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Chemotherapy of a tumor by optimal control approach

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Abstract

We study a model of tumor which grows or shrinks due the proliferation of cells which depends on nutrient concentration σ modeled by a diffusion equation. The tumor is assumed to be spherical shape and its boundary is unknown. From optimal control, we show some results and optimal control lying to the evolution of tumor. We use also some tools in shape and topological optimization to detect the evolution of the tumor and its shape and we do some numerical simulations.

Mathematics Subject Classification: 35R35, 92D29

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1 Introduction

We propose the use of the Optimal Control Theory to provide a complete explanation of the biological phenomena, not only of the relationships between bio-entities but also of the origin of these interrelationships. Optimal Control Theory is the contemporary setting for analysing and solving optimisation problems, born in the 1960s with the work of Pontryagin et al. (1962) on the basis of the previous contributions made by Lagrange (1788) and Hamilton (1827). In essence, Optimal Control Theory considers the problem of

how to attain an objective subject to external constraints, and it has mainly been used in Economics. To our knowledge, concerning Biosciences, Optimal Control Theory has been applied to the design of optimal therapies, optimal harvest policies and optimal investments in renewable-resources, but not to elucidate the origin of the observed biological behaviours. When designing an optimal therapy, an optimal harvest or an optimal investment, the purpose is to achieve an objective external to the involved biological entities -namely, to minimise the negative effects of drugs and illness and to maximise the present value of revenues, subject to the biological laws describing the existing cross effects. The suitable mathematical approach to this problem is therefore the Optimal Control Theory, and, indeed, in modern biomathematics there is large body of work developed to study optimal drug therapies and optimal harvest policies.
However, in addition to such well known applications, Optimal Control Theory also constitutes the most appropriate approach to study biological phenomena understood as the result of the behaviour of semi-autonomous bio-entities. Therefore, the optimal control theory provides a complete explanation of the observed behaviours: the bio-entities pursue their own specific objectives, the actions of a bio-entity affects the possibilities of the other entities to achieve their objectives, and as a result, all the behaviours are interrelated. However, the interpretation of biological phenomena as the result of a set of optimal control problems has not yet been considered by current biomathematics. In this respect, taking economic oligopolistic models as our starting point, the purpose of this paper is to show how this application of Optimal Control Theory is a promising approach to the analysis of biomedical questions, specially to tumor.

The mathematical modeling of tumor has been approached by a few number of researchers using a variety of models over the past decades.

In [26], G.Swan presents a review of the ways in which optimal control theory interacts with cancer chemotherapy. There are three broad areas of investigation. One involves miscellaneous growth kinetic models, the second involves cell cycle models, and the third is a classification of "other models." Both normal and tumor cell populations are included in a number of the models. The concepts of deterministic optimal control theory are applied to each model in such a way as to present a cohesive picture. There are applications to both experimental and clinical tumors. He presents also suggestions for designing better chemotherapy strategies.

In [27], G.Swan introduced a performance criterion to measure the effectiveness of therapy while penalizing excessive usage of drug. He use optimal control theory to obtain information on the nature of the controller, which is related to the amount of drug to be infused from a drug-delivery device. In [19] Urszula L. and Heinz S. analyze non cell-cycle specific mathematical models for drug resistance in cancer chemotherapy. Distinguishing between sensitive and resistant cells they consider a model which includes interactions of two killing agents which generate separate resistant populations. They formulate an associated optimal control problem for chemotherapy and analyze the qualitative structure of corresponding optimal controls.

In [9] De Pillis, L.G and Radunskaya,A. using optimal control theory with constraints and numerical simulations, they obtain new therapy protocols that we then compare with traditional pulsed periodic treatment. The optimal control generated therapies produce larger oscillations in the tumor population over time. However, by the end of the treatment period, they show the total tumor size is smaller than that achieved through traditional pulsed therapy, and the normal cell population suffers nearly no oscillations.

In [18], according to Kimmel,M. and Swierniak,A. proved the major obstacles against successful chemotherapy of cancer are cell-cycle-phase dependence of treatment, and emergence of resistance of cancer cells to cytotoxic agents. One way to understand and overcome these two problems is to apply optimal control theory to mathematical models of cell cycle dynamics. These models should include division of the cell cycle into subphases and/or the mechanisms of drug resistance. They review their results in mathematical modeling and control of the cell cycle and of the mechanisms of gene amplification (related to drug resistance), and estimation of parameters of the constructed models.

The structure of this paper is as follow : after this introduction, Section 2 describes the model of the tumor growth. Section 3 briefly describes the proposed application of the Optimal Control Theory. Once the approach has been explained and making use of very simple examples and some numerical simulations are given In Section 4, the topological optimization approach gives us an alternative to study and to do simulations in order to locate and get geometrical topological distributions of the tumors.

2 A model of tumor growth

The tumors appear after a change of the material genetic of a cell. This change encourages the uncontrolled division. The cancerous cells acquire the capacity to produce of the growth signals and are less receptive to the signals of anti-growth. In order to divide, a cell needs nutrients (such as oxygen), which is obtained from its close environment in the avascular phase. As the tumor grows, some cells do not get any more enough nutrient and turn to a quiescent state where they no longer divide waiting for the environment to become favorable again. Therefore, for a realistic description of cancer growth, one has to describe the evolution of the concentration of nutrients. From now we consider some models continuous. Every species (nutrient, cellular types...) is described by its density depending on the time and the space i.e $N = N(t,x)$. To describe the evolution of the system, one must write an equation of evolution on N. The cellular division is described by a linear, exponential or logistical term. By conservation law equation, one can write

$$\partial_t N + f(N) = \alpha(1-N)N \tag{1}$$

where $f(N)$ is a function an unknown depending on N. One can consider the two following cases :

Case with reaction diffusive term

$$\partial_t N + \nabla J = \alpha - \beta = \gamma \tag{2}$$

α, β, γ are respectively birth rate,death rate and demographic rate. J is the total flow of cells i.e the density of cells enter and/or exit of every elementary volume.

Let at first consider that $J = J_1 = -D\nabla N$ and (2) becomes

$$\partial_t N + \nabla(-D\nabla N) = \gamma \tag{3}$$

And in a second case that $J = J_2 = -D|\nabla N|^{m-2}\nabla N$ and (2) becomes

$$\partial_t N + \nabla(-D|\nabla N|^{m-2}\nabla N) = \gamma \tag{4}$$

D is a diffusive coefficient term with depend on the biological considerations. To model the movement of cells, one can replace the diffusive term by advection term.

Case with advection term

$$\partial_t N + \nabla(vN) = \gamma$$

Let us consider the following problems.

$$\begin{cases} \frac{\partial\sigma}{\partial t} - \Delta\sigma + \sigma = -\overline{\sigma} & \text{in} \quad]0,T[\times\Omega \\ \sigma = 0 & \text{on} \quad]0,T[\times\partial\Omega \\ \sigma(0,x) = \sigma_0 & \text{in} \quad \Omega \end{cases} \tag{5}$$

where σ is the nutrient concentration of cells proliferating (for more details see [24]) and we assume like in [10] that in the tumor region $\Omega(t)$ there are tree types of cells : proliferating cells with density p, quiescent cells with density q and necrotic cells with density r.

