcal{P}^2\|\sigma\|^2_{L^2(\Omega)} + c\|\varphi\|^2_{L^2(\Omega)} + \alpha^2\|u\|^2_{L^2(\Omega)}$$

and

$$\frac{d}{dt}\|\sigma\|^2_{L^2(\Omega)} + 2\|\sigma\|^2_{L^2(\Omega)} \leq \mathcal{C}^2M^2\|\varphi\|^2_{L^2(\Omega)} + \|\sigma\|^2_{L^2(\Omega)}.$$

Combining the last inequalities, we have

$$\frac{d}{dt}\left(\|\varphi\|^2_{L^2(\Omega)} + \|\sigma\|^2_{L^2(\Omega)}\right) + 2B\|\nabla\varphi\|^2_{L^2(\Omega)} + 2\|\nabla\sigma\|^2_{L^2(\Omega)} \leq$$
$$(1+\mathcal{P}^2)\|\sigma\|^2_{L^2(\Omega)} + c\|\varphi\|^2_{L^2(\Omega)} + \alpha^2\|u\|^2_{L^2(\Omega)}.$$

Putting $c' = max(1+\mathcal{P}^2; c)$, integrating over $[0,t]$ and thanks to Gronwall's inequality, we find

$$\|\sigma(t)\|^2_{L^2(\Omega)} + \|\varphi(t)\|^2_{L^2(\Omega)} + 2\|\nabla\sigma\|^2_{L^2(0,t;L^2(\Omega))} + 2B\|\nabla\varphi\|^2_{L^2(0,t;L^2(\Omega))} \leq \alpha^2 \|u\|^2_{L^2(0,t;L^2(\Omega))} e^{c't}.$$

We can write

$$\begin{aligned}\|\sigma\|^2_{L^2(0,t;L^2(\Omega))} + \|\varphi\|^2_{L^2(0,t;L^2(\Omega))} &= \int_0^t \|\sigma(s)\|^2_{L^2(\Omega)}\, ds + \int_0^t \|\varphi(s)\|^2_{L^2(\Omega)}\, ds \\ &\leq \frac{\alpha^2}{c'} \|u\|^2_{L^2(0,t;L^2(\Omega))} \left(e^{c't} - 1\right).\end{aligned}$$

Moreover, putting $\xi = \partial_t\phi$ in (2.21), and $\xi = \partial_t\sigma$, we find

$$\|\partial_t\varphi\|^2_{L^2(\Omega)} + B\frac{d}{dt}\|\nabla\varphi\|^2_{L^2(\Omega)} \leq \frac{d}{dt}\|\varphi\|^2_{L^2(\Omega)} + \mathcal{P}^2\|\sigma\|^2_{L^2(\Omega)} + \alpha^2\|u\|^2_{L^2(\Omega)} + cM^2\|\varphi\|^2_{L^2(\Omega)} \tag{2.22}$$

and

$$\|\partial_t\sigma\|^2_{L^2(\Omega)} + \frac{d}{dt}\|\nabla\sigma\|^2_{L^2(\Omega)} \leq c\|\sigma\|^2_{L^2(\Omega)} + c'\|\varphi\|^2_{L^2(\Omega)}. \tag{2.23}$$

Putting $\xi = 1$ in (2.21) yields

$$\frac{d}{dt}\langle\varphi\rangle = \langle f(\varphi_1) - f(\varphi_2)\rangle - \langle\mathcal{P}h(\varphi_1)\sigma\rangle + \langle(\mathcal{P}\sigma_2 - \mathcal{A} - \alpha u_1)(h(\varphi_1) - h(\varphi_2))\rangle - \langle\alpha h(\varphi_2)u\rangle.$$

Using Assumption (B), in addition to the following inequality

$$\|f(\varphi_1) - f(\varphi_2)\|^2_{L^2(\Omega)} \leq \|f'(c)\varphi\|^2_{L^2(\Omega)},$$

it follows that

$$\left(\frac{d}{dt}\langle\varphi\rangle\right)^2 \leq \|f'(c)\varphi\|^2_{L^2(\Omega)} + \mathcal{P}^2\|h(\varphi_1)\|^2_{L^\infty(\Omega)}\|\sigma\|^2_{L^2(\Omega)}$$

$$+M^2\|\mathcal{P}\sigma_2 - \mathcal{A} - \alpha u_1\|^2_{L^\infty(\Omega)}\|\varphi\|^2_{L^2(\Omega)} + \alpha^2\|h(\varphi_2)\|^2_{L^\infty(\Omega)}\|u\|^2_{L^2(\Omega)}.$$

Now, we can write

$$\left(\frac{d}{dt}\langle\varphi\rangle\right)^2 + \langle\varphi\rangle^2 \leq c\|\varphi\|^2_{L^2(\Omega)} + \mathcal{P}^2\|\sigma\|^2_{L^2(\Omega)} + \alpha^2\|u\|^2_{L^2(\Omega)}.$$

Adding the last inequality with (2.22), we find

$$\|\partial_t\varphi\|^2_{L^2(\Omega)} + c\frac{d}{dt}\|\varphi\|^2_{H^1(\Omega)} \leq \frac{d}{dt}\|\varphi\|^2_{L^2(\Omega)} + 2\mathcal{P}^2\|\sigma\|^2_{L^2(\Omega)} + 2\alpha^2\|u\|^2_{L^2(\Omega)} + c\|\varphi\|^2_{L^2(\Omega)}.$$

Combining (2.23) and the above equation, and integrating over $[0,t]$, we have

$$\|\partial_t\varphi\|^2_{L^2(0,t;L^2(\Omega))} + \|\partial_t\sigma\|^2_{L^2(0,t;L^2(\Omega))} + c\|\varphi(t)\|^2_{H^1(\Omega)} + \|\nabla\sigma(t)\|^2_{L^2(\Omega)} \leq \alpha^2\|u\|^2_{L^2(0,t;L^2(\Omega))}\left(ce^{c't} + c''\right).$$

In addition, we know that

$$\|\varphi\|^2_{L^2(0,s;H^2(\Omega))}$$

$$\leq k\left(\|\partial_t\varphi\|^2_{L^2(0,s;L^2(\Omega))} + \alpha^2\|u\|^2_{L^2(0,s;L^2(\Omega))} + \|\varphi\|^2_{L^2(0,s;L^2(\Omega))} + \|\varphi\|^2_{L^2(0,s;H^1(\Omega))}\right)$$

and

$$\|\sigma\|^2_{L^2(0,s;H^2(\Omega))} \leq k\left(\|\partial_t\sigma\|^2_{L^2(0,s;L^2(\Omega))} + \|\sigma\|^2_{L^2(0,s;L^2(\Omega))}\right).$$

Finally, we have

$$\|\varphi\|^2_{L^2(0,s;H^2(\Omega))} + \|\sigma\|^2_{L^2(0,s;H^2(\Omega))} \leq c\,\|u\|^2_{L^2(0,s;L^2(\Omega))}.$$

□

2.3 Existence of a minimizer

Theorem 2.2

Assume that Assumptions (A) and (B) hold and let $\mathcal{J}_r$ be defined by (2.7). Then there exist $(u^*, \tau^*) \in \mathcal{U}_{ad} \times [r, T]$ such that

$$\mathcal{J}_r(u^*, \tau^*) \leq \mathcal{J}_r(u, \tau), \quad \text{for every } (u, \tau) \in \mathcal{U}_{ad} \times [r, T].$$

Proof. The cost functional $\mathcal{J}_r$ is bounded from below, and therefore it has a finite infimum. Consider a minimizing sequence $\{(u_n, \tau_n)\}_{n\in\mathbb{N}}$ with $u_n \in \mathcal{U}_{ad}$ and $\tau_n \in [r, T]$ and the corresponding weak solutions $(\varphi_n, \sigma_n)_{n\in\mathbb{N}}$ on the interval $[0, T]$ with $\varphi_n(0) = \varphi_0$ and $\sigma_n(0) = \sigma_0$, $n \in \mathbb{N}$, such that

$$\lim_{n\to\infty} \mathcal{J}_r(\varphi_n, \tau_n, u_n) = \inf_{(\phi,w,s)} \mathcal{J}_r(\phi, w, s).$$

We have, $u_n \in \mathcal{U}_{ad}$, then $0 \leq u_n \leq 1$, a.e in Q, for all $n \in \mathbb{N}$. Since $\{\tau_n\}_n$ is a bounded sequence, then there exists a relabeled subsequence τ_n satisfying

$$\lim_{n\to\infty} \tau_n = \tau_* \ \in \ [r, T].$$

We also have

$$\begin{cases} u_n \to u_* & \text{weakly in} \quad L^2(0,T;L^2(\Omega)), \\ \varphi_n \to \varphi_* & \text{strongly in} \quad C([0,T];L^2(\Omega)) \cap L^2(0,T;L^2(\Omega)), \\ \sigma_n \to \sigma_* & \text{strongly in} \quad C([0,T];L^2(\Omega)) \cap L^2(0,T;L^2(\Omega)), \end{cases}$$

where the couple (φ_*, σ_*) satisfy (2.3)-(2.6), with $0 \leq u_*, \sigma_* \leq 1$, a.e. in Q.

Applying Lebesgue dominated convergence theorem, we obtain

$$\begin{cases} \chi_{[0,\tau_n]}(t) \to \chi_{[0,\tau_*]}(t) & \text{strongly in} \quad L^p(0,T) \quad p \in [1,\infty) \\ \chi_{[\tau_n - r,\tau_n]}(t) \to \chi_{[\tau_* - r,\tau_*]}(t) & \text{strongly in} \quad L^p(0,T) \quad p \in [1,\infty). \end{cases}$$

Passing to the limit, we get

$$\int_0^{\tau_n}\int_\Omega |\varphi_n - \varphi_Q|^2 dx\,dt = \int_0^T \|\varphi_n - \varphi_Q\|^2_{L^2(\Omega)}\,\chi_{[0,\tau_n]}(t)dt$$

$$\to \int_0^T \|\varphi_* - \varphi_Q\|^2_{L^2(\Omega)} \chi_{[0,\tau_*]}(t)dt = \int_0^{\tau_*}\int_\Omega |\varphi_* - \varphi_Q| dx\, dt \quad \text{as } n \to \infty \text{ in } L^2(0,T;L^2(\Omega))$$

and

$$\frac{1}{r}\int_{\tau_n - r}^{\tau_n} \left(\frac{\beta_\Omega}{2} \|\varphi_n - \varphi_\Omega\|^2_{L^2(\Omega)} + \frac{\beta_S}{2}\int_\Omega (1+\varphi_n) dx \right) dt$$

$$\to \frac{1}{r}\int_{\tau_* - r}^{\tau_*} \left(\frac{\beta_\Omega}{2} \|\varphi_* - \varphi_\Omega\|^2_{L^2(\Omega)} + \frac{\beta_S}{2}\int_\Omega (1+\varphi_*) dx \right) dt \quad \text{as } n \to \infty \text{ in } L^2(0,T;L^2(\Omega)).$$

Furthermore, using the weak lower semicontinuity of the $L^2(Q)$ norm, and the fact that $\tau_n \to \tau_*$ as $n \to \infty$, we find

$$\liminf_{n\to\infty} \int_0^{\tau_n} \|u_n\|^2_{L^2(\Omega)}\, dt - \int_0^{\tau_*} \|u_*\|^2_{L^2(\Omega)}\, dt \geq 0.$$

After passing to the limit in $\mathcal{J}_r(\varphi_n, u_n, \tau_n)$, we obtain

$$\inf_{(\phi,w,s)} \mathcal{J}_r(\phi, w, s) = \lim_{n\to\infty} \mathcal{J}_r(\varphi_n, u_n, \tau_n) \geq \mathcal{J}_r(\varphi_*, u_*, \tau_*),$$

which implies that (u_*, τ_*) is a minimizer of the problem. □

2.4 Well-posedness of the linearized system

In order to establish the existence of the Fréchet derivative of the control-to-state operator with respect to the control, we consider the linearized system at (φ^*, σ^*) associated to the control u^*, for $w \in L^2(0,T;L^2(\Omega))$.

$$\begin{cases} \partial_t \Phi - B\Delta\Phi + \Phi f'(\varphi^*) = (\mathcal{P}\Sigma - \alpha w)h(\varphi^*) + (\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*)\Phi h'(\varphi^*), & \text{in } Q, \\ \partial_t \Sigma = \Delta\Sigma - \mathcal{C}\Sigma h(\varphi^*) - \mathcal{C}\sigma^*\Phi h'(\varphi^*) - \beta\Sigma, & \text{in } Q, \\ \partial_\nu \Sigma = \partial_\nu \Phi = 0, & \text{on } \Gamma \times (0,T), \\ \Sigma(0) = \Phi(0) = 0, & \text{in } \Omega, \end{cases} \tag{2.24}$$

satisfying the following variational formulations, for $\xi \in H^1(\Omega)$,

$$\begin{aligned} \int_\Omega \partial_t\Phi\, \xi\, dx + B\int_\Omega \nabla\Phi\cdot\nabla\xi\, dx + \int_\Omega f'(\varphi^*)\Phi\xi\, dx = \int_\Omega (\mathcal{P}\Sigma - \alpha w)h(\varphi^*)\, \xi\, dx \\ + \int_\Omega (\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*)\Phi h'(\varphi^*)\xi\, dx \end{aligned} \tag{2.25}$$

and

$$\int_\Omega \partial_t\Sigma\, \xi dx + \int_\Omega \nabla\Sigma\cdot\nabla\xi\, dx = -\int_\Omega \left((\mathcal{C}h(\varphi^*) + \beta)\, \Sigma + \mathcal{C}\sigma^*\Phi h'(\varphi^*)\, \xi \right) dx. \tag{2.26}$$

Theorem 2.3

Let $u^* \in \mathcal{U}_{ad}$. Then, System (2.24) admits a unique solution

$$(\Phi, \Sigma) \text{ in } \left(L^2(0,T;H^2(\Omega)) \cap H^1(0,T;L^2(\Omega)) \cap C([0,T];L^2(\Omega))\right)^2.$$

Proof. As we did before, we will use Galerkin method. Reconsider the finite dimentional space spanned by the first n eigenfunctions $\{\omega_i\}_i$ associated to the first n eigenvalues of $-\Delta$ operator. We are looking for the functions of the form

$$\Phi_n(x,t) = \sum_{i=1}^{n} a_{n,i}(t)\omega_i(x) \text{ and } \Sigma_n(x,t) = \sum_{i=1}^{n} b_{n,i}(t)\omega_i(x)$$

satisfying

$$\int_\Omega (\partial_t \Phi_n v + B\nabla\Phi_n \cdot \nabla v - h(\varphi^*)(\mathcal{P}\Sigma_n - \alpha w)v)\, dx$$
$$- \int_\Omega (h'(\varphi^*)(\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*)\Phi_n - f'(\varphi^*)\Phi_n)\, v\, dx = 0$$

and

$$\int_\Omega (\partial_t \Sigma_n v + \nabla\Sigma_n \cdot \nabla v + \mathcal{C}h(\varphi^*)\Sigma_n v + \mathcal{C}\sigma^* h'(\sigma)\Phi_n v + \beta\Sigma_n v)\, dx = 0.$$

Let $\Phi_{n,0} = P_{V_n}\Phi_0$, and $\Sigma_{n,0} = P_{V_n}\Sigma_0$ such that $\Phi_{n,0} \longrightarrow \Phi_0$, and $\Sigma_{n,0} \longrightarrow \Sigma_0$ in $L^2(\Omega)$. Substituting $\omega_j \in V_n$, $j = 1, \ldots, n$, for v in both equations to have

$$\int_\Omega (\partial_t \Phi_n \omega_j + B\nabla\Phi_n \cdot \nabla\omega_j - h(\varphi^*)(\mathcal{P}\Sigma_n - \alpha w\omega_j)\, dx$$
$$- \int_\Omega (h'(\varphi^*)(\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*)\Phi_n - f'(\varphi^*)\Phi_n)\, \omega_j dx = 0$$

and

$$\int_\Omega (\partial_t \Sigma_n \omega_j + \nabla\Sigma_n \cdot \nabla\omega_j + \mathcal{C}h(\varphi^*)\Sigma_n\omega_j + \mathcal{C}\sigma^* h'(\varphi^*)\Phi_n\omega_j + \beta\Sigma_n\omega_j)\, dx = 0.$$

Consequently,

$$\begin{aligned} &\int_\Omega \left(\frac{d}{dt}\sum_{i=1}^{n} a_{n,i}(t)\omega_i\omega_j + B\sum_{i=1}^{n} a_{n,i}(t)\nabla\omega_i \cdot \nabla\omega_j - h(\varphi^*)\left(\mathcal{P}\sum_{i=1}^{n} b_{n,i}(t)\omega_i - \alpha w\right)\omega_j\right) dx \\ &- \int_\Omega h'(\varphi^*)\left(\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*\right)\sum_{i=1}^{n} a_{n,i}(t)\omega_i\omega_j dx - \int_\Omega f'(\varphi^*)\sum_{i=1}^{n} a_{n,i}(t)\omega_i\omega_j dx = 0 \end{aligned} \tag{2.27}$$

and

$$\begin{aligned} &\int_\Omega \left(\frac{d}{dt}\sum_{i=1}^{n} b_{n,i}(t)\omega_i\omega_j + \sum_{i=1}^{n} b_{n,i}(t)\nabla\omega_i \cdot \nabla\omega_j + \mathcal{C}h(\varphi^*)\sum_{i=1}^{n} b_{n,i}(t)\omega_i\omega_j\right) dx \\ &+ \int_\Omega \left(\mathcal{C}\sigma^* h'(\varphi^*)\sum_{i=1}^{n} a_{n,i}(t)\omega_i\omega_j + \beta\sum_{i=1}^{n} b_{n,i}(t)\omega_i\omega_j\right) dx = 0 \end{aligned} \tag{2.28}$$

Its vector form is

$$\frac{d}{dt}a_n(t)I_n + Ba_n(t)J_n = h(\varphi^*)\mathcal{P}b_n(t)I_n + h(\varphi^*)\alpha W_n$$

$$+h'(\varphi^*)\left(\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*\right)a_n(t)I_n - f'(\varphi^*)a_n(t)I_n$$

and

$$\frac{d}{dt}b_n(t)I_n + b_n(t)J_n = -\mathcal{C}h(\varphi^*)b_n(t)I_n - \mathcal{C}\sigma^* h'(\varphi^*)a_n(t)I_n - \beta b_n(t)I_n,$$

where

$$(J_n)_{i,j} = \int \nabla\omega_i \cdot \nabla\omega_j dx \quad \text{and} \quad (W_n)_{i,j} = \int w\omega_j dx.$$

Equivalently

$$\begin{cases} a_n'(t) = \left(h(\varphi^*)\mathcal{P}b_n(t) + h'(\varphi^*)\left(\mathcal{P}\sigma^* - A - \alpha u^*\right)a_n(t) - f'(\varphi^*)a_n(t)\right)I_n \\ \qquad\qquad + h(\varphi^*)\alpha W_n - Ba_n(t)J_n = f(t, a_n, b_n) \\ b_n'(t) = -b_n(t)J_n - \left(\mathcal{C}h(\varphi^*) + \beta\right)b_n(t)I_n - \mathcal{C}\sigma^* h'(\varphi^*)a_n(t)I_n = g(t, a_n, b_n). \end{cases}$$

It is easy to see that the function $F = (f(t, a_n, b_n), g(t, a_n, b_n)$ is locally Lipschitz with respect to a_n and b_n, so the ODE system admits a unique local in time solution. Multiplying Equation (2.27) by $a_{n,j}(t)$ and (2.28) by $b_{n,j}(t)$, and summing over j from 1 to n, moreover, due to the fact that α is positive, $\beta, \mathcal{C}, \mathcal{P}, \mathcal{A}$ are non negative, we obtain

$$\begin{aligned} &\frac{1}{2}\frac{d}{dt}\left\|\Phi_n\right\|^2_{L^2(\Omega)} + B\left\|\nabla\Phi_n\right\|^2_{L^2(\Omega)} \leq \frac{1}{2}\left\|h(\varphi^*)\right\|_\infty \mathcal{P}^2\left\|\Sigma_n\right\|^2_{L^2(\Omega)} + \left\|\Phi_n\right\|^2_{L^2(\Omega)} \\ &+\frac{1}{2}\left\|h(\varphi^*)\right\|_\infty \alpha^2\left\|w\right\|^2_{L^2(\Omega)} + \left|h'(\varphi^*)\mathcal{P}\sigma^*\right|\left\|\Phi_n\right\|^2_{L^2(\Omega)} + \left|f'(\varphi^*)\right|\left\|\Phi_n\right\|^2_{L^2(\Omega)} \end{aligned} \tag{2.29}$$

and

$$\frac{1}{2}\frac{d}{dt}\left\|\Sigma_n\right\|^2_{L^2(\Omega)} + \left\|\Sigma_n\right\|^2_{H^1(\Omega)} \leq \frac{1}{2}\left(\left|\mathcal{C}\sigma^* h'(\varphi^*)\right|\left\|\Sigma_n\right\|^2_{L^2(\Omega)} + \left\|\Phi_n\right\|^2_{L^2(\Omega)}\right).$$

Adding (2.29) to the last inequality, we get

$$\frac{1}{2}\frac{d}{dt}\left(\left\|\Phi_n\right\|^2_{L^2(\Omega)} + \left\|\Sigma_n\right\|^2_{L^2(\Omega)}\right) + B\left\|\nabla\Phi_n\right\|^2_{L^2(\Omega)} + \left\|\Sigma_n\right\|^2_{H^1(\Omega)}$$

$$\leq c\left\|\Sigma_n\right\|^2_{L^2(\Omega)} + c'\left\|\Phi_n\right\|^2_{L^2(\Omega)} + c''\left\|w\right\|^2_{L^2(\Omega)}.$$

Integrating the above equation with respect to time leads to

$$\left\|\Phi_n(s)\right\|^2_{L^2(\Omega)} + \left\|\Sigma_n(s)\right\|^2_{L^2(\Omega)} + \int_0^s 2\left(B\left\|\nabla\Phi_n(t)\right\|^2_{L^2(\Omega)} + \left\|\Sigma_n(t)\right\|^2_{H^1(\Omega)}\right)dt$$

$$\leq \left\|\Phi_n(0)\right\|^2_{L^2(\Omega)} + \left\|\Sigma_n(0)\right\|^2_{L^2(\Omega)} + C_3\left\|w\right\|^2_{L^2(0,s;L^2(\Omega))} + \int_0^s \left(C_1\left\|\Sigma_n(t)\right\|^2_{L^2(\Omega)} + C_2\left\|\Phi_n(t)\right\|^2_{L^2(\Omega)}\right)dt,$$

for $s \in (0, T]$. By virtue of Gronwall's lemma, we obtain

$$\left\|\Phi_n(s)\right\|^2_{L^2(\Omega)} + \left\|\Sigma_n(s)\right\|^2_{L^2(\Omega)} + \int_0^s \left(B\left\|\nabla\Phi_n(t)\right\|^2_{L^2(\Omega)} + \left\|\nabla\Sigma_n(t)\right\|^2_{L^2(\Omega)}\right)dt$$

$$\leq \left(c + c\left\|w\right\|^2_{L^2(0,s;L^2(\Omega))}\right)e^{cs}.$$

Putting $\xi = 1$ in (2.26), and multiplying it by $\dfrac{1}{\mathrm{Vol}(\Omega)}$, we find

$$\frac{d}{dt}\langle\Phi\rangle = -\langle f'(\varphi)\Phi\rangle + \langle \mathcal{P}h(\varphi^*)\Sigma\rangle - \alpha\langle wh(\varphi^*)\rangle + \langle (\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*)\, h'(\varphi^*)\Phi\rangle,$$

so that

$$\left(\frac{d}{dt}\langle\Phi\rangle\right)^2 \leq c\,\|\Phi\|^2_{L^2(\Omega)} + \mathcal{P}^2\,\|\Sigma\|^2_{L^2(\Omega)} + \alpha^2\,\|w\|^2_{L^2(\Omega)}\,.$$

Consequently,

$$2\langle\Phi\rangle\frac{d}{dt}\langle\Phi\rangle \leq c\,\|\Phi\|^2_{L^2(\Omega)} + \mathcal{P}^2\,\|\Sigma\|^2_{L^2(\Omega)} + \alpha^2\,\|w\|^2_{L^2(\Omega)}\,. \tag{2.30}$$

Multiplying (2.27) and (2.28) by $a'_{n,j}$ and $b'_{n,j}$, respectively, and summing over j from 1 to n, we find

$$\left\|\frac{d\Phi_n}{dt}\right\|^2_{L^2(\Omega)} + \frac{B}{2}\frac{d}{dt}\,\|\nabla\Phi_n\|^2_{L^2(\Omega)} \leq \frac{1}{2}\,\|h(\varphi^*)\|_{L^\infty(\Omega)}\left(\mathcal{P}^2\,\|\Sigma_n\|^2_{L^2(\Omega)} + \alpha^2\,\|w\|^2_{L^2(\Omega)} + \left\|\frac{d\Phi_n}{dt}\right\|^2_{L^2(\Omega)}\right)$$

$$+\frac{1}{2}\,\|h'(\varphi^*)\,(\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*)\|_\infty\,\frac{d}{dt}\,\|\Phi_n\|^2_{L^2(\Omega)} + \frac{1}{2}\,\|f'(\varphi^*)\|_\infty\,\frac{d}{dt}\,\|\Phi_n\|^2_{L^2(\Omega)}\,.$$

Adding (2.30) to the last inequality, we find

$$\left\|\frac{d\Phi_n}{dt}\right\|^2_{L^2(\Omega)} + c\frac{d}{dt}\,\|\Phi_n\|^2_{H^1(\Omega)} \leq 2\mathcal{P}^2\,\|\Sigma\|^2_{L^2(\Omega)} + c\frac{d}{dt}\,\|\Phi_n\|^2_{L^2(\Omega)} + 2\alpha^2\,\|w\|^2_{L^2(\Omega)}\,. \tag{2.31}$$

On the other hand, we have

$$\left\|\frac{d\Sigma_n}{dt}\right\|^2_{L^2(\Omega)} + \frac{d}{dt}\,\|\nabla\Sigma_n\|^2_{L^2(\Omega)} \leq \frac{|\mathcal{C}h(\varphi^*)| + \beta}{2}\,\|\Sigma_n\|^2_{L^2(\Omega)} + \frac{1}{2}\,(\mathcal{C}\sigma^* h'(\varphi^*))^2\,\|\Phi_n\|^2_{L^2(\Omega)}\,.$$

Combining (2.31) and the last inequality, and integrating over $[0,t]$, we find

$$\left\|\frac{d\Phi_n}{dt}\right\|^2_{L^2(0,t;L^2(\Omega))} + \left\|\frac{d\Sigma_n}{dt}\right\|^2_{L^2(0,t;L^2(\Omega))} + c\,\|\Phi_n(t)\|^2_{H^1(\Omega)} + \|\nabla\Sigma_n(t)\|^2_{L^2(\Omega)}$$

$$\leq 2\alpha^2\,\|w\|^2_{L^2(0,t;L^2(\Omega))} + c\,\|\Phi_n(0)\|^2_{H^1(\Omega)} + \|\nabla\Sigma_n(0)\|^2_{L^2(\Omega)}$$

$$+c'\,\|\Sigma_n\|^2_{L^2(0,t;L^2(\Omega))} + c''\,\|\Phi_n\|^2_{L^2(0,t;L^2(\Omega))}\,.$$

Consequently, $\{\Phi_n\}$ and $\{\Sigma_n\}$ are uniformly bounded in

$$L^\infty(0,T;H^1(\Omega)) \cap H^1(0,T;L^2(\Omega)),$$

therefore, the solution is global in time. Moreover, there exists a relabeled subsequence such that

$$\Phi_n \overset{*}{\rightharpoonup} \Phi \text{ weakly star in } L^\infty(0,T;H^1(\Omega)) \cap H^1(0,T;L^2(\Omega))$$

and

$$\Sigma \overset{*}{\rightharpoonup} \Sigma \text{ weakly star in } L^\infty(0,T;H^1(\Omega)) \cap H^1(0,T;L^2(\Omega)).$$

Since this system is linear, it is easy to pass to the limit. Let $\{(\Phi_i, \Sigma_i)\}_{i=1,2}$ be two weak solutions to (2.25)-(2.26). Setting $\Phi := \Phi_1 - \Phi_2$ and $\Sigma := \Sigma_1 - \Sigma_2$ with $w = 0$, then Σ and Φ satisfy (2.25) and (2.26), respectively. Therefore, regularity estimates still hold and it implies

$$\|\Phi\|_{L^\infty(0,T;L^2(\Omega))\cap L^2(0,T;H^1(\Omega))} + \|\Sigma\|_{L^\infty(0,T;L^2(\Omega))\cap L^2(0,T;H^1(\Omega))} \leq 0,$$

hence $\Phi = \Sigma = 0$. □

2.5 Fréchet Differentiability of control-to-state operator with respect to the control

Let $w \in L^2(Q)$, set $(\varphi^w, \sigma^w) := S(u^* + w)$, $(\varphi^*, \sigma^*) := S(u^*)$ and $u^w := u^* + w$. We express the remainders ρ and θ as $\theta = \varphi^w - \varphi^* - \Phi$, and $\rho = \sigma^w - \sigma^* - \Sigma$.

Theorem 2.4

Let (Φ, Σ) be the solution of the linearized system at u^*, then the remainders θ and ρ satisfy

$$\|(\theta, \rho)\|^2_{\mathcal{Y}} \leq c \|w\|^4_{L^2(Q)},$$

with

$$\mathcal{Y} := L^2(0, s; H^2(\Omega)) \cap H^1(0, s; L^2(\Omega)) \cap L^\infty(0, s; H^1(\Omega)),\ s \in (0, T).$$

Then the control-to-state operator is Fréchet differentiable with respect to the control.

