SIAM J. APPL. MATH.
Vol. 81, No. 3, pp. 1077–1097

OPTIMAL CHEMOTHERAPY FOR BRAIN TUMOR GROWTH IN A REACTION-DIFFUSION MODEL*

MOHSEN YOUSEFNEZHAD†, CHIU-YEN KAO‡, AND SEYYED ABBAS MOHAMMADI§

Abstract. In this paper we address the question of determining optimal chemotherapy strategies to prevent the growth of brain tumor population. To do so, we consider a reaction-diffusion model which describes the diffusion and proliferation of tumor cells and a minimization problem corresponding to it. We shall establish that the optimization problem admits a solution and obtain a necessary condition for the minimizer. In a specific case, the optimizer is calculated explicitly, and we prove that it is unique. Then, a gradient-based efficient numerical algorithm is developed in order to determine the optimizer. Our results suggest a bang-bang chemotherapy strategy in a cycle which starts at the maximum dose and terminates with a rest period. Numerical simulations based upon our algorithm on a real brain image show that this is in line with the maximum tolerated dose (MTD), a standard chemotherapy protocol.

Key words. reaction-diffusion equation, brain tumor, optimal chemotherapy strategy

AMS subject classifications. 35K57, 49J20, 49M05, 35Q92

DOI. 10.1137/20M135995X

1. Introduction.

Brain tumor remains one of the most lethal diseases, causing many deaths worldwide every year. Glioblastoma multiforme (GBM) is a highly invasive brain tumor, producing life expectancies from 6 to 12 months [2, 7, 12, 25]. An essential component of the postoperative treatments administered to patients is chemotherapy [1]. Indeed, most patients will first undergo a surgical procedure for diagnostic and treatment purposes. Then, the recurrence of the tumor, even after radical excision, makes postoperative therapeutic strategies such as radiotherapy and chemotherapy a necessity to reduce tumor progression [23]. To increase the survival rate of patients, it is necessary to develop novel therapies to improve conventional treatments.

Mathematical modeling is a viable tool which can be used to develop a better understanding of how different parameters contribute to GBM growth [13, 23, 25, 30, 31, 32]. In addition to predicting disease progression, simulation can be extremely helpful in analyzing factors that may contribute to the disease growth and control of postoperative treatment [15, 23, 25]. Spatial macroscopic models that rely on partial differential equations (PDEs) have been used vastly to describe the proliferation and invasion of the tumor cells' density in the brain tissue; see [26, 28, 30, 32] and the references therein.

In this paper, we consider a reaction-diffusion model proposed in [26] which describes the diffusion and proliferation of tumor cells in addition to the effects of

*Received by the editors August 17, 2020; accepted for publication (in revised form) March 9, 2021; published electronically June 3, 2021. The U.S. Government retains a nonexclusive, royalty-free license to publish or reproduce the published form of this contribution, or allow others to do so, for U.S. Government purposes. Copyright is owned by SIAM to the extent not limited by these rights.
https://doi.org/10.1137/20M135995X
Funding: The work of the second author was partially supported by NSF grant DMS-1818948.
†Department of Mathematics, College of Sciences, Shiraz University, Shiraz, Iran (m.yousefnezhad@shirazu.ac.ir).
‡Department of Mathematical Sciences, Claremont McKenna College, Claremont, CA 91711 USA (ckao@cmc.edu).
§Department of Mathematics, College of Sciences, Yasouj University, Yasouj, 75918-74934, Iran (mohammadi@yu.ac.ir).

precisely delivered chemotherapy. To do so, let $\tilde{u}(\mathbf{x},t)$ be the tumor cell density $\left(\text{cell}\cdot\text{mm}^{-3}\right)$ in the whole brain domain, Ω; then the rate of change of the tumor cell density with chemotherapy can be considered in the following way:

$$\tilde{u}_t = \text{diffusion} + \text{net increase due to proliferation} - \text{death due to chemotherapy},$$

which is a conservation equation for the population [21, 22]. We consider the following equation with a logistic growth term and a net proliferation rate $\rho > 0$ $\left(\text{day}^{-1}\right)$ in the brain domain Ω:

$$\tilde{u}_t - \nabla\cdot(D(\mathbf{x})\nabla\tilde{u}) = \rho\left(1 - \frac{\tilde{u}}{K}\right)\tilde{u} \qquad \text{in } \Omega, \tag{1.1}$$

where K $\left(\text{cell}\cdot\text{mm}^{-3}\right)$ represents the carry capacity of the tissue, which provides an upper limit on the number of tumor cells capable of occupying any cubic millimeter of brain. The function $D(\mathbf{x})$ $\left(\text{mm}^2\cdot\text{day}^{-1}\right)$ is the diffusion coefficient at the position $\mathbf{x}$, and there is a constant θ such that

$$D(\mathbf{x}) \in L^\infty(\Omega), \qquad D(\mathbf{x}) > \theta > 0. \tag{1.2}$$

We assume that Ω can be partitioned into two subregions corresponding to tumor tissue and healthy tissue. According to [29], in order to consider the effect of the chemotherapy, we add a loss term corresponding to it on the right-hand side of (1.1), and we arrive at the following equation:

$$\begin{cases} \tilde{u}_t - \nabla\cdot(D(\mathbf{x})\nabla\tilde{u}) = \rho\left(1 - \dfrac{\tilde{u}}{K}\right)\tilde{u} - C(t)\tilde{u}, & (\mathbf{x},t)\in\Omega\times(0,T),\\ \dfrac{\partial\tilde{u}}{\partial\mathbf{n}} = 0, & (\mathbf{x},t)\in\partial\Omega\times(0,T),\\ \tilde{u}(\mathbf{x},0) = \tilde{u}_0(\mathbf{x}), & \mathbf{x}\in\Omega, \end{cases} \tag{1.3}$$

where $C(t)$ $\left(\text{day}^{-1}\right)$ denotes the distribution of the chemotherapy on the tissue during the time interval $[0,T]$, $0 < T < \infty$, and $\tilde{u}_0(\mathbf{x})$ is the tumor cell density at the beginning. Indeed, $C(t)$ defines the temporal profile of the chemotherapy in the single cycle $[0,T]$. The zero flux boundary condition prevents cells from leaving the brain domain at its boundary. For the sake of simplicity in our notation, we set $u = \frac{\tilde{u}}{K}$, and so (1.3) transforms into the following equation:

$$\begin{cases} u_t - \nabla\cdot(D(\mathbf{x})\nabla u) = \rho\left(1 - u\right)u - C(t)u, & (\mathbf{x},t)\in\Omega\times(0,T),\\ \dfrac{\partial u}{\partial\mathbf{n}} = 0, & (\mathbf{x},t)\in\partial\Omega\times(0,T),\\ u(\mathbf{x},0) = u_0(\mathbf{x}), & \mathbf{x}\in\Omega. \end{cases} \tag{1.4}$$

In order to avoid unacceptable toxicity, assume that the maximum of chemotherapy allowable at time t is $A > 0$, and the total amount of chemotherapy effort on $[0,T]$ is considered to be $B > 0$. Therefore, we should consider the chemotherapy function in the following admissible set:

$$\mathcal{M} = \left\{ C(t)\in L^\infty(0,T) \mid 0 \le C(t) \le A, \quad \int_0^T C(t)\,dt = B \right\}. \tag{1.5}$$

Actually, B is the mean value of the chemotherapy over a cycle, and A is the highest applicable chemotherapy. It is well known that $\mathcal{M}$ is convex and weakly compact in $L^2(\Omega)$ [6]. As the solution u of (1.4) depends on C, we use the notation u_C to emphasize this dependence.

From a biological point of view, it is interesting to know how the chemotherapy affects the population size of tumor cells. More precisely, our goal is to determine optimal chemotherapy strategies to prevent the growth of tumor population. Indeed, we want to find an optimal strategy which minimizes the population size of tumor cells. Consider

$$\mathcal{J}(C) = \int_0^T \int_\Omega u_C(\mathbf{x}, t) d\mathbf{x} dt,$$

the total population of tumor cells in the time interval $[0, T]$, as our objective functional; we should find a solution for the following minimization problem:

$$\min_{C \in \mathcal{M}} \mathcal{J}(C). \tag{1.6}$$

We shall prove that (1.6) admits a solution invoking a direct approach of calculus of variation. By obtaining the derivative of the functional $\mathcal{J}(C)$ with respect to C and defining an adjoint problem, a necessary condition for the minimizer is determined. In the diffusion-free case that (1.4) is reduced to an ODE form, the optimizer is calculated explicitly, and it is proved that the solution is unique. Then, a gradient-based numerical algorithm is developed in order to compute the optimizer. Numerical illustrations reveal the efficiency and applicability of the method.

The question of how chemotherapy protocols should be scheduled to optimize their effect has been investigated in many studies; see [3, 4, 5, 14, 15, 19, 20, 10], to name just a few. They yield the concept of the maximum tolerated dose (MTD), a commonly used chemotherapy protocol in medical practice [29]. In line with the previous studies and clinical experiments, the results of this paper confirm the MTD strategy, which typically includes repeated cycles of chemotherapy at the MTD without causing unacceptable toxicity. The optimal solution of (1.6) suggests a bang-bang chemotherapy strategy in a cycle which starts at the maximum dose and terminates with a rest period. Employing this strategy, we observe that during the time that chemotherapy is being administered, the population size of tumor cells is decreasing, while the tumor continues to grow with no chemotherapy. We illustrate this phenomenon with a numerical simulation based upon our algorithm on a real brain image.