Nutrient with concentration σ is diffusing in $\Omega(t)$ and affects the transition of cells one type to another :

$p \to q$ at rate $k_Q(\sigma)$, $q \to p$ at rate $k_p(\sigma)$,

$p \to r$ and $q \to r$ at rates $k_A(\sigma)$ and $k_D(\sigma)$ respectively and $p \to p$ at proliferate

rate $k_B(\sigma)$. Necrotic cells are removed from the tumor at constant rate k_R. By conservation of mass,

$$\begin{cases} \frac{\partial p}{\partial t} + div(p\overrightarrow{v}) = [k_B(\sigma) - k_Q(\sigma) - k_A(\sigma)]p + k_p q & \text{in} \quad]0,T[\times\Omega \\ \frac{\partial q}{\partial t} + div(q\overrightarrow{v}) = k_Q(\sigma)p - [k_p(\sigma) + k_D(\sigma)]q & \text{in} \quad]0,T[\times\Omega \\ \frac{\partial r}{\partial t} + div(r\overrightarrow{v}) = k_A(\sigma)p + k_D(\sigma)q - k_R r & \text{in} \quad]0,T[\times\Omega \\ p + q + r = 1 \end{cases} \tag{6}$$

Where $\overrightarrow{v}$ is the velocity of the cells, caused by motions due to the proliferation and removal of cells.
Let us denote by M the density of sane tissue. It satisfies :

$$\partial_t M + \nabla(vM) = 0$$

Making the sum of the three first equations of (6) and using the fourth equation of (6), we obtain :

$$div(\overrightarrow{v}) = k_B(\sigma)p - k_R r \tag{7}$$

and for more considerations (see [24] or [10]) we take $\overrightarrow{v} = -\nabla\mathcal{P}$ et $k_B(\sigma) = \mu(\sigma - \widetilde{\sigma})$ where $\mathcal{P}$ is the pressure with appear due to motions of cells.
And then with these notations, equation (7) becomes

$$-\Delta\mathcal{P} = \mu(\sigma - \widetilde{\sigma})p - k_R r \tag{8}$$

3 Optimal control with the evolution of tumors

In this paper, the optimal control problems are formulated and solved as J.L.Lions approach for details see [21]. We are interested an internal optimal control that is the intensity of the radiation issuing or injected dose at the target domain (internal control) or a surface treatment for example the application of an ointment on the skin(boundary control). We show how to control the system via an equation of stated this approach has been started by J.L.Lions for details see [21]. To illustrate our approach, we present some examples and numerical simulations.

3.1 Optimal control problem

First express a general manner how one can write an optimal control problem. Let us consider Ω an nonempty set and bounded of $\mathbb{R}^N$ and C^2 class. Let $\Gamma = \partial\Omega$

the border of Ω. Let us consider the following systems :

$$\left\{ \begin{array}{lll} Ay = f & \text{in} & \Omega \\ By = 0 & \text{on} & \partial\Omega \end{array} \right. \tag{9}$$

$Ay = f$ the equation verified in Ω by the state of the system
f is given ; $f : \Omega \to \overline{\mathbb{R}}$;In large cases f is $L^2(\Omega)$
y is the state of the system
$By = 0$ represents the boundaries conditions
Let y_d a reference state, a desired state ; $y_d : \Omega \to \overline{\mathbb{R}}$
We want to act to the equation (9) such that the new state $\tilde{y}$ be the nearest of y_d. The notion of near must be define of different maner :

Internal control
$u \in \mathcal{U} \subset \mathcal{F}(\Omega, \overline{\mathbb{R}})$

$$\left\{ \begin{array}{lll} Ay = f + u & \text{in} & \Omega \\ By = 0 & \text{on} & \partial\Omega \end{array} \right. \tag{10}$$

Our objective it is $y(u)$nearest possible of $y_d$with the costs the least

$$J(u) = j(y(u) - y_d) + c(u) \tag{11}$$

where j and c are given functions.
The problem is solve $\overline{u} \in \mathcal{U}$ such that :

$$J(\overline{u}) = \min_{u \in \mathcal{U}} J(u)$$

$\mathcal{U}$ = admissible control set.
$\overline{u}$ = optimal control that's mean control corresponding to the best cost.
$\overline{y} = y(\overline{u})$ = optimal state, state corresponding at the optimal control.
J = cost-function.
$J(\overline{u})$ = optimal cost, here the minimal cost.
Boundaries control
$\mathcal{V} \subset \mathcal{F}(\partial\Omega, \overline{\mathbb{R}})$, $v \in \mathcal{V}$
$\mathcal{V}$ = admissible control set.

$$\left\{ \begin{array}{lll} Ay = f & \text{in} & \Omega \\ By(v) = v & \text{on} & \partial\Omega \end{array} \right. \tag{12}$$

$y_d : \Omega \to \overline{\mathbb{R}}$, a reference function

$$J(v) = j(y(v) - y_d) + d(v) \tag{13}$$

where j and d are given functions. The problem is to solve $\overline{v} \in \mathcal{V}$ such that

$$J(\overline{v}) = \min_{v \in \mathcal{V}} J(v)$$

and the system of PDE(Partial Differential Equation) has solution. Here we make an internal control.

3.1.1 Optimal control problem for tumor growth

To avoid of the confusion in notations of problem (5), we take $-\overline{\sigma} = f$ and we make control of the following problem :

$$\left\{ \begin{array}{ccc} \frac{\partial \sigma}{\partial t} - \Delta\sigma + \sigma = f & \text{in} &]0,T[\times\Omega \\ \sigma = 0 & \text{on} &]0,T[\times\partial\Omega \\ \sigma(0,x) = \sigma_0 & \text{in} & \Omega \end{array} \right. \tag{14}$$

and let $\varphi_1, ..., \varphi_p \in L^\infty(Q_T)$, $u = (u_1, ..., u_n) \in \mathbb{R}^p$ et $\sigma(t,u)$ solution of the control problem

$$\left\{ \begin{array}{ccc} \frac{\partial \sigma}{\partial t} - \Delta\sigma + \sigma = f + \sum_{i=1}^p u_i\varphi_i(t) & \text{in} &]0,T[\times\Omega \\ \sigma = 0 & \text{on} &]0,T[\times\partial\Omega \\ \sigma(0,x) = \sigma_0 & \text{in} & \Omega \end{array} \right. \tag{15}$$

Let $\sigma_1 \in L^2(\Omega)$ the desired state

$$J_1(u) = \frac{1}{2}\int_\Omega (\sigma(T,u,x) - \sigma_1(x))^2 dx + \frac{\alpha}{2}\|u\|^2_{\mathbb{R}^p} \text{ où } \alpha > 0 \tag{16}$$

$$\begin{array}{rcl} J_2(\sigma, N, u) & = & \frac{1}{2}\int_{]0,T[\times\Omega}(N(t,u,x) - N_1(x))^2 dxdt \\ & + & \frac{1}{2}\int_{]0,T[\times\Omega}(\sigma(t,u,x) - \sigma_1(x))^2 dxdt + \frac{\alpha}{2}\int u^2 dx \end{array} \tag{17}$$

