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A Penalization Approach in Breast Cancer Chemotherapy: Preliminary Numerical Simulations

1st David Lassounon
 Univ Rennes, INSA, CNRS,
 IRMAR-UMR 6625, F-35000
 Rennes, France
 enagnon-david.lassounon@insa-rennes.fr

2nd Aziz Belmiloudi
 Univ Rennes, INSA, CNRS,
 IRMAR-UMR 6625, F-35000
 Rennes, France
 aziz.belmiloudi@insa-rennes.fr

3rd Mounir Haddou
 Univ Rennes, INSA, CNRS,
 IRMAR-UMR 6625, F-35000
 Rennes, France
 mounir.haddou@insa-rennes.fr

Abstract—In this paper, we discuss preliminary numerical simulation results that stem from an optimal control problem in breast cancer chemotherapy. The objective of this control problem is to minimize the growth of tumor cells while minimizing damage to normal tissue, considering that chemotherapeutic agents affect both tumor cells and healthy cells. The control variable is drug concentration, and the state variable is the tumor density in the breast. We first formulate the optimal control problem by specifying a performance criterion and various constraints and then investigate the necessary optimality conditions. Next, we present an optimization algorithm for solving the control problem. Finally, we present and discuss numerical simulations to demonstrate the importance of the suggested optimal control strategy for tumor cell eradication.

Index Terms—Optimal control problem, state constraint, cancer chemotherapy, nonlinear reaction-diffusion systems, malignant tumors, optimization algorithm, twin experiments, numerical simulations.

I. INTRODUCTION AND MOTIVATION

Breast cancer is a disease in which abnormal breast cells grow out of control and form a mass called a tumor, very localized or more invasive when the tumor cells spread to neighboring normal tissues until reaching the nearest lymph nodes. The majority of deaths attributable to breast cancer are due to a resistance of the tumor and invasion of tumor cells to other organs (lungs, liver, brain) by a metastatic process to reach and multiply in organs other than the one initially affected. There are several mathematical models of treatment response in the literature, notably [1]–[3]. The mathematical models of treatment responses integrate clinical and experimental data to predict tumor response to treatments and evaluate the effectiveness of different treatments. Systemic chemotherapy is one of the most commonly used methods for the treatment of breast tumors. Still, it presents three clinical difficulties: the drug’s toxicity to normal cells, the tumor’s resistance to the drug, and the tumor’s resistivity after treatment. Recently, in [1], an optimal control problem has been studied for breast cancer chemotherapy with an ordinary differential equation treatment response model. Even when we set constraints on the control, the tumoral density can have an uncontrolled behavior (decrease and grow during treatment) as shown in [1] for instance. It is therefore interesting to add a constraint on the density of tumor. For studying the growth of breast tumours

under treatment, we consider the following reaction–diffusion equation that can be described by

$$\begin{aligned} \frac{\partial \mathbf{u}}{\partial t} &= \operatorname{div}(D\nabla \mathbf{u}) - K_1 \mathbf{u}^{\rho_1} + K_2 \mathbf{u} - \alpha_0 \varphi \mathbf{u} \text{ in } \mathcal{Q}, \\ -D\nabla \mathbf{u} \cdot \mathbf{n} &= K_3 \mathbf{u}^{\rho_2} \text{ on } \Sigma, \end{aligned} \quad (1)$$

$$\mathbf{u}(0, \mathbf{x}) = u_0(\mathbf{x}) \text{ in } \Omega,$$

under the pointwise constraint

$$\mathbf{a}(\mathbf{x}) \leq \varphi(t, \mathbf{x}) \leq \mathbf{b}(\mathbf{x}) \quad a.e.(x, t) \in \mathcal{Q}. \quad (2)$$

and the state constraint

$$\mathcal{G}(\varphi) = \|\mathbf{u}(t, \cdot)\|_{L^2(\Omega)}^2 - \zeta(t) \leq 0 \quad a.e.t \in (0, T), \quad (3)$$

where the breast region Ω is an open bounded domain in \mathbb{R}^2 with a smooth boundary $\Gamma = \partial\Omega$, $T > 0$ is a fixed constant (a given final time), $\mathcal{Q} = (0, T) \times \Omega$, $\Sigma = (0, T) \times \Gamma$ and the vector \mathbf{n} is the outward normal to Γ .