Proof. The remainders θ and ρ could be expressed as, $\theta = \varphi^w - \varphi^* - \Phi$, and $\rho = \sigma^w - \sigma^* - \Sigma$, such that, for all $\xi \in H^1(\Omega)$, we have

$$\int_\Omega \partial_t \varphi^w \xi dx + B \int_\Omega \nabla \varphi^w \cdot \nabla \xi dx + \int_\Omega f(\varphi^w)\xi\, dx = \int_\Omega (\mathcal{P}\sigma^w - \mathcal{A} - \alpha u^w) h(\varphi^w)\, dx$$
$$\int_\Omega \partial_t \varphi^* \xi dx + B \int_\Omega \nabla \varphi^* \cdot \nabla \xi dx + \int_\Omega f(\varphi^*)\xi\, dx = \int_\Omega (\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*) h(\varphi^*)\, dx$$

and

$$\int_\Omega \partial_t \Phi \xi dx + B \int_\Omega \nabla \Phi \cdot \nabla \xi dx + \int_\Omega f'(\varphi^*)\Phi\xi\, dx$$
$$= \int_\Omega (\mathcal{P}\Sigma - \alpha w) h(\varphi^*)\, \xi dx + \int_\Omega (\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*)\, \Phi h'(\varphi^*)\, \xi dx.$$

Respectively,

$$\begin{cases} \int_\Omega \partial_t \sigma^w \xi dx + \int_\Omega \nabla \sigma^w \cdot \nabla \xi dx = -\mathcal{C} \int_\Omega \sigma^w h(\varphi^w) \xi dx + \beta \int_\Omega (\sigma_s - \sigma^w)\xi dx, \\ \int_\Omega \partial_t \sigma^* \xi dx + \int_\Omega \nabla \sigma^* \cdot \nabla \xi dx = -\mathcal{C} \int_\Omega \sigma^* h(\varphi^*) \xi dx + \beta \int_\Omega (\sigma_s - \sigma^*)\xi dx \\ \int_\Omega \partial_t \Sigma \xi dx + \int_\Omega \nabla \Sigma \cdot \nabla \xi dx = -\mathcal{C} \int_\Omega \Sigma h(\varphi^*) \xi dx - \mathcal{C} \int_\Omega \sigma^* \Phi h'(\varphi^*) \xi dx - \beta \int_\Omega \Sigma \xi dx. \end{cases}$$

Then the remainder $\theta = \varphi^w - \varphi^* - \Phi$ satisfies, for all $\xi \in H^1(\Omega)$

$$\begin{aligned}
&\int_\Omega \partial_t\theta\xi dx + B\int_\Omega \nabla\theta\cdot\nabla\xi dx + \int_\Omega \left(f(\varphi^w) - f(\varphi^*) - \Phi f'(\varphi^*)\right)\xi\, dx \\
&= \int_\Omega \left(\mathcal{P}\sigma^w - \mathcal{A} - \alpha u^w\right) h(\varphi^w)\xi dx - \int_\Omega \left(\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*\right) h(\varphi^*)\xi\, dx \\
&- \int_\Omega \left(\mathcal{P}\Sigma - \alpha w\right) h(\varphi^*)\xi\, dx - \int_\Omega \left(\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*\right)\Phi h'(\varphi^*)\xi dx.
\end{aligned}$$

Besides, we have that

$$\begin{aligned}
&\sigma^w h(\varphi^w) - \sigma^* h(\varphi^w) + \sigma^* h(\varphi^w) - \sigma^w h(\varphi^*) + \sigma^w h(\varphi^*) + \sigma^* h(\varphi^*) - \sigma^* h(\varphi^*) \\
&\quad + \sigma^* h(\varphi^*) - \Sigma h(\varphi^*) - \sigma^*\Phi h'(\varphi^*) \\
&= \sigma^w\left(h(\varphi^w) - h(\varphi^*)\right) - \sigma^*\left(h(\varphi^w) - h(\varphi^*)\right) + \sigma^w h(\varphi^*) - \sigma^* h(\varphi^*) \\
&\quad - \Sigma h(\varphi^*) + \sigma^* h(\varphi^w) - \sigma^* h(\varphi^*) - \sigma^*\Phi h'(\varphi^*) \\
&= \left(h(\varphi^w) - h(\varphi^*)\right)\left(\sigma^w - \sigma^*\right) + h(\varphi^*)\left(\sigma^w - \sigma^* - \Sigma\right) + \sigma^*\left(h(\varphi^w) - h(\varphi^*) - \Phi h'(\varphi^*)\right).
\end{aligned}$$

Thanks to Taylor expansion with integral remainder, we have

$$h(\varphi^w) - h(\varphi^*) - h'(\varphi^*)\Phi = h'(\varphi^*)\theta + (\varphi^w - \varphi^*)^2\int_0^1 h''(z(\varphi^w) + (1-z)\varphi^*)(1-z)dz.$$

The remainder

$$R = \int_0^1 h''(z(\varphi^w) + (1-z)\varphi^*)(1-z)dz$$

is bounded, with

$$\|R\|_\infty \leq c_R.$$

We then deduce that

$$\begin{aligned}
&\left(h(\varphi^w) - h(\varphi^*)\right)\left(\sigma^w - \sigma^*\right) + h(\varphi^*)\left(\sigma^w - \sigma^* - \Sigma\right) + \sigma^*\left(h(\varphi^w) - h(\varphi^*) - \Phi h'(\varphi^*)\right) \\
&= \left(h(\varphi^w) - h(\varphi^*)\right)\left(\sigma^w - \sigma^*\right) + h(\varphi^*)\rho + \sigma^*\left(h'(\varphi^*)\theta + (\varphi^w - \varphi^*)^2 R\right).
\end{aligned}$$

Therefore the variational formulation, for $\xi \in H^1(\Omega)$ is given by

$$\begin{aligned}
&\int_\Omega \partial_t\theta\xi dx + B\int_\Omega \nabla\theta\cdot\nabla\xi dx + \int_\Omega \left(f(\varphi^w) - f(\varphi^*) - \Phi f'(\varphi^*)\right)\xi\, dx \\
&= \mathcal{P}\int_\Omega \left(h(\varphi^w) - h(\varphi^*)\right)\left(\sigma^w - \sigma^*\right)\xi dx - \int_\Omega \alpha w\left(h(\varphi^w) - h(\varphi^*)\right)\xi\, dx \\
&+ \int_\Omega \left(\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*\right)\left(h'(\varphi^*)\theta + (\varphi^w - \varphi^*)^2 R\right)\xi dx + \int_\Omega \mathcal{P}h(\varphi^*)\rho\xi dx.
\end{aligned} \tag{2.32}$$

Now, put $\xi = \theta$ in (2.32), we get

$$\frac{1}{2}\frac{d}{dt}\|\theta\|^2_{L^2(\Omega)} + B\|\nabla\theta\|^2_{L^2(\Omega)} + \int_\Omega f'(\varphi^*)\theta^2\,dx + \int_\Omega (\varphi^w - \varphi^*)^2 R\theta\,dx$$
$$= \mathcal{P}\int_\Omega (h(\varphi^w) - h(\varphi^*))(\sigma^w - \sigma^*)\,\theta dx + \int_\Omega \mathcal{P}h(\varphi^*)\rho\theta\,dx$$
$$+ \int_\Omega (\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*)\,h'(\varphi^*)\theta^2\,dx + \int_\Omega (\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*)(\varphi^w - \varphi^*)^2 R\theta\,dx$$
$$-\alpha\int_\Omega w\,(h(\varphi^w) - h(\varphi^*))\,\theta dx.$$

Applying holder's inequality, and as well as Young's, and knowing that h is a Lipschitz function with constant M, and R is bounded by some c_R, we obtain

$$\frac{d}{dt}\|\theta\|^2_{L^2(\Omega)} + 2B\|\nabla\theta\|^2_{L^2(\Omega)} \le 2\mathcal{P}M\|\varphi^w - \varphi^*\|_{L^2(\Omega)}\|\sigma^w - \sigma^*\|_{L^\infty(\Omega)}\|\theta\|_{L^2(\Omega)}$$
$$+ \|h(\varphi^*)\|_{L^\infty}\left(\mathcal{P}^2\|\rho\|^2_{L^2(\Omega)} + \|\theta\|^2_{L^2(\Omega)}\right) + 2c\|h'(\varphi^*)\|_{L^\infty(\Omega)}\|\theta\|^2_{L^2(\Omega)}$$
$$+2c_R c\|\varphi^w - \varphi^*\|_{L^\infty(\Omega)}\|\varphi^w - \varphi^*\|_{L^2(\Omega)}\|\theta\|_{L^2(\Omega)}$$
$$+2M\|\varphi^w - \varphi^*\|_{L^\infty(\Omega)}\|w\|_{L^2(\Omega)}\|\theta\|_{L^2(\Omega)}.$$

Using the boundedness of $h'(\varphi^*), h(\varphi^*)$, and integrating with respect to time, we get

$$\|\theta(s)\|^2_{L^2(\Omega)} + 2B\|\nabla\theta\|^2_{L^2(0,s;L^2(\Omega))}$$
$$\le 2\mathcal{P}M\|\varphi^w - \varphi^*\|_{L^\infty(0,s;L^2(\Omega))}\|\sigma^w - \sigma^*\|_{L^2(0,s;L^\infty(\Omega))}\|\theta\|_{L^2(0,s;L^2(\Omega))}$$
$$+\mathcal{P}^2\|\rho\|^2_{L^2(0,s;L^2(\Omega))} + \|\theta\|^2_{L^2(0,s;L^2(\Omega))} + c\|\theta\|^2_{L^2(0,s;L^2(\Omega))}$$
$$+2c_R\|\varphi^w - \varphi^*\|_{L^2(0,s;L^\infty(\Omega))}\|\varphi^w - \varphi^*\|_{L^\infty(0,s;L^2(\Omega))}\|\theta\|_{L^2(0,s;L^2(\Omega))}$$
$$+2M\|\varphi^w - \varphi^*\|_{L^2(0,s;L^\infty(\Omega))}\|w\|_{L^2(0,s;L^2(\Omega))}\|\theta\|_{L^\infty(0,s;L^2(\Omega))}.$$

Using the embedding $L^2(0,s;H^2(\Omega)) \hookrightarrow L^2(0,s;L^\infty(\Omega))$, and applying Young's inequality, we obtain

$$\|\theta(s)\|^2_{L^2(\Omega)} + 2B\|\nabla\theta\|^2_{L^2(0,s;L^2(\Omega))} \le (\mathcal{P}M)^2\|\varphi^w - \varphi^*\|^2_{L^\infty(0,s;L^2(\Omega))}\|\sigma^w - \sigma^*\|^2_{L^2(0,s;H^2(\Omega))}$$
$$+\|\theta\|^2_{L^2(0,s;L^2(\Omega))} + \mathcal{P}\|\rho\|^2_{L^2(0,s;L^2(\Omega))} + \|\theta\|^2_{L^2(0,s;L^2(\Omega))} + c\|\theta\|^2_{L^2(0,s;L^2(\Omega))}$$
$$+c_R^2\|\varphi^w - \varphi^*\|^2_{L^2(0,s;H^2(\Omega))}\|\varphi^w - \varphi^*\|^2_{L^\infty(0,s;L^2(\Omega))} + \|\theta\|^2_{L^2(0,s;L^2(\Omega))}$$
$$+M^2\|\varphi^w - \varphi^*\|^2_{L^2(0,s;H^2(\Omega))}\|w\|^2_{L^2(0,s;L^2(\Omega))} + \frac{1}{2}\|\theta\|^2_{L^\infty(0,s;L^2(\Omega))}.$$

Therefore, it follows that

$$\begin{aligned}&\|\theta(s)\|^2_{L^2(\Omega)} + 2B\,\|\nabla\theta\|^2_{L^2(0,s;L^2(\Omega))}\\&\leq c_1\,\|w\|^4_{L^2(0,s;L^2(\Omega))} + c_2\,\|\theta\|^2_{L^2(0,s;L^2(\Omega))} + \mathcal{P}\,\|\rho\|^2_{L^2(0,s;L^2(\Omega))}.\end{aligned} \tag{2.33}$$

On the other hand, $\rho = \sigma^w - \sigma^* - \Sigma$ satisfies the following variational inequality, for $\xi \in H^1(\Omega)$

$$\begin{aligned}&\int_\Omega \partial_t\rho\xi dx + \int_\Omega \nabla\rho\cdot\nabla\xi dx = -\mathcal{C}\int_\Omega (\sigma^w-\sigma^*)\,(h(\varphi^w)-h(\varphi^*))\,\xi dx\\&-\mathcal{C}\int_\Omega h(\varphi^*)\rho\xi dx - \mathcal{C}\int_\Omega \sigma^* h'(\varphi^*)\theta\xi dx - \mathcal{C}\int_\Omega \sigma^*(\varphi^w-\varphi^*)^2 R\xi dx - \beta\int_\Omega \rho\xi dx.\end{aligned} \tag{2.34}$$

Putting $\xi = \rho$ in (2.34), we get

$$\begin{aligned}&\frac{1}{2}\frac{d}{dt}\,\|\rho\|^2_{L^2(\Omega)} + \|\nabla\rho\|^2_{L^2(\Omega)} + \beta\,\|\rho\|^2_{L^2(\Omega)}\\&\leq \mathcal{C}\,\|\sigma^w-\sigma^*\|_{L^\infty(\Omega)}\,\|h(\varphi^w)-h(\varphi^*)\|_{L^2(\Omega)}\,\|\rho\|_{L^2(\Omega)} + \mathcal{C}\,\|h(\varphi^*)\|_{L^\infty(\Omega)}\,\|\rho\|^2_{L^2(\Omega)}\\&+\frac{\mathcal{C}}{2}\,\|\sigma^*\|^2_{L^\infty(\Omega)}\,\|h'(\varphi^*)\|^2_{L^\infty(\Omega)}\,\|\theta\|^2_{L^2(\Omega)} + \frac{1}{2}\,\|\rho\|^2_{L^2(\Omega)}\\&+\mathcal{C}\,\|\sigma^*\|_{L^\infty(\Omega)}\,c_R\,\|\varphi^w-\varphi^*\|_{L^\infty(\Omega)}\,\|\varphi^w-\varphi^*\|_{L^2(\Omega)}\,\|\rho\|_{L^2(\Omega)}.\end{aligned}$$

Putting $c = min(1;\beta)$ and using the boundedness of $h(\varphi^*), h'(\varphi^*), \sigma^*$, in addition to the fact that h is Lipschitz with constant M, and the embedding $L^2(0,s;H^2(\Omega)) \hookrightarrow L^2(0,s;L^\infty(\Omega))$, then integrating on $[0,s)$ for $s\in[0,T]$, we get

$$\begin{aligned}&\|\rho(s)\|^2_{L^2(\Omega)} + 2c\,\|\rho\|^2_{L^2(0,s;H^1(\Omega))}\\&\leq (\mathcal{C}M)^2\,\|\sigma^w-\sigma^*\|^2_{L^2(0,s;H^2(\Omega))}\,\|\varphi^w-\varphi^*\|^2_{L^\infty(0,s;L^2(\Omega))} + \|\rho\|^2_{L^2(0,s;L^2(\Omega))}\\&+\mathcal{C}\,\|\rho\|^2_{L^2(0,s;L^2(\Omega))} + c\,\|\theta\|^2_{L^2(0,s;L^2(\Omega))} + \|\rho\|^2_{L^2(0,s;L^2(\Omega))}\\&+\mathcal{C}^2c_R^2\,\|\varphi^w-\varphi^*\|^2_{L^2(0,s;H^2(\Omega))}\,\|\varphi^w-\varphi^*\|^2_{L^\infty(0,s;L^2(\Omega))} + \|\rho\|^2_{L^2(0,s;L^2(\Omega))}\\&\leq c_3\,\|w\|^4_{L^2(0,s;L^2(\Omega))} + c_4\,\|\rho\|^2_{L^2(0,s;L^2(\Omega))} + c_5\,\|\theta\|^2_{L^2(0,s;L^2(\Omega))}.\end{aligned}$$

Combining (2.33) and the above inequality, we find

$$\begin{aligned}&\|\rho(s)\|^2_{L^2(\Omega)} + \|\theta(s)\|^2_{L^2(\Omega)} + 2c\,\|\rho\|^2_{L^2(0,s;H^1(\Omega))} + 2B\,\|\nabla\theta\|^2_{L^2(0,s;L^2(\Omega))}\\&\leq c_6\,\|w\|^4_{L^2(0,s;L^2(\Omega))} + c_7\,\|\rho\|^2_{L^2(0,s;L^2(\Omega))} + c_8\,\|\theta\|^2_{L^2(0,s;L^2(\Omega))}\\&\leq c_6\,\|w\|^4_{L^2(0,s;L^2(\Omega))} + c_9\left(\|\rho\|^2_{L^2(0,s;L^2(\Omega))} + \|\theta\|^2_{L^2(0,s;L^2(\Omega))}\right),\quad c_9\geq c_7 \text{ and } c_9\geq c_8.\end{aligned}$$

Applying Gronwall's inequality, we get

$$\|\rho(s)\|^2_{L^2(\Omega)} + \|\theta(s)\|^2_{L^2(\Omega)} + 2c\,\|\rho\|^2_{L^2(0,s;H^1(\Omega))} + 2B\,\|\nabla\theta\|^2_{L^2(0,s;L^2(\Omega))}$$

$$\leq c_6 e^{c_9 s}\,\|w\|^4_{L^2(0,s;L^2(\Omega))}\,,\ \ s\in[0,T].$$

Furthermore, putting $\xi=\partial_t\theta$ in (2.32), we obtain

$$\|\partial_t\theta\|^2_{L^2(\Omega)} + \frac{B}{2}\frac{d}{dt}\|\nabla\theta\|^2_{L^2(\Omega)} \leq \frac{1}{2}\frac{d}{dt}\|\theta\|^2_{L^2(\Omega)} + cc_R\,\|\varphi^w-\varphi^*\|_{L^\infty(\Omega)}\,\|\varphi^w-\varphi^*\|_{L^2(\Omega)}\,\|\partial_t\theta\|_{L^2(\Omega)}$$

$$+\mathcal{P}\,\|h(\varphi^w)-h(\varphi^*)\|_{L^\infty}\,\|\sigma^w-\sigma^*\|_{L^2(\Omega)}\,\|\partial_t\rho\|_{L^2(\Omega)} + \mathcal{P}^2\,\|h(\varphi^*)\|^2_\infty\,\frac{1}{2}\,\|\rho\|^2_{L^2(\Omega)} + c\frac{1}{2}\frac{d}{dt}\|\theta\|^2_{L^2(\Omega)}$$

$$+\alpha\,\|w\|_{L^2(\Omega)}\,\|h(\varphi^w)-h(\varphi^*)\|_{L^\infty}\,\|\partial_t\theta\|_{L^2(\Omega)}\,,$$

using the Lipschitz property of the function h, in addition to the boundedness of σ^*, $h'(\varphi^*)$, $h(\varphi^*)$, and R in addition to Young's inequality, and the continuous embedding $H^2(\Omega)\hookrightarrow L^\infty(\Omega)$, we get

$$\|\partial_t\theta\|^2_{L^2(\Omega)} + B\frac{d}{dt}\|\nabla\theta\|^2_{L^2(\Omega)} \leq \frac{d}{dt}\|\theta\|^2_{L^2(\Omega)} + 2cc^R\,\|\varphi^w-\varphi^*\|_{L^\infty}\,\|\varphi^w-\varphi^*\|_{L^2(\Omega)}\,\|\partial_t\theta\|_{L^2(\Omega)}$$

$$+2\mathcal{P}M\,\|\varphi^w-\varphi^*\|_{L^\infty}\,\|\sigma^w-\sigma^*\|_{L^2(\Omega)}\,\|\partial_t\rho\|_{L^2(\Omega)} + \mathcal{P}\,\|\rho\|^2_{L^2(\Omega)} + M^2\alpha^2\,\|w\|^2_{L^2(\Omega)}\,\|\varphi^w-\varphi^*\|^2_{H^2(\Omega)}\,.$$

Integrating over $[0,s)$, and applying Young's and Schwartz inequalities, as well as the embedding

$$L^2(0,s;H^2(\Omega))\hookrightarrow L^2(0,s;L^\infty(\Omega)),$$

we obtain

$$\|\partial\theta\|^2_{L^2(0,s;L^2(\Omega))} + B\,\|\nabla\theta(s)\|^2_{L^2(\Omega)} \leq cc_R\,\|\varphi^w-\varphi^*\|^2_{L^2(0,s;H^2(\Omega))}\,\|\varphi^w-\varphi^*\|^2_{L^\infty(0,s;L^2(\Omega))}$$

$$+c\,\|\theta(s)\|^2_{L^2(\Omega)} + (\mathcal{P}M)^2\,\|\varphi^w-\varphi^*\|^2_{L^2(0,s;H^2(\Omega))}\,\|\sigma^w-\sigma^*\|^2_{L^\infty(0,s;L^2(\Omega))} + \|\partial\rho\|^2_{L^2(0,s;L^2(\Omega))} \tag{2.35}$$

$$+\mathcal{P}\,\|\rho\|^2_{L^2(0,s;L^2(\Omega))} + (M\alpha)^2\,\|w\|^2_{L^2(o,s;L^2(\Omega))}\,\|\varphi^w-\varphi^*\|^2_{L^2(0,s;H^2(\Omega))}\,.$$

On the other hand, putting $\xi=\partial_t\rho$ in (2.34), and proceeding in the same way like above, we get

$$\|\partial_t\rho\|^2_{L^2(\Omega)} + \frac{d}{dt}\|\nabla\rho\|^2_{L^2(\Omega)} \leq (\mathcal{C}M)^2\,\|\sigma^w-\sigma^*\|^2_{L^\infty(\Omega)}\,\|\varphi^w-\varphi^*\|^2_{L^2(\Omega)} + \|\partial_t\rho\|^2_{L^2(\Omega)}$$

$$+\mathcal{C}\frac{d}{dt}\|\rho\|^2_{L^2(\Omega)} + c_{12}\,\|\theta\|^2_{L^2(\Omega)} + c\,\|\partial_t\rho\|^2_{L^2(\Omega)} + (\mathcal{C}c_R)^2\,\|\varphi^w-\varphi^*\|^2_{L^\infty}\,\|\varphi^w-\varphi^*\|^2_{L^2(\Omega)}\,.$$

Integrating with respect to time, using the embedding $L^2(0,s;H^2(\Omega))\hookrightarrow L^2(0,s;L^\infty(\Omega))$, and the continuous dependence on control, we obtain

$$\|\partial_t\rho\|^2_{L^2(0,s;L^2(\Omega))} + \|\nabla\rho(s)\|^2_{L^2(\Omega)} \leq c\,\|w\|^4_{L^2(0,s;L^2(\Omega))} + c'\,\|\theta\|^2_{L^2(0,s;L^2(\Omega))} + \mathcal{C}\,\|\rho(s)\|^2_{L^2(\Omega)}\,.$$

Combining (2.35) and the above inequality, we obtain

$$\|\partial_t\theta\|^2_{L^2(0,s;L^2(\Omega))} + \|\partial_t\rho\|^2_{L^2(0,s;L^2(\Omega))} + B\,\|\nabla\theta(s)\|^2_{L^2(\Omega)} + \|\nabla\rho(s)\|^2_{L^2(\Omega)}$$

$$\leq c\,\|w\|^4_{L^2(0,s;L^2(\Omega))} + c_1\,\|\rho\|^2_{L^2(0,s;L^2(\Omega))} + c_2\,\|\theta(s)\|^2_{L^2(\Omega)} + c_3\,\|\theta\|^2_{L^2(0,s;L^2(\Omega))} + \mathcal{C}\,\|\rho(s)\|^2_{L^2(\Omega)}\,.$$

Noting that, there exist a constant c_4 such that $c_4 \geq c_1$ and $c_4 \geq c_3$, we have

$$c_1 \|\rho\|^2_{L^2(0,s;L^2(\Omega))} + c_3 \|\theta\|^2_{L^2(0,s;L^2(\Omega))} \leq c_4 \left(\|\rho\|^2_{L^2(0,s;L^2(\Omega))} + \|\theta\|^2_{L^2(0,s;L^2(\Omega))}\right)$$
$$\leq c_4 \left(\int_0^s \left(\|\rho(t)\|^2_{L^2(\Omega)} + \|\theta(t)\|^2_{L^2(\Omega)}\right) dt\right) \leq c_4 \left(e^{c_9 s} - 1\right) \|w\|^4_{L^2(0,s;L^2(\Omega))}$$

and a constant c_5 such that $c_5 \geq c_2$ and $c_5 \geq \mathcal{C}$, we also have

$$c_2 \|\theta(s)\|^2_{L^2(\Omega)} + \mathcal{C} \|\rho(s)\|^2_{L^2(\Omega)} \leq c_5 \left(\|\theta(s)\|^2_{L^2(\Omega)} + \|\rho(s)\|^2_{L^2(\Omega)}\right)$$
$$\leq c_5 \left(c_9 e^{c_9 s} \|w\|^4_{L^2(0,s;L^2(\Omega))}\right).$$

Finally, we obtain

$$\|\partial_t \theta\|^2_{L^2(0,s;L^2(\Omega))} + \|\partial_t \rho\|^2_{L^2(0,s;L^2(\Omega))} + B \|\nabla\theta(s)\|^2_{L^2(\Omega)} + \|\nabla\rho(s)\|^2_{L^2(\Omega)} \leq c \|w\|^4_{L^2(0,s;L^2(\Omega))}.$$

One can view (2.32) and (2.34) as the weak formulations of the following problem

$$-B\Delta\theta = -\partial_t\theta + \mathcal{P}\left(h(\varphi^w) - h(\varphi^*)\right)\left(\sigma^w - \sigma^*\right) + h(\varphi^*)\rho + \sigma^* h'(\varphi^*)\theta + \left(\varphi^w - \varphi^*\right)^2 R$$

and

$$-\Delta\rho = -\partial_t\rho - \mathcal{C}\left(h(\varphi^w) - h(\varphi^*)\right)\left(\sigma^w - \sigma^*\right) - \mathcal{C}h(\varphi^*)\rho$$
$$-\mathcal{C}\sigma^* h'(\varphi^*)\theta - \mathcal{C}\sigma^*\left(\varphi^w - \varphi^*\right)^2 R - \beta\rho.$$

Thus, using elliptic regularity, we get

$$\|\theta\|^2_{L^2(0,s;H^2(\Omega))} + \left\|\rho^2\right\|_{L^2(0,s;H^2(\Omega))} \leq c \|w\|^4_{L^2(0,s;L^2(\Omega))}.$$

□

2.6 Differentiability of the cost functional

2.6.1 Differentiability of the cost functional with respect to time

The Fréchet derivative of the reduced cost functional at (u^*, τ^*) with respect to time is given as follows:

$$D_\tau \mathcal{J}_r(u^*, \tau^*) = \frac{\beta_Q}{2} \int_\Omega \left(|\varphi(\tau^*) - \varphi_Q(\tau^*)|^2 - |\varphi(0) - \varphi_Q(0)|^2\right) dx$$
$$+ \frac{\beta_\Omega}{2r} \int_\Omega \left(|\varphi(\tau^*) - \varphi_\Omega(\tau^*)|^2 - |\varphi(\tau^* - r) - \varphi_\Omega(\tau^* - r)|^2\right) dx$$
$$+ \frac{\beta_s}{2r} \int_\Omega \left(\varphi(\tau^*) - \varphi(\tau^* - r)\right) dx + \frac{\beta_u}{2} \int_\Omega |u^*(T)|^2 dx + \beta_T,$$

which is equivalent to

$$D_\tau \mathcal{J}_r(u^*, \tau^*) = \frac{\beta_Q}{2} \|\varphi(\tau^*) - \varphi_Q(\tau^*)\|^2_{L^2(\Omega)} + \frac{\beta_s}{2r} \int_\Omega \left(\varphi(\tau^*) - \varphi(\tau^* - r)\right) dx$$
$$+ \frac{\beta_u}{2} \|u(T)\|^2_{L^2(\Omega)} + \frac{\beta_\Omega}{2r} \left(\|\varphi(\tau^*) - \varphi_\Omega(\tau^*)\|^2_{L^2(\Omega)} - \left\|\varphi(\tau^* - r) - \varphi_\Omega(\tau^* - r)^2\right\|_{L^2(\Omega)}\right) + \beta_T,$$

the proof of the differentiability of the cost functional with respect to time follows as in [43].