In practice we use

$$\begin{array}{rcl} J_3(\sigma, N, u) & = & \frac{1}{2}\int_\Omega(N(T,u,x) - N_1(x))^2 dx \\ & + & \frac{1}{2}\int_\Omega(\sigma(T,u,x) - \sigma_1(x))^2 dx + \frac{\alpha}{2}\int u^2 dx \end{array} \tag{18}$$

Remark 3.1 *We can make the control at every moment of $[0,T]$ and take $\sigma(t,u,x)$ and $\sigma_1(t,x)$, but here we make the control by interesting to the final state (at the moment T)that's why we take $\sigma(T,u,x)$ and $\sigma_1(x)$*

Theorem 3.1 *There exists an optimal control $\overline{u}$ such that*

$$J(\overline{u}) = \min_{u \in \mathcal{U}} J(u)$$

$$\textit{where } J(u) = \frac{1}{2}\int_\Omega (\sigma(T,u,x) - \sigma_1(x))^2 dx + \frac{\alpha}{2}\|u\|^2_{\mathbb{R}^p} \ \textit{où } \alpha > 0$$

and an optimality system

$$\left\{\begin{array}{ccc} \frac{\partial \sigma}{\partial t} - \Delta\sigma + \sigma = f + \sum_{i=1}^p u_i\varphi_i(t) & in &]0,T[\times\Omega \\ \sigma = 0 & on &]0,T[\times\partial\Omega \\ \sigma(0,x) = \sigma_0 & in & \Omega \\ -\frac{\partial \overline{p}}{\partial t} - \Delta\overline{p} + \overline{p} = 0 & in &]0,T[\times\Omega \\ \overline{p} = 0 & on &]0,T[\times\partial\Omega \\ \overline{p}(T) = \sigma(T,\overline{u}) - \sigma_1 & in & \Omega \\ \overline{u}_i = -\frac{1}{\alpha}\int_0^T\int_\Omega \overline{p}(t,x)\varphi_i(t,x)dxdt & & \end{array}\right. \tag{19}$$

Proof 3.1

$$J : \mathbb{R}^p \to \mathbb{R}$$

$$J(u) = \frac{1}{2}\int_\Omega (\overline{\sigma}(T,x) + \mathcal{L}[f + \sum_{i=1}^p u_i\varphi_i] - \sigma_1(x))^2 dx + \frac{\alpha}{2}\|u\|^2_{\mathbb{R}^p}$$

$\mathcal{L}$ *as*

$$\mathcal{L} : L^2(Q_T) \to C([0,T], L^2(\Omega))$$

$$f \to \mathcal{L}(f) = z$$

$Q_T =]0,T[\times\Omega$
$\mathcal{L}$ *is linear and continu*
where $z \in C([0,T], L^2(\Omega))$ *is solution of the system*

$$\left\{\begin{array}{ccc} \frac{\partial z}{\partial t} - \Delta z + z = f & in &]0,T[\times\Omega \\ z = 0 & on &]0,T[\times\partial\Omega \\ z(0,x) = 0 & in & \Omega \end{array}\right. \tag{20}$$

$\overline{\sigma}$ *is solution of*

$$\left\{\begin{array}{ccc} \frac{\partial \overline{\sigma}}{\partial t} - \Delta\overline{\sigma} + \overline{\sigma} = 0 & in &]0,T[\times\Omega \\ \overline{\sigma} = 0 & on &]0,T[\times\partial\Omega \\ \overline{\sigma}(0,x) = \sigma_0 & in & \Omega \end{array}\right. \tag{21}$$

$$\textit{then } \sigma(t,x) = \overline{\sigma}(t,x) + \mathcal{L}f$$

where $\sigma(t,x)$ *verifies*

$$\left\{\begin{array}{ccc} \frac{\partial \sigma}{\partial t} - \Delta\sigma + \sigma = f & in &]0,T[\times\Omega \\ \sigma = 0 & on &]0,T[\times\partial\Omega \\ \sigma(0,x) = \sigma_0 & in & \Omega \end{array}\right. \tag{22}$$

J *is strictly convex*

$$J(u) \geq \frac{\alpha}{2}\|u\|^2_{\mathbb{R}^p}$$

$$\lim_{\|u\|_{\mathbb{R}^p}\to\infty} J(u) = +\infty$$

$$\exists\ !\ \overline{u} \in \mathbb{R}^p / J(\overline{u}) = \min_{u\in\mathbb{R}^p} J(u)$$

Optimality sytem : Let $v \in \mathbb{R}^p$.

$$\textit{We have : } J'(\overline{u}).v = \int_\Omega \sum_{i=1}^{p} \overline{u_i}\mathcal{L}(\varphi_i) \sum_{i=1}^{p} v_i \mathcal{L}(\varphi_i)dx$$

$$+\int_\Omega (\overline{\sigma}(T,x) + \mathcal{L}(f) - \sigma_1) \sum_{i=1}^{p} v_i\mathcal{L}(\varphi_i)dx + \alpha < \overline{u}, v >_{\mathbb{R}^p}$$

$$J'(\overline{u}).v = \int_\Omega [\overline{\sigma}(T,x) + \mathcal{L}(f) + \sum_{i=1}^{p} \overline{u_i}\mathcal{L}(\varphi_i) - \sigma_1] \sum_{i=1}^{p} v_i\mathcal{L}(\varphi_i)dx + \alpha < \overline{u}, v >_{\mathbb{R}^p} = 0$$

$$J'(\overline{u}).v = \int_\Omega [\overline{\sigma}(T,x) + \mathcal{L}(f + \sum_{i=1}^{p} \overline{u_i}\varphi_i) - \sigma_1] \sum_{i=1}^{p} v_i\mathcal{L}(\varphi_i)dx + \alpha < \overline{u}, v >_{\mathbb{R}^p} = 0$$

$$J'(\overline{u}).v = \int_\Omega [\sigma(T,\overline{u}) - \sigma_1]\mathcal{L}(\sum_{i=1}^{p} v_i(\varphi_i))(T)dx + \alpha < \overline{u}, v >_{\mathbb{R}^p} = 0$$

Here we want to have the expression $\sum_{i=1}^{p} v_i$ *in factor and for this we consider the adjoint state. Let then* $\overline{p}$ *solution of the following system*

$$\begin{cases} -\frac{\partial \overline{p}}{\partial t} - \Delta\overline{p} + \overline{p} = 0 & in \quad]0,T[\times\Omega \\ \overline{p} = 0 & on \quad]0,T[\times\partial\Omega \\ \overline{p}(T) = \sigma(T,\overline{u}) - \sigma_1 & in \quad \Omega \end{cases} \tag{23}$$