Here, $\mathbf{u}(t, \mathbf{x})$ is the tumor cell density at time t and location \mathbf{x} of the breast region Ω and K_1 is the tumor proliferation rate. The function K_2 denote the intrinsic growth rate with a growth coefficient ρ_1 and K_3 the invasion rate of the tumor or the migration capacity to other organs with a growth coefficient ρ_2 , where $\rho_i \geq 2$, for $i = 1, 2$, are integer numbers. The operator $\varphi \mathbf{u}$ is the treatment term describing the death of cells due to chemotherapy, in which the control value $\varphi(t, \mathbf{x})$ models the concentration of drugs in chemotherapy treatment at time t and location \mathbf{x} and u_0 is the initial density of the tumor at time $t = 0$. The diffusivity coefficient of the tumor is assumed to be variable in \mathcal{Q} and satisfies $\nu_1 \geq D(t, \mathbf{x}) \geq \nu_0 > 0$, (where ν_0 and ν_1 are two positives constants). Furthermore, the parameters ζ , \mathbf{a} and \mathbf{b} are sufficiently regular functions.

Remark 1.1:

- 1) The nonlinear problem (1) integrates a control dependent on time and space, which considers the capacity of invasion and migration of tumor cells to other organs modeled by the function K_3 . This aspect is often neglected (see, e.g., [1]–[3]). Indeed, for an intracranial brain tumor, the invasion rate $K_3 = 0$, but in the case of a breast tumor, $K_3 \neq 0$, since we can witness an increasing tumor flow which migrates towards other

organs through the lymph nodes which explains the risk of invasion of tumor cells to other organs.

- 2) The control limit functions \mathbf{a}, \mathbf{b} are medicinal and can be patient-specific (e.g., quality of life, comorbidities). The inequality constraint (2) imposed on the parameter φ makes it possible to avoid acute drug toxicity when the drug concentration exceeds a maximum value.

Note that in (1), we have ten biological data whose units are mentioned in the following

TABLE I: Table of units.

Biological Data	D	φ	K_1	K_2	K_3
Units	$mm^2 \cdot d^{-1}$	μM	d^{-1}	d^{-1}	$mm \cdot d^{-1}$
	α_0	\mathbf{x}	t		
	$\mu M^{-1} \cdot d^{-1}$	mm	$days (d)$		

Contribution

The main objective of our contribution is to minimize the tumor density by imposing two different constraints: a constraint on the control to limit the acute toxicity of drugs in patients and a constraint on the density of tumor satisfied at each treatment time to control the evolution of tumor density. The control is a spatiotemporal function modeling the concentration of therapeutic agents in breast tumor chemotherapy. The importance of constraining the density of tumor lies in the fact that even in the presence of a resistant tumor we can find an optimal therapeutic strategy with less damage to eradicate the tumors. Our numerical simulations have yielded excellent results, proving the effectiveness of our approach.

II. ASSUMPTIONS AND NOTATIONS

We introduce the following spaces (for $q \in]1, +\infty]$ and $\theta \in [0, 1/2[$)

$$\begin{aligned} L_+^q(\mathcal{Q}) &= \{v \in L^q(\mathcal{Q}); v \geq 0\}, \mathcal{H}_\theta = H^{2\theta+1}(\Omega), \\ \mathcal{V}_\theta &= L^2(0, T; \mathcal{H}_\theta), \mathcal{W}_\theta = H^1(0, T; \mathcal{H}'_\theta), \\ \mathbf{U}_\theta &= \mathcal{V}_\theta \cap \mathcal{W}_\theta \end{aligned}$$

where \mathcal{H}'_θ is the dual of \mathcal{H}_θ . We note v_+ the positive part of v by $v_+ = \max(v, 0)$.