2.6.2 Fréchet differentiability of the cost functional with respect to the control

Furthermore, the Fréchet derivative of the cost functional at (u^*, τ^*) with respect to the control is given as follows:

$$D_u\mathcal{J}_r(u^*,\tau^*)w = \beta_Q \int_0^{\tau^*}\int_\Omega |\varphi^* - \varphi_Q|\Phi^w\,dx\,dt + \beta_\Omega \int_{\tau^*-r}^{\tau^*}\int_\Omega |\varphi^* - \varphi_\Omega|\Phi^w\,dx\,dt$$
$$+\frac{\beta_s}{r}\int_{\tau^*-r}^{\tau^*}\int_\Omega \Phi^w\,dx\,dt + \beta_u\int_0^T\int_\Omega u\,w\,dx\,dt.$$

In order to eliminate the term Φ^w from the above equation, we apply Lagrangian principle, to this end, we define the Lagrangian function with respective Lagrangian multipliers p and q by

$$\mathcal{L}(\varphi,\sigma,u,p,q) = \mathcal{J}_r(\varphi,u) - \iint_Q (\partial_t\sigma - \Delta\sigma + \mathcal{C}\sigma h(\varphi) - \beta(\sigma_s - \sigma))\,q\,dx\,dt$$
$$-\iint_Q (\partial_t\varphi - B\Delta\varphi - (\mathcal{P}\sigma - \mathcal{A} - \alpha u)\,h(\varphi) + f(\varphi))\,p\,dx\,dt.$$

2.6.3 Adjoint system

The adjoint system is given as follows

$$D_\varphi\mathcal{L}(\varphi^*,\sigma^*,u^*,p,q)\varphi = 0$$

and

$$D_\sigma\mathcal{L}(\varphi^*,\sigma^*,u^*,p,q)\sigma = 0,$$

where

$$D_\varphi\mathcal{L}(\varphi^*,\sigma^*,u^*,p,q)\varphi = \frac{1}{2r}\int_0^{\tau^*}\int_\Omega \chi_{[\tau^*-r,\tau^*]}(t)\,(2\beta_\Omega\,(\varphi^* - \varphi_\Omega) + \beta_s)\,\varphi dx\,dt$$
$$\beta_Q\int_0^{\tau^*}\int_\Omega(\varphi^* - \varphi_Q)\varphi dx\,dt + \int_0^{\tau^*}\int_\Omega \partial_t p\varphi\,dx\,dt + B\int_0^{\tau^*}\int_\Omega \Delta p\varphi\,dx\,dt$$
$$+\int_0^{\tau^*}\int_\Omega (\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*)\,h'(\varphi^*)\,p\varphi\,dx\,dt - \int_0^{\tau^*}\int_\Omega f'(\varphi^*)p\varphi\,dx\,dt$$
$$-\int_0^{\tau^*}\int_\Omega \mathcal{C}\sigma^* h'(\varphi^*)q\varphi dx\,dt, \quad \tau^* \in [r,T]$$

and

$$D_\sigma\mathcal{L}(\varphi^*,\sigma^*,u^*,p,q)\sigma = \int_0^{\tau^*}\int_\Omega \partial_t q\sigma\,dx\,dt + \int_0^{\tau^*}\int_\Omega \Delta q\sigma\,dx\,dt + \int_0^{\tau}\int_\Omega \mathcal{P}h(\varphi^*)\,p\sigma\,dx\,dt$$
$$-\mathcal{C}\int_0^{\tau}\int_\Omega h(\varphi^*)q\sigma\,dx\,dt - \beta\int_0^{\tau}\int_\Omega q\sigma\,dx\,dt.$$

The adjoint system is then written as

$$\begin{cases} -\partial_t p - B\Delta p = (\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*)\, h'(\varphi^*)p + \beta_Q\,(\varphi^* - \varphi_Q) \\ +\dfrac{1}{2r}\chi_{[\tau^*-r,\tau^*]}(t)\,(2\beta_\Omega\,(\varphi^* - \varphi_\Omega) + \beta_s) - f'(\varphi^*)p - \mathcal{C}\sigma^* h'(\varphi^*)q, & \text{in } [0,T]\times\Omega, \\ -\partial_t q - \Delta q = \mathcal{P}h(\varphi^*)p - (\mathcal{C}h(\varphi^*) + \beta)\, q, & \text{in } [0,T]\times\Omega, \\ \partial_\nu p = \partial_\nu q = 0, & \text{on } [0,T]\times\Gamma, \\ p(\tau^*) = q(\tau^*) = 0, & \text{in } \Omega. \end{cases} \tag{2.36}$$

Theorem 2.5

Let u^* be an optimal control, and $(\varphi^*, \sigma^*) = \mathcal{S}(u^*)$ be the corresponding state. Then the adjoint Problem (2.36) has a unique solution

$$(p,q) \in \left(H^1(0,\tau^*; L^2(\Omega)) \cap L^\infty(0,\tau^*; H^1(\Omega)) \cap L^2(0,\tau^*; H^2(\Omega)) \cap C([0,\tau^*]; H^1(\Omega))\right)^2.$$

Proof. The variational formulations of the adjoint system, for $\xi \in H^1(\Omega)$, are given by:

$$\begin{aligned} &-\int_\Omega \partial_t p\,\xi dx + B\int_\Omega \nabla p\cdot\nabla\xi\,dx = \int_\Omega (\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*)\, h'(\varphi^*)p\,\xi\,dx + \int_\Omega \beta_Q\,(\varphi^* - \varphi_Q)\,\xi dx \\ &+\frac{1}{2r}\int_\Omega \chi_{[\tau^*-r,\tau^*]}(t)\,(2\beta_\Omega\,(\varphi^* - \varphi_\Omega) + \beta_s)\,\xi dx - \int_\Omega f'(\varphi^*)p\xi\,dx - \int_\Omega \mathcal{C}\sigma^* h'(\varphi^*)q\xi dx \end{aligned} \tag{2.37}$$

and

$$-\int_\Omega \partial_t q\,\xi\,dx + \int_\Omega \nabla q\cdot\nabla\xi\,dx = \int_\Omega \mathcal{P}h(\varphi^*)p\,\xi\,dx - \int_\Omega (\mathcal{C}h(\varphi^*) + \beta)\,q\,\xi\,dx. \tag{2.38}$$

Now, we will establish the a priori estimates for (2.36), for this purpose, we put $\xi = p$ in (2.37) and $\xi = q$ in (2.38) in addition to using $f'(\varphi^*)p^2 \geq -p^2$, to obtain

$$\begin{aligned} &\frac{d}{dt}\|p\|^2_{L^2(\Omega)} + 2B\|\nabla p\|^2_{L^2(\Omega)} \leq c\|p\|^2_{L^2(\Omega)} + \|\beta_Q(\varphi^* - \varphi_Q)\|^2_{L^2(\Omega)} \\ &+\left\|\frac{1}{2r}(2\beta_\Omega(\varphi^* - \varphi_\Omega)) + \beta_s\right\|^2_{L^2(\Omega)} + 2\|p\|^2_{L^2(\Omega)} + c'\left(\|p\|^2_{L^2(\Omega)} + \|q\|^2_{L^2(\Omega)}\right) \\ &\leq c\|p\|^2_{L^2(\Omega)} + c'\|q\|^2_{L^2(\Omega)} + c''. \end{aligned} \tag{2.39}$$

On the other hand, we have

$$\frac{d}{dt}\|q\|^2_{L^2(\Omega)} + 2\|\nabla q\|^2_{L^2(\Omega)} + 2\beta\|q\|^2_{L^2(\Omega)} = -2\int_\Omega \mathcal{C}h(\varphi^*)q^2 dx + \int_\Omega \mathcal{P}h(\varphi^*)pq\,dx.$$

Therefore

$$\frac{d}{dt}\|q\|^2_{L^2(\Omega)} + 2\|\nabla q\|^2_{L^2(\Omega)} \leq \mathcal{P}^2\|p\|^2_{L^2(\Omega)} + (2\mathcal{C}+1)\|q\|^2_{L^2(\Omega)}.$$

Combining (2.39) and the above inequality, and putting $c_0 = min(2; 2\beta)$, we obtain

$$\frac{d}{dt}\left(\|p\|^2_{L^2(\Omega)} + \|q\|^2_{L^2(\Omega)}\right) + 2B\|\nabla p\|^2_{L^2(\Omega)} + \|q\|^2_{H^1(\Omega)} \leq c\|p\|^2_{L^2(\Omega)} + c'\|q\|^2_{L^2(\Omega)} + c''$$
$$\leq c_1\left(\|p\|^2_{L^2(\Omega)} + \|q\|^2_{L^2(\Omega)}\right) + c'',$$

where c_1 is a constant depending on $\mathcal{P}, \mathcal{C}, \mathcal{A}, \alpha, \beta$, so that $c \leq c_1$ and $c' \leq c_1$. Integrating over time and applying Gronwall's lemma, we find

$$\|p(s)\|^2_{L^2(\Omega)} + \|q(s)\|^2_{L^2(\Omega)} + 2B\|\nabla p\|^2_{L^2(0,s;L^2(\Omega))} + \|q\|^2_{L^2(0,s;H^1(\Omega))} \leq c''e^{c_1 s}, \quad s \in (0, \tau^*], \tag{2.40}$$

where c_2 depends on c'', $\|p_0\|^2_{L^2(\Omega)}$ and $\|q_0\|^2_{L^2(\Omega)}$. Furthermore, putting $\xi = \partial_t p$ in (2.37) and $\xi = \partial_t q$ in (2.38), we obtain

$$\|\partial_t p\|^2_{L^2(\Omega)} + B\frac{d}{dt}\|\nabla p\|^2_{L^2(\Omega)} + \|\partial_t q\|_{L^2(\Omega)} + \frac{d}{dt}\|\nabla q\|^2_{L^2(\Omega)}$$
$$\leq c\|p\|^2_{L^2(\Omega)} + c'\|\partial_t p\|^2_{L^2(\Omega)} + c_1\|q\|^2_{L^2(\Omega)} + c_2\|\partial_t q\|^2_{L^2(\Omega)} + c\frac{d}{dt}\|p\|^2_{L^2(\Omega)} + c''.$$

Consequently,

$$\|\partial_t p\|^2_{L^2(0,s;L^2(\Omega))} + B\|\nabla p(s)\|^2_{L^2(\Omega)} + \|\nabla q(s)\|^2_{L^2(\Omega)} + \|\partial_t q\|_{L^2(0,s;L^2(\Omega))} \leq c\|p\|^2_{L^2(0,s;L^2(\Omega))}$$
$$+c_1\|q\|^2_{L^2(0,s;L^2(\Omega))} + c\|p(s)\|^2_{L^2(\Omega)} + c''s + B\|\nabla p(0)\|^2_{L^2(\Omega)} + B\|\nabla q(0)\|^2_{L^2(\Omega)}. \tag{2.41}$$

However, due to (2.40), we have

$$\|p\|^2_{L^2(0,s;L^2(\Omega))} + \|q\|^2_{L^2(0,s;L^2(\Omega))} = \int_0^s \|p(t)\|^2_{L^2(\Omega)}\,dt + \int_0^s \|q(t)\|^2_{L^2(\Omega)}\,dt \leq \int_0^s c''e^{c_1 t}dt \leq c\left(e^{c_1 s} - 1\right).$$

As well, we know that

$$\left(\frac{d}{dt}\langle p\rangle\right)^2 + \langle p\rangle^2 \leq c\|p\|^2_{L^2(\Omega)} + \|\beta_Q(\varphi^* - \varphi_Q)\|^2_{L^2(\Omega)} + c\|q\|^2_{L^2(\Omega)}$$
$$+\left\|\frac{1}{2r}\left(2\beta_\Omega(\varphi^* - \varphi_\Omega) + \beta_s\right)\right\|^2_{L^2(\Omega)}.$$

Adding the above inequality to (2.41), and integrating over $[0, t]$, we find

$$\|\partial_t p\|^2_{L^2(0,s;L^2(\Omega))} + B\|\nabla p(s)\|^2_{L^2(\Omega)} + \|q(s)\|^2_{H^1(\Omega)} + \|\partial_t q\|_{L^2(0,s;L^2(\Omega))} \leq c.$$

Therefore, we deduce that

$$(p, q) \in \left(H^1(0, \tau^*; L^2(\Omega)) \cap L^\infty(0, \tau^*; H^1(\Omega)) \cap C([0, \tau^*]; L^2(\Omega))\right)^2.$$

Rewriting the adjoint equations as

$$
\begin{aligned}
&-B\Delta p = \partial_t p + \left(\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*\right) h'(\varphi) p + \beta_Q \left(\varphi^* - \varphi_Q\right) \\
&+\frac{1}{2r}\chi_{[\tau^*-r,\tau^*]}(t)\left(2\beta_\Omega\left(\varphi^* - \varphi_\Omega\right) + \beta_s\right) - \mathcal{C}\sigma^* h'(\varphi^*) q - f'(\varphi^*) p, \quad \text{in } [0,T]\times\Omega, \\
&-\Delta q = \partial_t q + \mathcal{P} h(\varphi^*) p - \left(\mathcal{C} h(\varphi^*) + \beta\right) q, \qquad \text{in } [0,T]\times\Omega, \\
&\partial_\nu p = \partial_\nu q = 0, \qquad \text{on } [0,T]\times\Gamma, \\
&p(\tau^*) = q(\tau^*) = 0, \qquad \text{in } \Omega,
\end{aligned}
$$

and thanks to elliptic regularity, we deduce that $(p,q) \in \left(L^2(0,\tau^*, H^2(\Omega))\right)^2$.

Existence of solution for the adjoint system. We apply a Galerkin approximation and consider a basis $\{\omega_i\}_{i\in\mathbb{N}}$ of $H^1(\Omega)$ that is orthonormal in $L^2(\Omega)$. Look for the functions

$$
p_{n,i}(x,t) = \sum_{i=1}^{n} P_{n,i}(t)\omega_i(x) \quad \text{and} \quad q_{n,i}(t,x) = \sum_{i=1}^{n} Q_{n,i}(t)\omega_i(x)
$$

such that

$$
p_n(0) = p_0^n, \quad q_n(0) = q_0^n, \quad p_n(\tau^*) = q_n(\tau^*) = 0,
$$

which satisfy the following approximate problem:

$$
\begin{aligned}
&-\int_\Omega \partial_t p_n\, v\, dx + B\int_\Omega \nabla p_n \cdot \nabla v\, dx = \int_\Omega \left(\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*\right) h'(\varphi^*) p_n\, v\, dx \\
&+\int_\Omega \left(\beta_Q(\varphi^* - \varphi_Q) + \frac{1}{2r}\chi_{[\tau^*-r,\tau^*]}(t)\left(2\beta_\Omega\left(\varphi^* - \varphi_\Omega\right) + \beta_s\right)\right) v\, dx \\
&-\int_\Omega \mathcal{C}\sigma^* h'(\varphi^*) q_n\, v\, dx - \int_\Omega f'(\varphi^*) p_n v\, dx
\end{aligned}
\tag{2.42}
$$

and

$$
-\int_\Omega \partial_t q_n\, v\, dx + \int_\Omega \nabla q_n \cdot \nabla v\, dx = \int_\Omega \mathcal{P} h(\varphi^*) p_n\, v\, dx - \int_\Omega \left(\mathcal{C} h(\varphi^*) + \beta\right) q_n\, v\, dx, \tag{2.43}
$$

for all $v \in V_n = \text{span}\,\{\omega_i,\, i = 1,\ldots,n\}$. In particular, put $v = \omega_j$ in (2.42) and (2.43) to get, $\forall\ i,j = 1,\ldots,n$,

$$
\begin{aligned}
&-\frac{d}{dt}\sum_{i=1}^{n} P_{n,i}(t)\int_\Omega \omega_i(x)\,\omega_j(x)\,dx + B\sum_{i=1}^{n} P_{n,i}(t)\int_\Omega \nabla\omega_i(x)\cdot\nabla\omega_i(x)\,dx \\
&= \sum_{i=1}^{n} P_{n,i}(t)\int_\Omega \left(\mathcal{P}\sigma^* - \mathcal{A} - \alpha^*\right) h'(\varphi^*)\omega_i(x)\,\omega_j(x)dx \\
&+\int_\Omega \beta_Q(\varphi^* - \varphi_Q)\omega_j(x)\,dx + \int_\Omega \frac{1}{2r}\chi_{[\tau^*-r,\tau^*]}(t)\left(2\beta_\Omega\left(\varphi^* - \varphi_\Omega\right) + \beta_s\right)\omega_j(x)\,dx \\
&-\sum_{i=1}^{n} Q_{n,i}(t)\int_\Omega \mathcal{C}\sigma^* h'(\varphi^*)\omega_i(x)\,\omega_j(x)\,dx - \sum_{i=1}^{n} P_{n,i}(t)\int_\Omega f'(\varphi^*)\omega_i(x)\,\omega_j(x)\,dx
\end{aligned}
\tag{2.44}
$$

and

$$-\frac{d}{dt}\sum_{i=1}^{n} Q_{n,i}(t)\int_\Omega \omega_i\,\omega_j\,dx+\sum_{i=1}^{n} Q_{n,i}(t)\int_\Omega \nabla\omega_i(x)\cdot\nabla\omega_j(x)\,dx$$
$$=\sum_{i=1}^{n} P_{n,i}(t)\int_\Omega \mathcal{P}h(\varphi^*)\omega_i(x)\,\omega_j(x)\,dx-\sum_{i=1}^{n} Q_{n,i}(t)\int_\Omega (\mathcal{C}h(\varphi^*)+\beta)\,\omega_i(x)\,\omega_j(x)\,dx.$$

Consequently, the above equation and (2.44) are ODEs of the following forms:

$$-P_n(t)'I_n+BP_n(t)J=P_n(t)K+L+\chi_{[\tau^*-r,\tau^*]}(t)M-Q_n(t)H-P_n(t)F \tag{2.45}$$

and

$$-Q_n(t)'I_n+Q_n(t)J=P_n(t)N-Q_n(t)R, \tag{2.46}$$

with the conditions $p_n(x,\tau^*)=q_n(x,\tau^*)=0$. Here

$$\begin{cases} J_{i,j}=\displaystyle\int_\Omega \nabla\omega_i(x)\cdot\nabla\omega_j(x)\,dx,\ K_{i,j}=\int_\Omega (\mathcal{P}\sigma^*-\mathcal{A}-\alpha^*)\,h'(\varphi^*)\omega_i(x)\,\omega_j(x)dx,\\ N_{i,j}=\displaystyle\int_\Omega \mathcal{P}h(\varphi^*)\omega_i(x)\,\omega_j(x)\,dx,\ R_{i,j}=\int_\Omega (\mathcal{C}h(\varphi^*)+\beta)\,\omega_i(x)\,\omega_j(x)\,dx,\\ H_{i,j}=\displaystyle\int_\Omega \mathcal{C}\sigma^*h'(\varphi^*)\omega_i(x)\,\omega_j(x)\,dx,\ F_{i,j}=\int_\Omega f'(\varphi^*)\omega_i(x)\,\omega_j(x)\,dx,\\ L_j=\displaystyle\int_\Omega \beta_Q(\varphi^*-\varphi_Q)\,\omega_j(x)\,dx,\\ M_j=\displaystyle\int_\Omega \frac{1}{2r}\left(2\beta_\Omega\left(\varphi^*-\varphi_\Omega\right)+\beta_s\right)\omega_j(x)\,dx. \end{cases}$$

First, we will consider the Cauchy Problem (2.45)-(2.46) on the interval $(\tau^*-r,\tau^*]$, so that it has the form

$$P_n(t)'I_n=BP_n(t)J-P_n(t)K-L-M-Q_n(t)H+P_n(t)F$$

and

$$Q_n(t)'I_n=Q_n(t)J-P_n(t)N+Q_n(t)R.$$

In other words, we have

$$(x'(t),y'(t))^\top=(f(t,x(t),y(t)),g(t,x(t),y(t)))^\top.$$

The right hand side of the above equation is locally Lipschitz with respect to (x,y), hence according to Cauchy Lipschitz theorem, the Problem (2.45)-(2.46) has a unique solution on (τ^*-r,s), where $s\in(\tau^*-r,\tau^*]$.

As well, we consider the System (2.45)-(2.46) on the interval $(0,\tau^*-r)$, we have

$$P_n(t)'I_n=BP_n(t)J-P_n(t)K-L+Q_n(t)H \tag{2.47}$$

and

$$Q_n(t)'I_n=Q_n(t)J-P_n(t)N+Q_n(t)R. \tag{2.48}$$

We then rewrite System (2.47)-(2.48) as

$$(x'(t),y'(t))^\top=(f(t,x(t),y(t)),g(t,x(t),y(t)))^\top,$$

where $f(t,x(t),y(t)) = BxJ - xK - L + yH$ and $g(t,x(t),y(t)) = yJ - xN + yR$. The function $(f(t,x(t),y(t)), g(t,x(t),y(t)))^\top$ is locally Lipschitz with respect to (x,y), so Cauchy Lipschitz theorem implies that the System (2.47)-(2.48) has a unique solution on the interval $(0,s)$ where $s \in (0, \tau^* - r)$.

It follows from the a priori estimates derived formally in the previous section, but for the approximated solution (p_n, q_n), that the solution is global and is defined on the whole interval $[0,\tau^*]$. Then the a priori estimates yields that up to a relabeled subsequence,

$$(p_n, q_n) \overset{*}{\rightharpoonup} (p,q), \text{ weakly star in } L^\infty(0,\tau^*, L^2(\Omega))$$

and

$$(p_n, q_n) \rightharpoonup (p,q), \text{ weakly in } L^2(0,\tau^*, H^1(\Omega)).$$

Moreover $(p_n, q_n) \in C([0,\tau^*], L^2(\Omega))^2$.

Passing to the limit. Recall that, the variational formulations of the approximate system are given by

$$\begin{aligned}
&-\frac{d}{dt}(p_n, v)_{L^2(\Omega)} + B(\nabla p_n, \nabla v)_{L^2(\Omega)} = \left((\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*)\, h'(\varphi^*) p_n, v\right)_{L^2(\Omega)} \\
&+ \left(\left(\beta_Q(\varphi^* - \varphi_Q) + \frac{1}{2r}\chi_{[\tau^*-r,\tau^*]}(t)\left(2\beta_\Omega(\varphi^* - \varphi_\Omega) + \beta_s\right)\right), v\right)_{L^2(\Omega)} \\
&-(\mathcal{C}\sigma^* h'(\varphi^*) q_n, v)_{L^2(\Omega)} - (f'(\varphi^*)p, v)
\end{aligned}$$

and

$$-\frac{d}{dt}(q_n, v)_{L^2(\Omega)} + (\nabla q_n, \nabla v)_{L^2(\Omega)} = (\mathcal{P}h(\varphi^*)p, v)_{L^2(\Omega)} - ((\mathcal{C}h(\varphi^*) + \beta)\, q_n, v)_{L^2(\Omega)}.$$

Integrating by parts over $[0,\tau^*]$, $\forall\, \psi \in D([0,\tau^*))$, we obtain

$$\begin{aligned}
&\int_0^{\tau^*} (p_n(t), v\psi'(t))_{L^2(\Omega)}\, dt + B\int_0^{\tau^*} (\nabla p_n(t), \nabla v\psi(t))_{L^2(\Omega)}\, dt \\
&= \int_0^{\tau^*} \left((\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*)\, h'(\varphi^*) p_n(t), v\psi(t)\right)_{L^2(\Omega)} dt + (p_0^n, v\psi(0))_{L^2(\Omega)} \\
&+ \int_0^{\tau^*} \left(\beta_Q(\varphi^* - \varphi_Q) + \frac{1}{2r}\chi_{[\tau^*-r,\tau^*]}(t)\left(2\beta_\Omega(\varphi^* - \varphi_\Omega) + \beta_s\right), v\psi(t)\right)_{L^2(\Omega)} dt \\
&- \int_0^{\tau^*} (\mathcal{C}\sigma^* h'(\varphi^*) q_n, v\psi(t))_{L^2(\Omega)}\, dt - \int_0^{\tau^*} (f'(\varphi^*)p_n, v\psi(t))_{L^2(\Omega)}\, dt
\end{aligned}$$

and

$$\begin{aligned}
&\int_0^{\tau^*} (q_n(t), v\psi'(t))_{L^2(\Omega)} dt + \int_0^{\tau^*} (\nabla q_n(t), \nabla v\psi(t))_{L^2(\Omega)} dt = (q_0^n, v\psi(0))_{L^2(\Omega)} \\
&+ \int_0^{\tau^*} (\mathcal{P}h(\varphi^*)p_n(t), v\psi(t))_{L^2(\Omega)} dt - \int_0^{\tau^*} ((\mathcal{C}h(\varphi^*) + \beta)\, q_n(t), v\psi(t))_{L^2(\Omega)} dt.
\end{aligned}$$

Noting that

$$\begin{aligned}
&\int_0^{\tau^*} (p_n(t), v\psi'(t))_{L^2(\Omega)} dt + B\int_0^{\tau^*} (\nabla p_n(t), \nabla v\psi(t))_{L^2(\Omega)} dt \\
&\to \int_0^{\tau^*} (p(t), v\psi'(t))_{L^2(\Omega)} dt + B\int_0^{\tau^*} (\nabla p(t), \nabla v\psi(t))_{L^2(\Omega)} dt
\end{aligned}$$

and

$$\int_0^{\tau^*} ((\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*)\, h'(\varphi^*)p_n(t), v\psi(t))_{L^2(\Omega)}dt + (p_0^n, v\psi(0))_{L^2(\Omega)}$$
$$\to \int_0^{\tau^*} ((\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*)\, h'(\varphi^*)p(t), v\psi(t))_{L^2(\Omega)}dt + (p_0, v\psi(0))_{L^2(\Omega)}.$$

On the other hand

$$\int_0^{\tau^*} (q_n(t), v\psi'(t))_{L^2(\Omega)}dt + \int_0^{\tau^*} (\nabla q_n(t), \nabla v\psi(t))_{L^2(\Omega)}dt - (q_0^n, v\psi(0))_{L^2(\Omega)}$$
$$\to \int_0^{\tau^*} (q(t), v\psi'(t))_{L^2(\Omega)}dt + \int_0^{\tau^*} (\nabla q(t), \nabla v\psi(t))_{L^2(\Omega)}dt - (q_0, v\psi(0))_{L^2(\Omega)}$$

and

$$\int_0^{\tau^*} (\mathcal{P}h(\varphi^*)p_n(t), v\psi(t))_{L^2(\Omega)}dt - \int_0^{\tau^*} ((\mathcal{C}h(\varphi^*) + \beta)\, q_n(t), v\psi(t))_{L^2(\Omega)}dt$$
$$\to \int_0^{\tau^*} (\mathcal{P}h(\varphi^*)p(t), v\psi(t))_{L^2(\Omega)}dt - \int_0^{\tau^*} ((\mathcal{C}h(\varphi^*) + \beta)\, q(t), v\psi(t))_{L^2(\Omega)}dt.$$

Using (2.37) and (2.38), as well as the fact that $\bigcup_n V_n$ is dense in $H^1(\Omega)$, we find, for all $v \in V_n$, $\psi \in D([0, \tau^*])$

$$\int_0^{\tau^*} (p(t), v\psi'(t))_{L^2(\Omega)}dt + B\int_0^{\tau^*} (\nabla p(t), \nabla v\psi(t))_{L^2(\Omega)}dt = (p(0), v\psi(0))_{L^2(\Omega)}$$
$$+ \int_0^{\tau^*} ((\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*)\, h'(\varphi^*)p(t), v\psi(t))_{L^2(\Omega)}dt + \int_0^{\tau^*} (\beta_Q\,(\varphi^* - \varphi_Q)\,, v\psi(t))_{L^2(\Omega)}dt$$
$$+ \frac{1}{2r}\int_0^{\tau^*} (\chi_{[\tau^*-r,\tau^*]}(t)\,(2\beta_\Omega\,(\varphi^* - \varphi_\Omega) + \beta_s)\,, v\psi(t))_{L^2(\Omega)}dt$$
$$- \int_0^{\tau^*} (\mathcal{C}\sigma^* h'(\varphi^*)q, v\psi(t))_{L^2(\Omega)}dt - \int_0^{\tau^*} (f'(\varphi^*)p, v\psi(t))_{L^2(\Omega)}dt$$

and

$$\int_0^{\tau^*} (q(t), v\psi'(t))_{L^2(\Omega)}dt + \int_0^{\tau^*} (\nabla q(t), \nabla v\psi(t))_{L^2(\Omega)}dt = (q(0), v\psi(0))_{L^2(\Omega)}$$
$$+ \int_0^{\tau^*} (\mathcal{P}h(\varphi^*)p(t), v\psi(t))_{L^2(\Omega)}dt - \int_0^{\tau^*} ((\mathcal{C}h(\varphi^*) + \beta)\, q(t), v\psi(t))_{L^2(\Omega)}\, dt.$$

Thus, it follows that $p(0) = p_0$, and $q(0) = q_0$ a.e. in $L^2(\Omega)$. □

2.7 Simplification of the first-order necessary optimality condition for the control

Let (u^*, τ^*) be a minimizer of the problem with corresponding state variables $(\varphi^*, \sigma^*) = \mathcal{S}(u^*)$, and adjoint variables (p, q) associated to (φ^*, σ^*). Let $w := u - u^* \in L^2(Q)$ for any $u \in \mathcal{U}_{ad}$, and let (Φ, Σ) be the linearized state variables associated to w.

Proposition 2.1

The optimal control u^* and the optimal treatment time τ^* satisfy the following simplified first-order necessary optimality conditions

$$(D_u\mathcal{J}_r(u^*,\tau^*))(u-u^*) = \beta_u\int_0^T\int_\Omega u^*(u-u^*)\,dx\,dt+\alpha\int_0^{\tau^*}\int_\Omega h(\varphi^*)(u-u^*)p\,dx\,dt \geq 0.$$

and

$$D_\tau\mathcal{J}_r(u^*,\tau^*)(s-\tau^*)\geq 0,\ \forall\, s\ \in[r,T].$$

Proof. Setting $\varphi(t)=\varphi_0$ for $t\leq 0$, and $\varphi_Q\in H^1(0,T;L^2(\Omega)),\varphi^*,\varphi_\Omega\in H^1(-r,T;L^2(\Omega)$, then the cost functional (**??**) can be expressed as

$$\begin{aligned}\mathcal{J}_r(\varphi,u,\tau) &= \frac{\beta_u}{2}\|u\|^2_{L^2(Q)}+\beta_T\tau+\frac{\beta_Q}{2}\int_0^\tau\int_\Omega|(\varphi-\varphi_Q)(t)|^2dx\,dt\\ &+\frac{\beta_\Omega}{2r}\int_0^\tau\int_\Omega\left(|(\varphi-\varphi_\Omega)(t)|^2-|(\varphi-\varphi_\Omega)(t-r)|^2\right)dx\,dt\\ &+\frac{\beta_S}{2r}\int_0^\tau\int_\Omega(\varphi(t)-\varphi(t-r))\,dx\,dt+\frac{\beta_\Omega}{2r}\int_{-r}^0\int_\Omega(\varphi_0-\varphi_\Omega(t))\,dx\,dt\\ &+\frac{\beta_S}{2r}\int_{-r}^0\int_\Omega(1+\varphi_0)\,dx\,dt.\end{aligned}$$

We have

$$\begin{aligned}D_\tau\mathcal{J}_r(u^*,\tau^*) &= \beta_T+\frac{\beta_Q}{2}\|\varphi^*(\tau^*)-\varphi_Q(\tau^*)\|^2_{L^2(\Omega)}+\frac{\beta_S}{2r}\int_\Omega(\varphi^*(\tau^*)-\varphi^*(\tau^*-r))\,dx\\ &+\frac{\beta_\Omega}{2r}\left(\|(\varphi^*-\varphi_\Omega)(\tau^*)\|^2_{L^2(\Omega)}-\|(\varphi^*-\varphi_\Omega)(\tau^*-r)\|^2_{L^2(\Omega)}\right).\end{aligned}$$

So, the optimal control and time (u^*,τ^*) satisfy the following first order necessary optimality condition with respect to time

$$D_\tau\mathcal{J}_r(u^*,\tau^*)(s-\tau^*)\geq 0,\ \forall\, s\ \in[r,T].$$

This condition can be simplified by taking the following arguments on s. If $\tau^*\in(r,T)$, take $s=\tau^*+h$ or $s=\tau^*-h$ for $h>0$, then we obtain $D_\tau\mathcal{J}_r(u^*,\tau^*)=0$. If $\tau^*=r$, then $s-\tau^*\geq 0$ for any $s\in[r,T]$, so we have $D_\tau\mathcal{J}_r(u^*,\tau^*)\geq 0$. Finally, if $\tau^*=T$, we deduce that $D_\tau\mathcal{J}_r(u^*,\tau^*)\leq 0$.
The optimal control u^* satisfies the following first-order necessary optimality condition

$$\begin{aligned}&(D_u\mathcal{J}_r(u^*,\tau^*))(u-u^*)=(D_u\mathcal{J}_r(u^*,\tau^*))w=\beta_Q\int_0^{\tau^*}\int_\Omega(\varphi^*-\varphi_Q)\Phi dx\,dt\\ &+\frac{\beta_\Omega}{r}\int_{\tau^*-r}^{\tau^*}\int_\Omega(\varphi^*-\varphi_\Omega)\Phi dx\,dt+\frac{\beta_s}{2r}\int_{\tau^*-r}^{\tau^*}\int_\Omega\Phi dx\,dt+\beta_u\int_0^T\int_\Omega u^*(u-u^*)dx\,dt\geq 0.\end{aligned}\tag{2.49}$$

In order to simplify this condition, put $\xi = \Phi$ in (2.37), $\xi = \Sigma$ in (2.38) and integrate over $[0, \tau^*]$, which yields

$$\begin{aligned}
&-\int_0^{\tau^*}\int_\Omega \partial_t p\Phi\, dx\, dt = -B\int_0^{\tau^*}\int_\Omega \nabla p\cdot\nabla\Phi\, dx\, dt + \int_0^{\tau^*}\int_\Omega \left(\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*\right) h'(\varphi^*)p\Phi\, dx\, dt\\
&+\int_0^{\tau^*}\int_\Omega \beta_Q\left(\varphi^* - \varphi_Q\right)\Phi\, dx\, dt + \int_{\tau^*-r}^{\tau^*}\int_\Omega \frac{1}{2r}\left(2\beta_\Omega(\varphi^* - \varphi_\Omega) + \beta_s\right)\Phi\, dx\, dt\\
&-\int_0^{\tau^*}\int_\Omega \mathcal{C}\sigma^* h'(\varphi^*)q\Phi dx\, dt - \int_0^{\tau^*}\int_\Omega f'(\varphi^*)p\Phi dx\, dt
\end{aligned} \tag{2.50}$$

and

$$\begin{aligned}
&-\int_0^{\tau^*}\int_\Omega \partial_t q\Sigma\, dx\, dt = -\int_0^{\tau^*}\int_\Omega \nabla q\cdot\nabla\Sigma\, dx\, dt\\
&+\int_0^{\tau^*}\int_\Omega \mathcal{P}h(\varphi^*)p\Sigma\, dx\, dt - \int_0^{\tau^*}\int_\Omega \left(\mathcal{C}h(\varphi^*) + \beta\right)q\Sigma\, dx\, dt.
\end{aligned} \tag{2.51}$$

On the other hand, substituting ξ for p in (2.25) and q in (2.26) leads to

$$\begin{aligned}
&\int_0^{\tau^*}\int_\Omega \partial_t\Phi p\, dx\, dt + B\int_0^{\tau^*}\int_\Omega \nabla\Phi\cdot\nabla p\, dx\, dt = \int_0^{\tau^*}\int_\Omega \left(\mathcal{P}\Sigma - \alpha w\right)h(\varphi^*)p\, dx\, dt\\
&+\int_0^{\tau^*}\int_\Omega \left(\mathcal{P}\sigma^* - \mathcal{A} - \alpha u^*\right)h'(\varphi^*)\Phi p\, dx\, dt - \int_0^{\tau^*}\int_\Omega f'(\varphi^*)\Phi p dx\, dt
\end{aligned} \tag{2.52}$$

and

$$\begin{aligned}
&\int_0^{\tau^*}\int_\Omega \partial_t\Sigma q\, dx\, dt + \int_0^{\tau^*}\int_\Omega \nabla\Sigma\cdot\nabla q\, dx\, dt\\
&= -\int_0^{\tau^*}\int_\Omega \left(\mathcal{C}h(\varphi^*) + \beta\right)\Sigma q\, dx\, dt - \int_0^{\tau^*}\int_\Omega \mathcal{C}\sigma^* h'(\varphi^*)\Phi q\, dx\, dt.
\end{aligned} \tag{2.53}$$

Due to the facts that $p(\tau^*) = q(\tau^*) = 0$, and $\Phi(0) = \Sigma(0) = 0$, and upon integrating by parts with respect to time, we obtain

$$-\int_0^{\tau^*}\int_\Omega \partial_t p\Phi\, dx\, dt = \int_0^{\tau^*}\int_\Omega p\partial_t\Phi\, dx\, dt.$$

Consequently, substituting (2.50) into (2.52), we obtain

$$\begin{aligned}
&\int_0^{\tau^*}\int_\Omega \beta_Q(\varphi^* - \varphi_Q)\Phi\, dx\, dt + \int_{\tau^*-r}^{\tau^*}\int_\Omega \frac{1}{2r}\left(2\beta_\Omega(\varphi^* - \varphi_\Omega) + \beta_s\right)\Phi\, dx\, dt\\
&= \int_0^{\tau^*}\int_\Omega \left(\mathcal{P}\Sigma - \alpha w\right)h(\varphi^*)p\, dx\, dt + \int_0^{\tau^*}\int_\Omega \mathcal{C}\sigma^* h'(\varphi^*)q\Phi dx\, dt.
\end{aligned} \tag{2.54}$$

As well, upon substituting (2.51) into (2.53), we obtain

$$\int_0^{\tau^*}\int_\Omega \mathcal{P}h(\varphi^*)\Sigma p\, dx\, dt = -\int_0^{\tau^*}\int_\Omega \mathcal{C}\sigma^* h'(\varphi^*)\Phi q\, dx\, dt.$$

Combining (2.54) and the above equation leads to

$$\begin{aligned}
&\int_0^{\tau^*}\int_\Omega \beta_Q(\varphi^* - \varphi_Q)\Phi\, dx\, dt + \int_{\tau^*-r}^{\tau^*}\int_\Omega \frac{1}{2r}\left(2\beta_\Omega(\varphi^* - \varphi_\Omega) + \beta_s\right)\Phi\, dx\, dt\\
&+\alpha\int_0^{\tau^*}\int_\Omega h(\varphi^*)wp\, dx\, dt = 0.
\end{aligned}$$

Substituting the above equation into (2.49) to obtain

$$(D_u\mathcal{J}_r(u^*,\tau^*))(u-u^*) = \beta_u \int_0^T \int_\Omega u^*(u-u^*)\,dx\,dt + \alpha \int_0^{\tau^*} \int_\Omega h(\varphi^*)(u-u^*)p\,dx\,dt \geq 0.$$

□

Chapter 3

On an Optimal Control Problem Describing Lactate Production Inhibition

"Doing the best at this moment puts you in the best place for the next moment."