2. Preliminaries.

In what follows, Ω is a bounded smooth domain in the real d-space $\mathbb{R}^d$. For a given fixed time $0 < T < \infty$, let us denote $Q_T = \Omega \times (0, T)$. We denote by $H^k(\Omega)$, where k is a positive integer, the set of all functions u defined in Ω such that all of its distributional derivatives of order $s \leq k$ belong to $L^2(\Omega)$. Furthermore, $H^k(\Omega)$ is a Hilbert space with the following norm:

$$\|v\|_{H^k(\Omega)} = \left(\sum_{s \leq k} \int_\Omega \left| \frac{\partial^s v}{\partial \mathbf{x}^s} d\mathbf{x} \right|^2 \right)^{1/2}.$$

The space $L^p(0, T; H^k(\Omega))$, $p > 1$, consists of all functions v such that for almost every $t \in (0, T)$, the element $v(t) = v(\mathbf{x}, t)$ belongs to $H^k(\Omega)$. Furthermore, $L^p(0, T; H^k(\Omega))$ is a normed space with the norm

$$\|v\|_{L^p(0,T;H^k(\Omega))} = \left(\int_0^T \|v(t)\|^p_{H^k(\Omega)} dt \right)^{1/p}.$$

Let $H^1(\Omega)^*$ be the dual space of $H^1(\Omega)$. A solution of (1.4) is defined in the weak sense as follows.

Definition 2.1. *We say a function $u \in L^2\left(0,T;H^1(\Omega)\right)$ with $u_t \in L^2(0,T;H^1(\Omega)^*)$ and $u(\mathbf{x},0) = u_0(\mathbf{x})$ is a weak solution of* (1.4) *if*

$$\int_\Omega u_t\phi \; d\mathbf{x} + \int_\Omega D(\mathbf{x})\nabla u \cdot \nabla\phi \; d\mathbf{x} = \int_\Omega \left(\rho\,(1-u)\,u - C(t)u\right)\phi \; d\mathbf{x} \tag{2.1}$$

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

The following theorem addresses the existence and uniqueness of solutions to (1.4). For a proof, the reader is referred to [9].

Theorem 2.2. *Let $0 < T < \infty$, $u_0 \in L^\infty(\Omega) \cap H^1(\Omega)$, and $u_0(\mathbf{x}) \ge 0$. Then, for each $C \in \mathcal{M}$ there is a unique nonnegative weak solution $u = u_C(\mathbf{x},t)$ of the problem* (1.4)*. Moreover, there exists a constant $M > 0$ which depends only on θ, A, $|\Omega|$, T, d, and $\|u_0\|_{L^\infty(\Omega)}$ such that $\|u\|_{L^\infty(Q_T)} \le M$.*

Hereafter in this paper, M is a generic positive constant independent of u and C. The following lemma is needed for our later investigation.

Lemma 2.3. *Let $C \in \mathcal{M}$ and $u = u_C$ be the unique nonnegative solution of* (1.4) *corresponding to C. Then there exists a positive constant M independent of u and C such that $\|u\|_{L^\infty(0,T;L^2(\Omega))} + \|u\|_{L^2(0,T;H^1(\Omega))} + \|u_t\|_{L^2(0,T;H^1(\Omega)^*)} \le M$.*

Proof. Multiplying (1.4) by u and integrating over Ω, for all $t \in (0,T)$, we obtain

$$\frac{1}{2}\frac{d}{dt}\int_\Omega u^2 d\mathbf{x} + \int_\Omega D(\mathbf{x})|\nabla u|^2 \; d\mathbf{x} + \int_\Omega \rho u^3 \; d\mathbf{x} + \int_\Omega C(t)u^2 \; d\mathbf{x} = \rho\int_\Omega u^2 \; d\mathbf{x}. \tag{2.2}$$

From the above equality and the fact that $u \ge 0$, we obtain the following inequality:

$$\frac{d}{dt}\int_\Omega u^2 d\mathbf{x} \le 2\rho\int_\Omega u^2 \; d\mathbf{x}. \tag{2.3}$$

Using (2.3) and Grönwall's inequality, we deduce that for all $0 \le t \le T$

$$\|u(t)\|^2_{L^2(\Omega)} \le e^{2\rho t}\|u_0\|^2_{L^2(\Omega)},$$

and so we infer that

$$\|u\|_{L^\infty(0,T;L^2(\Omega))} \le e^{\rho T}\|u_0\|_{L^2(\Omega)}, \quad \|u\|^2_{L^2(0,T;L^2(\Omega))} \le \frac{1}{2\rho}\left(e^{2\rho T} - 1\right)\|u_0\|^2_{L^2(\Omega)}. \tag{2.4}$$

Returning again to (2.2), we integrate from 0 to T and employ (1.2) to find

$$\theta\int_0^T\int_\Omega |\nabla u|^2 \; d\mathbf{x}dt \le \int_0^T\int_\Omega D(\mathbf{x})|\nabla u|^2 \; d\mathbf{x}dt \le \frac{1}{2}\|u_0\|^2_{L^2(\Omega)} + \rho\|u\|^2_{L^2(0,T;L^2(\Omega))},$$

and so in view of (2.4) we obtain

$$\|\nabla u\|^2_{L^2(0,T;L^2(\Omega))} \le \frac{e^{2\rho T}}{2\theta}\|u_0\|^2_{L^2(\Omega)}. \tag{2.5}$$

Then, from (2.4) and (2.5) we deduce $\|u\|_{L^2(0,T;H^1(\Omega))} \leq M$. Multiplying (1.4) by $\phi \in L^2\left(0,T;H^1(\Omega)\right)$ and integrating over $\Omega \times (0,T)$ give

$$\int_0^T \int_\Omega u_t \phi \, d\mathbf{x}dt = -\int_0^T \int_\Omega D(\mathbf{x})\nabla u \cdot \nabla \phi \, d\mathbf{x}dt + \rho \int_0^T \int_\Omega u\phi \, d\mathbf{x}dt \\ - \rho \int_0^T \int_\Omega u^2 \phi \, d\mathbf{x}dt - \int_0^T \int_\Omega Cu\phi \, d\mathbf{x}dt.$$

Now, using inequalities (2.4) and (2.5), we obtain

$$\left| \int_0^T \int_\Omega u_t \phi \, d\mathbf{x}dt \right| \leq M \|\phi\|_{L^2(0,T;H^1(\Omega))}.$$

Therefore, it is deduced that

$$\|u_t\|_{L^2(0,T;H^1(\Omega)^*)} \leq M. \tag{2.6}$$

In view of (2.4) and (2.6),

$$\|u\|_{L^\infty(0,T;L^2(\Omega))} + \|u\|_{L^2(0,T;H^1(\Omega))} + \|u_t\|_{L^2(0,T;H^1(\Omega)^*)} \leq M$$

is obtained. ∎

We close this section by considering (1.4), the diffusion-free case that its solution does not depend on spatial variables. Indeed, it is recast into the ODE

$$u' = \rho u - \rho u^2 - C(t)u, \quad u(0) = u_0. \tag{2.7}$$

It is easy to check that

$$u(t) = \frac{u_0 \, \mathrm{e}^{\int_0^t \rho - c(s)\,\mathrm{d}s}}{1 + \rho u_0 \int_0^t \mathrm{e}^{\int_0^s \rho - c(s)\,\mathrm{d}s}\,\mathrm{d}s} \tag{2.8}$$

is an absolute continuous function which satisfies (2.7) almost everywhere. Moreover, one can verify that

$$\frac{u_0 e^{-B}}{1 + u_0 e^{\rho T}} \leq u(t) \leq u_0 e^{\rho T}. \tag{2.9}$$

Using standard methods of theory of ODEs (see [8]), we can prove that (2.7) has a unique solution. However, it is noteworthy that the uniqueness of a solution for (2.7) can be obtained in view of the fact that a solution of (1.4) is unique; see Theorem 2.2. Let $u = u(t)$ be a solution of (2.7), and consider the function $v(\mathbf{x},t)$ over Q_T such that $v(.,t) = u(t)$ with $v(\mathbf{x},0) = u_0$. The function $v(\mathbf{x},t)$ is a constant function in its spatial variables over Ω. Now, we observe that $v(\mathbf{x},t)$ satisfies (1.4) with the initial condition $u(\mathbf{x},0) \equiv u_0$ due to the fact that $\nabla v(.,t) \equiv 0$ and $u(t)$ is the solution of (2.7). This reveals that $u(t)$ is the unique solution of (2.7) since $v(\mathbf{x},t)$ is the unique solution of (1.4) with the initial condition $u(\mathbf{x},0) \equiv u_0$.

3. Existence of an optimal solution. This section is devoted to the existence of a solution for the minimization problem (1.6).

THEOREM 3.1. *Assume that* $0 < T < \infty$, $u_0 \in L^\infty(\Omega) \cap H^1(\Omega)$, *and* u_0 *is nonnegative. There exists an optimal solution* $C^* \in \mathcal{M}$ *for the problem* (1.6).