We can now state the following assumptions for functions K_i , for $i = 1, 3$ and parameters \mathbf{a} and \mathbf{b}

(H1) $K_1 \in L_+^\infty(\mathcal{Q})$, $K_3 \in L_+^\infty(\Sigma)$, $\mathbf{a}, \mathbf{b} \in L_+^{p_\rho}(\Omega)$, with $p_\rho = \frac{2\rho_1}{\rho_1-1}$. For the desired state u_d and the initial condition u_0 , we impose

(H2) $u_d \in L^\infty(0, T; L^2(\Omega))$ and $u_0 \in H^1(\Omega) \cap L_+^\infty(\Omega)$.

Finally, we assume that the parameter ζ is chosen such that

$$\zeta = \max(\|u_d\|_{L^\infty(0, T; L^2(\Omega))}^2; \|u_0\|_{L^2(\Omega)}^2). \quad (4)$$

According to assumptions **(H1)**-**(H2)** and [5] we have that problem (1) admits one and unique solution u in $\mathbf{U}_\theta \cap L^\infty(\mathcal{Q})$.

Outline of the paper

The rest of the paper is presented as follows. In Sec. III, we present the optimal control problem and its description. In IV, first, we present the optimization algorithm to resolve control problem and numerical simulation results to validate optimization algorithm. Afterward, we present the numerical simulations to optimal control problem for twin experiments and in the case of breast tumor eradication. Finally, the conclusion and future projections are presented in Sec. V.

III. OPTIMAL CONTROL PROBLEM

Let $\mathcal{S}_{ad} = \{\varphi \in L^{p_\rho}(\mathcal{Q}) : \mathbf{a}(\mathbf{x}) \leq \varphi(t, \mathbf{x}) \leq \mathbf{b}(\mathbf{x}), a.e., t \in [0, T]\}$ and $\mathcal{F} : \varphi \in \mathcal{S}_{ad} \mapsto \mathcal{F}(\varphi) \in \mathbf{U}_\theta \cap L^\infty(\mathcal{Q})$ such that $\mathbf{u} = \mathcal{F}(\varphi)$ is the unique solution of (1), corresponding to φ . Now we introduce the following objective (or cost) functional J , which measures the distance between pronostic variable \mathbf{u} and desired state u_d , by

$$J(\varphi) = \frac{1}{2} \int_{\mathcal{Q}} (\mathbf{u} - u_d)^2 d\mathbf{x}dt + \frac{\lambda}{p_\rho} \int_{\mathcal{Q}} |\varphi|^{p_\rho} d\mathbf{x}dt \quad (5)$$

where the parameter $\lambda > 0$ is the price we pay for control. The optimal control problem consists of obtaining a minimizer of functional J with respect to φ . Precisely, we will study the following problem : find $\varphi_{opt} \in \mathcal{S}_{ad}$ such that functional J is minimized with respect to φ subject to equations (1) and constraints (2) and (3).

Our control problem **(P)** is then

$$\begin{aligned} \inf_{\varphi \in \mathcal{S}_{ad}} J(\varphi); \\ s.t. \quad \mathcal{G}(\varphi) \leq 0. \end{aligned} \quad (6)$$

The existence of optimal solutions of **(P)** is proven in [5], as well as a differentiability result of solution map \mathcal{F} and the first-order necessary conditions of optimality under some conditions in [5].

Throughout the rest of this paper, we choose $\rho_1 = 3$, $\rho_2 = 2$, and then $p_\rho = \frac{2\rho_1}{\rho_1-1} = 3$.

IV. NUMERICAL SIMULATIONS

In this section, we present the numerical results obtained in two parts. In the first, we present and validate the optimization algorithm for solving the control problem. Afterward, we present the numerical simulations of the solution to the control problem in eradicating breast tumors. We used the implicit Euler and Newton methods for numerical resolution of the state problem. To consider the control and state constraints, we modified the cost function J by penalizing the state and control constraints to enforce them to be satisfied, resulting in the modified cost function

$$\begin{aligned} \tilde{J}(\varphi) &= J(\varphi) + \frac{\beta_1}{3} \int_{\mathcal{Q}} (a - \varphi)_+^3 d\mathbf{x}dt + \frac{\beta_2}{3} \int_{\mathcal{Q}} (\varphi - b)_+^3 d\mathbf{x}dt \\ &+ \frac{\beta_3}{4} \int_0^T \mathcal{G}(\varphi)_+^2 dt. \end{aligned} \quad (7)$$