Let us make the following variables change

$$\phi(t) = \overline{p}(T-t)$$

$$\textit{and then } \frac{\partial\phi}{\partial t} = -\frac{\partial\phi}{\partial t}(T-t)$$

$$-\Delta\phi = -\Delta\overline{p}(T-t)$$

ϕ *solution of the following problem :*

$$\begin{cases} \frac{\partial\phi}{\partial t} - \Delta\phi + \phi = -\frac{\partial\overline{p}}{\partial t} - \Delta\overline{p} + \overline{p} = 0 & in \quad]0,T[\times\Omega \\ \phi = 0 & on \quad]0,T[\times\partial\Omega \\ \phi(0) = \overline{p}(T) = \sigma(T,\overline{u}) - \sigma_1 & in \quad \Omega \end{cases} \tag{24}$$

$$\overline{p} \in C([0,T], L^2(\Omega)$$

$$\int_0^T\int_\Omega(-\frac{\partial\overline{p}}{\partial t}-\Delta\overline{p}+\overline{p})\mathcal{L}(\sum_{i=1}^p v_i(\varphi_i))(t)dx=0$$

$$\overline{p}\in C([0,T],L^2(\Omega)$$

$$=\int_0^T\int_\Omega-\frac{\partial\overline{p}}{\partial t}\mathcal{L}(\sum_{i=1}^p v_i(\varphi_i))(t)dx+\int_0^T\int_\Omega(-\Delta\overline{p}+\overline{p})\mathcal{L}(\sum_{i=1}^p v_i(\varphi_i))(t)dx$$

$$=\int_\Omega-\overline{p}(T)\mathcal{L}(\sum_{i=1}^p v_i(\varphi_i))(T)dx\underbrace{-\int_\Omega-\overline{p}(0)\mathcal{L}(\sum_{i=1}^p v_i(\varphi_i))(0)dx}_{=0}$$

$$-\int_0^T\int_\Omega-\overline{p}\frac{\partial}{\partial t}\mathcal{L}(\sum_{i=1}^p v_i(\varphi_i))(t)dx+\int_0^T\int_\Omega\overline{p}(-\Delta\mathcal{L})(\sum_{i=1}^p v_i(\varphi_i))(t)dxdt$$

$$\underbrace{-\int_0^T\int_{\partial\Omega}\frac{\partial\overline{p}}{\partial x}\mathcal{L}(\sum_{i=1}^p v_i(\varphi_i))(t)d\sigma dt}_{=0}+\underbrace{\int_0^T\int_{\partial\Omega}\overline{p}\frac{\partial}{\partial x}\mathcal{L}(\sum_{i=1}^p v_i(\varphi_i))(t)d\sigma dt}_{=0}$$

$$+\int_0^T\int_\Omega\overline{p}\mathcal{L}(\sum_{i=1}^p v_i(\varphi_i))(t)dxdt=0$$

$$\Rightarrow\int_\Omega\overline{p}(T)\mathcal{L}(\sum_{i=1}^p v_i(\varphi_i))(T)dx=$$

$$\int_0^T\int_\Omega\overline{p}(\underbrace{\frac{\partial}{\partial t}\mathcal{L}(\sum_{i=1}^p v_i(\varphi_i))-\Delta\mathcal{L}(\sum_{i=1}^p v_i(\varphi_i))+\mathcal{L}(\sum_{i=1}^p v_i(\varphi_i))}_{\sum_{i=1}^p v_i(\varphi_i)})dxdt$$

$$\int_\Omega\overline{p}(T)\mathcal{L}(\sum_{i=1}^p v_i(\varphi_i))(T)dx=\int_\Omega(\sigma(T,\overline{u})-\sigma_1)\mathcal{L}(\sum_{i=1}^p v_i(\varphi_i))(T)dx$$

$$=\int_0^T\int_\Omega\overline{p}\sum_{i=1}^p v_i(\varphi_i))dxdt$$

$$\Rightarrow\int_0^T\int_\Omega\overline{p}\sum_{i=1}^p v_i\varphi_i dxdt+\alpha\sum_{i=1}^p\overline{u}_i v_i=0$$

$$\Rightarrow\sum_{i=1}^p(\int_0^T\int_\Omega\overline{p}(t,x)\varphi_i(t,x)dxdt)v_i=-\alpha\sum_{i=1}^p\overline{u}_i v_i\qquad\forall v\in\mathbb{R}^p$$

$$\forall i\in\{1,..,p\},\ \overline{u}_i=-\frac{1}{\alpha}\int_0^T\int_\Omega\overline{p}(t,x)\phi_i(t,x)dxdt$$

Then we have the following optimality system :

$$\begin{cases} \frac{\partial\sigma}{\partial t} - \Delta\sigma + \sigma = f + \sum_{i=1}^{p} u_i\varphi_i(t) & in \quad]0,T[\times\Omega \\ \sigma = 0 & on \quad]0,T[\times\partial\Omega \\ \sigma(0,x) = \sigma_0 & in \quad \Omega \\ -\frac{\partial\overline{p}}{\partial t} - \Delta\overline{p} + \overline{p} = 0 & in \quad]0,T[\times\Omega \\ \overline{p} = 0 & on \quad]0,T[\times\partial\Omega \\ \overline{p}(T) = \sigma(T,\overline{u}) - \sigma_1 & in \quad \Omega \\ \overline{u}_i = -\frac{1}{\alpha}\int_0^T\int_\Omega \overline{p}(t,x)\varphi_i(t,x)dxdt & \end{cases}$$

3.2 Numerical simulations to the optimal control problem with the evolution of the tumors

Here we are going to make some simulations for the optimal control problem bound to the evolution of the tumors, for it we must simulate the system of optimality above. We have the following problem of control :

$$\begin{cases} \frac{\partial\sigma}{\partial t} - \Delta\sigma + \sigma = f + u_1 & \text{in} \quad]0,T[\times\Omega \\ \sigma = 0 & \text{on} \quad]0,T[\times\partial\Omega \\ \sigma(0,x) = \sigma_0 & \text{in} \quad \Omega \end{cases} \tag{25}$$

f is the source u_1 is the control.
we $\Omega =]0.5, 0.5[\times]0.5, 0.5[$, $T = 10$, $f = -1$ and $\sigma(0,x) = \sigma_0 = 0.5$ for every case and we determine u_1 . For the simulation of the optimality system we begin by

$$\begin{cases} -\frac{\partial\overline{p}}{\partial t} - \Delta\overline{p} + \overline{p} = 0 & \text{in} \quad]0,T[\times\Omega \\ \overline{p} = 0 & \text{on} \quad]0,T[\times\partial\Omega \\ \overline{p}(T) = \sigma(T,\overline{u}) - \sigma_1 & \text{in} \quad \Omega \end{cases} \tag{26}$$

Let us consider the following variables change:
$p_1(t,x) = \overline{p}(T-t,x)$ that's gives $\frac{\partial p_1}{\partial t} = -\frac{\partial\overline{p}}{\partial t}$ and $-\Delta p_1 = -\Delta\overline{p}$
One take $s = T - t \Rightarrow t = T - s$; $t \in [0,T]$, $-t \in [-T,0]$ et $T - t \in [0,T]$ this is gives us for the first case

$$\begin{cases} \frac{\partial p_1}{\partial t} - \Delta p_1 + p_1 = 0 & \text{in} \quad]0,T[\times\Omega \\ p_1 = 0 & \text{on} \quad]0,T[\times\partial\Omega \\ p_1(0) = 0 & \text{in} \quad \Omega \end{cases} \tag{27}$$

and the numeric representation of this system(27) is given by the figure 1. And one determine the control u_1 by $u_1 = -\frac{1}{\alpha}\int_0^T\int_\Omega p_1(t,x)\varphi(t,x)dxdt$ here we take $\varphi \equiv 1$, $\alpha = 20$,$\sigma_0 = 0.5$ and p_1 is solution of the system (27)
The representation of the controlled system :

$$\begin{cases} \frac{\partial\sigma}{\partial t} - \Delta\sigma + \sigma = f + u_1 & \text{in} \quad]0,T[\times\Omega \\ \sigma = 0 & \text{on} \quad]0,T[\times\partial\Omega \\ \sigma(0,x) = \sigma_0 & \text{in} \quad \Omega \end{cases} \tag{28}$$

is given at figure 2.

