Numerical Optimal Control

2 st Quarter 2022/2023, IST

Computational Project 2 – Gliobastoma + Radiotherapy

Remarks: The report should be as short as possible, answering item by item, and should remain within the limit of 10 to 15 pages. Direct answers are prefered, except when comments or justifications are required. Whenever is necessary, graphical representations and/or tables should be included. The algorithms should be implemented in *Freefem ++*. The corresponding scripts should be attached with file extension .edp. While answering, clearly explain how to run the code in order to reproduce the results shown.

Freefem ++ can be obtained here:

`https://www.ljll.math.upmc.fr/lehyaric/ffcs/install.htm`.

Report due on:

Glioblastoma, also known as glioblastoma multiforme (GBM), is the most common and aggressive type of primary brain tumor. It belongs to a group of tumors called gliomas, which originate in the glial cells that provide support and nourishment to the neurons in the brain. Glioblastoma tumors are characterized by their rapid growth, infiltrative nature, and high tendency to recur even after treatment.

Radiotherapy is a commonly used treatment for glioblastoma. It involves the use of high-energy radiation beams to target and kill cancer cells. The goal of radiotherapy is to destroy or shrink the tumor, alleviate symptoms, and prolong survival. It is usually administered after surgical removal of the tumor or in combination with other treatment modalities like chemotherapy.

The radiotherapy treatment for glioblastoma can be modeled as a system of PDEs that model the effects of a therapy on a brain tumor (glioblastoma). In this case, we use for simplicity that the tumor cell density verifies a linear parabolic PDE, which is coupled with another similar PDE for a cytotoxic agent. Control is distributed, its support is a small subdomain of the open that represents the brain and acts through the right side of the equation for the density.

Thus, this project will consist of solving the optimal control problem associated with said system, from the theoretical and practical point of view.

Let an open bounded, convex set $\Omega \subset \mathbb{R}^2$ to represent a brain section where tumor cells have been detected. We consider the following simplified system which describes the evolution of the brain tumor (glioblastoma) in $(0, T) \times \Omega$, $T > 0$

$$\begin{cases} c_t - \nabla \cdot (D(x)\nabla c) - a_1 c = -b_1 \beta \quad (t,x) \in (0,T) \times \Omega, \\ \beta_t - \mu \Delta \beta - a_2 \beta = v 1_\omega \quad (t,x) \in (0,T) \times \Omega, \\ c(0,x) = c_0(x), \quad \beta(0,x) = \beta_0(x) \quad x \in \Omega, \\ \dfrac{\partial c}{\partial n} = 0, \quad \dfrac{\partial \beta}{\partial n} = 0 \quad (t,x) \in (0,T) \times \partial\Omega. \end{cases} \tag{1}$$

Here $c(t,x)$ represents the density of tumor cells and we denote by $\beta(t,x)$ as the antibodies (cytotoxic agents) generated by the organism. The function $v(t,x)$ describes the action of the radiotherapy applied to a smaller part of the domain, ω. On the other hand, μ is the diffusion coefficient of the antibodies that we assume to be constant and positive. As to$D(x)$, it represent the diffusion coefficient of the tumor cells and in general it depends on the type of brain matter present at location x (gray or white matter). In our case we will assume that D is a definite positive matrix that takes a value in the control domain and another outside it:

$$D(x) := \begin{cases} D_1(x) \text{ if } x \in \Omega \setminus \omega, \\ D_2(x) \text{ if } x \in \omega, \end{cases}$$

where $D_1(x)$ and $D_2(x)$ are definite positive matrix and they are bounded.

1. Let us consider that a_1, b_1, b_2 are positive real numbers and c_0 and β_0 two data functions in $L^2(\Omega)$.

   Prove that (1) has an unique weak solution for each $v \in L^2(0,T;L^2(\Omega))$ by using the classical theorems for general parabolic equations.