Oprah Winfrey

ALTERED metabolism, characterized by high concentration levels of lactate enzyme, contributes to tumor development, malignancy, and metastasis and introduces metabolic liabilities that can be employed in cancer treatment. Here, this chapter aims to reach a desired lactate concentration, under the action of an optimal treatment dose, represented by a control, at an optimal treatment time. We consider an objective functional to be minimized associated with a system modeling lactate dynamics in the presence of control. We show the existence of a minimizer of this functional, and we derive a first-order necessary optimality condition.

3.1 Introduction

A common feature of tumor cells is the glycolytic abnormal metabolism known as the Warburg effect, by which and even in the presence of ample oxygen, cancer cells preferentially use glycolysis, unlike healthy cells which usually rely on oxidative phosphorylation to produce energy. The shift from oxidative phosphorylation towards glycolysis, which is accompanied by a high glucose uptake due to the lower energetic efficiency of glycolysis compared with oxidative phosphorylation, is one of the hallmarks of tumors. As a result, one observes elevated production levels of lactate which contributes to malignant progression, lowering PH for invasion and triggering immune escape.

LDH enzyme covers a central position in the metabolic reprogramming of tumor cells, playing a key role in the maintenance of altered glycolytic metabolism and permitting the survival of tumor cells when glycolysis represents the only energetic source. Structurally, the LDH enzyme is a tetrameric enzyme composed of two different kinds of subunits LDH-A and LDH-B. LDH-A has high activity in converting pyruvate into lactate whereas LDH-B is more efficient in the catalysis of the reverse reaction from lactate to pyruvate.

An isoform of LDHA, hLDH-5, was found to be overexpressed in a wide range of tumors linking its increase to aggressive tumor phenotype. Moreover, it has been established that

hLDH-5 may play an important role in the development and maintenance of metastatic tumors and serum hLDH-5 levels have been correlated with resistance to chemotherapy and radiotherapy. For these reasons hLDH-5 is now being considered a very promising therapeutic target for the treatment of cancer (see [17, 25, 30, 32, 39, 54, 57, 58, 72, 78]). Several LDHA inhibitors are mentioned in the literature for either type of tumors (see [45,56,67,68]). In this chapter, we are interested in gliomas, so we consider the treatment with gossypol which showed dose-dependent cytotoxic activity in diverse cancer cells and in particular in gliomas.

In [62], Miranville considered the following reaction-diffusion equation modeling lactate kinetics in one compartment

$$\partial_t u - \alpha\Delta u + \beta u + \frac{ku}{k' + u} = f(x,t).$$

Here u represents the intracellular lactate concentration. Furthermore, the non-linear term $ku\ (k'+u)^{-1}$ stands for lactate transport from capillary, where k is the maximum transport rate and k' is the Michaelis-Menten constant. The function f represents the creation and consumption of lactate and βu stands for the loss of lactate due to the convert of lactate to pyruvate by the LDHB enzyme (note that the above equation can also model the extra-cellular (capillary) lactate concentration, in which case βu corresponds to the blood flow). One can see that

$$\frac{ku}{k' + u} = k - \frac{kk'}{k' + u}.$$

Based on the previous model, we consider the following problem, for $T > 0$ in a bounded domain $\Omega \subset \mathbb{R}^3$ with C^3-boundary Γ

$$\partial_t u - \alpha\Delta u + \beta u - \frac{k}{k' + u} = J(x,t)(1 - \gamma v), \quad \text{in} \quad \Omega \times (0,T) =: Q, \tag{3.1}$$

$$\partial_\nu u = 0, \quad \text{on} \quad \Gamma \times (0,T), \tag{3.2}$$

$$u(0,x) = u_0(x), \quad \text{in} \quad \Omega. \tag{3.3}$$

Here, we introduce a control v which represents the concentration of gossypol inhibitor, where $v = 0$ stands for no dose and $v = 1$ stands for full dose. We further write $kk'\ (k'+u)^{-1}$ as $k\ (k'+u)^{-1}$ and note that $J = f - k$. Finally, $\gamma J(x,t)v$ is the inhibition of lactate production at rate γ. The cost functional to be minimized is given by

$$\mathcal{J}(u,v,\tau) = \frac{\beta_Q}{2}\int_0^\tau \int_\Omega |u-u_Q|^2 dx\,dt + \frac{\beta_\Omega}{2r}\int_{\tau-r}^\tau \int_\Omega |u-u_\Omega|^2 dx\,dt + \frac{\beta_v}{2}\int_0^T \int_\Omega |v|^2 dx\,dt, \tag{3.4}$$

where u_Q, u_Ω represent the desired evolution and distributional lactate concentrations both in $L^2(Q)$, $\tau \in (0,T]$ represents the treatment time, $T > 0$ is a fixed maximal time in which the patient is allowed to undergo treatment. The first two terms of (3.4) are of standard tracking type as often considered in the literature of parabolic optimal control (see [73]), the third term penalizes large concentrations of the applied inhibitor. Our problem becomes

$$\text{minimize } \mathcal{J} \text{ associated to (3.1) – (3.3).} \tag{3.5}$$

Cancer therapy is of interest to many researchers, particularly the application of optimal control theory to find an optimal treatment dose at an optimal time (see [43] and [23]), but most of these models target the cancer cell itself. In this work, we consider the cancer cell, its proliferation, malignancy, and metastasis from a different perspective, for example at the level of metabolism. To this end, we consider the parabolic problem in [62] the more lactate the cell produces, the more malignant it becomes. As excess lactate is transported to the capillaries with Michaelis-Menten kinetics, this promotes metastasis, malignancy, and resistance to therapy. Considering these facts, we think of inhibiting lactate production by finding a biologically relevant control to achieve our goal. Moreover, cancer treatment must not exceed or fall below a certain dose and treatment time. Thus, the goal of this work is to choose the control and treatment time such that the corresponding state $u(t,x)$ is the best possible approximation to a desired evolutionary lactate concentration and a stationary final lactate distribution in Ω. A mathematical difficulty lies in the singularity of the nonlinear term $k\ (k+u)^{-1}$, showing that our solution is non-negative is another challenge, however, we also emphasize that our objective functional depends on the free final time, which is also a challenge to show the differentiability of the coast functional with respect to time. So, in this work, we first show the well-posedness of (3.1)-(3.3), and consequently, we define the control-to-state operator, which we show is Fréchet differentiable with respect to the control v, we also prove that a minimizer of (3.4) exists. Moreover, the objective functional (3.4) is also Fréchet differentiable with respect to time and control. Finally, we derive a simplified first-order necessary optimality condition.

Assumptions

(C) The constants $k, \alpha \geq 0$, $\beta > 0$, $\gamma > 0$, and the function $J \in L^\infty(Q)$ are such that $J \geq -\dfrac{k'}{k}$ and $u_0 \geq 0$.

(D) The control $v \in \mathcal{V}_{ad} := \{v \in L^\infty(Q) :\ 0 \leq v \leq 1\}$.

3.2 Existence of solutions

In this section, we study the existence of a unique weak solution of System (3.1)-(3.3). More precisely, we will prove the following theorem:

Theorem 3.1 (Existence and uniqueness of weak solutions)

Assume that Assumptions (C) and (D) hold and that $u_0 \in H^1(\Omega)$. Then, Problem (3.1)-(3.3) admits a unique weak solution u such that $u \geq 0$ and

$$u \in \mathcal{Y} := L^2(0,T;H^2(\Omega)) \cap L^\infty(0,T;H^1(\Omega)) \cap H^1(0,T;L^2(\Omega)).$$

Moreover, the control-to-state operator

$$\begin{array}{rccc} S: & L^2(Q) & \longrightarrow & \mathcal{Y} \\ & v & \longmapsto & u \end{array}$$

is continuous.

Proof. The variational formulation of (3.1), for $u,\ \xi \in H^1(\Omega)$, is given by

$$\int_\Omega \partial_t u\xi\, dx + \alpha \int_\Omega \nabla u \cdot \nabla \xi\, dx + \beta \int_\Omega u\,\xi\, dx = \int_\Omega \frac{k}{k'+u}\xi\, dx + \int_\Omega J(x,t)(1-\gamma v)\xi\, dx. \quad (3.6)$$

Nonnegativity of u:

Estimate 1. Set $U = u + k'$. Then (3.1) is equivalent to

$$\partial_t U - \alpha\Delta U + \beta U - \frac{k}{U} = \beta k' + J(1-\gamma v).$$

Multiplying the above equation by $-\dfrac{1}{U}$ and integrate by parts to have

$$\frac{d}{dt}\int_\Omega \ln\frac{1}{U}dx + \alpha\int_\Omega \frac{|\nabla U|^2}{U^2}dx + \int_\Omega \frac{k}{U^2}dx = \beta \mathrm{Vol}(\Omega) - \int_\Omega \frac{\beta k'}{U}dx - \int_\Omega \frac{J(1-\gamma v)}{U}dx.$$

From the above equation, we deduce that

$$\frac{d}{dt}\int_\Omega \ln\frac{1}{U}dx \le c\left(1 + \|J\|^2_{L^\infty(\Omega)}\,\|1-\gamma v\|^2_{L^2(\Omega)}\right).$$

Whence, upon integrating over $[0,t]$, we find

$$\int_\Omega \ln\frac{1}{U(t)}dx \le \int_\Omega \ln\frac{1}{U_0}dx + c\left(t + \|J\|^2_{L^\infty(Q)}\,\|1-\gamma v\|^2_{L^2(Q)}\right).$$

This implies that $U > 0$, and thus $u > -k'$.

Estimate 2. Set $u^- = \max(0,-u)$. Then, multiplying Equation (3.1) by $-u^-$, and integrating over Ω, we get

$$\frac{1}{2}\frac{d}{dt}\left\|u^-\right\|^2_{L^2(\Omega)} + \alpha\left\|\nabla u^-\right\|^2_{L^2(\Omega)} + \beta\left\|u^-\right\|^2_{L^2(\Omega)} = -\int_\Omega\left(\frac{k}{k'+u} + J(1-\gamma v)\right)u^- dx.$$

If $u \ge 0$, then $u^- = 0$. On the contrary, from *Estimate 1*, we have $-k' < u \le 0$, and consequently $\dfrac{k}{k'+u} \ge \dfrac{k}{k'}$. So, by using Assumption (C) in the above equation, we deduce that

$$\frac{d}{dt}\left\|u^-\right\|^2_{L^2(\Omega)} \le 0.$$

It follows, from the fact that $u_0 \ge 0$, that

$$\sup_{\tau\in[0,T]}\left\|u^-(\tau)\right\|^2_{L^2(\Omega)} \le \left\|u^-(0)\right\|^2_{L^2(\Omega)} = 0.$$

Therefore $u^- = 0$, and hence $u \ge 0$ a.e. in Q.

Regularity estimates:

Estimate 1. Putting $\xi = 2u$ in (3.6) gives

$$\frac{d}{dt}\|u\|^2_{L^2(\Omega)} + 2\alpha\|\nabla u\|^2_{L^2(\Omega)} + 2\beta\|u\|^2_{L^2(\Omega)} = 2\int_\Omega \frac{ku}{k'+u}\,dx + 2\int_\Omega J(x,t)(1-\gamma v)u\,dx.$$

Let $\lambda = min(\alpha, \beta)$, we find

$$\frac{d}{dt}\|u\|^2_{L^2(\Omega)} + 2\lambda\|u\|^2_{H^1(\Omega)} \leq 2k\mathrm{Vol}(\Omega) + \|J\|^2_{L^\infty(\Omega)}\|1-\gamma v\|^2_{L^2(\Omega)} + \|u\|^2_{L^2(\Omega)}$$

$$\leq 2k\mathrm{Vol}(\Omega) + \|J\|^2_{L^\infty(\Omega)}\left(\mathrm{Vol}(\Omega) + \gamma^2\|v\|^2_{L^2(\Omega)}\right) + \|u\|^2_{L^2(\Omega)}.$$

Integrating over $[0,t)$, and applying Gronwall's lemma, we have

$$\|u(t)\|^2_{L^2(\Omega)} + 2\lambda\|u\|^2_{L^2(0,t;H^1(\Omega))} \leq \|u_0\|^2_{L^2(\Omega)}$$

$$+\int_0^t \left(2k\mathrm{Vol}(\Omega) + \|J\|^2_{L^\infty(\Omega)}\left(\mathrm{Vol}(\Omega) + \gamma\|v\|^2_{L^2(\Omega)}\right)\right)ds + \int_0^t \|u(s)\|^2_{L^2(\Omega)}\,ds.$$

Consequently, we get

$$\|u(t)\|^2_{L^2(\Omega)} + 2\lambda\|u\|^2_{L^2(0,t;H^1(\Omega))}$$

$$\leq \left(\|u_0\|^2_{L^2(\Omega)} + \int_0^t \left(2k\mathrm{Vol}(\Omega) + \|J\|^2_{L^\infty(\Omega)}\left(\mathrm{Vol}(\Omega) + \gamma\|v\|^2_{L^2(\Omega)}\right)\right)ds\right)e^t.$$

We deduce that u is bounded in $L^\infty(0,t;L^2(\Omega)) \cap L^2(0,t;H^1(\Omega))$.

Estimate 2. Putting $\xi = 2\partial_t u$ in (3.6), we find

$$\|\partial_t u\|^2_{L^2(\Omega)} + \alpha\frac{d}{dt}\|\nabla u\|^2_{L^2(\Omega)} + \beta\frac{d}{dt}\|u\|^2_{L^2(\Omega)}$$

$$\leq k\mathrm{Vol}(\Omega) + \|J\|^2_{L^\infty(\Omega)}\left(\mathrm{Vol}(\Omega) + \gamma^2\|v\|^2_{L^2(\Omega)}\right) + \|\partial_t u\|^2_{L^2(\Omega)}.$$

Taking $\lambda = min(\alpha, \beta)$, and integrating over $[0,t]$, we get

$$\|\partial_t u\|^2_{L^2(0,t;L^2(\Omega))} + \lambda\|u(t)\|^2_{H^1(\Omega)} \leq k\mathrm{Vol}(\Omega)t + \mathrm{Vol}(\Omega)\|J\|^2_{L^2(0,t;L^\infty(\Omega))}$$

$$+\gamma^2\|J\|^2_{L^\infty(0,t;L^\infty(\Omega))}\|v\|^2_{L^2(0,t;L^2(\Omega))} + \lambda\|u_0\|^2_{H^1(\Omega)}.$$

Therefore, we deduce that u is bounded in $L^\infty(0,t;H^1(\Omega))$, and $\partial_t u$ is bounded in $L^2(0,t;L^2(\Omega))$.

Estimate 3. We rewrite (3.1) in the form

$$-\alpha\Delta u = -\partial_t u - \beta u + \frac{k}{k'+u} + J(x,t)(1-\gamma v),$$

and since the right-hand side is in $L^2(\Omega)$, then elliptic regularity (see [36]), implies that $u \in H^2(\Omega)$. Moreover there exists some l so that

$$\|u\|_{H^2(\Omega)} \leq l\left(\|\partial_t u\|_{L^2(\Omega)} + \|u\|_{L^2(\Omega)} + \|v\|_{L^2(\Omega)} + \|J\|_{L^2(\Omega)}\right).$$

Consequently

$$\|u\|_{L^2(0,t;H^2(\Omega))} \leq l\left(\|\partial_t u\|_{L^2(0,t;L^2(\Omega))} + \|u\|_{L^2(0,t;L^2(\Omega))} + \|v\|_{L^2(0,t;L^2(\Omega))} + \|J\|_{L^2(0,t;L^2(\Omega))}\right).$$

Therefore, we infer that $u \in L^2(0,t;H^2(\Omega)) \cap L^\infty(0,t;H^1(\Omega))$ and $\partial_t u \in L^2(0,t;L^2(\Omega))$, hence $u \in C^0([0,t];H^1(\Omega))$ (see [8]).

Existence of solution. We have seen in the previous part that any regular solution of (3.1)-(3.3) is non-negative, so in the view of that, we set

$$\varphi(s) = \begin{cases} \dfrac{-k}{k'+s}; & \text{if} \quad s \geq 0, \\ -\dfrac{k}{k'} + \dfrac{s}{k'}; & \text{if} \quad s < 0, \end{cases}$$

and we consider the following problem

$$\begin{aligned} \partial_t u - \alpha\Delta u + \beta u + \varphi(u) = J(x,t)(1-\gamma v), \quad & \text{in } \Omega \times (0,T) =: Q, \\ \partial_\nu u = 0, \qquad & \text{on } \Gamma \times (0,T), \\ u(0,x) = u_0(x), \qquad & \text{in } \Omega. \end{aligned}$$

In order to establish the existence of solution, we will employ Faedo-Galerkin method, to this end, we consider $V_n = \text{Span}\{\omega_i\,;\, i = 1,\dots,n\}$ where $\{\omega_i\}_i$ form an orthonormal basis of $L^2(\Omega)$. Let P_n be the projection of $L^2(\Omega)$ on V_n. Set

$$u_0^n = P_n u_0,\ v_n = P_n v,\ J_n = P_n J, \text{ and } u_n = P_n u,$$

so that $u_n = \sum_{i=1}^{n} a_{n,i}(t)\omega_i(x)$, and $J_n \to J$ strongly in $L^2(Q)$, $u_0^n \to u_0$ strongly in $L^2(\Omega)$, and $v_n \to v$ strongly in $L^2(Q)$. Then the approximated variational problem is given by

$$\begin{aligned} &\frac{d}{dt}\sum_{i=1}^{n} a_{n,i}(t)\int_\Omega \omega_i\,\omega_j\,dx + \alpha\sum_{i=1}^{n} a_{n,i}(t)\int_\Omega \nabla\omega_i\cdot\nabla\omega_j\,dx + \beta\sum_{i=1}^{n} a_{n,i}(t)\int_\Omega \omega_i\,\omega_j\,dx \\ &= -\int_\Omega \varphi\left(\sum_{i=1}^{n} a_{n,i}(t)\omega_i\right)\omega_j\,dx + \int_\Omega J_n\,(1-\gamma v_n)\,\omega_j\,dx, \quad i,j = 1,\dots,n. \end{aligned} \tag{3.7}$$

Equivalently, we have

$$a_n'(t)I_n + \alpha a_n(t)M_n + \beta a_n(t)I_n = K_n + J_n - \gamma V_n, \tag{3.8}$$

where

$$\begin{cases} (I_n)_{i,j} = \displaystyle\int_\Omega \omega_i\,\omega_j\,dx, \quad (M_n)_{i,j} = \int_\Omega \nabla\omega_i\cdot\nabla\omega_j\,dx, \\ (K_n)_j = \displaystyle\int_\Omega \varphi\left(\sum_{i=1}^{n} a_{n,i}(t)\omega_i\right)\omega_j\,dx, \quad (J_n)_j = \int_\Omega J_n\omega_j\,dx, \quad (V_n)_j = \int_\Omega v_n\omega_j\,dx. \end{cases}$$

The Problem (3.8) can be written as the following form

$$a_n'(t) = f(t, a_n(t)), \tag{3.9}$$

with a vectorial function f Lipschitz with respect to the second variable $a_n(t)$. Then (3.9) admits a unique local solution over $[0,T^*]$, where $T^* \in [0,T]$.

Multiplying Equation (3.7) by $a_{n,j}$, and summing over j from 1 to n, and putting $\lambda = min(\alpha, \beta)$, we find

$$\frac{d}{dt}\|u_n\|^2_{L^2(\Omega)} + 2\lambda\|u_n\|^2_{H^1(\Omega)} \leq k\mathrm{Vol}(\Omega) + \|J_n\|^2_{L^\infty(\Omega)}\|1-\gamma v_n\|^2_{L^2(\Omega)} + 2\|u_n\|^2_{L^2(\Omega)}.$$

Hence

$$\begin{aligned}&\|u_n(T^*)\|^2_{L^2(\Omega)} + 2\lambda\|u_n\|^2_{L^2(0,T^*;H^1(\Omega))}\\ &\leq \left(\int_0^t \left(\|J_n\|^2_{L^\infty(\Omega)}\|1-\gamma v_n\|^2_{L^2(\Omega)} + k\mathrm{Vol}(\Omega)\right)ds + \|u_0^n\|^2_{L^2(\Omega)}\right)e^{2T^*}.\end{aligned}$$

Now, multiplying Equation (3.7) by $a'_{n,j}$, and summing over j from 1 to n, we have

$$2\|\partial_t u_n\|^2_{L^2(\Omega)} + \lambda\frac{d}{dt}\|u_n\|^2_{H^1(\Omega)} \leq k\mathrm{Vol}(\Omega) + \|J_n\|^2_{L^\infty(\Omega)}\|1-\gamma v_n\|^2_{L^2(\Omega)} + \|\partial_t u_n\|^2_{L^2(\Omega)}.$$

Equivalently, we have

$$\begin{aligned}&\|\partial_t u_n\|^2_{L^2(0,T^*;L^2(\Omega))} + \lambda\|u_n(T^*)\|^2_{H^1(\Omega)}\\ &\leq k\mathrm{Vol}(\Omega)T^* + \|J_n\|^2_{L^\infty(0,T^*;L^\infty(\Omega))}\|1-\gamma v_n\|^2_{L^2(0,T^*;L^2(\Omega))} + \lambda\|u_0^n\|^2_{H^1(\Omega)}.\end{aligned}$$

We deduce that u_n is bounded in $L^2(0,T^*;H^1(\Omega))$, and $\partial_t u_n$ is bounded in $L^2(0,T^*;L^2(\Omega))$, hence the solution a_n of the ODE (3.9) is global over $[0,T]$, and $u_n \in C^0([0,T];L^2(\Omega))$. Moreover, there exists some relabeled subsequence $\{u_n\}_n$ which converges weakly to u in $L^2(0,T;H^1(\Omega))$.

Passage to the limit. Let $\psi \in C_c^\infty([0,T])$, and $\xi \in H^1(\Omega)$, we have

$$\begin{aligned}&\int_0^T\int_\Omega \partial_t u_n \xi\psi dx\,dt + \alpha\int_0^T\int_\Omega (\nabla u_n\cdot\nabla\xi)\,\psi dx\,dt\\ &= -\beta\int_0^T\int_\Omega u_n\xi\psi dx\,dt + \int_0^T\int_\Omega \varphi(u_n)\xi\psi dx\,dt + \int_0^T\int_\Omega J_n(1-\gamma v_n)\xi\psi dx\,dt.\end{aligned} \tag{3.10}$$

Therefore

$$\int_0^T\int_\Omega \partial_t u_n\xi\psi dx\,dt = -\int_0^T\int_\Omega u_n\xi\psi' dx\,dt,$$

but

$$\int_0^T\int_\Omega u_n\xi\psi' dx\,dt \longrightarrow \int_0^T\int_\Omega u\xi\psi' dx\,dt = -\int_0^T\int_\Omega \partial_t u\xi\psi dx\,dt.$$

So,

$$\int_0^T\int_\Omega \partial_t u_n\xi\psi dx\,dt \longrightarrow -\int_0^T\int_\Omega \partial_t u\xi\psi dx\,dt.$$

Besides, we have that

$$\int_0^T\int_\Omega (\nabla u_n\cdot\nabla\xi)\,\psi dx\,dt \longrightarrow \int_0^T\int_\Omega (\nabla u\cdot\nabla\xi)\,\psi dx\,dt$$

and

$$-\beta\int_0^T\int_\Omega u_n\xi\psi dx\,dt + \int_0^T\int_\Omega J_n(1-\gamma v_n)\xi\psi dx\,dt \longrightarrow -\beta\int_0^T\int_\Omega u\,\xi\psi dx\,dt + \int_0^T\int_\Omega J(1-\gamma v)\xi\psi dx\,dt.$$

The compact embedding

$$W := \{u_n \in L^2(0,T;H^1(\Omega)), \partial_t u_n \in L^2(0,T;L^2(\Omega))\} \hookrightarrow L^2(0,T;L^2(\Omega))$$

(see [8]) yields that u_n converges strongly to u in $L^2(0,T;L^2(\Omega))$, and since $\varphi(u_n)$ is Lipschitz continuous, then

$$\int_0^T \int_\Omega \varphi(u_n)\xi\psi dx\, dt \longrightarrow \int_0^T \int_\Omega \varphi(u)\xi\psi dx\, dt.$$

Now choose $\psi \in C_c^\infty([0,T])$, so that $\psi(T) = 0$. Then, we have in (3.6)

$$\begin{aligned}&\int_0^T \int_\Omega \partial_t u\xi\psi dx\, dt + \alpha \int_0^T \int_\Omega (\nabla u \cdot \nabla \xi)\, \psi dx\, dt \\ &= -\beta \int_0^T \int_\Omega u\xi\psi dx\, dt + \int_0^T \int_\Omega \varphi(u)\xi\psi dx\, dt + \int_0^T \int_\Omega J(1-\gamma v)\xi\psi dx\, dt,\end{aligned}$$

which is equivalent to

$$\begin{aligned}&-\int_0^T \int_\Omega u\xi\psi' dx\, dt + \alpha \int_0^T \int_\Omega (\nabla u \cdot \nabla \xi)\, \psi dx\, dt = -\beta \int_0^T \int_\Omega u\xi\psi dx\, dt \\ &+ \int_0^T \int_\Omega \varphi(u)\xi\psi dx\, dt + \int_0^T \int_\Omega J(1-\gamma v)\xi\psi dx\, dt + \int_\Omega u(0)\xi\psi(0) dx.\end{aligned} \tag{3.11}$$

Similarly, we have in (3.10)

$$\begin{aligned}&-\int_0^T \int_\Omega u_n\xi\psi' dx\, dt + \alpha \int_0^T \int_\Omega (\nabla u_n \cdot \nabla \xi)\, \psi dx\, dt \\ &= -\beta \int_0^T \int_\Omega u_n\xi\psi dx\, dt + \int_0^T \int_\Omega \varphi(u_n)\xi\psi dx\, dt + \int_0^T \int_\Omega J_n(1-\gamma v_n)\xi\psi dx\, dt + \int_\Omega u_n(0)\xi\psi(0) dx.\end{aligned}$$

Passing to the limit in the above equation, we find

$$\begin{aligned}&-\int_0^T \int_\Omega u\xi\psi' dx\, dt + \alpha \int_0^T \int_\Omega (\nabla u \cdot \nabla \xi)\, \psi dx\, dt \\ &= -\beta \int_0^T \int_\Omega u\xi\psi dx\, dt + \int_0^T \int_\Omega \varphi(u)\xi\psi dx\, dt + \int_0^T \int_\Omega J(1-\gamma v)\xi\psi dx\, dt + \int_\Omega u_0\xi\psi(0) dx.\end{aligned}$$

Subtracting (3.11) and the above equation, we get

$$\int_\Omega u(0)\xi\psi(0) dx = \int_\Omega u_0\xi\psi(0) dx,$$

we deduce that $u(0) = u_0$ a.e in $L^2(\Omega)$.