And we consider the second case where we have the following system :

$$\left\{\begin{array}{ccc} \frac{\partial p_1}{\partial t} - \Delta p_1 + p_1 = 0 & \text{in} &]0,T[\times\Omega \\ p_1 = 0 & \text{on} &]0,T[\times\partial\Omega \\ p_1(0) = 1 & \text{in} & \Omega \end{array}\right. \tag{29}$$

and his representation is given at figure 3.
Always we determine u_1 by $u_1 = -\frac{1}{\alpha}\int_0^T\int_\Omega p_1(t,x)\varphi(t,x)dxdt$, $\varphi \equiv 1$, $\alpha = 20$, $\sigma_0 = 0.5$ and p_1 is solution of the system (29) and the representation of the controlled system :

$$\left\{\begin{array}{ccc} \frac{\partial \sigma}{\partial t} - \Delta \sigma + \sigma = f + u_1 & \text{in} &]0,T[\times\Omega \\ \sigma = 0 & \text{on} &]0,T[\times\partial\Omega \\ \sigma(0,x) = \sigma_0 & \text{in} & \Omega \end{array}\right. \tag{30}$$

is given at figure 4

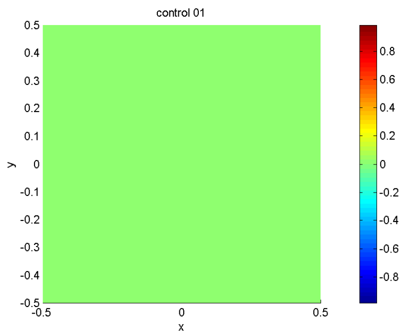

Figure 1: case 1 evolution of of p_1

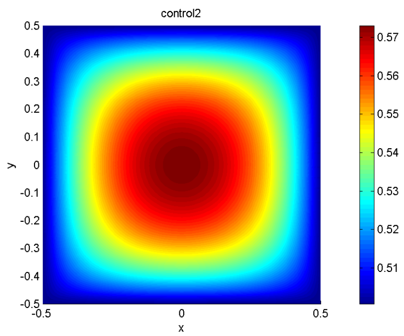

Figure 2: case 1 evolution of σ

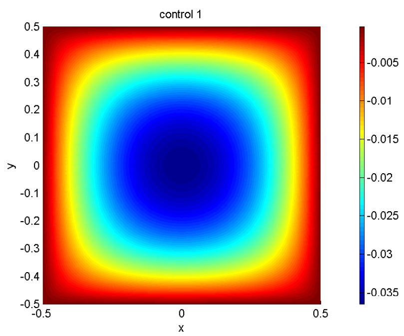

Figure 3: case 2 evolution of p_1

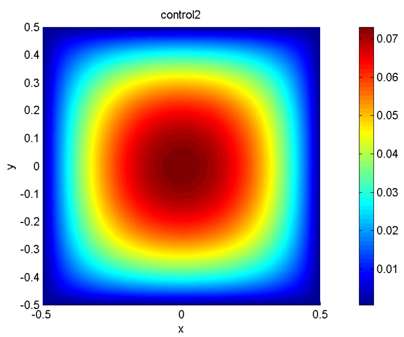

Figure 4: case 2 evolution of σ

4 Topological optimization

One looks for without any explicit or implicit restrictions on the geometry of the domains, the shape or the distribution of the tumors. Let us remark that the domain may change topology.
In this section we are going to use technics of topological optimization to get numerical simulations and therefore the representation of the domain.
We consider a set $\Omega \subset \mathbb{R}^N$ regular in which we put some small holes $\omega_\epsilon = B(x_0, \epsilon)$ depending on $\epsilon \in (0,1)$ and we introduce the set $\Omega_\epsilon = \Omega \setminus \bar{\omega_\epsilon}$. We evaluate the difference $J(\Omega_\epsilon) - J(\Omega)$ to obtain the topological derivative.
It is very difficult to obtain this topological derivative for surface functional. Let us consider a continuous function g and $\omega_\epsilon = B(x_0, \epsilon)$. For every $x_0 \in \Omega \subset \mathbb{R}^2$, one computes the following asymptotic development

$$J(\Omega_\epsilon) - J(\Omega) = g(x_0)f(\epsilon) + o(f(\epsilon))$$

where $f(\epsilon)$ is such that $\lim\limits_{\epsilon \longrightarrow 0} f(\epsilon) = 0$. The optimality condition then writes $g(x_0) \geq 0$. We refer to [13],[23] for details discussion of the topological derivative and for several applications to concrete problems.

4.1 An permanent case

The problem is to study :

$$\min_{\omega \in \Theta} J_\Omega(\sigma)$$

$$\text{where } J_\Omega(\sigma) = \int_\Omega |\sigma - \sigma_d|^2$$

where σ is solution of problem

$$\left\{ \begin{array}{lcll} -\Delta\sigma + \sigma & = & 0 & \text{in} \quad \Omega \\ \sigma & = & \overline{\sigma} & \text{on} \quad \partial\Omega \end{array} \right. \tag{31}$$

and :

$$\left\{ \begin{array}{lcll} \Delta p & = & -\mu(\sigma - \tilde{\sigma}) & \text{in} \quad \Omega \\ B_p & = & h & \text{on} \quad \partial\Omega \end{array} \right. \tag{32}$$

with

$$B_p = p \quad \text{or} \quad B_p = \frac{\partial p}{\partial \nu}$$

where Ω is a ball big enough and containing the region or the domain that we wish to identify and Θ an admissible sets.