We thus solve a modified optimal control problem ($\tilde{\mathbf{P}}$) without constraints given by

$$\inf_{\varphi \in L^3(\mathcal{Q})} \tilde{J}(\varphi). \quad (8)$$

To characterize the optimal control, we introduce the following adjoint problem corresponding to the state problem:

$$-\frac{\partial \tilde{u}}{\partial t} - \text{div}(D\nabla \tilde{u}) + (3K_1 \mathbf{u}^2 + \alpha_0 \varphi - K_2) \tilde{u} = (\mathbf{u} - u_d)$$

$$+ \beta_3 \mathbf{u} \mathcal{G}(\varphi)_+ \text{ in } \mathcal{Q},$$

$$-D\nabla \tilde{u} \cdot \mathbf{n} + 2K_3 \mathbf{u} \tilde{u} = 0 \text{ on } \Sigma,$$

$$\tilde{u}(T, \cdot) = 0 \text{ in } \Omega. \quad (9)$$

For a given desired function u_d and cost function \tilde{J} by using the successive resolutions of both the state and adjoint problem, we derive the gradient of \tilde{J} relative to the control variables φ by

$$\nabla \tilde{J}(\varphi) = \lambda \varphi^2 - \alpha_0 \mathcal{F}(\varphi) \tilde{u} - \beta_1 (a - \varphi)_+^2 + \beta_2 (\varphi - b)_+^2. \quad (10)$$

For the optimization process, we used BFGS¹ to solve ($\tilde{\mathbf{P}}$). For all the numerical simulations, we used the Freefem++². To calibrate the state problem, we used the following data:

$$D = D_0 e^{-\gamma_0 \sigma}; \quad \sigma = \sigma_0 e^{-\delta_0 |\mathbf{x}|^2 t} \text{ in } \mathcal{Q},$$

$$K_1 = \frac{k_1 - k_2 e^{-\gamma_0 \sigma}}{e^{-\gamma_0 \sigma} (1 - e^{-2\gamma_0 \sigma})}, \quad K_2 = \theta^2 K_1, \text{ in } \mathcal{Q},$$

$$\mathbf{a} = 0, \quad \mathbf{b}(\mathbf{x}) = b_0 e^{-b_1 [(x-x_1)^2 + (y-y_2)^2]}, \text{ in } \Omega, \\ \text{and } K_3 = k_3 K_1 \text{ on } \Sigma.$$

We choose the

$$u_0(\mathbf{x}) = e^{-\frac{1}{\epsilon} [(x-x_0)^2 + (y-y_0)^2]},$$

which represents the density of a tumor whose center is at (x_0, y_0) , (see Fig. 1 for his graph). The optimization algorithm can be summarized in table (III) and \tilde{J} is minimized until some convergence criteria are attained. For the desired state u_d , we build it as follows:

$$u_{d,\epsilon} = u \cdot (1 + \epsilon \cdot f_{per}), \quad (11)$$

where f_{per} a perturbation defined on \mathcal{Q} , u is the solution of the state problem given by the control ϕ_0 and ϵ a percentage parameter. The control ϕ_0 was used to obtain u_d .

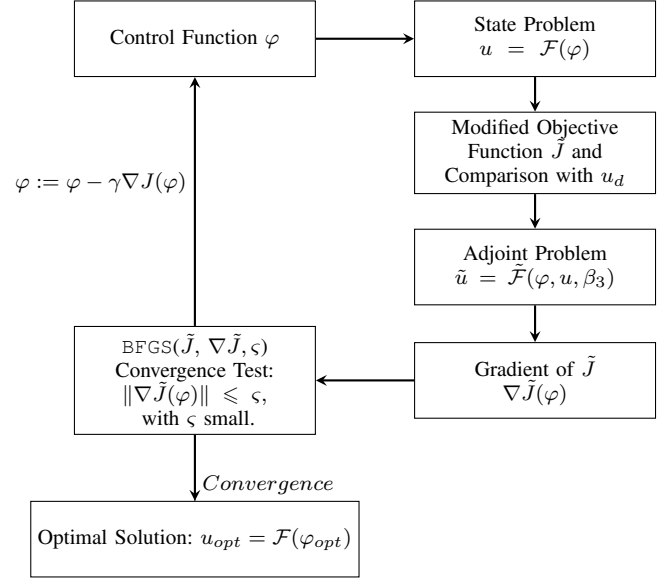
¹The solver BFGS solves the complex nonlinear optimization problem within FreeFEM++.