Continuity of the control-to-state operator. Let u_1, u_2 be two solutions of (3.1)-(3.3) with same initial data, and let v_1, v_2 be two controls. Set $u = u_1 - u_2$, and $v = v_1 - v_2$, set $\lambda = min(\alpha, \beta)$, we have

$$\int_\Omega \partial_t u\xi dx + \alpha \int_\Omega \nabla u \cdot \nabla \xi dx + \beta \int_\Omega u\xi\, dx = -\int_\Omega \frac{ku}{(k'+u_1)(k'+u_2)}\xi dx - \gamma \int_\Omega J(x,t)v\xi dx. \tag{3.12}$$

Put $\xi = 2u$ in (3.12), we obtain

$$\frac{d}{dt}\|u\|^2_{L^2(\Omega)} + 2\lambda \|u\|^2_{H^1(\Omega)} \leq \gamma^2 \|J\|^2_{L^\infty(\Omega)} \|v\|^2_{L^2(\Omega)} + 2\|u\|^2_{L^2(\Omega)}.$$

Thus, integrating with respect to time, and using Gronwall's inequality, we get

$$\|u(t)\|^2_{L^2(\Omega)} + 2\lambda \|u\|^2_{L^2(0,t;H^1(\Omega))} \leq \left(\gamma^2 \|J\|^2_{L^\infty(0,t;L^\infty(\Omega))} \|v\|^2_{L^2(0,t;L^2(\Omega))}\right) e^{2t}.$$

Put $\xi = 2\partial_t$ in (3.12), we have

$$\begin{aligned} 2\|\partial_t u\|^2_{L^2(\Omega)} + \lambda \frac{d}{dt}\|u\|^2_{H^1(\Omega)} &\leq -2\int_\Omega \frac{k}{(k'+u_1)(k'+u_2)} u\partial_t u\, dx - 2\gamma \int_\Omega J(x,t) v \partial_t u dx \\ &\leq 2\frac{d}{dt}\|u\|^2_{L^2(\Omega)} + \gamma^2 \|J\|^2_{L^\infty(\Omega)} \|v\|^2_{L^2(\Omega)} + \|\partial_t u\|^2_{L^2(\Omega)}. \end{aligned}$$

Hence

$$\|\partial_t u\|^2_{L^2(0,t;L^2(\Omega))} + \lambda \|u(t)\|^2_{H^1(\Omega)} \leq \gamma^2 \|J\|^2_{L^\infty(0,t;L^\infty(\Omega))} \|v\|^2_{L^2(0,t;L^2(\Omega))} \left(2e^{2t}+1\right).$$

Recall that

$$-\alpha\Delta u = -\partial_t u - \beta u + \frac{ku}{(k'+u_1)(k'+u_2)} - \gamma J(x,t) v.$$

Since the right-hand side lies in $L^2(\Omega)$, then elliptic regularity gives that $u \in H^2(\Omega)$, and there is a constant l so that

$$\|u\|_{H^2(\Omega)} \leq l\left(\|u\|_{L^2(\Omega)} + \|v\|_{L^2(\Omega)} + \|\partial_t u\|_{L^2(\Omega)}\right).$$

Finally, we get

$$\|u\|_{L^2(0,t;H^2(\Omega))} \leq l\left(\|u\|_{L^2(0,t;L^2(\Omega))} + \|v\|_{L^2(0,t;L^2(\Omega))} + \|\partial_t u\|_{L^2(0,t;L^2(\Omega))}\right),$$

and hence the desired result. □

3.3 Existence of a minimizer

The cost functional $\mathcal{J}$ defined by (3.4) is bounded from below, so consider a minimizing sequence $(v_n, \tau_n)_{n\in\mathbb{N}}$ with $v_n \in \mathcal{V}_{ad}$, and $\tau_n \in (0,T)$ such that $(u_n)_{n\in\mathbb{N}}$ are the corresponding solutions of (3.1)-(3.3) on the interval $[0,T]$ with $u_n(0) = u_0, \forall\, n \in \mathbb{N}$ such that

$$\lim_{n\to\infty} \mathcal{J}(u_n, v_n, \tau_n) = \inf_{(w,s)\in\mathcal{V}_{ad}\times[0,T]} \mathcal{J}(\phi, w, s),$$

where ϕ is the solution of (3.1)-(3.3) for the corresponding control w. In particular, $v_n \in \mathcal{V}_{ad}$ implies that $0 \leq v_n \leq 1$ in Q, $\forall\, n \in \mathbb{N}$. As $\{\tau_n\}_{n\in\mathbb{N}}$ is a bounded sequence, there exists a relabeled subsequence, such that

$$\tau_n \to \tau^* \in [0,T], \quad \text{as } n \to \infty.$$

We also have

$$v_n \to v^* \quad \text{weakly} \quad \text{in} \quad L^2(Q), \quad \text{as } n \to \infty$$

and

$$u_n \to u^* \quad \text{strongly in} \quad C^0([0,T]; L^2(\Omega)) \cap L^2(Q), \quad \text{as } n \to \infty,$$

where (u^*, v^*) satisfy (3.1)-(3.3), with $0 \leq v^* \leq 1$ a.e. in Q.

Lebesgue dominated convergence theorem gives, $\forall\ p\ \in [1,\infty)$,

$$\chi_{[0,\tau_n]}(t) \to \chi_{[0,\tau^*]}(t)$$

and

$$\chi_{[\tau_n-r,\tau_n]}(t) \to \chi_{[\tau^*-r,\tau^*]}(t),$$

strongly in $L^p(0,T)$. Thus, since $u_n - u_Q$ converges strongly to $u^* - u_Q$, and $u_n - u_\Omega$ converges strongly to $u^* - u_\Omega$ in $L^2(Q)$, in addition to the strong convergence of $\chi_{[0,\tau_n]}(t)$ to $\chi_{[0,\tau^*]}(t)$, and $\chi_{[\tau_n-r,\tau_n]}(t)$ to $\chi_{[\tau^*-r,\tau^*]}(t)$, also in $L^2(Q)$, we have

$$\begin{aligned}&\int_0^{\tau_n}\int_\Omega |u_n - u_Q|^2 dx\,dt = \int_0^T \|u_n - u_Q\|^2_{L^2(\Omega)}\,\chi_{[0,\tau_n]}(t)dt\\ &\to \int_0^T \|u^* - u_Q\|^2_{L^2(\Omega)}\,\chi_{[0,\tau^*]}(t)dt = \int_0^{\tau^*}\int_\Omega |u^* - u_Q|^2 dx\,dt,\end{aligned}$$

and

$$\begin{aligned}&\int_{\tau_n-r}^{\tau_n}\int_\Omega |u_n - u_\Omega|^2 dx\,dt = \int_0^T \|u_n - u_\Omega\|^2_{L^2(\Omega)}\,\chi_{[\tau_n-r,\tau_n]}(t)dt\\ &\to \int_0^T \|u^* - u_\Omega\|^2_{L^2(\Omega)}\,\chi_{[\tau^*-r,\tau^*]}(t)dt = \int_{\tau^*-r}^{\tau^*}\int_\Omega |u^* - u_\Omega|^2 dx\,dt.\end{aligned}$$

By passing to the limit in $\mathcal{J}(u_n, v_n, \tau_n)$, and using the lower semi continuity of the $L^2(Q)$ norm, we infer

$$\inf_{(w,s)\in\mathcal{V}_{ad}\times[0,T]} \mathcal{J}(\phi, w, s) = \lim_{n\to\infty} \mathcal{J}(u_n, v_n, \tau_n) \geq \mathcal{J}(u^*, v^*, \tau^*),$$

which implies that (u^*, τ^*) is a minimizer of (3.5).

3.4 Fréchet differentiability of the control to state operator

In order to establish the existence of the Fréchet derivative of the control-to-state operator with respect to the control, we consider the linearized system at u^* associated to the control v^*, for $w \in L^2(Q)$.

$$\begin{aligned}&\partial_t U - \alpha\Delta U + \beta U = -\frac{k}{(k'+u^*)^2}U - \gamma J w, && \text{in, } Q\\ &\partial_\nu U = 0, && \text{on, } \Gamma\times(0,T)\\ &U(0,x) = 0, && \text{in, } \Omega\end{aligned} \tag{3.13}$$

satisfying the following variational formulation, for $\xi \in H^1(\Omega)$,

$$\int_\Omega \partial_t U\,dx + \alpha\int_\Omega \nabla U\cdot\nabla\xi\,dx + \beta\int_\Omega U\,\xi\,dx = -\int_\Omega \frac{k}{(k'+u^*)^2}U\,\xi\,dx - \gamma\int_\Omega J(x,t)w\,\xi\,dx. \tag{3.14}$$

Theorem 3.2

Let $v^* \in \mathcal{V}_{ad}$. Then the System (3.13) admits a unique solution

$$U \in L^2(0,T;H^2(\Omega)) \cap H^1(0,T;L^2(\Omega)) \cap C([0,T];H^1(\Omega)).$$

Proof. Regularity estimates. Putting $\xi = 2U$ in (3.14), we have

$$\frac{d}{dt}\|U\|^2_{L^2(\Omega)} + 2\lambda\|U\|^2_{H^1(\Omega)} = -\int_\Omega \frac{2k}{(k'+u^*)^2}|U|^2dx - 2\gamma\int_\Omega J(x,t)wU\,dx$$

$$\leq \gamma^2\|J\|^2_{L^\infty(\Omega)}\|w\|^2_{L^2(\Omega)} + c\|U\|^2_{L^2(\Omega)}.$$

Hence

$$\|U(t)\|^2_{L^2(\Omega)} + 2\lambda\|U\|^2_{L^2(0,t;H^1(\Omega))} \leq \gamma^2\|J\|^2_{L^\infty(0,t;L^\infty(\Omega))}\|w\|^2_{L^2(0,t;L^2(\Omega))}e^{ct}. \tag{3.15}$$

On the other hand, putting $\xi = 2\partial_t U$ in (3.14) yields

$$2\|\partial_t U\|^2_{L^2(\Omega)} + \lambda\frac{d}{dt}\|U\|^2_{H^1(\Omega)} \leq 2\frac{d}{dt}\|U\|^2_{L^2(\Omega)} + \gamma^2\|J\|^2_{L^\infty(\Omega)}\|w\|^2_{L^2(\Omega)} + \|\partial_t U\|^2_{L^2(\Omega)}.$$

Integrating over $[0,t]$, $t \in [0,T]$, and using (3.15), we get

$$\|\partial_t U\|^2_{L^2(0,t;L^2(\Omega))} + \lambda\|U(t)\|^2_{H^1(\Omega)} \leq \gamma^2\|J\|^2_{L^\infty(0,t;L^\infty(\Omega))}\|w\|^2_{L^2(0,t;L^2(\Omega))}\left(2e^{ct}+1\right).$$

Consequently, we deduce that U is bounded in $L^\infty(0,t;H^1(\Omega)) \cap L^2(0,t;H^1(\Omega))$, and $\partial_t U$ is bounded in $L^2(0,t;L^2(\Omega))$. Rewrite (3.13) as

$$-\alpha\Delta U = -\partial_t U - \beta U - \frac{k}{(k'+u^*)^2}U - \gamma Jw,$$

and due to elliptic regularity (see [61]), we deduce that U is in $H^2(\Omega)$. Moreover there exists some l such that

$$\|U\|^2_{H^2(\Omega)} \leq l\left(\|\partial_t U\|^2_{L^2(\Omega)} + \|U\|^2_{L^2(\Omega)} + \|w\|^2_{L^2(\Omega)}\right).$$

Thus, we get

$$\|U\|^2_{L^2(0,t;H^2(\Omega))} \leq l\left(\|\partial_t U\|^2_{L^2(0,t;L^2(\Omega))} + \|U\|^2_{L^2(0,t;L^2(\Omega))} + \|w\|^2_{L^2(0,t;L^2(\Omega))}\right).$$

Therefore, $U \in L^2(0,t;H^2(\Omega)) \cap L^\infty(0,t;H^1(\Omega))$, and $\partial_t U \in L^2(0,t;L^2(\Omega))$, so that $U \in C([0,t];H^1(\Omega))$.

Existence. By applying Faedo-Galerkin method, one can easily show the existence of solution of a linear system (see [27]).

Uniqueness. Let U_1 and U_2 be two solutions of (3.13) with $w = 0$, set $U = U_1 - U_2$, we find

$$\|U\|^2_{L^\infty(0,t;L^2(\Omega))\cap L^2(0,t;H^1(\Omega))} \leq \gamma^2\|J\|^2_{L^\infty(0,t;L^\infty(\Omega))}\|w\|^2_{L^2(Q)}e^{ct} \leq 0,$$

hence $U = 0$. □

3.5 Fréchet Differentiability of control-to-state operator with respect to the control

Let $w \in L^2(Q)$, set $u^w := S(v^* + w)$, and $u^* := S(v^*)$.

Theorem 3.3

Let U be the solution of the linearized System (3.13) at v^*. Then the remainder ρ satisfy

$$\|\rho\|_{\mathcal{Y}}^2 \leq c\,\|w\|_{L^2(Q)}^4\,,$$

where

$$\mathcal{Y} := L^2(0,s;H^2(\Omega)) \cap H^1(0,s;L^2(\Omega)) \cap L^\infty(0,s;H^1(\Omega)).$$

Proof. The remainder ρ could be expressed as, $\rho = u^w - u^* - U$, and set $v^w = v^* + w$, such that for all, $\xi \in H^1(\Omega)$, we have

$$\int_\Omega \partial_t u^w \xi dx + \alpha \int_\Omega \nabla u^w \cdot \nabla \xi dx = -\beta \int_\Omega u^w \xi dx + \int_\Omega \frac{k}{k' + u^w} \xi dx + \int_\Omega J(x,t)\,(1 - \gamma v^w)\,\xi dx,$$

$$\int_\Omega \partial_t u^* \xi dx + \alpha \int_\Omega \nabla u^* \cdot \nabla \xi dx = -\beta \int_\Omega u^* \xi dx + \int_\Omega \frac{k}{k' + u^*} \xi dx + \int_\Omega J(x,t)\,(1 - \gamma v^*)\,\xi dx,$$

and

$$\int_\Omega \partial_t U \xi dx + \alpha \int_\Omega \nabla U \cdot \nabla \xi dx = -\beta \int_\Omega U \xi dx - \int_\Omega \frac{k}{(k' + u^*)^2} U \xi dx - \gamma \int_\Omega J(x,t) w \xi dx.$$

Then the remainder $\rho = u^w - u^* - U$ satisfies, for all $\xi \in H^1(\Omega)$

$$\int_\Omega \partial_t \rho \xi dx + \alpha \int_\Omega \nabla \rho \cdot \nabla \xi dx + \beta \int_\Omega \rho \xi dx = \int_\Omega \left(\frac{k}{k' + u^w} - \frac{k}{k' + u^*} + \frac{k}{(k' + u^*)^2 U} \right) \xi dx.$$

Setting $f(u) = \dfrac{k}{k' + u}$, Taylor with integral remainder gives

$$f(u^w) - f(u^*) - f'(u^*)U = f'(u^*)\rho + (u^w - u^*)^2 \int_0^1 f''\left(z u^w + (1-z)u^*\right)(1-z)\,dz.$$

However, the remainder

$$R := \int_0^1 f''\left(z u^w + (1-z)u^*\right)(1-z)\,dz$$

is bounded, so that

$$\|R\|_\infty \leq c_R.$$

Thus, ρ satisfies the variational formulation

$$\int_\Omega \partial_t \rho\, \xi dx + \alpha \int_\Omega \nabla \rho \cdot \nabla \xi dx + \beta \int_\Omega \rho\, \xi dx = \int_\Omega f'(u^*)\rho\, \xi dx + \int_\Omega (u^w - u^*)^2\, R\, \xi dx. \quad (3.16)$$

Estimates:

Estimate 1. Putting $\xi = 2\rho$ in (3.16), gives

$$\frac{d}{dt}\|\rho\|_{L^2(\Omega)}^2 + 2\alpha \|\nabla \rho\|_{L^2(\Omega)}^2 + 2\beta \|\rho\|_{L^2(\Omega)}^2 = -2\int_\Omega \frac{k}{(k' + u^*)^2} |\rho|^2 dx + 2\int_\Omega (u^w - u^*)^2\, R\, \rho\, dx.$$

Consequently, taking $\lambda = min(\alpha, \beta)$, we find

$$\frac{d}{dt}\|\rho\|_{L^2(\Omega)}^2 + 2\lambda \|\rho\|_{H^1(\Omega)}^2 \leq 2\|\rho\|_{L^2(\Omega)}^2 + 2c_R \|u^w - u^*\|_{L^\infty(\Omega)} \|u^w - u^*\|_{L^2(\Omega)} \|\rho\|_{L^2(\Omega)}.$$

Integrating over $[0,t)$, we obtain

$$\|\rho(t)\|^2_{L^2(\Omega)} + 2\lambda \|\rho\|^2_{L^2(0,t;H^1(\Omega))} \leq \|\rho\|^2_{L^2(\Omega)} + 2c_R \int_0^t \|u^w - u^*\|_{L^\infty(\Omega)} \|u^w - u^*\|_{L^2(\Omega)} \|\rho\|_{L^2(\Omega)} \, ds$$
$$\leq \|\rho\|^2_{L^2(\Omega)} + 2c_R \|u^w - u^*\|_{L^\infty(0,t;L^2(\Omega))} \int_0^t \|u^w - u^*\|_{L^\infty(\Omega)} \|\rho\|_{L^2(\Omega)} \, ds.$$

Applying Holder's and Young's inequalities, and using the embedding

$$L^2(0,t;H^2(\Omega)) \hookrightarrow L^2(0,t;L^\infty(\Omega)),$$

we find

$$\|\rho(t)\|^2_{L^2(\Omega)} + 2\lambda \|\rho\|^2_{L^2(0,t;H^1(\Omega))} \leq c \|u^w - u^*\|^2_{L^\infty(0,t;L^2(\Omega))} \|u^w - u^*\|^2_{L^2(0,t;H^2(\Omega))} + c' \|\rho\|^2_{L^2(0,t;L^2(\Omega))}.$$

Consequently

$$\|\rho(t)\|^2_{L^2(\Omega)} + 2\lambda \|\rho\|^2_{L^2(0,t;H^1(\Omega))} \leq c \|w\|^4_{L^2(0,t;L^2(\Omega))} e^{c't}. \tag{3.17}$$

Estimate 2. Putting $\xi = 2\partial_t \rho$ in (3.16), and taking $\lambda = min(\alpha, \beta)$, we find

$$2\|\partial_t \rho\|^2_{L^2(\Omega)} + \lambda \frac{d}{dt} \|\rho\|^2_{H^1(\Omega)} \leq \frac{d}{dt} \|\rho\|^2_{L^2(\Omega)} + \int_\Omega (u^w - u^*)^2 R \, \partial_t \rho \, dx$$
$$\leq \frac{d}{dt} \|\rho\|^2_{L^2(\Omega)} + c_R \|u^w - u^*\|_{L^\infty(\Omega)} \|u^w - u^*\|_{L^2(\Omega)} \|\partial_t \rho\|_{L^2(\Omega)}.$$

Hence and using (3.17), we get

$$\|\partial_t \rho\|^2_{L^2(0,t;L^2(\Omega))} + \lambda \|\rho(t)\|^2_{H^1(\Omega)} \leq \|\rho(t)\|^2_{L^2(\Omega)} + c_R^2 \|u^w - u^*\|^2_{L^2(0,t;L^\infty(\Omega))} \|u^w - u^*\|^2_{L^\infty(0,t;L^2(\Omega))}$$
$$\leq c \|w\|^4_{L^2(0,t;L^2(\Omega))} e^{c't} + c \|u^w - u^*\|^2_{L^2(0,t;H^2(\Omega))} \|u^w - u^*\|^2_{L^\infty(0,t;L^2(\Omega))}$$
$$\leq c \|w\|^4_{L^2(0,t;L^2(\Omega))}.$$

Estimate 3. We can view the variational formulation as a variational formulation of an elliptic problem

$$-\alpha \Delta \rho = -\partial_t \rho - \beta \rho + f'(u^*)\rho + (u^w - u^*)^2 R.$$

Since the right-hand side lies in $L^2(\Omega)$, the elliptic regularity of the Neumann problem yields that ρ lies in $H^2(\Omega)$. Moreover, there is a constant l, so that

$$\|\rho\|_{H^2(\Omega)} \leq l \left(\|\rho\|_{L^2(\Omega)} + \|\partial_t \rho\|_{L^2(\Omega)} + \|w\|^2_{L^2(\Omega)} \right).$$

Consequently

$$\|\rho\|_{L^2(0,t;H^2(\Omega))} \leq l \left(\|\rho\|_{L^2(0,t;L^2(\Omega))} + \|\partial_t \rho\|_{L^2(0,t;L^2(\Omega))} + \|w\|^2_{L^2(0,t;L^2(\Omega))} \right).$$

□

3.6 Differentiability of the cost functional

3.6.1 Differentiability of the cost functional with respect to time

For any function $f \in L^1(0,\tau,L^1(\Omega))$, we have the following relation

$$\begin{aligned}\int_{\tau-r}^{\tau}\int_\Omega f(s)dx\,ds &= \int_{\tau-r}^{0}\int_\Omega f(s)dx\,ds + \int_0^\tau\int_\Omega f(s)dx\,ds\\ &= \int_{\tau}^{-r}\int_\Omega f(s)dx\,ds + \int_{-r}^{0}\int_\Omega f(s)dx\,ds + \int_0^\tau\int_\Omega f(s)dx\,ds\\ &= \int_0^\tau\int_\Omega (f(s)-f(s-r))\,dx\,ds + \int_{-r}^{0}\int_\Omega f(s)dx\,ds.\end{aligned}$$

So, we can rewrite the objective functional as

$$\begin{aligned}&\mathcal{J}(u,v,\tau) = \frac{\beta_v}{2}\|v\|^2_{L^2(Q)} + \frac{\beta_\Omega}{2r}\int_{-r}^{0}\int_\Omega |(u-u_\Omega)(t)|^2 dx\,dt\\ &+\frac{1}{2}\int_0^\tau\int_\Omega\left(\beta_Q|(u-u_Q)(t)|^2 + \beta_\Omega\left(|(u-u_\Omega)(t)|^2 - \frac{1}{r}|(u-u_\Omega)(t-r)|^2\right)\right)dx\,dt.\end{aligned}$$

The first two terms are independent of time, so they vanish when we compute the Fréchet derivative with respect to the time, for $f \in H^1(0,T) \hookrightarrow L^\infty(0,T)$ and $h>0$, so that for $\tau \in (0,T)$, $\tau+h \in (0,T)$, we find

$$\begin{aligned}&\int_0^{\tau+h}|f(s)|^2ds - \int_0^\tau |f(s)|^2ds - h|f(\tau)|^2 = \int_\tau^{\tau+h}|f(s)|^2ds - h|f(\tau)|^2\\ &= \int_\tau^{\tau+h}\left(|f(s)|^2 - |f(\tau)|^2\right)ds = \int_\tau^{\tau+h}(|f(s)|-|f(\tau)|)(|f(s)|+|f(\tau)|)\,ds\\ &\le 2\|f\|_{L^\infty(0,T)}\int_\tau^{\tau+h}(|f(s)|-|f(\tau)|)\,ds \le 2\|f\|_{L^\infty(0,T)}h^{\frac{3}{2}}\|\partial_t f\|_{L^2(0,T)}.\end{aligned}$$

Thus, we get

$$D_\tau\left(\int_0^\tau |f(t)|^2dt\right) = |f(\tau)|^2.$$

So, we deduce that

$$\begin{aligned}&D_\tau\mathcal{J}(v^*,\tau^*) = \frac{\beta_Q}{2}\|u^*(\tau^*)-u_Q(\tau^*)\|^2_{L^2(\Omega)}\\ &+\frac{\beta_\Omega}{2}\left(\|u^*(\tau^*)-u_\Omega(\tau^*)\|^2_{L^2(\Omega)} - \frac{1}{r}\|u^*(\tau^*-r)-u_\Omega(\tau^*-r)\|^2_{L^2(\Omega)}\right).\end{aligned}$$

For $u_Q \in H^1(0,T;L^2(\Omega)), u_\Omega, u^* \in H^1(-r,T;L^2(\Omega))$, we deduce the following first-order necessary optimality condition with respect to time

$$D_\tau\mathcal{J}(v^*,\tau^*)(s-\tau^*) \ge 0 \quad \forall\ s \in [0,T].$$

To simplify this condition, if $\tau^* \in (0,T)$, then $s-\tau^* \ge 0$ if $s \ge \tau^*$, and $s-\tau^* \le 0$ if $s \le \tau^*$, so that $D_\tau\mathcal{J}(v^*,\tau^*) = 0$. If $\tau^* = 0$, then $s-\tau^* \ge 0$ and hence $D_\tau\mathcal{J}(v^*,\tau^*) \ge 0$. If $\tau^* = T$, then $s-\tau^* \le 0$ and hence $D_\tau\mathcal{J}(v^*,\tau^*) \le 0$.

3.6.2 Differentiability of the cost functional with respect to the control

The Fréchet derivative of the reduced cost functional at (v^*, τ^*) with respect to the control v is given by

$$D_v J(v^*,\tau^*)w = \beta_Q \int_0^{\tau^*}\int_\Omega |u^*-u_Q|U\,dx\,dt+\beta_\Omega \int_{\tau^*-r}^{\tau^*}\int_\Omega |u^*-u_\Omega|U\,dx\,dt+\beta_v\int_0^T\int_\Omega v^*\,w\,dx\,dt.$$

In order to eliminate the term U from the above equation, we apply Lagrangian principle, to this end, we define the Lagrangian function with respective Lagrangian multiplier p by

$$\mathcal{L}(u,v,p) = J(u,v) - \iint_Q p\left(\partial_t u - \alpha\Delta u + \beta u - \frac{k}{k'+u} - J(x,t)(1-\gamma v)\right)dx\,dt$$

3.6.3 Adjoint system

The adjoint system is given by

$$D_u\mathcal{L}(u^*,v^*,p)u = 0,$$

where

$$\begin{aligned} D_u\mathcal{L}(u^*,v^*,p)u &= \beta_Q\int_0^{\tau^*}\int_\Omega |u^*-u_Q|u\,dx\,dt + \frac{\beta_\Omega}{r}\int_{\tau^*-r}^{\tau^*}\int_\Omega |u^*-u_\Omega|u\,dx\,dt \\ &\quad + \iint_Q (\partial_t p + \alpha\Delta p)\,u\,dx\,dt - \beta\iint_Q p\,u\,dx\,dt - \iint_Q \frac{k}{(k'+u^*)^2}p\,u\,dx\,dt, \quad \tau^* \in [0,T] \\ &= \int_0^{\tau^*}\int_\Omega \left(\beta_Q(u^*-u_Q) + \beta_\Omega\chi_{[\tau^*-r,\tau^*]}(t)(u^*-u_\Omega) + \partial_t p + \alpha\Delta p - \beta p - \frac{k}{(k'+u^*)^2}p\right)u\,dx\,dt. \end{aligned}$$

The adjoint system is then written as

$$\begin{cases} \partial_t p + \alpha\Delta p = \beta p + \dfrac{k\,p}{(k'+u^*)^2} - \beta_Q(u^*-u_Q) - \dfrac{\beta_\Omega}{r}\chi_{[\tau^*-r,\tau^*]}(t)(u^*-u_\Omega), & \text{in } [0,T]\times\Omega, \\ \partial_\nu p = 0, & \text{on } [0,T]\times\Gamma, \\ p(\tau^*) = 0, & \text{in } \Omega. \end{cases} \tag{3.18}$$

Theorem 3.4

Let v^* be an optimal control, and $u^* = \mathcal{S}(v^*)$ be the corresponding state. Then the adjoint Problem (3.18) has a unique solution

$$p \in H^1(0,\tau^*;L^2(\Omega)) \cap L^\infty(0,\tau^*;H^1(\Omega)) \cap L^2(0,\tau^*;H^2(\Omega)) \cap C([0,\tau^*];H^1(\Omega)).$$

Proof. The variational formulation of the adjoint system, for $\xi \in H^1(\Omega)$, is given by:

$$\begin{aligned} &-\int_\Omega \partial_t p\,\xi dx + \alpha\int_\Omega \nabla p\cdot\nabla\xi\,dx + \beta\int_\Omega p\,\xi\,dx = -\int_\Omega \frac{k}{(k'+u^*)^2}\xi\,dx \\ &+\beta_Q\int_\Omega (u^*-u_Q)\xi\,dx + \frac{\beta_\Omega}{r}\int_\Omega \chi_{[\tau^*-r,\tau^*]}(t)(u^*-u_\Omega)\xi\,dx. \end{aligned} \tag{3.19}$$

Regularity estimates:

Estimate 1. Put $\xi = 2p$ in (3.19), we find

$$\frac{d}{dt}\|p\|^2_{L^2(\Omega)} + 2\lambda\|p\|^2_{H^1(\Omega)} \leq \beta_Q^2\|u^* - u_Q\|^2_{L^2(\Omega)} + \left(\frac{\beta_\Omega}{r}\right)^2\|u^* - u_\Omega\|^2_{L^2(\Omega)} + c\|p\|^2_{L^2(\Omega)}.$$

Hence

$$\|p(t)\|^2_{\mathbb{L}^2(\Omega)} + 2\lambda\|p\|^2_{L^2(0,t;H^1(\Omega))}$$
$$\leq \left(\beta_Q^2\|u^* - u_Q\|^2_{L^2(0,t;L^2(\Omega))} + \left(\frac{\beta_\Omega}{r}\right)^2\|u^* - u_\Omega\|^2_{L^2(0,t;L^2(\Omega))} + \|p_0\|^2_{L^2(\Omega)}\right)e^{ct}.$$

We deduce that p is bounded in $L^\infty(0,t;L^2(\Omega)) \cap L^2(0,t;H^1(\Omega))$.

Estimate 2. Put $\xi = 2\partial_t p$ in (3.19), we have

$$2\|\partial_t p\|^2_{L^2(\Omega)} + \lambda\frac{d}{dt}\|p\|^2_{L^2(\Omega)} \leq \beta_Q^2\|u^* - u_Q\|^2_{L^2(\Omega)} + \left(\frac{\beta_\Omega}{r}\right)^2\|u^* - u_\Omega\|^2_{L^2(\Omega)} + \|\partial_t p\|^2_{L^2(\Omega)}.$$

Hence

$$\|\partial_t p\|^2_{L^2(0,t;L^2(\Omega))} + \|p(t)\|^2_{H^1(\Omega)} \leq \|p(0)\|^2_{H^1(\Omega)}$$
$$+\beta_Q^2\|u^* - u_Q\|^2_{L^2(0,t;L^2(\Omega))} + \left(\frac{\beta_\Omega}{r}\right)^2\|u^* - u_\Omega\|^2_{L^2(0,t;L^2(\Omega))}.$$

Therefore, p is bounded in $L^\infty(0,t;H^1(\Omega))$, and $\partial_t p$ is bounded in $L^2(0,t;L^2(\Omega))$.