Remark 4.1 *It is possible to consider the topological problem in the non permanent case. In this case, we have to add an initial condition on the boundary problem in σ and $\Omega =]0, T[\times D$ where D is a ball big enough. But we are going to focus our efforts on the stationary case.*

The problem is to detect the distribution of the concentration of σ in a given domain Ω and σ_d being the target (accepted concentration) which is given too.
After solving this problem we will able to recognize the region occupied by the tumors. Let us introduce the functional J :

$$J_{\Omega_\varepsilon}(\sigma_\varepsilon) = \int_{\Omega_\varepsilon} |\sigma_\varepsilon - \sigma_d|^2.$$

Where σ_ε is solution of the perturbed problem :

$$\begin{cases} -\Delta\sigma_\varepsilon + \sigma_\varepsilon & = & 0 & \text{in} & \Omega_\varepsilon \\ \sigma_\varepsilon & = & 0 & \text{in} & \omega_\varepsilon \\ \sigma_\varepsilon & = & \overline{\sigma} & \text{on} & \partial\Omega_\varepsilon \end{cases},$$

with :

$$\begin{cases} \Delta p_\varepsilon & = & -\mu(\sigma_\varepsilon - \tilde{\sigma}) & \text{in} & \Omega_\varepsilon \\ p_\varepsilon & = & 0 & \text{in} & \omega_\varepsilon \\ B_{p_\varepsilon} & = & h & \text{on} & \partial\Omega_\varepsilon. \end{cases}$$

Let Ω and ω be two domains in $\mathbb{R}^N$ with compact closures and $\partial\Omega$ and $\partial\omega$ are regulars boundaries We assume that:
$0 \in \omega \subset B_1 \subset B_2 \subset \Omega$ with $B_R = \{x \in \mathbb{R}^N / |x| \leq R\}$. We introduce the sets

$$\omega_\epsilon = \{x \in \mathbb{R}^N; \xi = \epsilon^{-1}x \in \omega\} \quad ; \quad \Omega(\epsilon) = \Omega \backslash \bar{\omega}_\epsilon$$

where ϵ is a small parameter belonging in (0,1). We obtain the topological derivative of the integral functional if we evaluate

$$\mathcal{T}(0) = \lim_{\epsilon \to 0} \frac{J_{\Omega_\epsilon}(\sigma_\epsilon) - J_\Omega(\sigma)}{f(\epsilon)}$$

where $f(\epsilon) \longrightarrow 0$ if $\epsilon \longrightarrow 0$.
We determine the topological gradient which give us the possibility to do numerical simulations which show the distribution of the tumor. And where the topological gradient is most negative will correspond to the zone which is more affected by the tumor.

In this step we need to determine the corresponding Green's function which will appear in the expression of the topological gradient.We have the following definition of Green's function.

Definition 4.1 - *Let Ω be an open and bounded domain given of $\mathbb{R}^N$, we call Green's function in Ω the function G defined in $\Omega \times \Omega \setminus D$ where $D = \{(x, y) \in \Omega \times \Omega; x = y\}$ is the diagonal of $\Omega \times \Omega$, by : $G(x, y) = E_N(x - y) - u(\phi_y)$, where for all $y \in \Omega, u(\phi_y)$ is the generalized solution of*

$$\begin{array}{ll} \Delta u = f & in\ \Omega \\ u = \phi & on\ \partial\Omega \end{array}$$

and

$$\phi_y(z) = E_n(z - y), z \in \Gamma,\ (\Gamma = \partial\Omega).$$

In this definition , E_n is the fundamental solution of $-\Delta E = \delta$, where δ represents Dirac's measure.

The operator $-\Delta + k^2$, $(k > 0)$ is coercive in $W^{1,2}(\Omega)$, for all open Ω of $\mathbb{R}^N$ and for any integer N. This hypothesis play in important role to solve the problem

$$\left\{ \begin{array}{llll} -\Delta u + k^2 u & = & v & \text{in} \quad \Omega \\ u & = & \varphi & \text{on} \quad \Gamma_0 \\ \frac{\partial u}{\partial \nu} & = & \psi & \text{on} \quad \Gamma \backslash \Gamma_0 \end{array} \right. \tag{33}$$

with (u, φ, ψ) bounded at the infinity. This allows us to define the Green's function for the problem related to $(\Omega, \Gamma_0, -\Delta + k^2)$.
Another formulation to solve the problem is the following lemma.

Lemma 4.1 *For all tempered distribution $v \in \mathcal{S}'(\mathbb{R}^N)$ on $\mathbb{R}^N$, there exists a unique distribution u on $\mathbb{R}^N$ such that $-\Delta u + k^2 u = v \ \in \mathcal{D}'(\mathbb{R}^N)$*

The Green's function for the Laplace operator in a ball $B(x_o, r_o)$ is given by :

$$G(x, x_o) = G(x_o, x) = E_N(x - x_o) - E_N(r_o), \text{ if } N \geq 3$$

$$G(x, x_o) = G(x_o, x) = \frac{1}{2\pi} log \frac{|x - x_o|}{r_o} \ , \text{ if } N = 2$$

see for details [8].

To compute the topological derivative (sensitivity), we use mainly the Propositions 3.1 ; 3.2 and the mains theorems 5.1, 5.2, 5.3,pp 163, 169 , 173 in [23]. We denote by :

$$F(x, \sigma(\varepsilon, x)) = |\sigma(\varepsilon, x) - \sigma_d|^{\ 2},$$

$$F'(x, \lambda(x)) = 2(\lambda(x) - \sigma_d),$$

$$\eta(x) = G(x, x_o) = G(x_o, x) = E_N(x - x_o) - E_N(r_o), \text{ if } N \geq 3.$$

For the case $N = 3$ the Green's function $\eta(x)$ becomes $\eta(x) = E_3(x - x_0) - E_3(r_0)$. Before going on, we give a precision about the fundamental solution E_N of $-\Delta E_N + E_N = \delta$ for the cases $N = 3$.
For $N = 3,\ E_3(x) = \frac{1}{4\pi|x|}e^{-|x|}$.
Then $E_3(x - x_0) - E_3(r_0) = \frac{1}{4\pi|x-x_0|}e^{-|x-x_0|} - \frac{1}{4\pi|r_0|}e^{-r_0}$.
Let us to determine the topological derivative. If $\Omega = B(x_0, r_0)$ with the ball $B_2 \subset B(x_0, r_0)$then the topological derivative is :

$$dJ = -\int_{B(x_0,r_0)} 2(\sigma - \sigma_d)(E_N(x - x_0) - E_N(r_o))\frac{meas(\partial\omega)}{1 + \frac{1}{4\pi}\int_\omega \frac{e^{|x|}}{|x|}dx}\ w(x_0)dx.$$

In 3 dimension, we have :

$$dJ = -\int_{B(x_0,r_0)} 2(\sigma - \sigma_d)(E_3(x - x_0) - E_3(r_o))\frac{meas(\partial\omega)}{1 + \frac{1}{4\pi}\int_\omega \frac{e^{|x|}}{|x|}dx}\ w(x_0)dx.$$

Hence

$$dJ = -\int_{B(x_0,r_0)} 2(\sigma-\sigma_d)(\frac{1}{4\pi|x - x_0|}e^{|x-x_0|}-\frac{1}{4\pi|r_0|}e^{r_0})\frac{meas(\partial\omega)}{1 + \frac{1}{4\pi}\int_\omega \frac{e^{|x|}}{|x|}dx}\ w(x_0)dx,$$

with w satisfies

$$\begin{cases} -\Delta w + w &= (\sigma - \sigma_d) \quad \text{in} \quad \Omega \\ w &= 0 \qquad\qquad \text{on} \quad \partial\Omega. \end{cases} \tag{34}$$

$$\text{Then } dJ = \int_{B(x_0,r_0)} F'(x, \sigma(x))\eta(x)\ m^\omega w(x_0)\ dx$$

$$\text{where } F'(x, \sigma(x)) = 2(\sigma(x) - \sigma_d)$$

$$\text{and } \eta(x) = \frac{1}{4\pi|x - x_0|}e^{|x-x_0|} - k\frac{1}{4\pi|r_0|}e^{r_0}$$

$$m^\omega = -\frac{meas(\partial\omega)}{1 + \frac{1}{4\pi}\int_\omega \frac{e^{|x|}}{|x|}dx}.$$