²<https://freefem.org/>

TABLE II: Data table

Parameters	Values and Definitions
D_0	0.09 $mm^2 \cdot d^{-1}$: Diffusion coefficient
σ_0	2.1 kPa: Mechanical coupling coefficient
γ_0	0.47 kPa^{-1} : Coupling constant
k_2	2.0 d^{-1} : Proliferation rate
k_1	4.0 d^{-1} : Coupling constant
k_3	3.0 mm : Coupling constant
δ_0	$5.55 \times 10^{-5} mm^{-2} \cdot d^{-1}$: Coupling constant
α_0	$1/d \cdot \mu M$: Coupling constant
T	20 days: The final horizon
b_0	$10^2 \mu M$: Coupling constant
b_1	0.90 mm^2 : Coupling constant
θ	3.16: Coupling constant

TABLE III: Optimization Algorithm

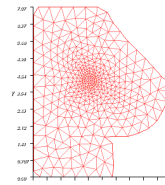


A. Validation of Our Approach

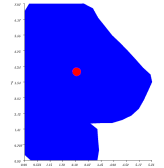
The objective of this subsection is to find an optimal control φ_{opt} that the optimal state $u_{opt} = u_d$, and satisfies the state constraint. We note by R_{Error1} (respectively R_{Error2}) the relative error between φ_{opt} and ϕ_0 in standard $L^3(\mathcal{Q})$ (respectively between u_{opt} and u_d in standard $L^2(\mathcal{Q})$):

$$R_{Error1} = \frac{\|\varphi_{opt} - \phi_0\|_{L^3(\mathcal{Q})}^3}{\|\phi_0\|_{L^3(\mathcal{Q})}^3}, \quad R_{Error2} = \frac{\|u_{opt} - u_d\|_{L^2(\mathcal{Q})}^2}{\|u_d\|_{L^2(\mathcal{Q})}^2}.$$

The table V displays the evolution of tumor density in the absence of treatment, i.e., for $\varphi = 0$ in (1) at several days.



Breast domain Ω .



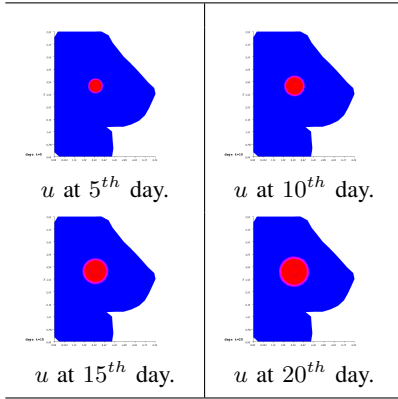
Initial tumor density u_0 .

Fig. 1: The domain Ω and initial tumor density u_0 .

TABLE IV: Discretization informations

Parameters	Value	Definitions
Δt	0.2 days (d)	Time Step
\mathbf{x}	$(x; y)$	2D space position
Δx	1 mm	Space Discretizations (x)
Δy	1 mm	Space Discretizations (y)
n_e	780	Total Mesh Elements
n_p	415	Total Mesh Points
$(x_0; y_0)$	$(7/3; 4)$	Tumor center
$(x_1; y_1)$	$(2; 3.5)$	
ε	0.01	

TABLE V: Tumor density without treatment



1) Optimal state u_{opt} and desired state u_d in absence of perturbation

This subsection presents the constraints satisfaction on the optimal control φ_{opt} and optimal state u_{opt} . The optimization parameters are as follows: $\lambda = 10^{-2}$; $\beta_1 = 10^3$; $\beta_2 = 3 \cdot 10^4$; $\beta_3 = 10^3$, and without perturbation i.e., $\varepsilon = 0$.