Proof. Due to the nonnegativity of u_C, we have $\mathcal{J}(C) \geq 0$. Therefore, we observe that

$$0 \leq \gamma = \inf_{C \in \mathcal{M}} \mathcal{J}(C) < \infty.$$

Suppose $\{C_i\}_1^\infty \subset \mathcal{M}$ is a minimizing sequence, i.e.,

$$\lim_{i\to\infty} \mathcal{J}(C_i) = \inf_{C\in\mathcal{M}} \mathcal{J}(C),$$

and $u_i = u_{C_i}(\mathbf{x}, t)$ is the unique solution of (1.4) corresponding to C_i. Employing Lemma 2.3, we have

$$\|u_i\|_{L^\infty(0,T;L^2(\Omega))} + \|u_i\|_{L^2(0,T;H^1(\Omega))} + \|\partial_t u_i\|_{L^2(0,T;H^1(\Omega)^*)} \leq M, \qquad i = 1, 2, 3, \dots. \tag{3.1}$$

Also, we see that

$$\|C_i\|_{L^\infty(0,T)} \leq A \qquad \text{for} \quad i = 1, 2, 3, \dots, \tag{3.2}$$

due to (1.5). Invoking (3.1) and (3.2) and by passing to a subsequence, one infers that there are $u^* \in L^2(0, T; H^1(\Omega))$ and $C^* \in \mathcal{M}$ such that

$$u_i \rightharpoonup u^* \quad \text{weakly in} \quad L^2(0, T; H^1(\Omega)), \tag{3.3}$$

$$\partial_t u_i \rightharpoonup \partial_t u^* \quad \text{weakly in} \quad L^2(0, T; H^1(\Omega)^*), \tag{3.4}$$

$$u_i \to u^* \quad \text{strongly in} \quad L^2(Q_T). \tag{3.5}$$

Furthermore, we have

$$C_i \rightharpoonup C^* \quad \text{with respect to the weak star topology on} \quad L^\infty(0, T). \tag{3.6}$$

We show that indeed $C^* \in \mathcal{M}$. In view of (3.6), it is inferred that $\int_0^T C^*(t)dt = B$. Let $E = \{t \in [0, T] : C^*(t) < 0\}$, and assume that $|E| > 0$. We observe that

$$0 \leq \lim_{i\to\infty} \int_0^T C_i(t)\chi_E(t)dt = \int_0^T C^*(t)\chi_E(t)dt < 0,$$

which is a contradiction. Hence, we have $C^*(t) \geq 0$ for $t \in [0, T]$. A similar argument establishes that $C^*(t) \leq A$ for $t \in [0, T]$. Therefore, we have $C^* \in \mathcal{M}$.

For each $\phi \in L^2\left(0, T; H^1(\Omega)\right)$ the solution u_i satisfies

$$\begin{aligned} &\int_0^T \int_\Omega \partial_t u_i \phi \; d\mathbf{x}dt + \int_0^T \int_\Omega D(\mathbf{x}) \nabla u_i \cdot \nabla \phi \; d\mathbf{x}dt \\ &= \int_0^T \int_\Omega \rho u_i \left(1 - u_i\right) \phi \; d\mathbf{x}dt - \int_0^T \int_\Omega C_i(t) u_i \phi \; d\mathbf{x}dt. \end{aligned} \tag{3.7}$$

Applying (3.3)–(3.5), it is deduced that

$$\begin{aligned} &\int_0^T \int_\Omega \partial_t u_i \phi \; d\mathbf{x}dt \to \int_0^T \int_\Omega \partial_t u^* \phi \; d\mathbf{x}dt, \\ &\int_0^T \int_\Omega D(\mathbf{x}) \nabla u_i \cdot \nabla \phi \; d\mathbf{x}dt \to \int_0^T \int_\Omega D(\mathbf{x}) \nabla u^* \cdot \nabla \phi \; d\mathbf{x}dt, \\ &\int_0^T \int_\Omega \rho u_i \phi \; d\mathbf{x}dt \to \int_0^T \int_\Omega \rho u^* \phi \; d\mathbf{x}dt, \end{aligned} \tag{3.8}$$

while $i \to \infty$.

Recall that $u_i(\mathbf{x},t) \to u^*(\mathbf{x},t)$ almost everywhere on Q_T using (3.5), and we know that $\|u_i\|_{L^\infty(Q_T)} \leq M$ employing Theorem 2.2. Then one can conclude that $\|u^*\|_{L^\infty(Q_T)} \leq M$. In view of Theorem 2.2, (3.3), and (3.5) as $i \to \infty$, we obtain

$$\left|\int_0^T \int_\Omega \left(u_i^2 - {u^*}^2\right) \phi \; d\mathbf{x}dt\right| \leq \left|\int_0^T \int_\Omega u_i \left(u_i - u^*\right) \phi \; d\mathbf{x}dt\right| + \left|\int_0^T \int_\Omega \left(u_i - u^*\right) u^* \phi \; d\mathbf{x}dt\right|$$
$$\leq M\|u_i - u\|_{L^2(Q_T)}\|\phi\|_{L^2(Q_T)} + \left|\int_0^T \int_\Omega \left(u_i - u^*\right) u^* \phi \; d\mathbf{x}dt\right| \to 0. \tag{3.9}$$

Also, we have

$$\int_0^T \int_\Omega \left(C_i u_i - C^* u^*\right) \phi \; d\mathbf{x}dt = \int_0^T \int_\Omega \left(C_i - C^*\right) u_i \phi \; d\mathbf{x}dt + \int_0^T \int_\Omega \left(u_i - u^*\right) C^* \phi \; d\mathbf{x}dt. \tag{3.10}$$

Equation (3.3) yields

$$\int_0^T \int_\Omega \left(u_i - u\right) C^* \phi \; d\mathbf{x}dt \to 0 \tag{3.11}$$

when $i \to \infty$. Moreover, we observe that

$$\int_0^T \int_\Omega \left(C_i - C^*\right) u_i \phi d\mathbf{x}dt = \int_0^T \int_\Omega \left(C_i - C^*\right) (u_i - u^*) \phi d\mathbf{x}dt + \int_0^T \int_\Omega \left(C_i - C^*\right) u^* \phi d\mathbf{x}dt$$
$$\leq M\|u_i - u\|_{L^2(Q_T)}\|\phi\|_{L^2(Q_T)} + \int_0^T \int_\Omega \left(C_i - C^*\right) u^* \phi d\mathbf{x}dt \to 0, \tag{3.12}$$

invoking (3.5) and (3.6).

Now, (3.11) and (3.12) lead us to

$$\int_0^T \int_\Omega \left(C_i u_i - C^* u^*\right) \phi \; d\mathbf{x}dt \to 0 \tag{3.13}$$

when $i \to \infty$. Equations (3.8), (3.9), and (3.13) yield that u^* is a weak solution of (1.4) corresponding to $C^* \in \mathcal{M}$. Therefore, we conclude that $J(C^*) = \inf_{C \in \mathcal{M}} \mathcal{J}(C)$.□

4. Necessary conditions. In this section, we characterize some properties of the optimal solution and a necessary condition for a minimizer. In the first step, we need to differentiate the map $C \in \mathcal{M} \to u_C(\mathbf{x},t)$ with respect to C.

THEOREM 4.1. *Let $C \in \mathcal{M}$, and $u = u_C$ is the corresponding solution of* (1.4). *Let $C_\epsilon = C + \epsilon\eta$, where $\epsilon > 0$ and $\eta \in L^\infty[0,T]$. The mapping $C \in \mathcal{M} \to u_C$ is differentiable in the following sense: there exists $\psi = \psi_{C,\eta} \in L^2\left(0,T;H^1(\Omega)\right)$, such that*

$$\psi_\epsilon \rightharpoonup \psi \quad \textit{weakly in} \quad L^2\left(0,T;H^1(\Omega)\right) \quad \textit{as} \quad \epsilon \to 0,$$

where $\psi_\epsilon = \frac{u_{C+\epsilon\eta} - u_C}{\epsilon}$ and the sensitivity ψ satisfies

$$\begin{cases} \psi_t - \nabla \cdot (D(\mathbf{x})\nabla\psi) - (\rho - 2\rho u - C)\,\psi = -\eta u & \textit{in} \quad \Omega \times (0,T), \\ \dfrac{\partial\psi}{\partial\mathbf{n}} = 0 & \textit{on} \quad \partial\Omega \times (0,T), \\ \psi(\mathbf{x},0) = 0 & \textit{in} \quad \Omega. \end{cases} \tag{4.1}$$

Moreover, we have

$$\mathcal{J}(C+\epsilon\eta)=\mathcal{J}(C)+\epsilon\int_0^T\int_\Omega \psi_{C,\eta}d\mathbf{x}dt+o(\epsilon). \tag{4.2}$$

Proof. Consider $u_\epsilon = u_{C_\epsilon}$ where $C_\epsilon = C+\epsilon\eta$, which satisfies the following equation in the weak sense:

$$\begin{cases}\partial_t u_\epsilon - \nabla\cdot(D(\mathbf{x})\nabla u_\epsilon)=\rho\,(1-u_\epsilon)\,u_\epsilon-(C+\epsilon\eta)\,u_\epsilon & \text{in} \quad \Omega\times(0,T),\\ \dfrac{\partial u_\epsilon}{\partial \mathbf{n}}=0 & \text{on} \quad \partial\Omega\times(0,T),\\ u_\epsilon(\mathbf{x},0)=u_0(\mathbf{x}) & \text{in} \quad \Omega,\end{cases} \tag{4.3}$$

and also $u=u_C$, where

$$\begin{cases}\partial_t u - \nabla\cdot(D(\mathbf{x})\nabla u)=\rho\,(1-u)\,u-Cu & \text{in} \quad \Omega\times(0,T),\\ \dfrac{\partial u}{\partial \mathbf{n}}=0 & \text{on} \quad \partial\Omega\times(0,T),\\ u(\mathbf{x},0)=u_0(\mathbf{x}) & \text{in} \quad \Omega.\end{cases} \tag{4.4}$$

Note that it follows from Theorem 2.2 and Lemma 2.3 that there is a constant $M>0$ independent of ϵ such that

$$\|u\|_{L^\infty(Q_T)}+\|\partial_t u\|_{L^2(0,T;H^1(\Omega)^*)}+\|u\|_{L^2(0,T;H^1(\Omega))}\le M,$$
$$\|u_\epsilon\|_{L^\infty(Q_T)}+\|\partial_t u_\epsilon\|_{L^2(0,T;H^1(\Omega)^*)}+\|u_\epsilon\|_{L^2(0,T;H^1(\Omega))}\le M.$$

Reasoning as in the proof of Theorem 3.1 and by the uniqueness of the solution $u=u_C$, we have

$$\begin{aligned}&u_\epsilon \rightharpoonup u \quad \text{weakly in} \quad L^2\left(0,T;H^1(\Omega)\right),\\ &\partial_t u_\epsilon \rightharpoonup \partial_t u \quad \text{weakly in} \quad L^2\left(0,T;H^1(\Omega)^*\right),\\ &u_\epsilon \to u \quad \text{strongly in} \quad L^2(Q_T),\end{aligned}$$

while $\epsilon\to 0$. It is noteworthy that

$$\frac{u_\epsilon^2-u^2}{\epsilon}=(u_\epsilon+u)\,\frac{u_\epsilon-u}{\epsilon}. \tag{4.5}$$