4.2 An evolutive case

The problem is to study :

$$\min_{\omega\in\Theta} J_\Omega(\sigma) = \int_\Omega |\sigma_1(x, T) - \sigma_d|^2$$

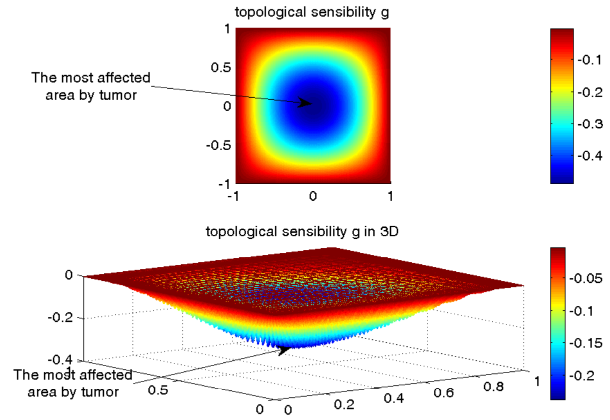

Figure 5: *Topological sensibility g respectively in 2D and 3D without therapy.*

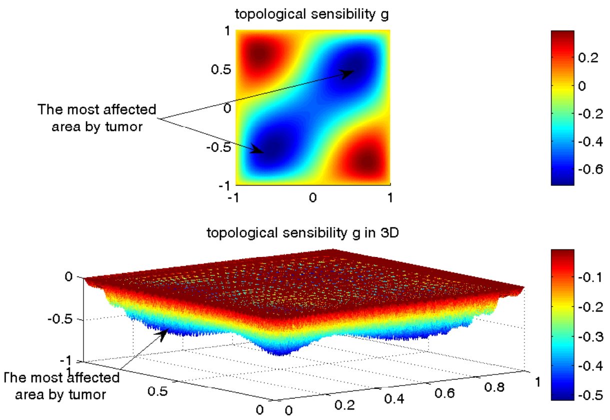

Figure 6: Topological sensibility g respectively in 2D and 3D after first therapy.

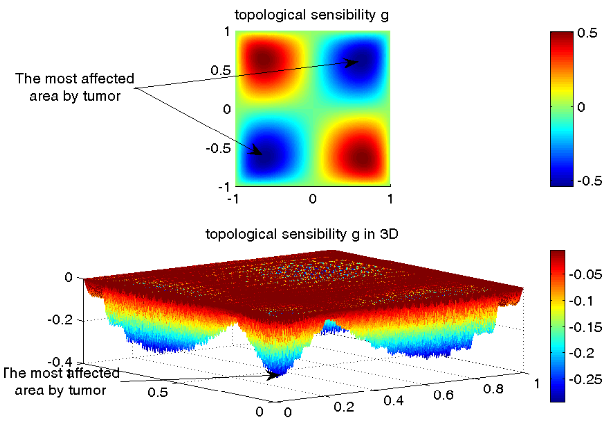

Figure 7: Topological sensibility g respectively in 2D and 3D after second therapy.

where σ is solution of problem :

$$\begin{cases} \frac{\partial \sigma_1}{\partial t} - \Delta\sigma_1 + \sigma_1 = f & \text{in } \Omega \\ \sigma_1 = g & \text{in } \partial\Omega \end{cases} \tag{35}$$

where $f \in L^2(\Omega)$ and $g \in L^2(\partial\Omega)$. For a given $x_0 \in \Omega$, we define the set $\omega_\varepsilon = x_0 + \varepsilon\omega$, where ω is a bounded open set containing the origin and the perforated domain $\Omega_\varepsilon = \Omega \setminus \overline{\omega_\varepsilon}$.
In Ω_ε, the new field is solution to the problem

$$\begin{cases} \frac{\partial u_\varepsilon}{\partial t} - \Delta u_\varepsilon + u_\varepsilon = f & \text{in } \Omega_\varepsilon \\ u_\varepsilon = g & \text{in } \partial\Omega \\ u_\varepsilon = 0 \text{ or } \frac{\partial u_\varepsilon}{\partial n} = 0 & \text{in } \partial\omega_\varepsilon \end{cases} \tag{36}$$

Multiplying the fisrt equation of (36) by a test function v and integrating over Ω_ε,

$$\frac{d}{dt}\int_{\Omega_\varepsilon} u_\varepsilon v + \int_{\Omega_\varepsilon} \nabla u_\varepsilon \nabla v + \int_{\Omega_\varepsilon} u_\varepsilon v - \int_{\partial\Omega_\varepsilon} \frac{\partial u_\varepsilon}{\partial n} = \int_{\Omega_\varepsilon} fv.$$

We define $a_\varepsilon(u_\varepsilon, v) = \frac{d}{dt}\int_{\Omega_\varepsilon} u_\varepsilon v + \int_{\Omega_\varepsilon} \nabla u_\varepsilon \nabla v + \int_{\Omega_\varepsilon} u_\varepsilon v$ and $l_\varepsilon(v) = \int_{\Omega_\varepsilon} fv$, $\forall v \in \mathcal{V}_\rho$.
We define $\mathcal{V}_\varepsilon = \{v \in H^1(\Omega),\ v = 0 \text{ on } \partial\Omega\ \ v|\partial\omega_\varepsilon = 0\}$.
The variational problem associated to problem (36) is for $u_\varepsilon \in \mathcal{V}_\varepsilon$ such that

$$a_\varepsilon(u_\varepsilon, v) = l_\varepsilon(v)\ \forall\ v \in \mathcal{V}_\varepsilon \tag{37}$$

We will consider for all $\varepsilon \geq 0$. The functional J_ε defined in $H^1(\Omega_\varepsilon)$ by $j(\varepsilon) = J_\varepsilon(u_\varepsilon)$ where u_ε is solution to (37). We will consider for $j(\varepsilon)$, the following functional

$$j(\varepsilon) = \int_{\Omega_\varepsilon} |u_\varepsilon - u_d|^2 dx$$

4.3 Adjoint method

Let γ an Hilbert space. Consider the bilinear form a_ε and coercive and a linear form l_ε continue on $\mathcal{V}_\varepsilon$: $\exists\ \alpha > 0$, $M > 0$, $L > 0$ not depending on ε such that for all $\rho > 0$

$$\begin{cases} a_\varepsilon(u, v) \leq M\|u\|\|v\| & \forall\ u,\ v \in \mathcal{V} \\ a_\varepsilon(u, v) \geq \alpha\|u\|^2 & \forall\ u\ \in \mathcal{V} \\ l_\varepsilon(v) \leq L\|v\| & \forall\ v \in \mathcal{V} \end{cases} \tag{38}$$