Estimate 3. Rewrite (3.18) in the elliptic form using the Neumann boundary conditions

$$-\alpha\Delta p = \partial_t p - \beta p - \frac{k}{(k' + u^*)^2}p + \beta_Q(u^* - u_Q) + \beta_\Omega\chi_{[\tau^*-r,\tau^*]}(t)(u^* - u_\Omega),$$

since the right-hand side of this equation is in $L^2(\Omega)$, so using elliptic regularity, we deduce that $p \in H^2(\Omega)$, and there is a constant l such that

$$\|p\|_{H^2(\Omega)} \leq l\left(\|p\|_{L^2(\Omega)} + \|u^*\|_{L^2(\Omega)} + \|\partial_t p\|_{L^2(\Omega)}\right).$$

Consequently

$$\|p\|_{L^2(0,t;H^2(\Omega))} \leq l\left(\|p\|_{L^2(0,t;L^2(\Omega))} + \|u^*\|_{L^2(0,t;L^2(\Omega))} + \|\partial_t p\|_{L^2(0,t;L^2(\Omega))}\right).$$

Existence of solution for the adjoint system. We apply a Galerkin approximation and for this purpose, we consider a basis $\{\omega_i\}_{i\in\mathbb{N}}$ of $H^1(\Omega)$ that is orthonormal in $L^2(\Omega)$. Look for the function $p_{n,i}(x,t) = \sum_{i=1}^{n} P_{n,i}(t)\omega_i(x)$, $p_n(0) = p_0^n$ so that $p_0^n \to p_0$ strongly in $L^2(\Omega)$ and $p_n(\tau^*) = 0$, which satisfy the following approximate problem:

$$-\int_\Omega \partial_t p_n\, v\, dx + \alpha\int_\Omega \nabla p_n \cdot \nabla v\, dx = -\beta\int_\Omega p_n\, v\, dx$$
$$-\int_\Omega \frac{k}{(k' + u^*)^2}p_n\, v\, dx + \beta_Q\int_\Omega\left((u^* - u_Q) + \frac{\beta_\Omega}{r}\chi_{[\tau^*-r,\tau^*]}(u^* - u_\Omega)\right)v\, dx.$$

for all $v \in V_n = \text{span}\,\{\omega_i,\, i = 1\ldots, n\}$. In particular, put $v = \omega_j$ in the above equation to get, $\forall\ i, j = 1, \ldots, n$,

$$\begin{aligned}
&-\frac{d}{dt}\sum_{i=1}^{n} P_{n,i}(t)\int_\Omega \omega_i(x)\,\omega_j(x)\,dx + \alpha\sum_{i=1}^{n} P_{n,i}(t)\int_\Omega \nabla\omega_i(x)\cdot\nabla\omega_i(x)\,dx\\
&= -\beta\sum_{i=1}^{n} P_{n,i}(t)\int_\Omega \omega_i\,\omega_j\,dx - \sum_{i=1}^{n} P_{n,i}(t)\int_\Omega \frac{k}{(k'+u^*)^2}\omega_i\,\omega_j\,dx\\
&+\beta_Q\int_\Omega (u^*-u_Q)\omega_j\,dx + \frac{\beta_\Omega}{r}\int_\Omega \chi_{[\tau^*-r,\tau^*]}(t)(u^*-u_\Omega)\omega_j\,dx.
\end{aligned}$$

Consequently, we can write the above equation in the form

$$-P_n(t)'I_n + \alpha P_n(t)J_n = -\beta P_n(t)I_n - P_n(t)K_n + \beta_Q U_Q + \frac{\beta_\Omega}{r}\chi_{[\tau^*-r,\tau^*]}(t)U_\Omega \tag{3.20}$$

with the condition $P_n(\tau^*) = 0$, where

$$\begin{cases}
(I_n)_{i,j} = \displaystyle\int_\Omega \omega_i\,\omega_j\,dx, \quad (J_n)_{i,j} = \int_\Omega \nabla\omega_i\cdot\omega_j\,dx, \quad (K_n)_{i,j} = \int_\Omega \frac{k}{(k'+u^*)^2}\omega_i\,\omega_j\,dx,\\
(U_Q)_j = \displaystyle\int_\Omega (u^*-u_Q)\omega_j\,dx, \quad (U_\Omega)_j = \int_\Omega (u^*-u_\Omega)\omega_j\,dx
\end{cases}$$

We rewrite (3.20) as

$$P'(t) = f(t, P_n(t)).$$

It is easy to see that f is Lipschitz with respect to P_n, so by Cauchy Lipschitz theorem, we deduce that (3.20) has unique solution over $[0, s)$, $s \in (0, \tau^*]$. With estimates similar to the regularity estimates, we can show that this solution is global over $[0, \tau^*]$, and that p_n is bounded in $L^2(0, \tau^*; H^2(\Omega))$, so there exists a relabeled subsequence $(p_n)_n$, so that

$$p_n \rightharpoonup p, \text{ weakly in } L^2(0, \tau^*, H^2(\Omega)).$$

Moreover, $p_n \in C([0, \tau^*], L^2(\Omega))$.

Passage to the limit. Let $\psi \in C_c^\infty(0, \tau^*; H^1(\Omega))$, we find

$$\begin{aligned}
&-\int_0^{\tau^*}\int_\Omega \partial_t p_n\psi\,dx\,dt + \alpha\int_0^{\tau^*}\int_\Omega \nabla p_n\cdot\nabla\psi\,dx\,dt + \int_0^{\tau^*}\int_\Omega \frac{k}{(k'+u^*)^2}p_n\,\psi\,dx\,dt\\
&+\beta\int_0^{\tau^*}\int_\Omega p_n\psi\,dx\,dt - \beta_Q\int_0^{\tau^*}\int_\Omega (u^*-u_Q)\psi\,dx\,dt - \frac{\beta_\Omega}{r}\int_0^{\tau^*}\int_\Omega \chi_{[\tau^*-r,\tau^*]}(t)(u^*-u_\Omega)\psi\,dx\,dt
\end{aligned} \tag{3.21}$$

$$\begin{aligned}
\longrightarrow\ &-\int_0^{\tau^*}\int_\Omega \partial_t p\psi\,dx\,dt + \alpha\int_0^{\tau^*}\int_\Omega \nabla p\cdot\nabla\psi\,dx\,dt + \beta\int_0^{\tau^*}\int_\Omega p\psi\,dx\,dt\\
&+\int_0^{\tau^*}\int_\Omega \frac{k}{(k'+u^*)^2}p\,\psi\,dx\,dt - \beta_Q\int_0^{\tau^*}\int_\Omega (u^*-u_Q)\psi\,dx\,dt\\
&-\frac{\beta_\Omega}{r}\int_0^{\tau^*}\int_\Omega \chi_{[\tau^*-r,\tau^*]}(t)(u^*-u_\Omega)\psi\,dx\,dt.
\end{aligned} \tag{3.22}$$

In particular, choose ψ so that $\psi(\tau^*) = 0$, and integrate (3.21) by parts with respect to time, we get

$$\int_0^{\tau^*}\int_\Omega p_n\partial_t\psi\,dx\,dt + \alpha\int_0^{\tau^*}\int_\Omega \nabla p_n\cdot\nabla\psi\,dx\,dt = \int_\Omega p_n(0)\psi(0)\,dx - \beta\int_0^{\tau^*}\int_\Omega p_n\psi\,dx\,dt$$
$$-\int_0^{\tau^*}\int_\Omega \frac{k}{(k'+u^*)^2}p_n\,\psi\,dx\,dt + \beta_Q\int_0^{\tau^*}\int_\Omega (u^*-u_Q)\psi\,dx\,dt$$
$$+\frac{\beta_\Omega}{r}\int_0^{\tau^*}\int_\Omega \chi_{[\tau^*-r,\tau^*]}(t)(u^*-u_\Omega)\psi\,dx\,dt.$$

Passing to the limit, we get

$$\int_0^{\tau^*}\int_\Omega p\partial_t\psi\,dx\,dt + \alpha\int_0^{\tau^*}\int_\Omega \nabla p\cdot\nabla\psi\,dx\,dt = \int_\Omega p_0\psi(0)\,dx - \beta\int_0^{\tau^*}\int_\Omega p\psi\,dx\,dt$$
$$-\int_0^{\tau^*}\int_\Omega \frac{k}{(k'+u^*)^2}p\,\psi\,dx\,dt + \beta_Q\int_0^{\tau^*}\int_\Omega (u^*-u_Q)\psi\,dx\,dt \tag{3.23}$$
$$+\frac{\beta_\Omega}{r}\int_0^{\tau^*}\int_\Omega \chi_{[\tau^*-r,\tau^*]}(t)(u^*-u_\Omega)\psi\,dx\,dt.$$

Similarly, integrating (3.22) with by parts with respect to time, we obtain

$$\int_0^{\tau^*}\int_\Omega p\partial_t\psi\,dx\,dt + \alpha\int_0^{\tau^*}\int_\Omega \nabla p\cdot\nabla\psi\,dx\,dt = \int_\Omega p(0)\psi(0)\,dx - \beta\int_0^{\tau^*}\int_\Omega p\psi\,dx\,dt$$
$$-\int_0^{\tau^*}\int_\Omega \frac{k}{(k'+u^*)^2}p\,\psi\,dx\,dt + \beta_Q\int_0^{\tau^*}\int_\Omega (u^*-u_Q)\psi\,dx\,dt$$
$$+\frac{\beta_\Omega}{r}\int_0^{\tau^*}\int_\Omega \chi_{[\tau^*-r,\tau^*]}(t)(u^*-u_\Omega)\psi\,dx\,dt.$$

We infer, after subtracting (3.23) and the above equation that

$$\int_\Omega p(0)\psi(0)dx - \int_\Omega p_0\psi(0)\,dx = 0,$$

hence, we have $p(0) = p_0$ a.e. in $L^2(\Omega)$. □

3.7 Simplification of the first-order necessary optimality condition for the control

Let (v^*, τ^*) be a minimizer of the problem with corresponding state variable $u^* = \mathcal{S}(v^*)$, and adjoint variable p associated to u^*. Let $w := v - v^* \in L^2(Q)$ for any $v \in \mathcal{V}_{ad}$, and let U be the linearized state variables associated to w.

Proposition 3.1

The optimal control v^* satisfies the following simplified first-order necessary optimality condition

$$(D_v\mathcal{J}(v^*,\tau^*))(v-v^*) = \beta_v\int_0^T\int_\Omega v^*(v-v^*)\,dx\,dt \geq 0.$$

Proof. The optimal control v^* satisfies the following first-order necessary optimality condition

$$\begin{aligned}(D_u\mathcal{J}(v^*,\tau^*))(v-v^*) = (D_u\mathcal{J}(v^*,\tau^*))w = \beta_Q\int_0^{\tau^*}\int_\Omega (u^*-u_Q)U dx\,dt\\ +\frac{\beta_\Omega}{r}\int_{\tau^*-r}^{\tau^*}\int_\Omega (u^*-u_\Omega)U dx\,dt + \beta_v\int_0^T\int_\Omega v^*(v-v^*)dx\,dt \geq 0.\end{aligned} \tag{3.24}$$

In order to simplify this condition, put $\xi = U$ in (3.19), and integrate over $[0,\tau^*]$, which yields

$$\begin{aligned}&-\int_0^{\tau^*}\int_\Omega \partial_t pU\,dx\,dt + \alpha\int_0^{\tau^*}\int_\Omega \nabla p\cdot\nabla U\,dx\,dt = -\beta\int_0^{\tau^*}\int_\Omega p\,U\,dx\,dt\\ &-\int_0^{\tau^*}\int_\Omega \frac{k}{(k'+u^*)^2}p\,U\,dx\,dt + \beta_Q\int_0^{\tau^*}\int_\Omega (u^*-u_Q)\,U\,dx\,dt\\ &+\frac{\beta_\Omega}{r}\int_0^{\tau^*}\int_\Omega \chi_{[\tau^*-r,\tau^*]}(t)(u^*-u_\Omega)U\,dx\,dt,\end{aligned} \tag{3.25}$$

and put $\xi = p$ in (3.13), then integrate over $[0,\tau^*]$, we find

$$\begin{aligned}&-\int_0^{\tau^*}\int_\Omega \partial_t U\,p\,dx\,dt + \alpha\int_0^{\tau^*}\int_\Omega \nabla U\cdot\nabla p\,dx\,dt\\ &= -\beta\int_0^{\tau^*}\int_\Omega U\,p\,dx\,dt - \int_0^{\tau^*}\int_\Omega \frac{k}{(k'+u^*)^2}U\,p\,dx\,dt - \gamma\int_0^{\tau^*}\int_\Omega J(x,t)w\,p\,dx\,dt.\end{aligned} \tag{3.26}$$

Using the fact that $p(\tau^*)=0$ and $U(0)=0$, we have

$$-\int_0^{\tau^*}\int_\Omega \partial_t p\,U\,dx\,dt = \int_0^{\tau^*}\int_\Omega p\,\partial_t U\,dx\,dt.$$

Substituting, and comparing with (3.25) and (3.26), we get

$$\begin{aligned}&-\beta\int_0^{\tau^*}\int_\Omega p\,U\,dx\,dt - \int_0^{\tau^*}\int_\Omega \frac{k}{(k'+u^*)^2}p\,U\,dx\,dt = -\beta\int_0^{\tau^*}\int_\Omega p\,U\,dx\,dt\\ &-\int_0^{\tau^*}\int_\Omega \frac{k}{(k'+u^*)^2}p\,U\,dx\,dt + \beta_Q\int_0^{\tau^*}\int_\Omega (u^*-u_Q)U\,dx\,dt\\ &+\frac{\beta_\Omega}{r}\int_0^{\tau^*}\int_\Omega \chi_{[\tau^*-r,\tau^*]}(t)(u^*-u_\Omega)U\,dx\,dt.\end{aligned}$$

Thus, we have

$$\beta_Q\int_0^{\tau^*}\int_\Omega (u^*-u_Q)U\,dx\,dt + \frac{\beta_\Omega}{r}\int_0^{\tau^*}\int_\Omega \chi_{[\tau^*-r,\tau^*]}(t)(u^*-u_\Omega)U\,dx\,dt = 0.$$

Consequently, upon substituting the above equation into (3.24), we obtain

$$\begin{aligned}D_v\mathcal{J}(v^*,\tau^*)w = \beta_Q\int_0^{\tau^*}\int_\Omega (u^*-u_Q)U dx\,dt + \frac{\beta_\Omega}{r}\int_{\tau^*-r}^{\tau^*}\int_\Omega (u^*-u_\Omega)U dx\,dt\\ +\beta_v\int_0^T\int_\Omega v^*(v-v^*)dx\,dt \geq 0,\end{aligned}$$

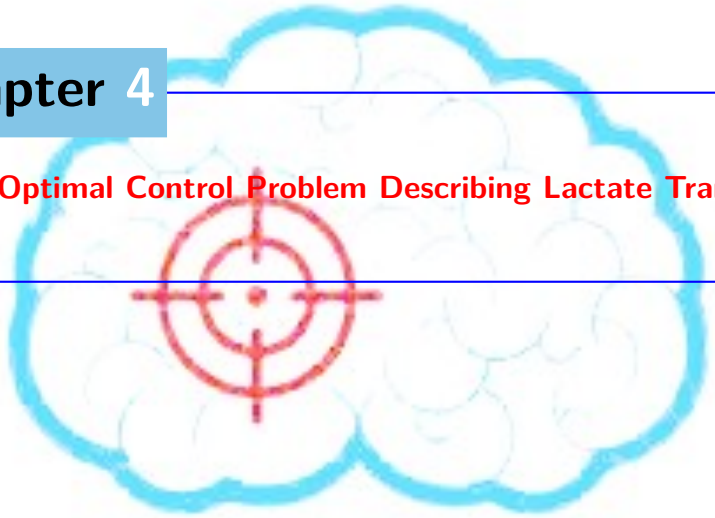
therefore

$$\beta_v\int_0^T\int_\Omega v^*(v-v^*)dx\,dt \geq 0.$$

□

Chapter 4

On an Optimal Control Problem Describing Lactate Transport Inhibition



"Strong, deeply rooted desire is the starting point of all achievement."

Napoleon Hill

In this chapter, the effect of inhibition of monocarboxylate transporters on intracellular and extracellular lactate concentration is investigated using an optimal control problem. A control term that represents the concentration of the inhibitor is used in an ODE model that models the lactate kinetics between the cell and the capillary. Finally, some numerical simulations were performed to confirm the efficiency of the control term for the problem.

4.1 Introduction

Tumor cancer cells take up high amounts of glucose to generate sufficient ATP to maintain cell proliferation and, as a result, produce large amounts of lactate in a process known as aerobic glycolysis.

To maintain proliferation, highly glycolytic cancer cells prevent intracellular acidification by exporting lactate to the extracellular space via monocarboxylate transporters (especially MCT1 and MCT4). This, in turn, leads to acidification of the extracellular PH in the tumor microenvironment, which indeed promotes metastasis, angiogenesis, and, most importantly, immunosuppression (see [28] and [7]).

A potential therapeutic target in cancer is therefore MCT1/4 inhibition, as it has been shown in [7] that cell proliferation is reduced both in vitro and in vivo by pharmacological or genetic MCT1/4 inhibition. Syronsingopine, an antihypertensive drug, is a dual MCT1/4 inhibitor that can be used to treat cancer. For more information on therapeutic approaches in lactate metabolism, please see the following and the references therein. [17, 25, 30, 32, 39, 54, 57, 58, 72, 78].

In this work, we consider the model presented in [46], which describes the lactate kinetics between a cell and the capillary network in its neighborhood. Here, u represents the intracellular lactate concentration, v the capillary lactate concentration and ϵ represents the volume separating the compartments. Lactate cotransport through brain blood is

taken into account by a simplified version of the equation for carrier-mediated symport. This nonlinear term depends on the maximum blood-cell transport rate, κ, and the modified Michaelis-Menten positive constant for both the intracellular and capillary lactate concentrations (k and k', respectively).

Our main goal is to add a control term w at a rate γ representing the desired treatment with syrosingopine, where $w = 0$ represents no dosing and $w = 1$ represents full dosing. Here, we add the control to the term representing the transport of lactate out of the cell into the capillary employing MCT inhibitor.

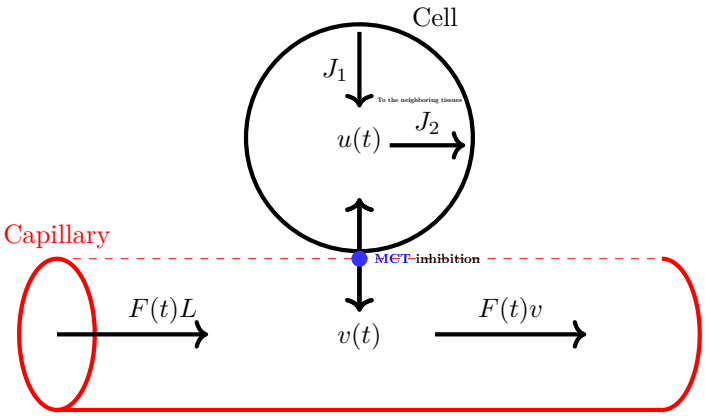


Figure 4.1 – Lactate transport inhibition from the cell to the capillary

Referring to [47], J_1 and J_2 denote lactate production and diffusion to the neighboring tissues, respectively, so that $J(t, u(t)) = J_1 - J_2$. In addition, $F(t) = 2CBF$, where CBF is the cerebral blood flow, L is the lactate arterial concentration so that $F(t)L$ represents the flow of lactate from arteries, $F(t)v$, the flow of lactate to the veins.

The dynamics treated in Figure 4.1 is given in the following system, that is, for $T > 0$.

$$u'(t) = J(t, u(t)) - \kappa \left((1 - \gamma w) \frac{u(t)}{k + u(t)} - \frac{v(t)}{k' + v(t)} \right), \quad \text{in } (0, T), \tag{4.1}$$

$$\epsilon v'(t) = F(t)(L - v(t)) + \kappa \left((1 - \gamma w) \frac{u(t)}{k + u(t)} - \frac{v(t)}{k' + v(t)} \right) \quad \text{in } (0, T), \tag{4.2}$$

$$(u(0), v(0)) = (u_0, v_0) \in \mathbb{R}_+ \times \mathbb{R}_+. \tag{4.3}$$

And the cost functional to be minimized is given by

$$\mathcal{J}(v, w, \tau) = \frac{1}{2} \int_0^\tau \|(v - v_Q)(t)\|^2 \, dt + \frac{1}{2r} \int_{\tau - r}^\tau \|(v - v_d)(t)\|^2 \, dt + \frac{1}{2} \int_0^\tau \|w(t)\|^2 \, dt. \tag{4.4}$$

Here r is a positive constant, the function v_Q corresponds to the desired evolution capillary lactate concentration and v_d to the desired final capillary lactate concentration. Targeting lactate transport from the cell to the capillary leads to acidification of the intracellular domain, which in turn is lethal to the tumor and its proliferation. At the same time, the

lower the lactate concentration in the capillary, the lower the malignancy of the tumor. Moreover, a patient undergoes several cycles of treatment, so that each cycle is followed by a resting period during which the healthy cells can recover, so that τ is the treatment time of each cycle and T is the final treatment time. So our main problem is

$$\text{minimize } \mathcal{J} \text{ associated to } \quad (4.1)-(4.3),\ w \in \mathcal{W}_{ad},\ \tau \in [r, T]. \tag{4.5}$$

In this chapter, we first show the well-posedness of the System (4.1)-(4.3), then, we define the control-to-state operator S which is continuous, Fréchet differentiable with respect to the control w. We show the existence of a solution to our Problem (4.5), Fréchet differentiability of the objective functional with respect to time and control. Then, we derive a simplified first-order necessary optimality condition. Finally, we support the result with numerical simulations.

Assumptions

(E) The constants $\kappa, L > 0$, $k, k' \geq 0$, $0 \leq \gamma \leq 1$, and the function F is positive bounded continuous function; i.e., there exist two positive constants F_1 and F_2, such that $F_1 < F < F_2$. The function J is Lipschitz with respect to u such that J_u, the derivative of J with repect to u, is bounded.

(F) The control $w \in \mathcal{W}_{ad} := \{w \in L^2(0, T; \mathbb{R}_+) :\ 0 \leq w \leq 1\}$..

Notations

- $((\cdot, \cdot))$ and $\|\cdot\|$ represent the usual inner product and norm of $\mathbb{R}_+$, respectively.
- We write $A \lesssim B$, if there exists a constant $C > 0$ independent of A and B, such that

$$A \leq CB.$$

4.2 Well-posedness

In this section, we investigate the existence of a unique solution of the System (4.1)-(4.3).

Definition 4.1

An ODE system $x'(t) = f(t, x(t))$ on $\mathbb{R}^n$, $x = (x_1, \ldots, x_n)^\top$, $f = (f_1, \ldots, f_n)^\top$ is called quasipositive, if the condition

$$x \geq 0,\ x_k = 0 \implies f_k(t, x(t)) \geq 0,$$

is verified for all $k = 1, \ldots, n$.

Theorem 4.1 (Existence and uniqueness of solution)

Assume that Assumptions (E) and (F) hold and that $(u_0, v_0) \in \mathbb{R}_+ \times \mathbb{R}_+$. Then, System (4.1)-(4.3) admits a unique solution (u, v), satisfying

$$(u, v) \in (C^1([0, T], \mathbb{R}_+)^2.$$

Moreover, the control-to-state operator

$$\begin{array}{rccc} S: & \mathcal{U}_{ad} & \longrightarrow & C^1([0,T],\mathbb{R}_+)^2 \\ & w & \longmapsto & (u,v), \end{array}$$

is continuous.

Proof.

• **The solution is nonnegative.** System (4.1)-(4.3) can be viewed as

$$u'(t) = f(t,u(t),v(t))$$

$$v'(t) = g(t,u(t),v(t)).$$

For $u=0$, $v\geq 0$, then

$$f(t,0,v) = J + \kappa\frac{v}{k'+v} \geq 0.$$

For $u\geq 0$, $v=0$, then

$$g(t,u,0) = FL + \kappa(1-\gamma w)\frac{u}{k+u} \geq 0.$$

Hence, the system is quasi-positive and so the solution

$$(u,v) \in \mathbb{R}_+ \times \mathbb{R}_+ \quad \forall\, t>0.$$

• **Existence of solution.** System (4.1)-(4.3) can be rewritten in the form

$$\begin{cases} X'(t) = F(t,X(t)) \\ \\ X(0) = X_0, \end{cases}$$

where $X(t) := (u(t),v(t))$ and $F(t,X(t)) := (f(t,u,v),g(t,u,v))$. We know that, for nonnegative u_1 and u_2

$$\frac{u_1}{k+u_1} - \frac{u_2}{k+u_2} = \frac{u_1(k+u_2)-u_2(k+u_1)}{(k+u_1)(k+u_2)} = \frac{k(u_1-u_2)}{(k+u_1)(k+u_2)}$$

and, for nonnegative v_1 and v_2

$$\frac{v_1}{k'+v_1} - \frac{v_2}{k'+v_2} \quad = \frac{k'(v_1-v_2)}{(k'+v_1)(k'+v_2)}.$$

As well, using Assumption (E), we have

$$\left| J(t,u_1) - J(t,u_2) - \kappa(1-\gamma w)\frac{k(u_1-u_2)}{(k+u_1)(k+u_2)} + \kappa\frac{k'(v_1-v_2)}{(k'+v_1)(k'+v_2)} \right|$$

$$\lesssim |u_1-u_2| + |v_1-v_2|$$

and

$$\frac{1}{\epsilon}\left|F(v_1-v_2)+\kappa(1-\gamma w)\frac{k(u_1-u_2)}{(k+u_1)(k+u_2)}-\kappa\frac{k'(v_1-v_2)}{(k'+v_1)(k'+v_2)}\right|$$

$$\lesssim |u_1-u_2|+|v_1-v_2|$$

We deduce that F is globally Lipschitz with respect to u and v, so System (4.1)-(4.3) admits a unique solution $(u,v)\in C^1([0,T],\mathbb{R}_+)^2$.

• **Continuous dependence on control.** Let w_1, w_2 be two controls in $\mathcal{U}_{ad}$ and (u_1,v_1), (u_2,v_2) be their corresponding solutions of System (4.1)-(4.3) with same initial data. Set $u=u_1-u_2$, $v=v_1-v_2$, and $w=w_1-w_2$, then, we have

$$u'=J(t,u_1)-J(t,u_2)-\kappa\left(\frac{ku}{(k+u_1)(k+u_2)}-\gamma\frac{k\,(w_1u+u_2w)}{(k+u_1)(k+u_2)}-\frac{k'v}{(k'+v_1)(k'+v_2)}\right) \tag{4.6}$$

and

$$\epsilon v'=-Fv+\kappa\left(\frac{ku}{(k+u_1)(k+u_2)}-\gamma\frac{k\,(w_1u+u_2w)}{(k+u_1)(k+u_2)}-\frac{k'v}{(k'+v_1)(k'+v_2)}\right). \tag{4.7}$$

Step one. Multiply Equation (4.6) by u in $\mathbb{R}_+$, we find

$$\begin{aligned}((u',u))=((J(t,u_1)-J(t,u_2),u))-\kappa\left(\left(\frac{ku}{(k+u_1)(k+u_2)},u\right)\right)\\ -\kappa\gamma\left(\left(\frac{k\,(w_1u+u_2w)}{(k+u_1)(k+u_2)},u\right)\right)-\kappa\left(\left(\frac{k'v}{(k'+v_1)(k'+v_2)},u\right)\right),\end{aligned}$$

Thanks to Cauchy Schwartz inequality, we get

$$\begin{aligned}&\frac{1}{2}\frac{d}{dt}\|u\|^2\le\|J(t,u_1)-J(t,u_2)\|\,\|u\|+\kappa k\left\|\frac{u}{(k+u_1)(k+u_2)}\right\|\|u\|\\ &+\kappa k\gamma\left\|\frac{w_1u}{(k+u_1)(k+u_2)}\right\|\|u\|+\kappa\gamma\left\|\frac{u_2w}{(k+u_1)(k+u_2)}\right\|\|u\|+\kappa k'\left\|\frac{k'v}{(k'+v_1)(k'+v_2)}\right\|\|u\|.\end{aligned}$$

Now using Assumption (E) and Young's inequality, we have

$$\frac{d}{dt}\|u\|^2\lesssim\|u\|^2+\|w\|^2+\|v\|^2. \tag{4.8}$$

On the other hand, multiplying Equation (4.7) by v in $\mathbb{R}_+$, using Assumption (E) and Young's inequality, we get

$$\frac{d}{dt}\|v\|^2\lesssim\|u\|^2+\|w\|^2+\|v\|^2. \tag{4.9}$$

Combining Equation (4.8) and Equation (4.9), then integrating over $[0,t]$, where $t\in[0,T]$, we get

$$\|u(t)\|^2+\|v(t)\|^2\lesssim\int_0^t\|w(s)\|^2\,ds+\int_0^t\left(\|u(s)\|^2+\|v(s)\|^2\right)ds.$$

So, owing to Gronwall's inequality, we obtain

$$\|u(t)\|^2+\|v(t)\|^2\lesssim\|w\|^2_{L^2(0,t;\mathbb{R}_+)}\,e^{ct},\quad t\in[0,T]. \tag{4.10}$$

On the other hand, since

$$\|u\|^2_{L^2(0,t;\mathbb{R}_+)} = \int_0^t \|u(s)\|^2 ds,$$

then, using Equation (4.10), we find

$$\int_0^t \|u(s)\|^2 ds \lesssim \int_0^t \|w\|^2_{L^2(0,s;\mathbb{R}_+)} e^{cs} ds \lesssim \|w\|^2_{L^2(0,t;\mathbb{R}_+)} (e^{ct} - 1), \quad \forall t \in [0,T]. \tag{4.11}$$

Similarly, we have

$$\|v\|^2_{L^2(0,t;\mathbb{R}_+)} \lesssim \|w\|^2_{L^2(0,t;\mathbb{R}_+)} (e^{ct} - 1). \tag{4.12}$$

Step two. Similarly to Step one, multiplying Equation (4.6) and Equation (4.7) by u' and v', respectively, we get

$$\begin{aligned}\|u'\|^2 &\leq \|J(t,u_1) - J(t,u_2)\| \|u'\| + \frac{c}{2}\frac{d}{dt}\|u\|^2 + c\|w\|\|u'\| + c\|v\|\|u'\| \\ &\lesssim \|u\|\|u'\| + \frac{d}{dt}\|u\|^2 + \|w\|\|u'\| + \|v\|\|u'\|.\end{aligned}$$

Let $\delta > 0$. Applying Young's inequality, we obtain

$$(1 - c\delta)\|u'\|^2 \lesssim \|u\|^2 + \frac{d}{dt}\|u\|^2 + \|w\|^2 + \|v\|^2.$$

Where $c > 0$ constant independent of δ. Choosing $\delta << 1$ such that $1 - c\delta = \frac{1}{2}$, we obtain

$$\frac{1}{2}\|u'\|^2 \lesssim \|u\|^2 + \frac{d}{dt}\|u\|^2 + \|w\|^2 + \|v\|^2. \tag{4.13}$$

By similar way, we obtain

$$\epsilon\|v'\|^2 \lesssim \frac{d}{dt}\|v\|^2 + c\|u\| + \|w\|. \tag{4.14}$$

Further, integrating (4.13) and (4.14) over $[0,t]$, $t \in [0,T]$, and using (4.10), we get

$$\|u'\|^2_{L^2(0,t;\mathbb{R}_+)} \lesssim \|u\|^2_{L^2(0,t;\mathbb{R}_+)} + \|u(t)\|^2 + \|v\|^2_{L^2(0,t;\mathbb{R}_+)} + \|w\|^2_{L^2(0,t;\mathbb{R}_+)} \lesssim \|w\|^2_{L^2(0,t;\mathbb{R}_+)}$$

and

$$\epsilon\|v'\|^2_{L^2(0,t;\mathbb{R}_+)} \lesssim \|v(t)\|^2 + \|u\|^2_{L^2(0,t;\mathbb{R}_+)} + \|w\|^2_{L^2(0,t;\mathbb{R}_+)},$$

hence

$$\|v'\|^2_{L^2(0,t;\mathbb{R}_+)} \lesssim \|w\|^2_{L^2(0,t;\mathbb{R}_+)}.$$

The proof is thus complete. □

4.3 Existence of a minimizer

In this section, we want to prove the existence of optimal control and time; i.e., we will prove the following result.