Using (4.5), subtracting (4.4) from (4.3), and dividing by ϵ, we get the linear parabolic problem

$$\begin{cases}\partial_t \psi_\epsilon - \nabla\left(D(\mathbf{x})\nabla \psi_\epsilon\right)-(\rho-\rho u_\epsilon-\rho u-C)\,\psi_\epsilon=-\eta u_\epsilon & \text{in} \quad \Omega\times(0,T),\\ \dfrac{\partial \psi_\epsilon}{\partial \mathbf{n}}=0 & \text{on} \quad \partial\Omega\times(0,T),\\ \psi_\epsilon(\mathbf{x},0)=0 & \text{in} \quad \Omega.\end{cases} \tag{4.6}$$

From the classical theory of linear parabolic problems, (4.6) has a unique weak solution (e.g., see Theorem 1.1.2 in [24]) such that $\psi_\epsilon\in L^2\left(0,T;H^1(\Omega)\right)$ with $\partial_t\psi_\epsilon\in L^2\left(0,T;H^1(\Omega)^*\right)$. Also, we have

$$\frac{1}{2}\|\psi_\epsilon\|^2_{L^2(\Omega)}+\int_0^t\int_\Omega D(\mathbf{x})|\nabla\psi_\epsilon|^2\,d\mathbf{x}dt\le\rho\int_0^t\|\psi_\epsilon\|^2_{L^2(\Omega)}\,dt+\|u_\epsilon\|_{L^\infty(Q_T)}\int_0^t\int_\Omega|\eta\psi_\epsilon|\,d\mathbf{x}dt. \tag{4.7}$$

Now, Cauchy's inequality yields that

$$\int_0^t \int_\Omega |\eta\psi_\epsilon| \, d\mathbf{x}dt \leq \frac{1}{2}|\Omega| \int_0^t \eta^2 dt + \frac{1}{2}\int_0^t \|\psi_\epsilon\|^2_{L^2(\Omega)} \, dt. \tag{4.8}$$

From (4.7) and (4.8), we can get

$$\begin{aligned} &\frac{1}{2}\|\psi_\epsilon\|^2_{L^2(\Omega)} + \int_0^t \int_\Omega D(\mathbf{x})|\nabla\psi_\epsilon|^2 \, d\mathbf{x}dt \\ &\leq \rho \int_0^t \|\psi_\epsilon\|^2_{L^2(\Omega)} \, dt + \frac{|\Omega|}{2}\|\eta\|_{L^2(0,T)}\|u_\epsilon\|_{L^\infty(Q_T)} + \frac{1}{2}\|u_\epsilon\|_{L^\infty(Q_T)} \int_0^t \|\psi_\epsilon\|^2_{L^2(\Omega)} \, dt. \end{aligned} \tag{4.9}$$

In view of (4.9), we obtain

$$\|\psi_\epsilon\|^2_{L^2(\Omega)} \leq B_1 \int_0^t \|\psi_\epsilon\|^2_{L^2(\Omega)} + B_2, \tag{4.10}$$

where

$$\begin{aligned} B_1 &= 2\rho + \|u_\epsilon\|_{L^\infty(Q_T)}, \\ B_2 &= |\Omega|\|\eta\|_{L^2(0,T)}\|u_\epsilon\|_{L^\infty(Q_T)}. \end{aligned}$$

Using (4.10) and Grönwall's inequality, we infer that

$$\|\psi_\epsilon\|^2_{L^2(\Omega)} \leq B_2 \left(1 + B_1 T e^{B_1 T}\right). \tag{4.11}$$

Thus, we conclude from (4.7) and (4.11) that

$$\|\psi_\epsilon\|_{L^2(0,T;H^1(\Omega))} \leq M, \tag{4.12}$$

where M is a positive constant independent of ϵ. By reasoning similar to that in the proof of inequality (2.5), there exists a positive constant M independent of ϵ such that

$$\|\partial_t\psi_\epsilon\|_{L^2(0,T;H^1(\Omega)^*)} \leq M. \tag{4.13}$$

Therefore, by passing to a subsequence, we can assume that there exists a function ψ such that

$$\begin{aligned} &\psi_\epsilon \rightharpoonup \psi \quad \text{weakly in} \quad L^2\left(0,T;H^1(\Omega)\right), \\ &\partial_t\psi_\epsilon \rightharpoonup \partial_t\psi \quad \text{weakly in} \quad L^2\left(0,T;H^1(\Omega)^*\right), \end{aligned}$$

while $\epsilon \to 0$. Using arguments similar to that in the proof of Theorem 3.1, we can prove that ψ satisfies problem (4.1). This completes the proof of the lemma. ◻

For our next analysis, we need an adjoint equation which is introduced in the following theorem.

THEOREM 4.2. *Let $C \in \mathcal{M}$, and consider $u = u_C$. There exists a nonpositive function $w = w_C \in L^2\left(0,T;H^1(\Omega)\right)$ with $w_t \in L^2\left(0,T;H^1(\Omega)^*\right)$ such that*

$$\begin{cases} w_t + \nabla\cdot(D(\mathbf{x})\nabla w) + (\rho - 2\rho u - C)\, w = 1 & \text{in} \quad \Omega\times(0,T), \\ \dfrac{\partial w}{\partial \mathbf{n}} = 0 & \text{on} \quad \partial\Omega\times(0,T), \\ w(\mathbf{x},T) = 0 & \text{in} \quad \Omega. \end{cases} \tag{4.14}$$

Furthermore,

$$\|w\|_{L^\infty(0,T:L^2(\Omega))} + \|\partial_t w\|_{L^2(0,T;H^1(\Omega)^*)} + \|w\|_{L^2(0,T;H^1(\Omega))} \leq M,$$

where the positive constant M depends on ρ, $|\Omega|$, and T.

Proof. Let us denote $v(\mathbf{x},t) = -w(\mathbf{x},T-t)$; then it follows that v solves the problem

$$\begin{cases} v_t - \nabla\cdot(D(\mathbf{x})\nabla v) - (\rho - 2\rho u(\mathbf{x},T-t) - C(T-t))\, v = 1 & \text{in} \quad \Omega\times(0,T), \\ \dfrac{\partial v}{\partial \mathbf{n}} = 0 & \text{on} \quad \partial\Omega\times(0,T), \\ v(\mathbf{x},0) = 0 & \text{in} \quad \Omega. \end{cases} \tag{4.15}$$

The existence and uniqueness for the weak solution of (4.15) follow by the classical theory of linear parabolic problems (e.g., see Theorem 1.1.2 in [24]). Then we can obtain the existence of a unique weak solution to the problem (4.14).

Multiplying the first equation in (4.15) by $-v^- = \frac{v-|v|}{2}$ and integrating over Ω, we get

$$\frac{1}{2}\frac{d}{dt}\int_\Omega |v^-|^2\, d\mathbf{x} + \int_\Omega D(\mathbf{x})|\nabla v^-|^2\, d\mathbf{x} + \int_\Omega (2\rho u(\mathbf{x},T-t) + C(\mathbf{x},T-t))\,|v^-|^2\, d\mathbf{x}$$
$$= \int_\Omega \rho|v^-|^2\, d\mathbf{x} - \int_\Omega v^-\, d\mathbf{x}.$$

Using the fact that $(2\rho u(\mathbf{x},T-t) + C(\mathbf{x},T-t)) \geq 0$ a.e. in Q_T, the above equality gives

$$\frac{d}{dt}\int_\Omega |v^-|^2\, d\mathbf{x} \leq 2\rho\int_\Omega |v^-|^2\, d\mathbf{x}.$$

Hence, Grönwall's inequality implies that

$$\int_\Omega |v^-|^2\, d\mathbf{x} = 0$$

for almost every $t\in[0,T]$. We deduce that $v^- = 0$, and then v is nonnegative. Now, from the definition of v, we conclude that $w \leq 0$ for almost every $(\mathbf{x},t)\in Q_T$.

Multiplying the first equation in (4.15) by v, we get

$$\frac{1}{2}\frac{d}{dt}\int_\Omega v^2\, d\mathbf{x} + \int_\Omega D(\mathbf{x})|\nabla v|^2\, d\mathbf{x} + \int_\Omega (2\rho u(\mathbf{x},T-t) + C(\mathbf{x},T-t))\, v^2\, d\mathbf{x}$$
$$= \int_\Omega \rho v^2\, d\mathbf{x} + \int_\Omega v\, d\mathbf{x}. \tag{4.16}$$

From Cauchy's inequality,

$$\int_\Omega v\, d\mathbf{x} \leq \frac{|\Omega|}{2} + \frac{1}{2}\int_\Omega v^2\, d\mathbf{x}. \tag{4.17}$$

From (4.16) and (4.17), we obtain

$$\frac{d}{dt}\int_\Omega v^2\, d\mathbf{x} \leq (2\rho+1)\int_\Omega v^2\, d\mathbf{x} + |\Omega|.$$

Using Grönwall's inequality, we have

$$\int_{\Omega} v^2(\mathbf{x},t)d\mathbf{x} \le e^{(2\rho+1)T}T|\Omega| \tag{4.18}$$

for every $t \in [0,T]$. Using (4.18), we obtain that

$$\|v\|_{L^\infty(0,T:L^2(\Omega))} \le M. \tag{4.19}$$

Moreover, integrating (4.16) over $(0,T)$ and employing (4.19), we deduce that

$$\|v\|_{L^2(0,T;H^1(\Omega))} \le M. \tag{4.20}$$

Invoking reasoning similar to that for proving (2.5), we infer that

$$\|\partial_t v\|_{L^2(0,T;H^1(\Omega)^*)} \le M.$$

The generic positive constant M in the above inequalities depends on ρ, $|\Omega|$, and T. This completes the proof. ∎

Multiply both sides of (4.1) by w and integrate. Now, multiply both sides of (4.14) by ψ and integrate. Adding the resulting equations, it is easily verified that

$$\int_0^T \int_{\Omega} \psi d\mathbf{x}dt = \int_0^T \int_{\Omega} \eta uw d\mathbf{x}dt, \tag{4.21}$$

which will be needed for our study.