In this case, the desired function u_d satisfies (1), and Fig. 2 proves that all constraints are satisfied. The optimal control φ_{opt} and state u_{opt} satisfy all constraints.

Fig. 3 presents the relative errors R_{Error1} and R_{Error2} for various values of λ , and proves that u_{opt} near u_d for small values of λ .

The graph of the optimal control and optimal state are given respectively in table VI and table VII at several days.

TABLE VI: The optimal control φ_{opt} .

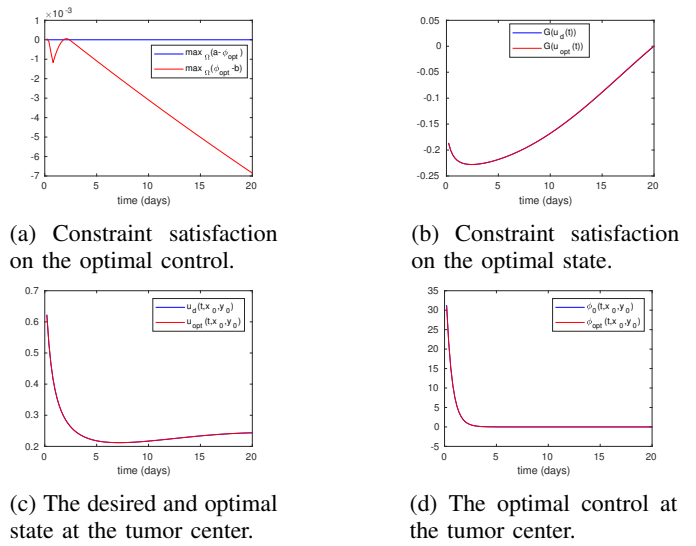
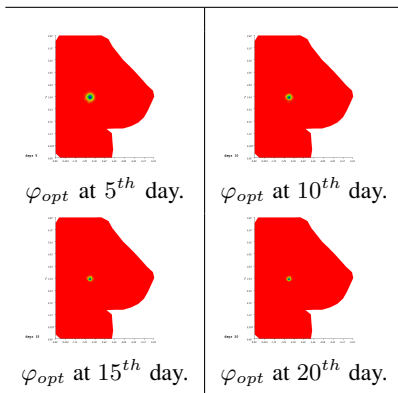


Fig. 2: Constraints satisfaction and the evolution of desired and optimal state.

TABLE VII: The desired state u_d and optimal state u_{opt} .

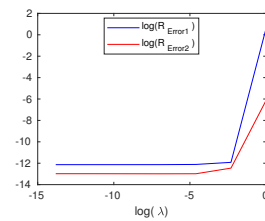
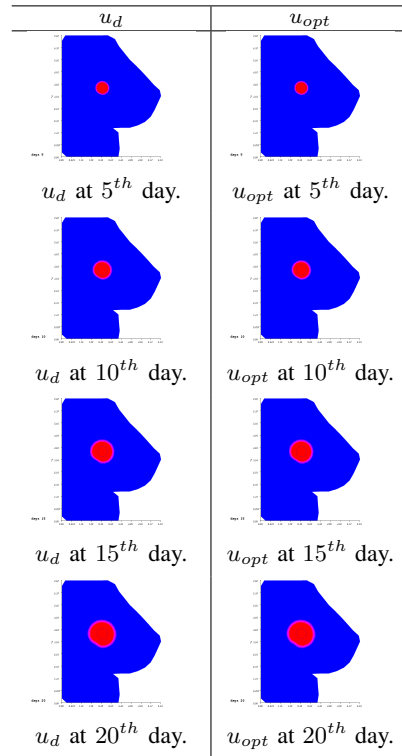


Fig. 3: The relative errors R_{Error1} and R_{Error2} .

2) *Optimal state u_{opt} and desired state u_d in presence of perturbation*

This subsection presents the constraints satisfaction on the optimal control and state in the presence of the perturbation, i.e., $\epsilon = 0.1$. The optimization parameters are as follows: $\lambda = 10^{-2}$; $\beta_1 = 10^2$; $\beta_2 = 3 \cdot 10^4$; and $\beta_3 = 10^4$.