Proposition 4.1

Let $w \in \mathcal{W}_{ad}$ and $\tau \in [r,T]$, and let (u,v) be the solution of System (4.1)-(4.3) corresponding to w. Then there exist $w_* \in \mathcal{W}_{ad}$ and $\tau_* \in [r,T]$, such that

$$\inf_{(w,\tau)\in \mathcal{W}_{ad}\times[r,T]} \mathcal{J}(v,w,\tau) = \mathcal{J}(v_*,w_*,\tau_*),$$

where (u_*,v_*) is the solution of (4.1)-(4.3) corresponding to w_*.

Proof. The cost functional $\mathcal{J}$ defined by (4.4) is bounded from below, consequently, we consider a minimizing sequence $(w_n,\tau_n)_{n\in\mathbb{N}}$ with $w_n \in \mathcal{W}_{ad}$ and $\tau_n \in [r,T]$, such that $(v_n)_{n\in\mathbb{N}}$ are the corresponding solutions of (4.1)-(4.3) on the interval $[0,T]$ with $v_n(0) = v_0, \forall\, n \in \mathbb{N}$, such that where (ψ,ϕ) is the solution of System (4.1)-(4.3) for the corresponding control w. In particular $w_n \in \mathcal{W}_{ad} \forall\, n \in \mathbb{N}$. As $\{\tau_n\}_{n\in\mathbb{N}}$ is a bounded sequence, there exists a relabeled subsequence such that

$$\lim_{n\to\infty} \mathcal{J}(v_n,w_n,\tau_n) = \inf_{(w,\tau)\in \mathcal{W}_{ad}\times[r,T]} \mathcal{J}(v,w,\tau),$$

where (u,v) is the solution of (4.1)-(4.3) for the corresponding control w. As $\{\tau_n\}_{n\in\mathbb{N}}$ is a bounded sequence, there exists a relabeled subsequence such that

$$\tau_n \to \tau_* \in [r,T], \quad \text{as } n \to \infty.$$

Since $w_n \in \mathcal{W}_{ad}$. Then there exists $w_* \in \mathcal{W}_{ad}$ such that

$$w_n \to w_* \quad \text{weakly} \quad \text{in} \quad L^2([0,T],\mathbb{R}_+), \quad \text{as } n \to \infty.$$

On the other hand, from Theorem 4.2, there exists $(u_*,v_*) \in C^1([0,T];\mathbb{R}_+)^2$ solution of System (4.1)-(4.3) associated to w_*. Further, we have

$$v_n \to v_* \quad \text{strongly in} \quad L^2([0,T];\mathbb{R}_+), \quad \text{as } n \to \infty.$$

Moreover, from Lebesgue dominated convergence theorem, we have

$$\chi_{[0,\tau_n]}(t) \to \chi_{[0,\tau_*]}(t), \quad \text{strongly in } L^2(0,T)$$

and

$$\chi_{[\tau_n-r,\tau_n]}(t) \to \chi_{[\tau_*-r,\tau_*]}(t), \quad \text{strongly in } L^2(0,T).$$

It follows from the strong convergence of v_n to v_* in $L^2([0,T];\mathbb{R}_+)$, that

$$\begin{aligned}\int_0^{\tau_n} \|v_n - v_Q\|^2\, dt &= \int_0^T \|v_n - v_Q\|^2\, \chi_{[0,\tau_n]}(t)dt \\ &\to \int_0^T \|v_* - v_Q\|^2\, \chi_{[0,\tau_*]}(t)dt = \int_0^{\tau_*} \|v_* - v_Q\|^2\, dt\end{aligned}$$

and

$$\begin{aligned}\int_{\tau_n-r}^{\tau_n} \|v_n - v_d\|^2\, dt &= \int_0^T \|v_n - v_d\|^2\, \chi_{[\tau_n-r,\tau_n]}(t)dt \\ &\to \int_0^T \|v_* - v_d\|^2\, \chi_{[\tau_*-r,\tau_*]}(t)dt = \int_{\tau_*-r}^{\tau_*} |v_* - v_d|^2 dt.\end{aligned}$$

Finally, passing to the limit in $\mathcal{J}(v_n, w_n, \tau_n)$, and using the lower semi continuity of the norm of $L^2(0,T,\mathbb{R}_+)$ along with the weak convergence of w_n to w_*, we infer

$$\inf_{(w,\tau)\in\mathcal{W}_{ad}\times[r,T]} \mathcal{J}(v,w,\tau) = \lim_{n\to\infty} \mathcal{J}(v_n,w_n,\tau_n) \geq \mathcal{J}(v_*,w_*,\tau_*),$$

which implies that (w_*, τ_*) is a minimizer of (4.5). □

4.4 Fréchet differentiability of the control to state operator

The natural approach consists in proving that the control-to-state operator S is Fréchet differentiable at w_* and applying the chain rule to $\mathcal{J}(v,w) = \mathcal{J}(S(v),v)$. So, let $w_* \in \mathcal{W}_{ad}$ be an optimal control in (4.5), with corresponding state (u^*, v^*), and let $h \in \mathcal{W}_{ad}$. In order to establish the existence of the Fréchet derivative of S at w_*, we consider the following linearized system

$$U' = J_u(t,u^*)U - \kappa\left(-\gamma h\frac{u^*}{k+u^*} + (1-\gamma w_*)\frac{k\,U}{(k+u^*)^2} - \frac{k'\,V}{(k'+v^*)^2}\right), \quad \text{on } [0,T], \tag{4.15}$$

$$\epsilon V' = -FV + \kappa\left(-\gamma h\frac{u^*}{k+u^*} + (1-\gamma w_*)\frac{k\,U}{(k+u^*)^2} - \frac{k'\,V}{(k'+v^*)^2}\right), \quad \text{on } [0,T], \tag{4.16}$$

$$U(0) = V(0) = 0. \tag{4.17}$$

Theorem 4.2

Let $w^* \in \mathcal{W}_{ad}$. Then, System (4.15)-(4.17) admits a unique solution

$$(U,V) \in C^1([0,T],\mathbb{R}_+)^2.$$

Proof. Let (U_1,V_1), (U_2,V_2) be two solutions of the System (4.15)-(4.17), which can be written in the form

$$X' = H(t,X(t)),$$

where $X=(U,V)$ and $H(t,U,V) = (F(t,U,V), G(t,U,V))$, we know that

$$\begin{aligned}
&|F(t,U_1,V_1) - F(t,U_2,V_2)| + |G(t,U_1,V_1) - G(t,U_2,V_2)| \\
&= \left|J_u(t,u^*)\,(U_1-U_2) - \kappa\left((1-\gamma w_*)\frac{k}{(k+u^*)^2} - \frac{k'}{(k'+v^*)^2}\,(V_1-V_2)\right)\right| \\
&+\frac{1}{\epsilon}\left|F(V_1-V_2) + \kappa\left((1-\gamma w_*)\frac{k}{(k+u^*)^2} - \frac{k'}{(k'+v^*)^2}\,(V_1-V_2)\right)\right| \\
&\leq \left(||J_u||_\infty + \left(\kappa+\frac{\kappa}{\epsilon}\right)\right)|U_1-U_2| + \left(\kappa+\frac{\kappa}{\epsilon}\right)|V_1-V_2| \\
&\leq \left(||J_u||_\infty + \left(\kappa+\frac{\kappa}{\epsilon}\right)\right)||U_1-U_2, V_1-V_2||,
\end{aligned}$$

which yields that H is lipchitz with respect to X, and therefore the System (4.15)-(4.17) admits a unique solution $(U,V) \in C^1([0,T],\mathbb{R}_+)^2$ (see [18]). □

4.5 Fréchet Differentiability of control-to-state operator with respect to the control

Let $h \in \mathcal{W}_{ad}$, set $(u_h, v_h) := S(w^* + h)$ and $(u_*, v_*) := S(w^*)$ and $(U, V) = D_w S(w^*)h$.

Theorem 4.3

Let (U, V) be the solution of the linearized system (4.15)-(4.17) corresponding to w^*. Then the remainders ρ and θ defined by

$$\rho = u_h - u_* - U \quad \text{and} \quad \theta = v_h - v_* - V,$$

satisfy

$$\|(\rho, \theta)\|^2_{L^\infty(0,T;\mathbb{R}_+)\cap H^1(0,T;\mathbb{R}_+)} \leq c \|h\|^4_{L^2(0,T;\mathbb{R}_+)},$$

and thus the control-to-state operator is fréchet differentiable.

Proof. The remainders ρ_h and θ_h satisfy

$$\rho' = J(t, u_h) - J(t, u_*) - J_u U - \kappa\left((1-\gamma w_*)\left(\frac{u_h}{k+u_h} - \frac{u_*}{k+u_*} - \frac{k}{(k+u_*)^2}U\right)\right)$$
$$+\kappa\left(\frac{v_h}{k'+v_h} - \frac{v_*}{k'+v_*} - \frac{k'}{(k'+v_*)^2}V + \gamma h\left(\frac{u_h}{k+u_h} - \frac{u_*}{k+u_*}\right)\right)$$

and

$$\epsilon\theta_h' = -F\theta_h + \kappa\left((1-\gamma w_*)\left(\frac{u_h}{k+u_h} - \frac{u_*}{k+u_*} - \frac{k}{(k+u_*)^2}U\right)\right)$$
$$-\kappa\left(\left(\frac{v_h}{k'+v_h} - \frac{v_*}{k'+v_*} - \frac{k'}{(k'+v_*)^2}V\right) - \gamma h\left(\frac{u_h}{k+u_h} - \frac{u_*}{k+u_*}\right)\right).$$

Setting $f(u) = \dfrac{k}{k+u}$ and $g(v) = \dfrac{k'}{k'+v}$, Taylor with integral remainder gives

$$f(u_h) - f(u_*) - f'(u_*)U = f'(u_*)\rho + (u_h - u_*)^2 \int_0^1 f''\left(zu_h + (1-z)u_*\right)(1-z)\,dz$$

and

$$g(v_h) - g(v_*) - g'(v_*)V = g'(v_*)\theta + (v_h - v_*)^2 \int_0^1 g''\left(zv_h + (1-z)v_*\right)(1-z)\,dz.$$

However, the remainders

$$R_1 := \int_0^1 f''\left(zu_h + (1-z)u_*\right)(1-z)\,dz \quad \text{and} \quad R_2 := \int_0^1 g''\left(zv_h + (1-z)v_*\right)(1-z)\,dz,$$

are bounded, so that

$$\|R_1\|_\infty \leq c_{R_1} \quad \text{and} \quad \|R_2\|_\infty \leq c_{R_2}.$$

Thus, ρ satisfies

$$\rho_h' = J_u(t, u_*)\rho_h + (u_h - u_*)^2 R_1 - \kappa\left((1-\gamma w_*)\left(f'(u_*)\rho_h + (u_h - u_*)^2 R_1\right)\right)$$
$$+\kappa\left(g'(v_*)\theta_h + (v_h - v_*)^2 R_2 + \gamma h\left(f(u_h) - f(u_*)\right)\right).$$

Equivalently, we have

$$\begin{aligned}\rho_h' &= J_u(t,u_*)\rho_h + (u_h-u_*)^2R_1 - \kappa\left((1-\gamma w_*)\left(f'(u_*)\rho_h + (u_h-u_*)^2R_1\right)\right)\\ &+\kappa\left(g'(v_*)\theta_h + (v_h-v_*)^2R_2 + \gamma h\left(f'(u_*)\left(u_h-u_*\right)\right) + (u_h-u_*)^2R_1\right)\end{aligned} \tag{4.18}$$

and θ satisfies

$$\begin{aligned}\epsilon\theta_h' &= -F\theta_h + \kappa(1-\gamma w_*)\left(f'(u_*)\rho_h + (u_h-u_*)^2R_1\right)\\ &-\kappa\left(g'(v_*)\theta_h + (v_h-v_*)^2R_2 + \gamma h\left(f(u_h)-f(u_*)\right)\right).\end{aligned}$$

Which is equivalent to

$$\begin{aligned}\epsilon\theta_h' &= -F\theta_h + \kappa(1-\gamma w_*)\left(f'(u_*)\rho_h + (u_h-u_*)^2R_1\right)\\ &-\kappa\left(g'(v_*)\theta_h + (v_h-v_*)^2R_2 + \gamma h\left(f'(u_*)(u_h-u_*) + (u_h-u_*)^2R_1\right)\right).\end{aligned} \tag{4.19}$$

We need to prove some estimates.

Estimate 1. Multiplying (4.18) by ρ_h and (4.19) by θ_h, we find

$$\begin{aligned}((\rho_h',\rho_h)) &= ((J_u(t,u_*)\rho_h,\rho_h)) + (((u_h-u_*)^2R_1,\rho_h)) - \kappa(((1-\gamma w_*)f'(u_*)\rho_h,\rho_h))\\ &-\kappa(((1-\gamma w_*)(u_h-u_*)^2R_1,\rho_h)) + \kappa((g'(v_*)\theta_h,\rho_h)) + \kappa(((v_h-v_*)^2R_2,\rho_h))\\ &+\kappa((\gamma h f'(u_*)(u_h-u_*),\rho_h)) + \kappa((h(u_h-u_*)^2R_1,\rho_h))\end{aligned}$$

and

$$\begin{aligned}((\epsilon\theta_h',\theta_h)) &= -((F\theta_h,\theta_h)) + \kappa(((1-\gamma w_*)f'(u_*)\rho_h,\theta_h))\\ &+\kappa(((1-\gamma w_*)(u_h-u_*)^2R_1,\theta_h)) - \kappa((g'(v_*)\theta_h,\theta_h)) - \kappa(((v_h-v_*)^2R_2,\theta_h))\\ &-\kappa((\gamma h f'(u_*)(u_h-u_*),\theta_h)) - \kappa((\gamma h(u_h-u_*)^2R_1,\theta_h)).\end{aligned}$$

Consequently, after using Assumptions (E) and (F), and Cauchy Schwartz inequality, we get

$$\begin{aligned}\frac{d}{dt}\|\rho_h\|^2 &\lesssim \|\rho_h\|^2 + \|u_h-u_*\|^2\|\rho_h\| + \|\theta_h\|\|\rho_h\|\\ &+c\|v_h-v_*\|^2\|\rho_h\| + \|h\|\|u_h-u_*\|\|\rho_h\| + \left\|h(u_h-u_*)^2\right\|\|\rho_h\|\end{aligned} \tag{4.20}$$

and

$$\begin{aligned}\epsilon\frac{d}{dt}\|\theta_h\|^2 &\lesssim \|\theta_h\|^2 + \|\rho_h\|\|\theta_h\| + \|u_h-u_*\|^2\|\theta_h\| + \|v_h-v_*\|^2\|\theta_h\|\\ &+\|h\|\|u_h-u_*\|\|\theta_h\| + \left\|h(u_h-u_*)^2\right\|\|\theta_h\|.\end{aligned} \tag{4.21}$$

Combining (4.20) and (4.21), integrating over $[0,t]$, and using Holder's inequality, we get

$$\begin{aligned}
&\|\rho_h(t)\|^2+\epsilon\|\theta_h(t)\|^2\lesssim\|\rho_h\|^2_{L^2(0,t;\mathbb{R}_+)}+\|\theta_h(s)\|^2_{L^2(0,t;\mathbb{R}_+)}+\|\theta_h\|_{L^2(0,t;\mathbb{R}_+)}\|\rho\|_{L^2(0,t;\mathbb{R}_+)}\\
&+\|u_h-u_*\|_{L^\infty(0,t;\mathbb{R}_+)}\|u_h-u_*\|_{L^2(0,t;\mathbb{R}_+)}\left(\|\rho_h\|_{L^2(0,t;\mathbb{R}_+)}+\|\theta_h\|_{L^2(0,t;\mathbb{R}_+)}\right)\\
&+\|v_h-v_*\|_{L^\infty(0,t;\mathbb{R}_+)}\|v_h-v_*\|_{L^2(0,t;\mathbb{R}_+)}\left(\|\rho_h\|_{L^2(0,t;\mathbb{R}_+)}+\|\theta_h\|_{L^2(0,t;\mathbb{R}_+)}\right)\\
&+\|h\|_{L^2(0,t;\mathbb{R}_+)}\|u_h-u_*\|_{L^\infty(0,t;\mathbb{R}_+)}\left(\|\rho_h\|_{L^2(0,t;\mathbb{R}_+)}+\|\theta_h\|_{L^2(0,t;\mathbb{R}_+)}\right)\\
&+\|h\|_{L^2(0,t;\mathbb{R}_+)}\|u_h-u_*\|^2_{L^\infty(0,t;\mathbb{R}_+)}\left(\|\rho_h\|_{L^2(0,t;\mathbb{R}_+)}+\|\theta_h\|_{L^2(0,t;\mathbb{R}_+)}\right).
\end{aligned}$$

Consequently, using Young's inequality, Assumption (F), Equations (4.10), (4.11), and (4.12), we have

$$\begin{aligned}
&\|\rho_h(t)\|^2+\epsilon\|\theta_h(t)\|^2\lesssim c\|\rho_h\|^2_{L^2(0,t;\mathbb{R}_+)}+\|\theta_h\|^2_{L^2(0,t;\mathbb{R}_+)}+c\|h\|^4_{L^2(0,t;\mathbb{R}_+)}\\
&+\|h\|^6_{L^2(0,t;\mathbb{R}_+)}\lesssim\|h\|^4_{L^2(0,t;\mathbb{R}_+)}.
\end{aligned}\tag{4.22}$$

Estimate 2. Multiplying (4.18) by ρ_h', and (4.19) by θ_h', we find

$$\begin{aligned}
((\rho_h',\rho_h'))&=((J_u(t,u_*)\rho_h,\rho_h'))+(((u_h-u_*)^2R_1,\rho_h'))-\kappa(((1-\gamma w_*)f'(u_*)\rho_h,\rho_h'))\\
&-\kappa(((1-\gamma w_*)(u_h-u_*)^2R_1,\rho_h'))+\kappa((g'(v_*)\theta_h,\rho_h'))+\kappa(((v_h-v_*)^2R_2,\rho_h'))\\
&+\kappa((\gamma hf'(u_*)(u_h-u_*),\rho_h'))+\kappa((h(u_h-u_*)^2R_1,\rho_h'))
\end{aligned}$$

and

$$\begin{aligned}
((\epsilon\theta_h',\theta_h'))&=-((F\theta_h,\theta_h'))+\kappa(((1-\gamma w_*)f'(u_*)\rho_h,\theta_h'))\\
&+\kappa(((1-\gamma w_*)(u_h-u_*)^2R_1,\theta_h'))-\kappa((g'(v_*)\theta_h,\theta_h'))-\kappa(((v_h-v_*)^2R_2,\theta_h'))\\
&-\kappa((\gamma hf'(u_*)(u_h-u_*),\theta_h'))-\kappa((\gamma h(u_h-u_*)^2R_1,\theta_h')).
\end{aligned}$$

Then, using Cauchy Schwartz inequality, we get

$$\begin{aligned}
\|\rho_h'\|^2\lesssim\frac{d}{dt}\|\rho_h\|^2+\|\theta_h\|\|\rho_h'\|+\|u_h-u_*\|^2\|\rho_h'\|+\|v_h-v_*\|^2\|\rho_h'\|\\
+\|h\|\|u_h-u_*\|\|\rho_h'\|+\|h\|\|u_h-u_*\|^2\|\rho_h'\|
\end{aligned}\tag{4.23}$$

and

$$\begin{aligned}
\epsilon\|\theta_h'\|^2\lesssim\frac{d}{dt}\|\theta_h\|^2+\|\rho_h\|\|\theta_h'\|+\|u_h-u_*\|^2\|\theta_h'\|+\|v_h-v_*\|^2\|\theta_h'\|\\
+\|h\|\|u_h-u_*\|\|\theta_h'\|+\|h\|\|u_h-u_*\|^2\|\theta_h'\|.
\end{aligned}\tag{4.24}$$

Combining (4.23) and (4.24), and integrating over $[0,t]$. In addition to that, using Assumption (F) and Young's inequality, we have

$$\|\rho_h'\|^2_{L^2(0,t;\mathbb{R}_+)} + \epsilon\,\|\theta_h'\|^2_{L^2(0,t;\mathbb{R}_+)} \lesssim \|\rho_h(t)\|^2_{L^2(0,t;\mathbb{R}_+)} + \|\theta_h(t)\|^2 + \|\theta_h\|^2_{L^2(0,t;\mathbb{R}_+)} + \|\rho_h\|^2_{L^2(0,t;\mathbb{R}_+)}$$

$$+ \|u_h - u_*\|^2_{L^\infty(0,t;\mathbb{R}_+)}\,\|u_h - u_*\|^2_{L^2(0,t;\mathbb{R}_+)} + \|v_h - v_*\|^2_{L^\infty(0,t;\mathbb{R}_+)}\,\|v_h - v_*\|^2_{L^2(0,t;\mathbb{R}_+)}$$

$$+ \|h\|^2_{L^2(0,t;\mathbb{R}_+)}\,\|u_h - u_*\|^2_{L^\infty(0,t;\mathbb{R}_+)} + \|h\|^2_{L^2(0,t;\mathbb{R}_+)}\,\|u_h - u_*\|^4_{L^\infty(0,t;\mathbb{R}_+)}\,.$$

Further, using Equations (4.22), (4.10), (4.11), and (4.12), we infer

$$\|\rho_h'\|^2_{L^2(0,t;\mathbb{R}_+)} + \epsilon\,\|\theta_h'\|^2_{L^2(0,t;\mathbb{R}_+)} \lesssim \|h\|^4_{L^2(0,t;\mathbb{R}_+)}\,,$$

and hence the result. □

4.6 First-Order Necessary Optimality Condition

The purpose of this section is to derive a first-order necessary optimality condition in the form of a variational inequality for an admissible control to be an optimal control. We divide this section into two subsections.

4.6.1 Differentiability of the cost functional with respect to time

Proposition 4.2

Let $v_Q \in H^1(0,T;\mathbb{R}_+)$, v_d and $v_* \in H^1(-r,T;\mathbb{R}_+)$. Then the mapping $\mathcal{J} : \mathcal{W}_{ad} \times [r,T] \longrightarrow \mathbb{R}_+$ is continuously Fréchet differentiable with respect to τ and

$$D_\tau \mathcal{J}(w_*,\tau_*) = \frac{1}{2}\,\|v_*(\tau_*) - v_Q(\tau_*)\|^2 + \frac{1}{2}\left(\|v_*(\tau_*) - v_d(\tau_*)\|^2 - \frac{1}{r}\,\|v_*(\tau_* - r) - v_d(\tau_* - r)\|^2\right).$$

In addition, assume that

$$D_\tau \mathcal{J}(w_*,\tau_*)\,(s - \tau_*) \geq 0 \quad \forall\ s \in [r,T].$$

Proof. For any function $f \in L^1(0,\tau,\mathbb{R}_+)$, we have the following relation

$$\begin{aligned}\int_{\tau-r}^{\tau} f(s)\,ds &= \int_{\tau-r}^{0} f(s)\,ds + \int_0^{\tau} f(s)\,ds \\ &= \int_{\tau}^{-r} f(s)\,ds + \int_{-r}^{0} f(s)\,ds + \int_0^{\tau} f(s)\,ds \\ &= \int_0^{\tau} (f(s) - f(s-r))\,ds + \int_{-r}^{0} f(s)\,ds.\end{aligned}$$

So, we can rewrite the objective functional as

$$\begin{aligned}\mathcal{J}(v,w,\tau) = \frac{1}{2}\,\|w\|^2_{L^2(0,T;\mathbb{R}_+)} + \frac{1}{2r}\int_{-r}^{0}\left(\|(v - v_d)(t)\|^2\right)dt \\ + \frac{1}{2}\int_0^{\tau}\left(\|(v - v_Q)(t)\|^2 + \left(\|(v - v_d)(t)\|^2 - \frac{1}{r}\,\|(v - v_d)(t - r)\|^2\right)\right)dt.\end{aligned}$$

Since the first two terms are independent of time, consequently, they vanish after computing the Fréchet derivative with respect to time. For $f \in H^1(0,T) \hookrightarrow L^\infty(0,T)$ and $h>0$, so that for $\tau \in (0,T)$, $\tau+h \in (0,T)$, we find

$$\begin{aligned}
\int_0^{\tau+h}|f(s)|^2ds-\int_0^{\tau}|f(s)|^2ds-h|f(\tau)|^2 &= \int_\tau^{\tau+h}|f(s)|^2ds-h|f(\tau)|^2\\
&= \int_\tau^{\tau+h}\left(|f(s)|^2-|f(\tau)|^2\right)ds\\
&= \int_\tau^{\tau+h}\left(|f(s)|-|f(\tau)|\right)\left(|f(s)|+|f(\tau)|\right)ds\\
&\leq 2\,\|f\|_{L^\infty(0,T)}\int_\tau^{\tau+h}\left(|f(s)|-|f(\tau)|\right)ds\\
&\leq 2\,\|f\|_{L^\infty(0,T)}\,h^{\frac{3}{2}}\,\|\partial_t f\|_{L^2(0,T)}\,.
\end{aligned}$$

Thus, we obtain

$$D_\tau\left(\int_0^\tau|f(t)|^2dt\right)=|f(\tau)|^2.$$

So, we deduce that

$$D_\tau\mathcal{J}(w_*,\tau_*)=\frac{1}{2}\,\|v_*(\tau_*)-v_Q(\tau_*)\|^2+\frac{1}{2}\left(\|v_*(\tau_*)-v_d(\tau_*)\|^2-\frac{1}{r}\,\|v_*(\tau_*-r)-v_d(\tau_*-r)\|^2\right).$$

Simplification of the first-order necessary optimality condition with respect to time. For $v_Q \in H^1(0,T;\mathbb{R}_+)$, v_d and $v_* \in H^1(-r,T;\mathbb{R}_+)$, we deduce the following first-order necessary optimality condition with respect to time

$$D_\tau\mathcal{J}(w_*,\tau_*)(s-\tau^*)\geq 0 \quad \forall\ s\in[r,T].$$

In fact, if $\tau_* \in (r,T)$, then $s-\tau_*\geq 0$ if $s\geq\tau_*$ and $s-\tau_*\leq 0$ if $s\leq\tau_*$, so $D_\tau\mathcal{J}(w_*,\tau_*)=0$. If $\tau_*=r$, then $s-\tau_*\geq 0$ and hence $D_\tau\mathcal{J}(w_*,\tau_*)\geq 0$, if $\tau_*=T$, then $s-\tau_*\leq 0$ and hence $D_\tau\mathcal{J}(w_*,\tau_*)\leq 0$. The proof is thus complete. □

4.6.2 Differentiability of the cost functional with respect to the control

Proposition 4.3

Let (w_*,τ_*) be a minimizer of $\mathcal{J}$, $h\in\mathcal{W}_{ad}$ so that $h=w-w_*$, and let (U,V) be a solution of the linearized System (4.1)-(4.3). Then the Fréchet derivative of the cost functional at (w_*,τ_*) with respect to the control w is given by

$$D_w\mathcal{J}(w_*,\tau_*)h=\int_0^{\tau_*}(v_*-v_Q)V\,dt+\frac{1}{r}\int_{\tau_*-r}^{\tau_*}(v_*-v_d)V\,dt+\int_0^T w_*\,h\,dt. \qquad (4.25)$$

Proof. By direct calculations, we get the above Fréchet derivative of the Functional (4.5). □

To eliminate the term V from Equation (4.25), we apply the Lagrangian principle. Using the Lagrangian function, we can formally eliminate the equality constraints given by the

state System (4.1)-(4.4), for which we define the Lagrangian function with respective Lagrangian multipliers p and q by

$$\mathcal{L}(u,v,w,p,q) = \mathcal{J}(v,w) - \int_0^T p\left(u' - J(t,u) + \kappa\left((1-\gamma w)\frac{u}{k+u} - \frac{v}{k'+v}\right)\right)dt$$
$$- \int_0^T q\left(\epsilon v' - F(L-v) - \kappa\left((1-\gamma w)\frac{u}{k+u} - \frac{v}{k'+v}\right)\right)dt.$$

Proposition 4.4

Let (w_*, τ_*) be a solution of Problem (4.5), (u_*, v_*) be the solution of System (4.1)-(4.4) associated to w_*, and let (p,q) be two multipliers of $\mathcal{L}$. Then the adjoint system is given by

$$-p' = J_u(u_*,t)p - \kappa(1-\gamma w)\frac{k}{(k+u_*)^2}p + \kappa(1-\gamma w)\frac{k}{(k+u_*)^2}q, \quad \text{in } [0,T], \tag{4.26}$$

$$-\epsilon q' = (v_* - v_Q) + \frac{1}{r}\chi_{[\tau^*-r,\tau^*]}(t)(v_* - v_d) + \kappa\frac{k'}{k'+v_*}(p-q) - Fq, \quad \text{in } [0,T], \tag{4.27}$$

$$p(\tau_*) = q(\tau_*) = 0. \tag{4.28}$$

Proof. The adjoint system verifies

$$\begin{cases} \mathcal{R}_1 := D_u\mathcal{L}(u_*,v_*,w_*,p,q)u &= 0 \\ \mathcal{R}_2 := D_v\mathcal{L}(u_*,v_*,w_*,p,q)v &= 0, \end{cases}$$

where

$$\begin{aligned}\mathcal{R}_1 &= \int_0^{\tau_*} p'u\,dt + \int_0^{\tau_*} J_u(u_*,t)pu\,dt - \kappa\int_0^{\tau_*}(1-\gamma w)\frac{k}{(k+u_*)^2}up\,dt \\ &\quad +\kappa\int_0^{\tau_*}(1-\gamma w)\frac{k}{(k+u_*)^2}uq\,dt, \quad \tau^* \in [0,T] \\ &= \int_0^{\tau_*}\left(p' + J_u(u_*,t)p - \kappa(1-\gamma w)\frac{k}{(k+u_*)^2}p + \kappa(1-\gamma w)\frac{k}{(k+u_*)^2}q\right)u\,dt\end{aligned}$$

and

$$\begin{aligned}\mathcal{R}_2 &= \int_0^{\tau_*}(v_* - v_Q)v\,dt + \frac{1}{r}\int_0^{\tau_*}\chi_{[\tau^*-r,\tau^*]}(t)(v_* - v_d)v\,dt \\ &= \quad +\kappa\int_0^{\tau_*}\frac{k'}{k'+v_*}v(p-q)\,dt + \int_0^{\tau_*}\epsilon q'v\,dt - F\int_0^{\tau_*}qv\,dt \\ &= \int_0^{\tau_*}\left((v_* - v_Q) + \frac{1}{r}\chi_{[\tau^*-r,\tau^*]}(t)(v_* - v_d) + \kappa\frac{k'}{k'+v_*}(p-q) + \epsilon q' - Fq\right)v\,dt.\end{aligned}$$

□

Theorem 4.4

Let w_* be an optimal control, and $(u_*, v_*) = S(w_*)$ be the corresponding states. Then the adjoint Problem (4.26) has a unique solution

$$(p, q) \in C^1([0, \tau^*]; \mathbb{R}_+)^2.$$

4.7 Simplification of the first-order necessary optimality condition for the control

Let (w_*, τ_*) be a solution of Problem (4.5) with corresponding state variables $(u_*, v_*) = S(w_*)$, and adjoint variables p and q related to u_* and v_* respectively. Let $h := w - w_* \in \mathcal{W}_{ad}$ for any $w \in \mathcal{W}_{ad}$, and (U, V) be the linearized state variables associated to h.