Next, we provide an optimality condition for a minimizer. In what follows, $\mathcal{B}(C,\epsilon)$ is a ball in $L^2(0,T)$ centered at C with radius $\epsilon > 0$. Also, a level set of a function $f(t)$ is the set $\{t: \ f(t)=\alpha\}$, where α is a constant.

THEOREM 4.3. *Let C^* be a local minimizer of $\mathcal{J}$ such that*

$$\mathcal{J}(C^*) \le \mathcal{J}(C) \quad \text{for all} \quad C \in \mathcal{B}(C^*,\epsilon) \cap \mathcal{M}.$$

Let $f^*(t) = \int_{\Omega} u_{C^*}(\mathbf{x},t) w_{C^*}(\mathbf{x},t)d\mathbf{x}$. Then, we have
(i)

$$\int_0^T C^*(t)f^*(t)dt \le \int_0^T C(t)f^*(t)dt \quad \text{for all} \quad C \in \mathcal{M}.$$

(ii) *If every level set of $f^*(t)$ has zero measure, then we have $C^*(t) = A\chi_{I^*}(t)$ such that*

$$I^* = \{t \in [0,T]: \ f^*(t) \le \tau\} \quad \text{and} \quad |I^*| = B/A.$$

Proof. (i) Consider an arbitrary function $C \in \mathcal{M}$. Setting $\eta = C - C^*$, we obtain

$$\mathcal{J}(C^* + \epsilon\eta) = \mathcal{J}(C^*) + \epsilon \int_0^T \int_{\Omega} \psi_{C^*,\eta} d\mathbf{x}dt + o(\epsilon), \tag{4.22}$$

employing (4.2). Since $\mathcal{J}(C^*)$ is a minimum value, there exists a small enough positive ϵ such that $\int_0^T \int_{\Omega} \psi_{C^*,\eta} d\mathbf{x}dt \ge 0$ for every $C \in \mathcal{M}$. Now applying (4.21), we arrive at

$$\int_0^T \int_{\Omega} \psi_{C^*,\eta} d\mathbf{x}dt = \int_0^T C(t)f^*(t)dt - \int_0^T C^*(t)f^*(t)dt, \tag{4.23}$$

which completes the proof of part (i).

(ii) Part (i) reveals that C^* is a minimizer of the functional $L(C) = \int_0^T C(t)f^*(t)dt$ over $\mathcal{M}$. Due to the fact that every level set of $f^*(t)$ has zero measure, one can conclude that there is a decreasing function $\xi : \mathbb{R} \to \mathbb{R}$ such that $\xi(f^*)$ is the unique minimizer of $L(C)$ over the set $\mathcal{N} = \{A\chi_I : I \subset [0,t],\ |I| = B/A\}$; see [6, Lemma 2.4 and 2.9]. It is well known that $\mathcal{M}$ is the weak closure of $\mathcal{N}$ in $L^2[0,T]$. Since L is weakly continuous in $L^2[0,T]$, it is inferred that indeed $\xi(f^*)$ is the unique minimizer of L over $\mathcal{M}$. This yields that $C^* = \xi(f^*)$, and then $C^* = A\chi_{I^*}$ is the unique minimizer of $L(h)$. Since $C^* = A\chi_{I^*} = \xi(f^*)$, it is easy to check that

$$\xi(s) = \begin{cases} 1, & s \le \tau, \\ 0, & s > \tau, \end{cases}$$

and $I^* = \{t \in [0,T] : \ f^*(t) \le \tau\}$ and $|I^*| = B/A$. □

Let us investigate this issue for the case that $u = u(t)$ and $w = w(t)$ are solutions of (1.4) and (4.14) in their ODE form, and then $f^*(t) = u_{C^*}(t)w_{C^*}(t)$. The following theorem ensures that level sets of $f^*(t)$ are of zero measure.

THEOREM 4.4. *Consider* (1.4) *and* (4.14) *in their ODE form. Let* $f_0 = u_0 w(0)$. *Then, level sets of* $f(t) = u(t)w(t)$ *are of zero measure, and the minimization problem* (1.6) *has a unique solution*

$$C^*(t) = A\chi_{[0,\frac{B}{A}]}(t).$$

Proof. Recall that u and w satisfy the following differential equations in the weak sense:

$$u' = \rho\,(1-u)\,u - C(t)u, \quad u(0) = u_0,$$
$$w' + (\rho - 2\rho u - C)\,w = 1, \quad w(T) = 0.$$

Now, using these equations, it can be easily verified that $f' = u'w + uw' = \rho(uw)u + u$ or

$$f'(t) - \rho u(t) f(t) = u(t) \quad \text{for every} \quad t \in [0,T]. \tag{4.24}$$

Define $v(t) = \int u(t)dt$, the antiderivative of u, and set $v_0 = v(0)$. By straightforward calculations, one can find that

$$f(t) = \left(f_0 + \frac{1}{\rho}\right) e^{\rho(v(t)-v_0)} - \frac{1}{\rho},$$

and then we conclude that

$$f'(t) = \left(f_0 + \frac{1}{\rho}\right) \rho u(t) e^{\rho(v(t)-v_0)}. \tag{4.25}$$

We consider three different cases. At first assume that $(f_0 + \frac{1}{\rho}) = 0$. Then (4.25) yields that f is constant, and indeed $f \equiv 0$ in view of $f(T) = 0$. This is a contradiction. Now let $(f_0 + \frac{1}{\rho}) < 0$. Then (4.25) says that $f(t)$ is a decreasing function. Since $f(T) = 0$, then $f(t)$ should be a positive function over $[0,T]$, which is a contradiction due to Theorems 2.2–4.2. Therefore, we can conclude that $(f_0 + \frac{1}{\rho}) > 0$, and so f is an increasing function because of (4.25). Since $f'(t) > 0$, it is inferred that a level set of $f(t)$ cannot be of positive measure due to Lemma 7.7 in [11]. Recall that $f(t)$ is continuous since $u(t)$ and $w(t)$ are continuous. Continuity, monotonicity of $f(t)$, and Theorem 4.3(ii) yield the assertion of the theorem. □

5. Numerical algorithm. This section is devoted to our numerical algorithm. The algorithm is a gradient-type one in which a descent direction is followed in each iteration.

Given $C \in \mathcal{M}$ and $\epsilon > 0$, (4.2) provides a descent direction while the quantity $\int_0^T \int_\Omega \psi_{C,\eta} d\mathbf{x}dt$ is negative and ϵ is small enough. Assume C is not a local minimizer of $\mathcal{J}(C)$, and consider $\tilde{C} \in \mathcal{M}$. Then $C + \epsilon(\tilde{C} - C)$ belongs to $\mathcal{M}$ since it is a convex set. Setting $\eta = \tilde{C} - C$ and invoking (4.21), we arrive at

$$\int_0^T \int_\Omega \psi_{C,\eta} d\mathbf{x}dt = \int_0^T \int_\Omega \tilde{C} u_C w_C d\mathbf{x}dt - \int_0^T \int_\Omega C u_C w_C d\mathbf{x}dt. \tag{5.1}$$

This reveals that $\eta = \tilde{C} - C$ is a descent direction if $\tilde{C}$ is a solution of the following optimization problem:

$$\inf_{C \in \mathcal{M}} \int_0^T C(t) f(t) dt, \tag{5.2}$$

where $f(t) = \int_\Omega u_C(\mathbf{x}, t) w_C(\mathbf{x}, t) d\mathbf{x}$. In view of the bathtub principle [17], minimization problem (5.2) has a solution of the form $A\chi_I$, where $A|I| = B$ and

$$\{t \in [0, T] : \ f(t) < \tau\} \subset I \subset \{t \in [0, T] : \ f(t) \leq \tau\}, \tag{5.3}$$

such that

$$\tau = \inf\{s \in \mathbb{R} : \ |\{t : f(t) \leq s\}| \geq B/A\}. \tag{5.4}$$

Hence, starting from C, $\eta = \tilde{C} - C$ is a direction for functional $\mathcal{J}(C)$ with steepest descent. One can use a line search algorithm to determine the maximum amount to move along the given descent direction such that the condition $\mathcal{J}(C + \epsilon\eta) < \mathcal{J}(C)$ is fulfilled. The resulting algorithm is presented in Algorithm 5.1.

Algorithm 5.1 Minimization algorithm

Given $A, B, \rho, D(\mathbf{x})$, and $TOL > 0$, choose an initial $C_0 \in \mathcal{M}$.
1. Set $i = 0$.
2. Compute $u_i = u_{C_i}$ and $\mathcal{J}(C_i)$ using a finite element method.
3. Set $\rho - 2\rho u_i - C_i$ as the coefficient in (4.14) and compute $w_i = w_{C_i}$ using a finite element method.
4. Set $f(t) = \int_\Omega u_i(\mathbf{x}, t) w_i(\mathbf{x}, t) d\mathbf{x}$ and derive I_i employing formulas (5.3) and (5.4).
5. Set $\eta_i = A\chi_{I_i} - C_i$ and $\epsilon = 1$.
6. Set $C_{i+1} = C_i + \epsilon\eta_i$ and compute $u_{i+1} = u_{C_{i+1}}$ and $\mathcal{J}(C_{i+1})$ using a finite element method.
7. While $J(u_{i+1}) > J(u_i)$ do
Set $\epsilon = \epsilon/2$.
Set $C_{i+1} = C_i + \epsilon\eta_i$ and compute $u_{i+1} = u_{C_{i+1}}$ and $\mathcal{J}(C_{i+1})$ using a finite element method.
8. If $\mathcal{J}(C_i) - \mathcal{J}(C_{i+1}) < TOL$, stop the algorithm. Otherwise set $i = i + 1$, and go to step 3.