We note that in this case, the desired state u_d is a low perturbed of the solution of (1), and Fig. 4 proves that all constraints are satisfied, and u_{opt} near u_d .

The graph of φ_{opt} and u_{opt} are given respectively in table VIII and table IX at several days.

Fig. 5 illustrates the error between the solution of the state problem and the perturbed state u_d^ϵ for various values of ϵ , where u_d^ϵ does not satisfy (1). From this, we can infer that the desired state can be achieved for low perturbations.

The results obtained in both situations confirm our expectations and validate our approach.

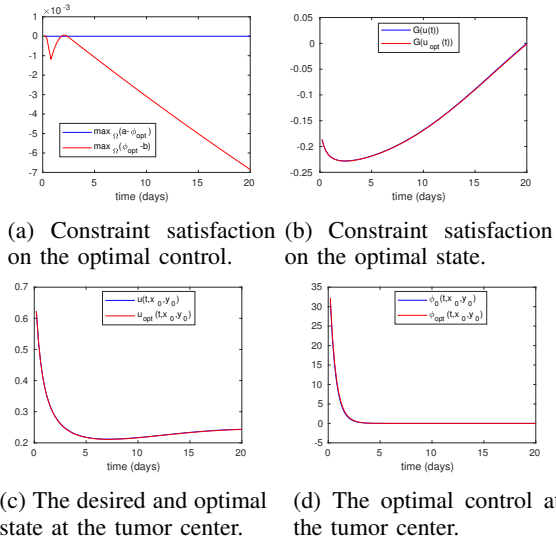


Fig. 4: Constraints satisfaction and the evolution of desired and optimal state.

TABLE VIII: The optimal control φ_{opt} .

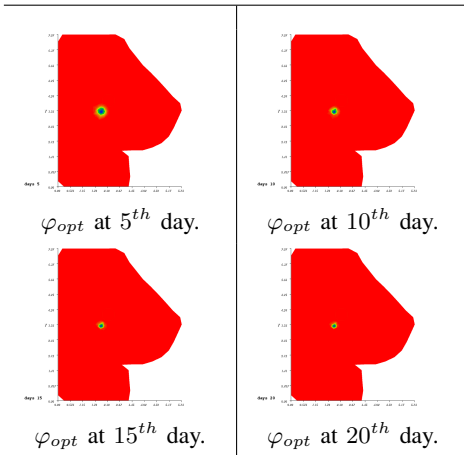


TABLE IX: The desired state u_d and optimal state u_{opt} .

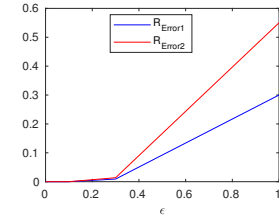
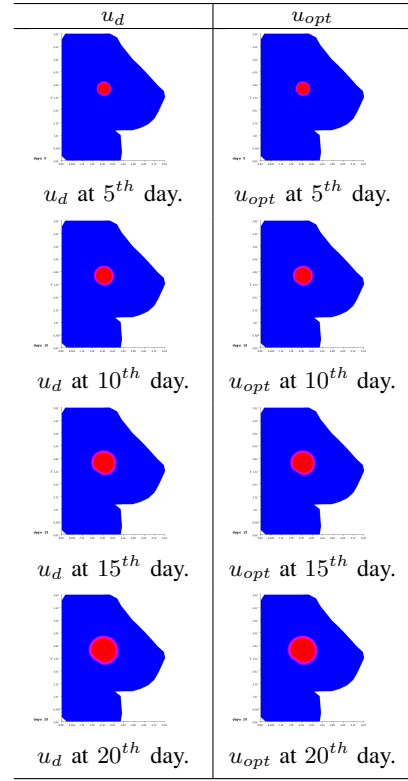


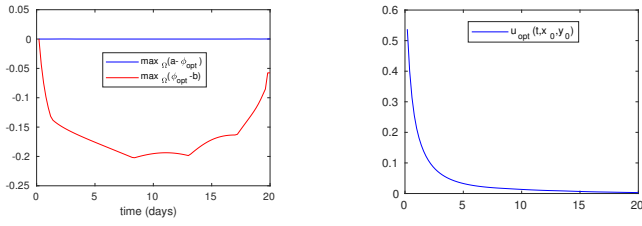
Fig. 5: The relative errors R_{Error1} and R_{Error2} .