Proposition 4.5

The optimal control w_* satisfies the following simplified first-order necessary optimality condition

$$D_w\mathcal{J}(w_*, \tau_*)h = \int_0^{\tau_*} w_*\, h\, dt + \kappa \int_0^{\tau_*} \gamma h \frac{u_*}{k + u_*}(p - q)\, dt \geq 0.$$

Proof. The optimal control w_* satisfies the following first-order necessary optimality condition

$$\begin{aligned}(D_u\mathcal{J}(w_*, \tau_*))(w - w_*) &= (D_u\mathcal{J}(w_*, \tau_*))h \\ &= \int_0^{\tau_*} (v_* - v_Q)V\, dt + \frac{1}{r}\int_{\tau_* - r}^{\tau_*} (v_* - v_d)V\, dt + \int_0^{\tau_*} w_* h\, dt \geq 0.\end{aligned}$$

To simplify this condition, multiply Equation (4.26) by U and Equation (4.15) by p and integrate over $[0, \tau_*]$, which after taking advantage of the fact that $p(\tau_*) = q_(\tau_*) = 0$ and $U(0) = V(0) = 0$, gives

$$-\int_0^{\tau_*} pU'\, dt + \int_0^{\tau_*} J_u(u_*, t)pU\, dt - \kappa \int_0^{\tau_*} (1 - \gamma w_*)\frac{k}{(k + u_*)^2}(p - q)U\, dt = 0 \qquad (4.29)$$

and

$$\begin{aligned}&\int_0^{\tau_*} pU'\, dt - \int_0^{\tau_*} J_u(u_*, t)Up\, dt \\ &\quad + \kappa \int_0^{\tau_*} \left(-\gamma h \frac{u_*}{k + u_*} + (1 - \gamma w_*)\frac{k}{(k + u_*)^2}U - \frac{k'}{(k' + v_*)^2}V\right) p\, dt = 0.\end{aligned}$$

Adding (4.29) and the above equation, we find

$$\kappa \int_0^{\tau_*} (1 - \gamma w_*)\frac{k}{(k + u_*)^2} qU\, dt = \kappa \int_0^{\tau_*} \left(\gamma h \frac{u_*}{k + u_*} + \frac{k'}{(k' + v_*)^2}V\right) p\, dt. \qquad (4.30)$$

Similarly, multiplying Equation (4.27) by V and Equation (4.16) by q and integrating over $[0, \tau_*]$, we obtain

$$\begin{aligned} -\epsilon \int_0^{\tau_*} qV'\,dt - \int_0^{\tau_*} FqV\,dt - \kappa \int_0^{\tau_*} \frac{k'}{k'+v_*}(q-p)V\,dt \\ + \int_0^{\tau_*} (v_* - v_Q)V\,dt + \int_0^{\tau_*} \chi_{[\tau_*-r],\tau_*}(t)(v_* - v_d)V\,dt = 0 \end{aligned} \tag{4.31}$$

and

$$\begin{aligned} \epsilon \int_0^{\tau_*} qV'\,dt + \int_0^{\tau_*} FVq\,dt + \kappa \int_0^{\tau_*} \gamma h \frac{u_*}{k+u_*} q\,dt \\ -\kappa \int_0^{\tau_*} \left((1-\gamma w_*)\frac{k}{(k+u_*)^2}U - \frac{k'}{(k'+v_*)^2}V \right) q dt = 0. \end{aligned}$$

Adding (4.31) and the above equation, we infer

$$\begin{aligned} \kappa \int_0^{\tau_*} \frac{k'}{k'+v_*} Vp\,dt + \int_0^{\tau^*} (v_* - v_Q)V\,dt + \int_0^{\tau_*} \chi_{[\tau_*-r,\tau_*]}(v_* - v_d)V\,dt \\ +\kappa \int_0^{\tau_*} \gamma h \frac{u_*}{k+u_*} q\,dt - \kappa \int_0^{\tau_*} (1-\gamma w_*)\frac{k}{(k+u_*)^2} Uq\,dt = 0. \end{aligned}$$

Substituting (4.30) into the above equation, we find

$$\int_0^{\tau_*} (v_* - v_Q)V\,dt + \int_0^{\tau_*} \chi_{[\tau_*-r,\tau_*]}(v_* - v_d)V\,dt = \kappa \int_0^{\tau^*} \gamma h \frac{u_*}{k+u_*}(p-q)\,dt.$$

Consequently, the simplified first-order necessary optimality condition is given by

$$D_w \mathcal{J}(w_*, \tau_*)h = \int_0^{\tau_*} w_*\, h\,dt + \kappa \int_0^{\tau_*} \gamma h \frac{u_*}{k+u_*}(p-q)\,dt \geq 0.$$

□

4.8 Numerical Simulations

As aforementioned, high concentrations of lactate lead to over-acidification of the intracellular milieu that is lethal for the cell, this is prevented by the cotransport of both protons and lactate from the cells by MCTs. Moreover, acidification of the extracellular domain promotes tumor malignancy and metastasis. Therefore, targeting MCTs leads to lactate accumulation in the intracellular domain, which induces apoptosis or inhibits lactate uptake by aerobic cells, reducing tumor angiogenesis, metastasis, the deleterious effects of extracellular lactate on immune cells, and invasion (see [70]).

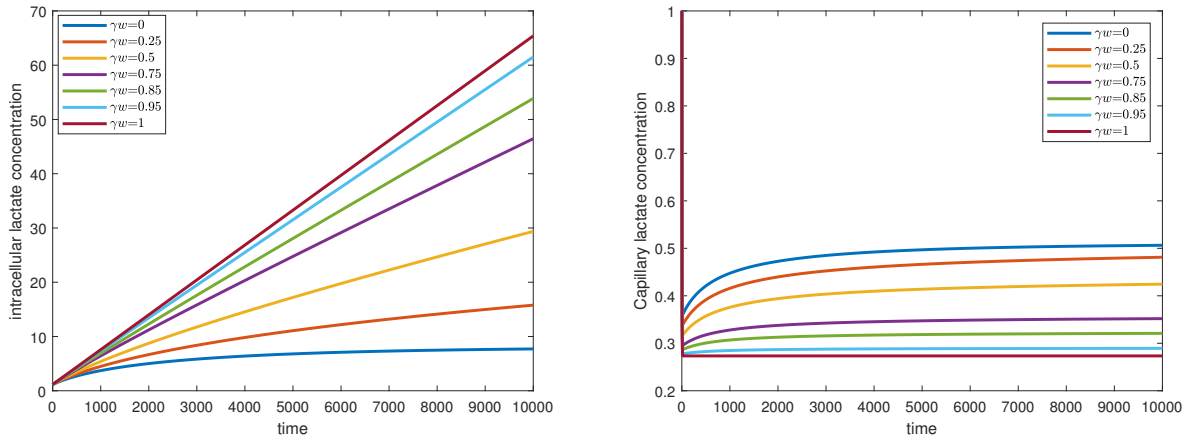
Thus, in this section, the effect of adding the control term, which represents the concentration of the therapeutic drug given at a certain rate, on the intracellular and capillary lactate concentrations is shown through some numerical simulations. For this purpose, we leverage from the parameters proposed in [46], then, we proceed by assuming two cases.

Numerical simulations with F and J constants. We assume that F and J are constants, then, we consider the parameters in Table 4.1:

Parameter	κ	k	k'	L	J	F	ϵ
value	0.01	3.5	3.5	0.3	0.0057	0.0272	0.1
Unit	mM.s^{-1}	mM	mM	mM	mM.s^{-1}	s^{-1}	s^{-1}

Table 4.1 – Parameters values.

When the control is zero, we get the same results as in [46], however, in Figure 4.2a, we can observe that the intracellular lactate concentration increases when the control value is close to 1 until it reaches a constant value. Simultaneously, in Figure 4.2b, the capillary lactate concentration decreases until it reaches a constant value, which illustrates the mode of action of the control (syronsigopine) on both intracellular and extracellular lactate concentration in this case.



(a) Intracellular lactate concentration

(b) Extracellular lactate concentration

Figure 4.2 – Intracellular and capillary lactate concentrations for several values of γw

Numerical simulations with non-constant F and J. We assume that it is biologically relevant to take a function J that does not depend on t since it is to be expected that a cell controls its lactate concentration by the amount, but not by the duration of the experiment. Moreover, we expect a cell to import more lactate when its lactate concentration is low. Thus, we consider the function J (see [46]) as follows

$$J \begin{cases} \mathbb{R}_+ & \longrightarrow \quad \mathbb{R}_+ \\ x & \longmapsto \quad G_J - L_J + \dfrac{C_J}{x + \epsilon_J}, \end{cases}$$

which contains a creation term, a consumption term, and an import term. This function, J, is a bounded and Lipschitz continuous function. Moreover, we follow [4] and define the

function

$$F\begin{cases}\mathbb{R}_+ \longrightarrow \mathbb{R}_+ \\ t \longrightarrow \begin{cases} F_0\left(1+\alpha_f\right) & \text{if} \quad \exists N \in \mathbb{N}/\left(N-1\right)t_f + t_i < t < Nt_f, \\ F_0 & \text{if not.} \end{cases}\end{cases}$$

The parameters of these functions are given in Table 4.2:

Parameter	F_0	α_f	t_i	t_f	C_J	ϵ_J	G_J	L_J
value	0.012	0.5	50	100	5.7×10^{-5}	0.01	0.02	0.01
Unit	s^{-1}	1	s	s	$mM^2.s^{-1}$	mM	$mM^2.s^{-1}$	$mM^2.s^{-1}$

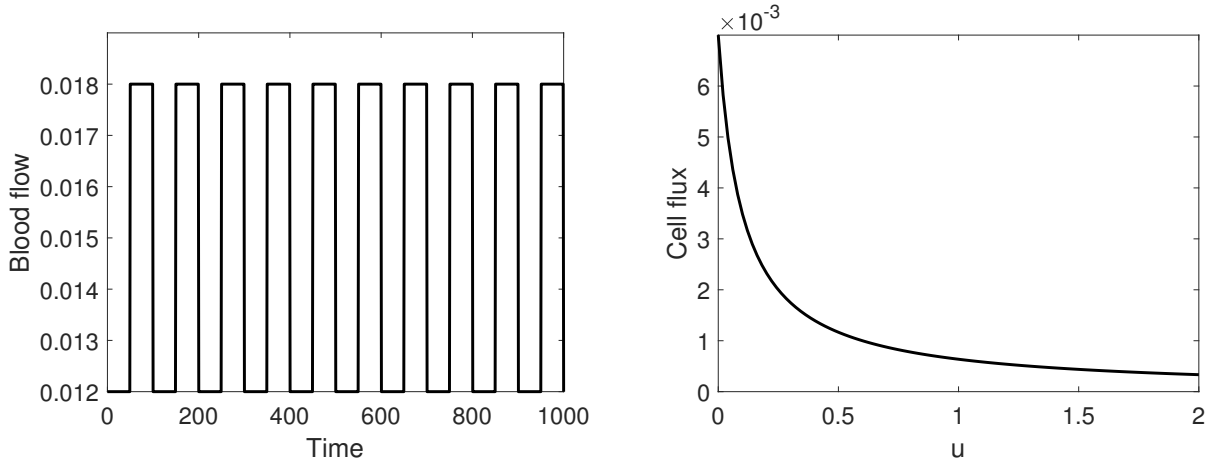
Table 4.2 – Parameters for F and J.

We also consider the parameters given in [5] and [50]. In that case, $(u_0, v_0) = (1.15, 1)$ and the parameters' values are given in Table 4.3:

Parameter	κ	k	k'	L	ϵ
value	0.01	3.5	3.5	0.3	0.001
Unit	$mM.s^{-1}$	mM	mM	mM.	s^{-1}

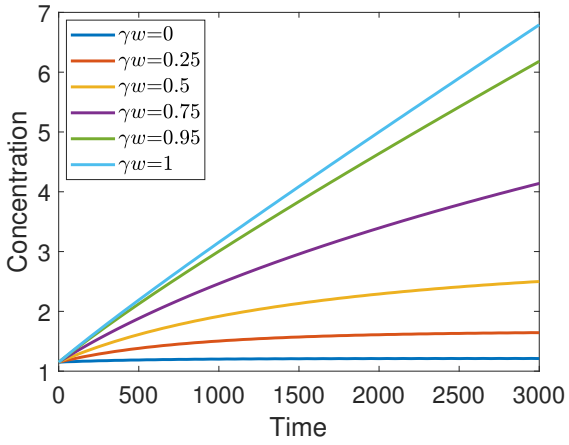
Table 4.3 – Parameters values.

The Functions F and J are given in Figure 4.3:

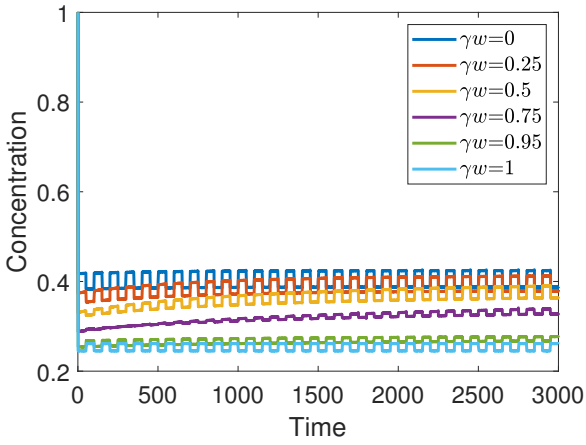


(a) F is a periodic function

(b) J is a monotone decreasing function



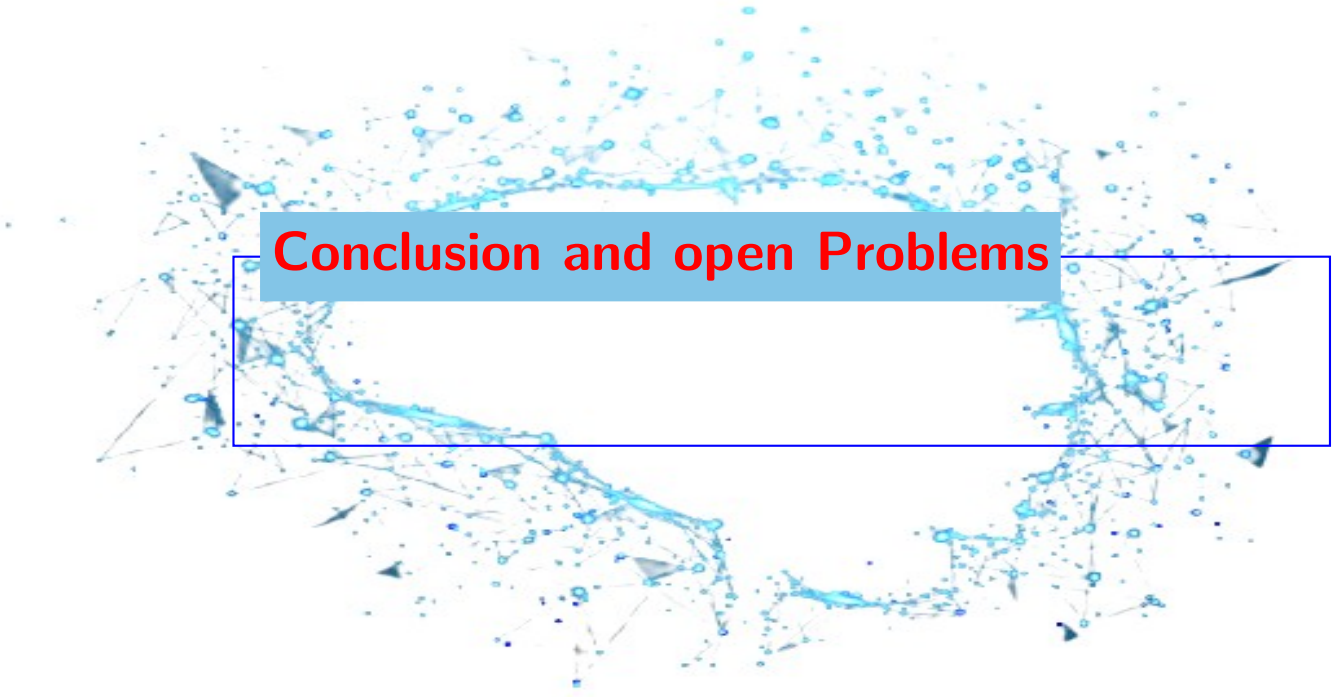
(c) Intracellular lactate concentration



(d) Extracellular lactate concentration

Figure 4.3 – Intracellular and capillary lactate concentrations for several values of γw when F and J are non-constants

Also, if we assume that the control is zero, then, we have the same results as those obtained in [46]. Moreover, in Figure 4.3c with an increasing value of γw, we can observe that the lactate concentration increases with time, simultaneously, the extracellular lactate concentration decreases with time and emerges in a sinusoidal form as shown in Figure 4.3d.



Conclusion and open Problems

"Do the best you can until you know better. Then when you know better, do better."

Maya Angelou

The objective of this thesis was to investigate three optimal control problems that describe glioma therapy directly, and at the level of metabolism. First, we showed in Chapter 2 the well-posedness of a state system that couples an Allen-Cahn equation modeling the tumor growth in the presence of a cytotoxic drug as a control term with a reaction-diffusion equation. This allowed us to define the control-to-state operator, which we proved to be continuous on a suitable topology. Next, we proved the existence of a minimizer (u^*, τ^*) using the lower semicontinuity of the L^2-norm, then, we proved the existence of a unique Fréchet derivative through a linearized system at u^* for any $w \in L^2(Q)$. Moreover, the control-to-state operator is Fréchet differentiable. On the other hand, we have proved that the cost functional is Fréchet differentiable for both time and control. Consequently, we have shown the existence of regular multipliers by employing an adjoint system. At the end of Chapter 2, we simplified the first-order necessary optimality condition.

In Chapter 3, we first modeled our optimal control problem, for this purpose, we considered the PDE model in [62] and added a biologically relevant control term with a given rate and set an objective functional to be minimized, which is the usual functional in optimal control theory (see [73]). Then, we studied the well-posedness of the state system, which allowed us to define the control-to-state operator. Consequently, we have

$$\mathcal{J}(u, v) = \mathcal{J}(S(v), v),$$

Moreover, we established the existence of a minimizer for $\mathcal{J}$, the existence of Fréchet derivative of the control-to-state operator S by means of the existence and uniqueness of solution for a linearized system at v^*. As well, we showed that S is Fréchet differentiable with respect to the control. Regarding the functional $\mathcal{J}$, we have shown that this functional is Fréchet differentiable with respect to time and control, moreover, to reduce the first-order necessary optimality condition, we have considered an adjoint system, shown that this system is well-posed, and derived the simplified first-order necessary optimality

condition.

Finally, in Chapter 4, we considered the ODE model provided in [46], but added the control term to inhibit lactate transport to the capillaries and thus acidify the intracellular domain, contributing to tumor regression.

Then, we set up an objective functional equivalent to the conventional functional used in optimal control theory. In this chapter, we first showed that the system is quasi-positive, and therefore we have a non-negative solution starting from non-negative initial data, then, we used Cauchy-Lipschitz theory to show the existence of a solution for our ODE system, and then we defined the control-to- state operator S. In addition, we demonstrated the existence of a minimizer, then the existence of the Fréchet derivative of the operator S using a linearized system of our ODE-model at the minimizer w^*. Since the unique Fréchet derivative exists, we have then shown the Fréchet differentiability of the operator S. Moreover, the objective functional is Fréchet differentiable with respect to time and control, respectively. Since this is a constrained problem, the existence of regular multipliers was proved by means of an adjoint system. Then, the simplified first-order necessary optimality condition was demonstrated. Finally, to verify our results, we performed some numerical simulations by considering two cases where, in one case the functions F and J are constant in the model, and in the other case J is a monotonically decreasing function and F is a periodic function. The results are shown in Figures 4.2a-4.2b and Figures 4.3c-4.3d, respectively.

As we mentioned earlier in this chapter, cancer cells transport excess lactate into the capillaries to maintain their proliferation and malignancy, in addition to resistance to therapy. In this way, we consider in Chapter 4 the ODE model provided in [46] and searched for a biologically relevant control whose main purpose is to inhibit lactate transport into the capillaries, thus acidifying the intracellular domain, which contributes to tumor regression. The main goal here is to choose the control, which is the concentration of the inhibitor, and the treatment time so that the capillary lactate concentration is the best approximation of the desired concentration during and at the end of treatment.

To this end, we set up an objective functional, $\mathcal{J}$, equivalent to the conventional functional used in optimal control theory, such that we seek some (w_*, τ_*) that minimizes $\mathcal{J}$. In this chapter, we first showed that the state system is quasi-positive, and hence we have a non-negative solution starting from non-negative initial data. Furthermore, we have used the Cauchy-Lipschitz theory to show the existence and uniqueness of a solution to our ODE system, so we have defined the control-to-state operator S. Moreover, we have shown the existence of a minimizer of $\mathcal{J}$ and then proved the existence of the Fréchet derivative of the operator S with respect to the control using a linearized system of our ODE-model at w^*. Since the unique Fréchet derivative exists, we have then shown the Fréchet differentiability of the operator S. Moreover, the objective functional is Fréchet differentiable with respect to time and control, respectively. Since this is a constrained problem, the existence of regular multipliers was proved by means of an adjoint system. Consequently, the simplified first-order necessary optimality condition was demonstrated. Finally, to verify the efficiency of our control, we performed some numerical simulations by considering two cases: In one case, the functions F and J are assumed to be constants in the model, and in the other case J is a monotonically decreasing function and F is a periodic function. The results are shown in Figures 4.2a-4.2b and Figures 4.3c-4.3d

respectively.

Therapeutic strategies of various cancers using the theory of optimal control are very interesting, starting from the behavior of the cell, what affects its proliferation, malignancy, and metastasis, in other words, knowing the key helps in deciphering the puzzle.

As open problems, we can emerge from the ones we have studied. For example, in Problem (4.1)-(4.3), we can also target lactate production, leading to two controls, moreover, we can also consider the spatial diffusion of lactate by a reaction-diffusion equation.

As well, Problem (3.1)-(3.3) may also model lactate transport inhibition by changing the position of the control in the equation.

Although this science is vast, and perhaps, sometimes require more complex models to target cancer, but a little is still better than nothing, and as we aforesaid, mathematical modeling is a major player in helping clinicians and physicians fight cancer. For this, we can recite Cohen's adage which says:"Mathematics' is Biology's next microscope; only better. Biology is mathematics' next Physics; only better."



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Titre: Etude et controle optimal de modeles de croissance de cellules gliales

Mots Clès: Croissance tumorale; modèle d'Allen-Cahn; métabolisme altéré; traitement du gliome; lactate déshydrogénase; équation de réaction-diffusion; conditions d'optimalité nécessaires de premier ordre.

Résumé: Cette thèse aborde différentes approches thérapeutiques pour les gliomes, soit directement, soit au niveau du métabolisme en utilisant la théorie du contrôle optimal. En effet, nous considérons tout d'abord un système couplant une équation d'Allen-Cahn modélisant la croissance tumorale, avec une équation d'évolution pour la dynamique des nutriments. Le traitement des gliomes est considéré en termes de contrôle qui représente la concentration du médicament cytotoxique à un taux donné. Notre objectif dans cette partie est de choisir le contrôle et le temps de traitement de telle sorte que la croissance tumorale correspondante et sa distribution finale soient la meilleure approximation possible des valeurs désirées. Notre première étape est donc consacrée à l'étude du caractère bien posé de notre système d'état, ce qui nous permet de définir l'opérateur contrôle-état qui est continu. Ensuite, nous montrons l'existence d'un minimiseur de notre fonction de coût, où notre opérateur contrôle-état est différentiable au sens de Fréchet. Ensuite, notre fonctionnelle de coût est également différentiable au sens de Fréchet par rapport au temps et au contrôle. Enfin, pour simplifier la condition d'optimalité nécessaire du premier ordre, nous considérons un système adjoint utilisant le principe de Lagrange pour lequel ce système a une solution régulière. D'autre part, nous savons que la progression et la malignité des gliomes sont liées au métabolisme, en particulier au déchet de glycolyse et de lactate. Ainsi, nous soulignons d'abord le fait que plus le gliome produit de lactate, plus il transporte l'excès dans le capillaire pour soutenir la prolifération, les métastases et la malignité. Par conséquent, nous considérons l'équation d'état comme un problème parabolique modélisant la dynamique du lactate intracellulaire. Notre premier défi consiste à ajouter un contrôle biologiquement pertinent qui agit comme une concentration d'un certain médicament pour inhiber la production de lactate. Puisque la dose de médicament et le temps ne doivent pas dépasser ou descendre en dessous d'un certain seuil dans le traitement du cancer, nous essayons de choisir le meilleur contrôle au moment le plus opportun afin que la concentration de lactate intracellulaire correspondante soit aussi proche que possible de notre évolution souhaitée et de la distribution finale du lactate. Cependant, comme nous l'avons dit plus haut, la cellule retire l'excès de lactate en le transportant à travers la membrane plasmique de la cellule dans le capillaire pour maintenir sa prolifération. Ceci nous a inspiré à cibler le transport du lactate en utilisant un inhibiteur de MCTs qui agit comme un terme de contrôle dans un système couplé de type EDO qui modélise la dynamique du lactate dans les domaines intracellulaire et capillaire. Nous abordons la question de savoir combien de temps un patient doit être traité et quelle est la dose optimale de médicament pour atteindre la concentration de lactate capillaire souhaitée. Pour atteindre notre objectif, nous considérons un problème de minimisation avec une fonction de coût conventionnelle associée au système d'EDO susmentionné. Tout d'abord, nous montrons l'existence d'une solution régulière unique et non négative de notre système EDO, puis nous définissons l'opérateur contrôle-état et montrons qu'il est continu sur la topologie correspondante. Puis, nous montrons l'existence d'une solution à notre problème de minimisation sous des contraintes données. Nous étudions ensuite l'existence d'une dérivée unique de l'opérateur contrôle-état et sa différentiabilité de Fréchet. Nous montrons ensuite la différentiabilité de Fréchet de la fonctionnelle de coût par rapport au temps et au contrôle. De plus, nous définissons le système adjoint par le principe de Lagrange, nous simplifions la condition d'optimalité nécessaire au premier ordre, et enfin, nous mettons en évidence le choix du terme de contrôle par des simulations numériques.

Keywords. Tumor growth; Allen-Cahn model; Altered metabolism; glioma treatment; lactate dehydrogenase; reaction-diffusion equation; first-order necessary optimality conditions.

Abstract: This thesis addresses different therapeutic approaches for gliomas, either directly or at the level of metabolism using optimal control theory. Indeed, we first consider an Allen-Cahn equation modeling tumor growth, and since the structure of the model can change in the presence of nutrients, it is then coupled with an evolution equation for nutrient dynamics. In addition, the treatment of gliomas is considered in terms of control that represents the concentration of the cytotoxic drug at a given rate. Our goal in this part is to choose the control and the treatment time such that the corresponding tumor growth and its final distribution are the best possible approximation to the desired values. Our first step is thus devoted to the study of the well-posedness of our state system, which allows us to define the control-to-state operator that is continuous. Then, we show the existence of a minimizer of our cost functional, where our control-to-state operator is Fréchet differentiable. Next, our cost functional is also Fréchet differentiable with respect to time and control; finally, to simplify the first-order necessary optimality condition, we consider an adjoint system using Lagrange's principle for which this system has a regular solution. On the other hand, we know that the progression and malignancy of gliomas are related to metabolism, in particular to the waste product of glycolysis, lactate. Thus, we first emphasize the fact that the more lactate the glioma produces, the more it transports the excess into the capillary to sustain proliferation, metastasis, and malignancy. Therefore, we consider the state equation as a parabolic problem modeling intracellular lactate dynamics. Our first challenge is to add a biologically relevant control that acts as a concentration of a certain drug to inhibit lactate production. Since the drug dose and time must not exceed or fall below a certain threshold in cancer treatment, we try to choose the best control at the most convenient time so that the corresponding intracellular lactate concentration is as close as possible to our desired evolution and final distribution of lactate. However, as aforesaid, the cell withdraws excess lactate by transporting it across the plasma cell membrane into the capillary to maintain its proliferation. This has inspired us to target lactate transport using an MCTs inhibitor that acts as a control term in a coupled ODE system that models lactate dynamics in both the intracellular and capillary domains. We address the question of how long a patient needs to be treated and what is the optimal drug dose to achieve the desired capillary lactate concentration. To attain our goal, we consider a minimization problem with a conventional cost functional associated with the ODE system aforementioned. First, we show the existence of a unique regular non-negative solution of our ODE system, then we define the control-to-state operator and show that it is continuous on the corresponding topology. Next, we show the existence of a solution to our minimization problem under given constraints. Then we study the existence of a unique derivative of the control-to-state operator and its Fréchet differentiability. We then show the Fréchet differentiability of the cost functional with respect to time and control. Moreover, we define the adjoint system by Lagrange's principle, simplify the first-order necessary optimality condition, and finally, we emphasize the choice of the control term with numerical simulations.