We address the convergence of Algorithm 5.1 in the following theorem.

THEOREM 5.1. *Consider the sequences* $\{C_i(t)\}_1^\infty$, $\{u_i(\mathbf{x}, t)\}_1^\infty$, *and* $\{w_i(\mathbf{x}, t)\}_1^\infty$ *generated by Algorithm* 5.1. *Then, the following hold.*

(i) *There exist* $C^*(t) \in \mathcal{M}$, $u^* \in L^2\left(0,T;H^1(\Omega)\right)$, *and* $w^* \in L^2\left(0,T;H^1(\Omega)\right)$ *such that* $C_i \rightharpoonup C^*$ *weakly in* $L^2(\Omega)$, $u_i \to u^*$, $w_i \to w^*$ *strongly in* $L^2(Q_T)$, *and* $J(C_i) \to J(C^*)$.

(ii) *If the level sets of* $f^*(t) = \int_\Omega u^*(\mathbf{x},t)w^*(\mathbf{x},t)d\mathbf{x}$ *are of zero measure, then* $C_i \to C^*$ *strongly in* $L^2[0,T]$.

Proof. (i) The proof is similar to that for Theorem 3.1 and so is omitted.

(ii) According to Algorithm 5.1, we have $J(C_i) > J(C_{i+1})$, and hence

$$J(C^*) = \inf \{J(C_i) :\ i \in \mathbb{N}\}. \tag{5.5}$$

This yields that

$$\int_0^T C^*(t)f^*(t)dt \le \int_0^T C(t)f^*(t)dt \quad \text{for every} \quad C \in \mathcal{M}, \tag{5.6}$$

since otherwise, due to Algorithm 5.1, one can find $\tilde{C} \in \mathcal{M}$ such that $J(\tilde{C}) < J(C^*)$, which is in contradiction to (5.5). Inequality (5.6) says that C^* is a minimizer of the functional $L(C) = \int_0^T C(t)f^*(t)dt$ over $\mathcal{M}$. Now, similar to the proof of Theorem 4.3(ii), we can conclude that $C^*(t) = A\chi_{I^*}(t)$, and it is the unique minimizer of the functional.

Recall that $\mathcal{M}$ is the weak closure of $\mathcal{N} = \{A\chi_I :\ I \subset [0,t],\ |I| = B/A\}$. For every $C \in \mathcal{M}$ there is sequence $\{h_i\}_1^\infty \subset \mathcal{N}$ such that $h_i \rightharpoonup C$ in $L^2(\Omega)$. It is easy to check that the L^2-norm of all functions in $\mathcal{N}$ equals to $\sqrt{AB}$. Employing the weak lower semicontinuity of the norm, we have

$$\|C\|_{L^2(\Omega)} \le \liminf_{i\to\infty} \|h_i\|_{L^2(\Omega)} = \sqrt{AB}.$$

Now, it is inferred that

$$\begin{aligned}\lim_{i\to\infty} \|C_i - C^*\|^2_{L^2[0,T]} &= \lim_{i\to\infty} \left(\|C_i\|^2_{L^2[0,T]} + \|C^*\|^2_{L^2[0,T]} - 2\int_0^T C_i C^* dt \right) \\ &\le AB + AB - 2AB = 0,\end{aligned}$$

in view of the weak convergence $C_i \rightharpoonup C^*$. This reveals that $C_i \to C^*$ in $L^2[0,T]$. ∎

5.1. Numerical results. This section is devoted to the implementation of Algorithm 5.1. Here, we use parameters estimated in [29]. We start with solving ODE problems on $t \in [0, t_{\max}]$, where $t_{\max}$ is chosen as a length of one chemotherapy cycle: 42 days. The maximum chemotherapy is chosen as $A = 0.084$, which is the strength of the effective chemotherapy in white matter. The total chemotherapy is $B = 1.26 = 0.084 \times 15$, which comes from applying the effective chemotherapy for 15 days. The growth rate is $\rho = 0.012\ \text{day}^{-1}$. In Figures 1 and 2, the results are shown for $u(0) = 0.5$ and two different choices of chemotherapy functions, $C_0(t) = \frac{B}{42} = 0.03$ and $C_0(t) = 0.03 + 0.025\sin(\frac{4\pi t}{t_{\max}})$, respectively. These two choices represent a constant dose and an oscillatory dose of chemotherapy, respectively. The corresponding $u(t)$ and $w(t)$ are also shown. For both cases, the optimized $C(t)$ is a step function $C(t) = 0.084\chi_{[0,15]}$ and $J^\star = 9.4385$. Notice that the solution $u(t) \approx 0.2$ at the end of the chemotherapy cycle, $t = 42$, is smaller than $u(0) = 0.5$ in the beginning of the chemotherapy cycle regardless of whether the chemotherapy is constant, oscillatory, or bang-bang (the optimized one). The solution u which corresponds to the optimized

$C(t)$ decreases more rapidly in the beginning of the cycle, compared to the ones which correspond to the constant and oscillatory chemotherapy, and increases gradually after the chemotherapy is off. The total population over the cycle $\mathcal{J}(C)$ is minimized when $C(t) = 0.084\chi_{[0,15]}$ which represents applying the effective chemotherapy in the beginning of the chemotherapy cycle for 15 consecutive days. The bang-bang chemotherapy has the best average effectiveness in terms of tumor cell population over the cycle and is easy to implement compared to the oscillatory chemotherapy. For these two numerical simulations, it only takes one iteration to reach the optimal $C(t)$. Indeed, the numerical results coincide with our analytical findings in Theorem 4.4.

The results of PDE problems show similar behaviors. In Figures 3 and 4, we solve (1.4) on $\Omega = [0,1]$ mm with $C_0(t) = 0.03$ with different initial conditions. The diffusion constant is chosen as 0.65 mm^2.day^{-1} [29]. The initial conditions are $u(x,0) = 0.5\chi_{[0,0.5]}$ and $u(x,0) = 0.5 + 0.5\cos^2(\pi x)$ in Figure 3 and Figure 4, respectively. In Figure 5, the result is shown with an oscillatory chemotherapy $C_0(t) = 0.03 + 0.025\sin(\frac{4\pi t}{42})$. Due to the diffusion effect, all solutions approach a constant at the later time. Again, the optimal $C(t)$ which minimizes the total population over the cycle $\mathcal{J}(C)$ is a bang-bang function which prefers MTD in the beginning.

In the last example, we show a calculation on a brain image to find the optimal drug treatment in time. The MRI dataset that we used is included in MRIcron, a cross-platform NIFTI format image viewer [27] developed by Professor Chris Rorden and his group. We first use MATLAB to load the dataset and generate an axial view of the image "ch2bet.nii" of size $181 \times 217 \times 181$ mm^3 at the slice $z = 95$mm shown in the original image in Figure 6. We use the segmentation approach in [16] to identify grey matter (GM) and white matter (WM) regions, which are shown in the middle of the first row in Figure 6, and then prepare a triangle mesh for finite element calculation to solve (1.4) on the brain. The problem that we study here corresponds to the homogeneous drug delivery case that was discussed in [29], and the parameters in [29] are used in our simulation. The diffusion coefficients are 0.13 and 0.65 mm^2.day^{-1} in GM and WM, respectively. The total growth rate is $\rho = 0.012$ day^{-1}, and the length of chemotherapy is 42 days for a cycle. No flux boundary is applied on the boundary of brain. The initial tumor cell density is chosen to be

$$u(x,0) = e^{-\frac{(x-x_0)^2+(y-y_0)^2}{4\sigma}},$$

where $\sigma = 100$, $(x_0, y_0) = (140, 100)$, $A = 0.084$, $B = 1.26$, and $C_0(t) = 0.03$ for $0 \le t \le 42$. With this constant drug dose, we see that the quantity $\int_\Omega u d\mathbf{x}$ is monotone decreasing in time while $\int_\Omega w d\mathbf{x}$ is monotone increasing in time as shown in the second row of Figure 6. The optimal drug dose is shown in the third row, which indicates that the bang-bang drug dose function is again preferable. The maximal drug dose is implemented in the beginning of the chemotherapy treatment cycle. The last two rows show the solution $u(\mathbf{x}, t)$ at various times for the constant drug dose and the optimal drug dose. One can observe that the total tumor cell population over the cycle is indeed smaller for the optimal bang-bang treatment as $J = 29949.3116$ for the constant chemotherapy treatment while $J = 20535.5933$ for the MTD chemotherapy treatment. At time $t = 14$, the function $\int_\Omega u(\mathbf{x}, t)d\mathbf{x}$ has magnitude less than 400 already for the bang-bang drug dose while $\int_\Omega u(\mathbf{x}, t)d\mathbf{x}$ is about 800 for the constant chemotherapy. This confirms that the MTD strategy, which typically includes repeated cycles of chemotherapy at the MTD without causing unacceptable toxicity,

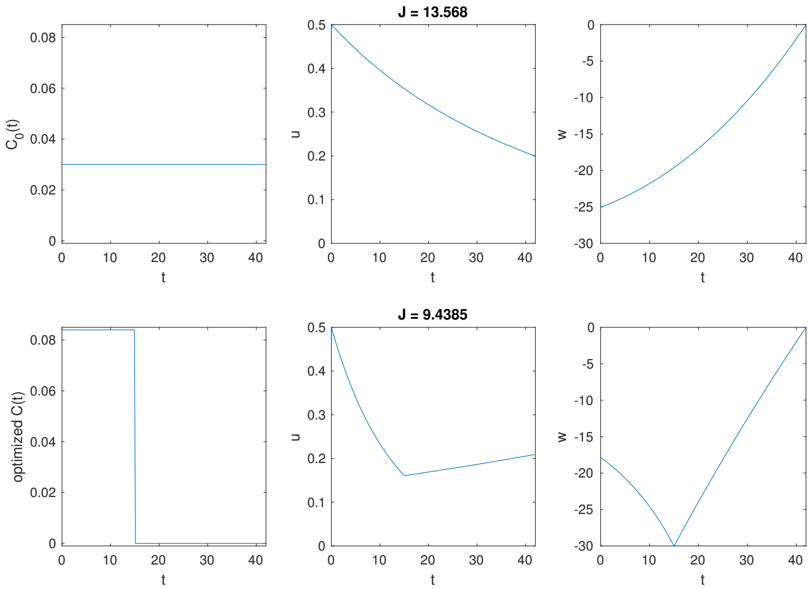

Fig. 1. *The chosen parameters are* $u(0) = 0.5$, $A = 0.084$, $B = 1.26$, $\rho = 0.012$. *The first row shows the initial* $C_0(t) = 0.03$ *and its corresponding* $J = 13.568$, $u(t)$, *and* $w(t)$. *The second row shows the optimized* $C(t)$ *and its corresponding* $J = 9.4385$, $u(t)$, *and* $w(t)$.

helps to reduce the total tumor cell population.