2. Now, we consider the optimal control problem associated to (1), where $v \in L^2(0,T;L^2(\Omega))$ is the control that guide the state to a desired state. Then,

$$(P) \begin{cases} \min\ J(v) := J(c,v) = \dfrac{\alpha_1}{2} \displaystyle\iint_{(0,T)\times\Omega} |c - c_d|^2 + \dfrac{\alpha_2}{2} \int_\Omega |c(T) - c_d(T)|^2 + \dfrac{\alpha_3}{2} \iint_{(0,T)\times\Omega} |v|^2 \\ \text{s.t.} \quad (c,\beta,v) \text{ solves (1).} \end{cases}$$

   with data $\alpha_1, \alpha_2, \alpha_3 > 0$, $c_d \in L^2(0,T;L^2(\Omega))$ and $c_d(T) \in L^(\Omega)$.

   The function J can be interpreted as an average of the difference between the amount of cancer cells remaining during treatment and a desired amount of cancer cells and the intensity of the medication. The weights α_i are determined by the importance of each term.

   Prove that (P) has a unique minimum.

3 Check that

$$\begin{cases} c_t - \nabla \cdot (D(x)\nabla c) - a_1 c = -b_1 \beta \quad (t,x) \in (0,T) \times \Omega, \\ \beta_t - \mu \Delta \beta - a_2 \beta = v 1_\omega \quad (t,x) \in (0,T) \times \Omega, \\ c(0,x) = c_0(x), \quad \beta(0,x) = \beta_0(x) \quad x \in \Omega, \\ \dfrac{\partial c}{\partial n} = 0, \quad \dfrac{\partial \beta}{\partial n} = 0 \quad (t,x) \in (0,T) \times \partial\Omega. \end{cases}$$

and

$$\begin{cases} -p_t - \nabla \cdot (D(x)\nabla p) - a_1 p = \alpha_1(c - c_d) \quad (t,x) \in (0,T) \times \Omega, \\ -q_t - \mu \Delta q - a_2 q = -b_1 p \quad (t,x) \in (0,T) \times \Omega, \\ p(T,x) = \alpha_2(c(T,x) - c_d(T,x)), \quad q(T,x) = 0 \quad x \in \Omega, \\ \dfrac{\partial p}{\partial n} = 0, \quad \dfrac{\partial q}{\partial n} = 0 \quad (t,x) \in (0,T) \times \partial\Omega. \end{cases}$$

and

$$q + \alpha_3 v = 0, \quad (t,x) \in (0,T) \times \omega.$$

is the associated optimality system (by using the adjoint approach and the Lagrange approach)

3. Determine the gradient algorithm with optimal step for the computation of the minimum and write the respective discretized systems by using finite differences in time and P_1 Lagrange finite element in space.

4. Solve the problem for the data:

$$D(x) := \begin{cases} D_1(x) \text{ if } x \in \Omega \setminus \omega, \\ D_2(x) \text{ if } x \in \omega, \end{cases}$$

where $D_1(x) = 0.0002Id$ and $D_2(x) = 0.001Id$.

$$\alpha_1 = \alpha_3 = 0.05, \quad \alpha_2 = 0.9, \quad T = 150 \ (days), Nt = 30,$$

$$\mu = 0.5, \quad a_1 = 0.001, \quad b_1 = 0.00005, \quad a_2 = 0.001.$$

As to the desired number of tumor cells c_d, due to lack of resolution, there is a threshold at which we stop being able to count the number of cells. We assume that level to be 13 tens of thousands per cm^2. So, we consider that our goal is to drive an initial concentration of $c_0 = 14$ with $\beta_0(x) = 0$ to a desired tumor cell density near to $c_d = 13$ by adjusting v.

As a solution method, consider the optimal step gradient method using a constant initial control $v = 1.$. To solve each equation, use $FreeFem++$. Use the stopping criteria

$$\|v^n - v^{n-1}\| \leq 0.05$$

to terminate the algorithm.

Draw the final solution c in the final time and the solution c without any control v. Generate two files: *cobserved.txt* and *cobservednocontrol.txt* that contain the maximum beteween zero and the difference of the solution in the final time (with and without control) and the desired density cell in the final time. Compare these two files and comment the effect of the therapy.