Hypothesis :
Let us suppose that there exists a bilinear and continus form δ_a, a linear continus form δ_l and a function δ_J and a function $f(\varepsilon)$ define in $\mathbb{R}^+$ such that :

$$\lim_{\varepsilon \to 0} f(\varepsilon) = 0$$

$$\|a_\varepsilon - a_0 - f(\varepsilon)\delta_a\|_{L'(\mathcal{V})} = o(f(\varepsilon))$$
$$\|l_\varepsilon - l_0 - f(\varepsilon)\delta_L\|_{L'(\mathcal{V})} = o(f(\varepsilon))$$
$$J_\varepsilon(v) - J_0(v) = DJ_0(u)(v-u) + f(\varepsilon)\delta_J(u) + o(\|v_u\| + f(\varepsilon))$$

Define the Lagrangian $\mathcal{L}_\rho$ by : $\mathcal{L}_\rho(u,v) = J_\rho(u) + a_\rho(u,v) - l\rho(v)$

Theorem 4.1 *We have*

$$j(\varepsilon) - j(0) = f(\varepsilon)\delta_L(u,v) + o(f(\varepsilon))$$

where

$$\delta_L(u,v) = \delta_J(u) + \delta_a(u,v) - \delta_l(v)$$

and v is the solution of the adjoint problem : find $v \in \mathcal{V}$ such that

$$a_0(w,v) = -DJ_0(u)w \ \forall \ w \in \mathcal{V}$$

This type of problem are studied by Amstutz and Masmoudi by using a particular class of functional. For there functional, the value of δ_L are given. Let give the following theorem which can be found in [1].

Theorem 4.2 *Let u and v the direct and the adjoint states. Suppose that u, v are of class $\mathcal{C}^2$ in the neighborhood of the origin then the cost function j has the following asymptotic expansion:*

$$j(\rho) - j(0) = \frac{-1}{ln\rho}[2\pi u(0)v(0) + \delta_J + o(\frac{-1}{ln\rho})] where\ \Omega \subset \mathbb{R}^2$$

The terms δ_J, depend only on the functional. If Ω is a bounded domain connected domain of $\mathbb{R}^2$, we have the following asymptotic expansion

$$j(\rho) - j(0) = \rho\ [Pu(0)v(0) + \delta_J] + o(\rho)$$

where $P = \int_{\partial\omega} \widehat{\eta} ds$, $\widehat{\eta} \in H^{-1/2}(\partial\omega)$ is the solution of

$$\int_{\partial\omega} E(x-y)\widehat{\eta}(y)ds(y) = 1 \ \forall \ x \in \partial\omega$$

For the following, let us give the value of δ_J If $j(\varepsilon) = J(u_\varepsilon) = \int_{\Omega_\varepsilon} |u-u_d|^2 dx$, then

$$\delta_J = 0 \tag{39}$$

Then we have

$$\delta_L(u,v) = \delta_a(u,v) - \delta_l(v)$$

4.4 An second evolutive case

$$J(\sigma_\Omega) = \int_0^T \int_\Omega (\sigma_\Omega - \sigma_d)^2 dxdt \tag{40}$$

where σ_Ω solution of the problem

$$\begin{cases} \frac{\partial \sigma_\Omega}{\partial t} - \Delta\sigma_\Omega + \sigma_\Omega = f & \text{in} \quad]0,T[\times\Omega \\ \sigma_\Omega = 0 & \text{on} \quad]0,T[\times\partial\Omega \\ \sigma(0,x) = \sigma_0 & \text{in} \quad \Omega \end{cases} \tag{41}$$

The perturbative problem

$$J(\sigma_\Omega^\varepsilon) = \int_0^T \int_{\Omega_\varepsilon} (\sigma_\Omega^\varepsilon - \sigma_d)^2 dxdt \tag{42}$$

where $\sigma_\Omega^\varepsilon$ solution of the problem

$$\begin{cases} \frac{\partial \sigma_\Omega^\varepsilon}{\partial t} - \Delta\sigma_\Omega^\varepsilon + \sigma_\Omega = f & \text{in} \quad]0,T[\times\Omega_\varepsilon \\ \sigma_\Omega^\varepsilon = 0 & \text{on} \quad]0,T[\times\omega_\varepsilon \\ \sigma_\Omega^\varepsilon = 0 & \text{on} \quad]0,T[\times\partial\Omega_\varepsilon \\ \sigma(0,x) = \sigma_0 & \text{in} \quad \Omega \end{cases} \tag{43}$$

Variation of the cost functional

$$J(\sigma_\Omega^\varepsilon) - J(\sigma_\Omega) = \int_0^T \int_{\Omega_\varepsilon} (\sigma_\Omega^\varepsilon - \sigma_d)^2 dxdt - \int_0^T \int_\Omega (\sigma_\Omega - \sigma_d)^2 dxdt$$

$$= \int_0^T \int_{\Omega_\varepsilon} (\sigma_\Omega^\varepsilon - \sigma_d)(\sigma_\Omega^\varepsilon + \sigma_d - 2\sigma_d) dxdt + \int_0^T \int_{\omega_\varepsilon} (\sigma_\Omega - \sigma_d)^2 dxdt$$

Variation of the bilinear form and Variation of the linear form
The variationnal formulation of (41) gives :

$$\frac{d}{dt} < \sigma_\Omega, \varphi > + \int_\Omega \nabla\sigma_\Omega \nabla\varphi + \sigma_\Omega\varphi - < \sigma_\Omega, \varphi >= 0$$

Let

$$a(\sigma_\Omega, \varphi) = \frac{d}{dt} < \sigma_\Omega, \varphi > + \int_\Omega \nabla\sigma_\Omega \nabla\varphi + \sigma_\Omega\varphi$$

and

$$l(\varphi) =< \sigma, \varphi >$$

where

$$< \sigma, \varphi >= \int_\Omega \sigma\varphi dx$$

$$a_\varepsilon(\sigma_\Omega^\varepsilon, \varphi) = \frac{d}{dt} < \sigma_\Omega^\varepsilon, \varphi > + \int_{\Omega_\varepsilon} \nabla\sigma_\Omega^\varepsilon \nabla\varphi + \sigma_\Omega^\varepsilon \varphi$$

and

$$l_\varepsilon(\varphi) =< \sigma_\Omega^\varepsilon, \varphi >= \int_{\Omega_\varepsilon} \sigma_\Omega^\varepsilon \varphi dx$$

The expansion of

$$a_\varepsilon(\sigma_\Omega^\varepsilon, \varphi) - a(\sigma_\Omega, \varphi)$$

permits us to obtain the term δ_a and the expansion of

$$l_\varepsilon(\varphi) - l(\varphi)$$

permits to obtain δ_l.
Define the Lagrangian $\mathcal{L}$ by : $\mathcal{L}(u, v) = J(u) + a(u, v) - l(v)$, the variation of the Lagrangian is given by : $\delta_{\mathcal{L}} = \delta_J + \delta_a - \delta_l$.

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