6. Conclusion. In order to find an optimal chemotherapy strategy that minimizes the population size of tumor cells, an optimization problem corresponding to a reaction-diffusion PDE has been considered. It has been proved that the minimization problem has a solution and a necessary condition for the optimizer can be determined. For the diffusion-free case, we have calculated the optimizer explicitly and established the uniqueness of the solution. Then, we have developed a gradient-based numerical algorithm in order to compute the optimizer.

Standard chemotherapy plans involve giving drug at the maximum tolerated dose (MTD) and typically consist of repeated cycles of chemotherapy at the highest possible dose without causing unacceptable toxicity [15]. Mathematically, these plans correspond to so-called bang-bang controls that are given at the maximum dose $C^* = C_{\max}$ with rest periods $C^* = 0$. The results presented in this paper, in particular the one involving a real brain image, are in line with the MTD treatment schedule for chemotherapy. More precisely, if a homogeneous tumor population is assumed and other aspects, like tumor heterogeneity and the tumor microenvironment, are ignored, then mathematical models confirm the MTD strategy.

There are a variety of extensions and future directions of this work. One important direction would be to find an optimal radiotherapy fractionation scheme [25]. A possible criterion for the optimality is minimizing the total number of tumor cells remaining after application of radiotherapy; another is to minimize the tumor control probability [18]. These important optimization problems have yet to be addressed.

Acknowledgment. The authors would like to thank the reviewers for their constructive suggestions to improve the presentation of the paper.

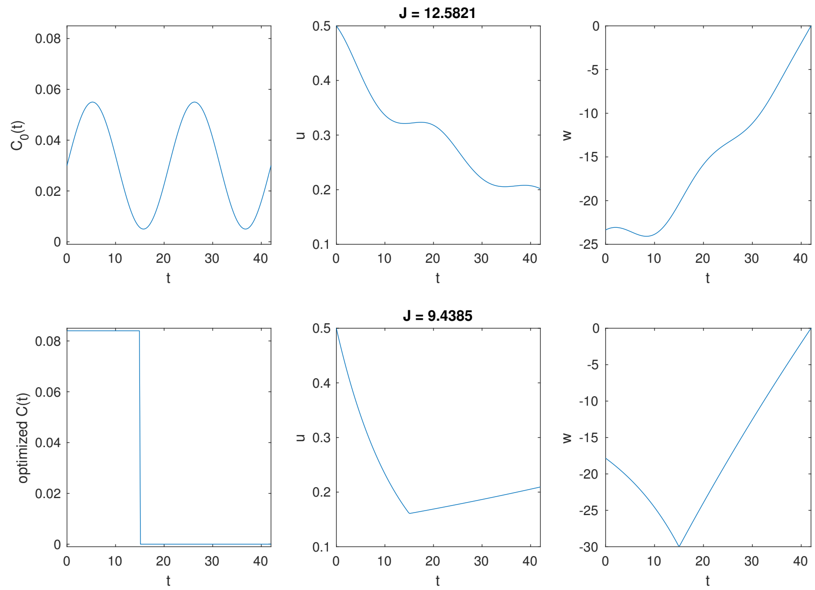

FIG. 2. *The chosen parameters are* $u(0) = 0.5$, $A = 0.084$, $B = 1.26$, $\rho = 0.012$. *The first row shows the initial* $C_0(t) = 0.03 + 0.025\sin(\frac{4\pi t}{42})$ *and its corresponding* $J = 12.5821$, $u(t)$, *and* $w(t)$. *The second row shows the optimized* $C(t)$ *and its corresponding* $J = 9.4385$, $u(t)$, *and* $w(t)$.

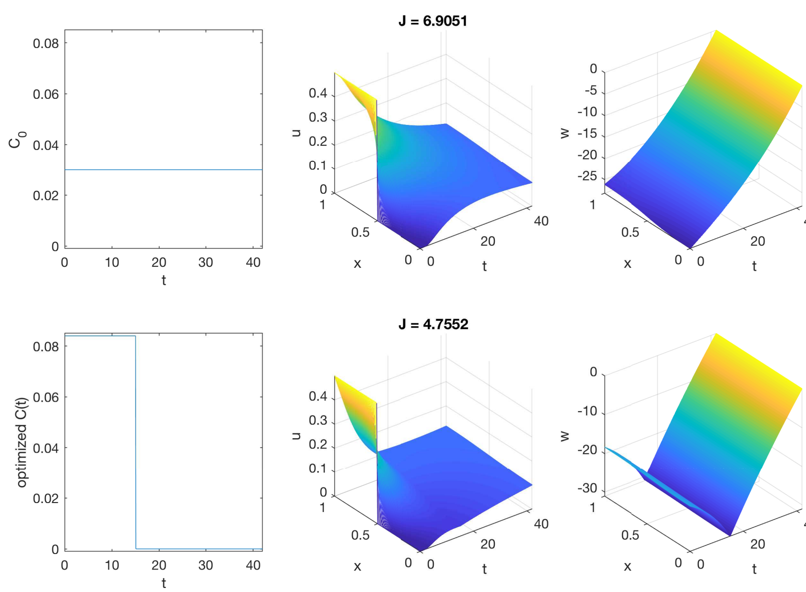

FIG. 3. *The chosen parameters are* $u(0) = 0.5\chi_{[0,0.5](x)}$, $A = 0.084$, $B = 1.26$, $\rho = 0.012$. *The first row shows the initial* $C_0(t) = 0.03$ *and its corresponding* $J = 6.9051$, $u(t)$, *and* $w(t)$. *The second row shows the optimized* $C(t)$ *and its corresponding* $J = 4.7552$, $u(t)$, *and* $w(t)$.

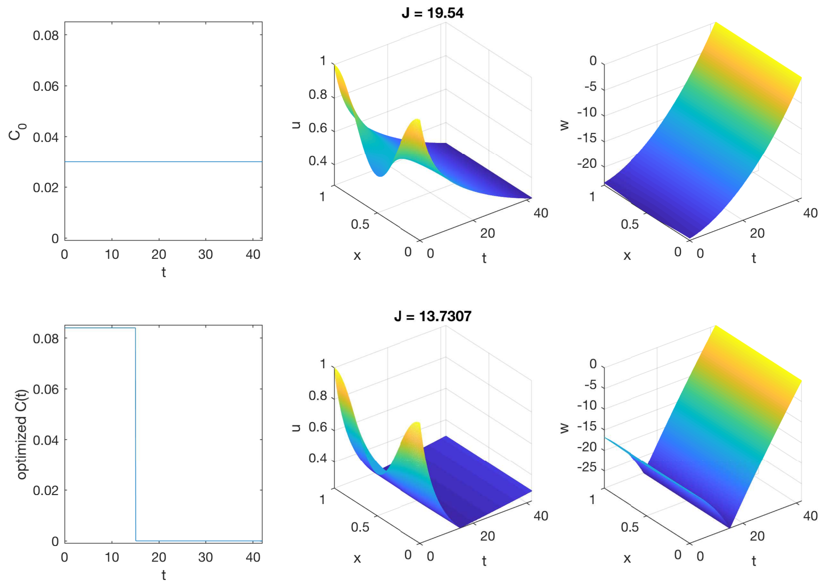

FIG. 4. *The chosen parameters are* $u(x,0) = 0.5+0.5\cos^2(\pi x)$, $A = 0.084$, $B = 1.26$, $\rho = 0.012$. *The first row shows the initial* $C_0(t) = 0.03$ *and its corresponding* $J = 19.54$, $u(t)$, *and* $w(t)$. *The second row shows the optimized* $C(t)$ *and its corresponding* $J = 13.7307$, $u(t)$, *and* $w(t)$.