B. *Eradication of Breast Tumor*

In this subsection, we aim to eradicate the breast tumor by finding an optimal control φ_{opt} such that the optimal state u_{opt} near the desired state $u_d = 0$. For this, the optimization parameters are: $\lambda = 10^{-2}$; $\beta_1 = 10^3$; $\beta_2 = 10^8$; $\beta_3 = 10^6$.

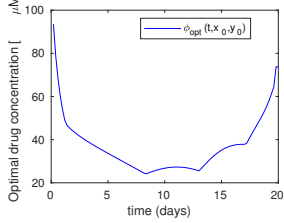
Fig. 6 proves that all constraints are satisfied, and the optimal tumor density u_{opt} decreases to 0, the desired state.

The graph of the optimal control φ_{opt} and optimal state u_{opt} at several days are given respectively in table X and table XI. We can observe that the optimal concentration of drugs migrating into the tumor, proving the effectiveness of localized treatment. This instance proves that our approach is very promising for a continuous 20-day therapeutic regimen, corresponding to localized metronomic chemotherapy (see, e.g., [4]). We have successfully treated many cases using this type of treatment, including cure-based treatment (i.e., specific treatments on certain days followed by rest on others), with promising results.

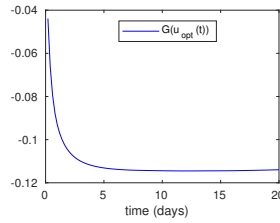


(a) Constraint satisfaction on the optimal control.

(b) The evolution of the optimal state at the tumor center.



(c) The evolution of the optimal control at the tumor center.



(d) Constraint satisfaction on the optimal state.

Fig. 6: Constraints satisfaction on the optimal control and state and the evolution of the optimal control and state at the tumor center.

V. CONCLUSION

This paper presents a new method to control tumor density in breast cancer chemotherapy. This method uses an optimal control problem with state constraint. We first conducted numerical simulations to validate the optimization algorithm by doing twin experiments. Then, we proved the importance of state constraints in eradicating breast tumors. For such an approach, some useful mathematical properties have been analyzed, and numerical experiments prove the efficiency of our study. We must still adapt our methodology to realistic treatment protocols.

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TABLE X: The optimal control φ_{opt} .

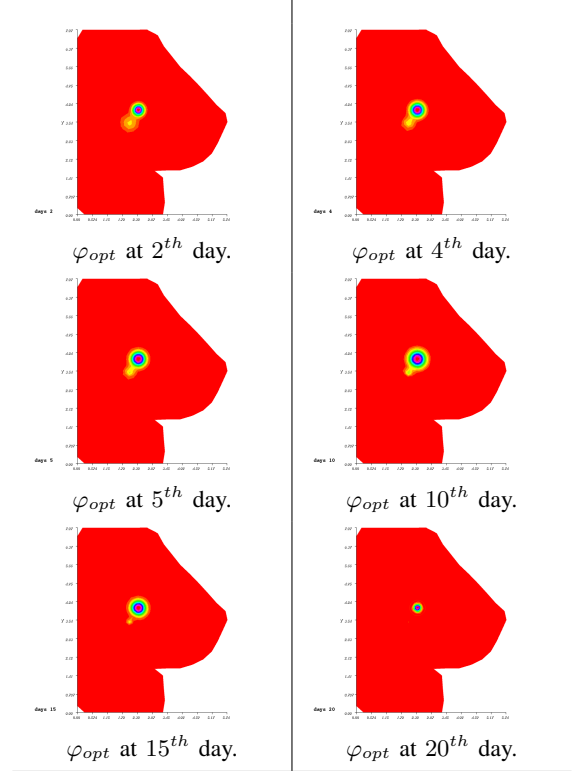


TABLE XI: The optimal state u_{opt} .