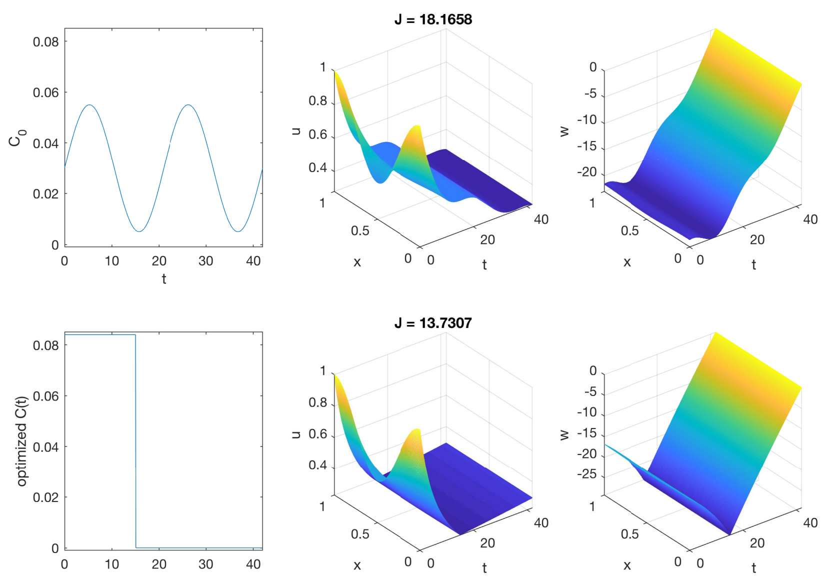

FIG. 5. *The chosen parameters are* $u(x,0) = 0.5+0.5\cos^2(\pi x)$, $A = 0.084$, $B = 1.26$, $\rho = 0.012$. *The first row shows the initial* $C_0(t) = 0.03+0.025\sin(\frac{4\pi t}{42})$ *and its corresponding* $J = 18.1658$, $u(t)$, *and* $w(t)$. *The second row shows the optimized* $C(t)$ *and its corresponding* $J = 13.7307$, $u(t)$, *and* $w(t)$.

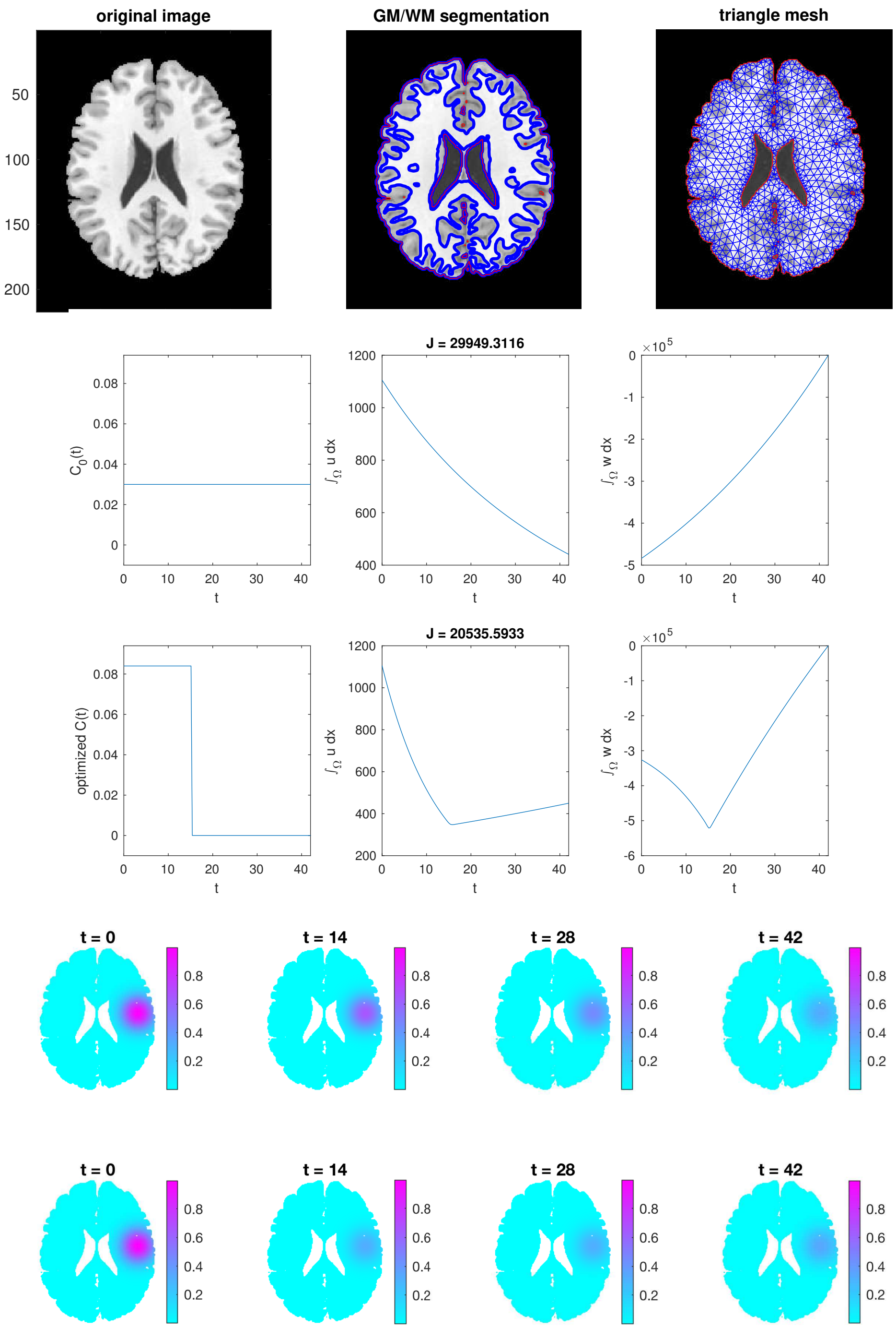

FIG. 6. *The first row shows a brain image in an axial view, its grey matter (GM) and white matter (WM) segmentation result, and a triangle mesh on the brain. The second row shows the initial* $C_0(t) = 0.03$ *and its corresponding* $J = 29949.3116$, $\int_\Omega u(\mathbf{x},t)d\mathbf{x}$, *and* $\int_\Omega w(\mathbf{x},t)d\mathbf{x}$. *The third row shows the optimized* $C(t)$ *and its corresponding* $J = 20535.5933$, $\int_\Omega u(\mathbf{x},t)d\mathbf{x}$, *and* $\int_\Omega w(\mathbf{x},t)d\mathbf{x}$. *The fourth row and the fifth row show the solution* $u(\mathbf{x},t)$ *at various times for* $C(t) = 0.03$ *and the optimized* $C(t)$, *respectively.*

REFERENCES

[1] A. Alvarez-Arenas, K. E. Starkov, G. F. Calvo, and J. Belmonte-Beitia, *Ultimate dynamics and optimal control of a multi-compartment model of tumor resistance to chemotherapy*, Discrete Contin. Dyn. Syst. Ser. B, 24 (2019), pp. 2017–2038.

[2] E. Alvord, *Patterns of growth of gliomas*, Amer. J. Neuroradiol., 16 (1995), pp. 1013–1017.

[3] F. Billy, J. Clairambault, and O. Fercoq, *Optimisation of cancer drug treatments using cell population dynamics*, in Mathematical Methods and Models in Biomedicine, Springer, New York, 2013, pp. 265–309.

[4] A. Bratus, I. Samokhin, I. Yegorov, and D. Yurchenko, *Maximization of viability time in a mathematical model of cancer therapy*, Math. Biosci., 294 (2017), pp. 110–119.

[5] A. S. Bratus, S. Y. Kovalenko, and E. Fimmel, *On viable therapy strategy for a mathematical spatial cancer model describing the dynamics of malignant and healthy cells*, Math. Biosci. Engrg., 12 (2015), pp. 163–183.

[6] G. Burton, *Variational problems on classes of rearrangements and multiple configurations for steady vortices*, Ann. Inst. H. Poincaré Anal. Non Linéaire, 6 (1989), pp. 295–319.

[7] M. E. Davis, *Glioblastoma: Overview of disease and treatment*, Clin. J. Oncol. Nurs., 20 (2016), pp. S2–S8.

[8] A. F. Filippov, *Differential Equations with Discontinuous Righthand Sides: Control Systems*, Math. Appl. 18, Springer, Dordrecht, The Netherlands, 1988.

[9] H. Finotti, S. Lenhart, and T. Van Phan, *Optimal control of advective direction in reaction-diffusion population models*, Evol. Equ. Control Theory, 1 (2012), pp. 81–107.

[10] K. R. Fister and J. C. Panetta, *Optimal control applied to competing chemotherapeutic cell-kill strategies*, SIAM J. Appl. Math., 63 (2003), pp. 1954–1971, https://doi.org/10.1137/S0036139902413489.

[11] D. Gilbarg and N. S. Trudinger, *Elliptic Partial Differential Equations of Second Order*, Springer, New York, 2015.

[12] E. C. Holland, *Glioblastoma multiforme: The terminator*, Proc. Natl. Acad. Sci. USA, 97 (2000), pp. 6242–6244.

[13] J. Jacobs, R. C. Rockne, A. J. Hawkins-Daarud, P. R. Jackson, S. K. Johnston, P. Kinahan, and K. R. Swanson, *Improved model prediction of glioma growth utilizing tissue-specific boundary effects*, Math. Biosci., 312 (2019), pp. 59–66.

[14] U. Ledzewicz and H. Schättler, *A review of optimal chemotherapy protocols: From MTD towards metronomic therapy*, Math. Model. Nat. Phenom., 9 (2014), pp. 131–152.

[15] U. Ledzewicz, H. Schättler, M. R. Gahrooi, and S. M. Dehkordi, *On the MTD paradigm and optimal control for multi-drug cancer chemotherapy*, Math. Biosci. Engrg., 10 (2013), pp. 803–819.

[16] C. Li, C.-Y. Kao, J. C. Gore, and Z. Ding, *Minimization of region-scalable fitting energy for image segmentation*, IEEE Trans. Image Process., 17 (2008), pp. 1940–1949.

[17] E. H. Lieb and M. Loss, *Analysis*, Grad. Stud. Math. 14, AMS, Providence, RI, 1997.

[18] C. Meaney, M. Stastna, M. Kardar, and M. Kohandel, *Spatial optimization for radiation therapy of brain tumours*, PloS ONE, 14 (2019), e0217354.

[19] H. Moradi, M. Sharifi, and G. Vossoughi, *Adaptive robust control of cancer chemotherapy in the presence of parametric uncertainties: A comparison between three hypotheses*, Comput. Biol. Med., 56 (2015), pp. 145–157.

[20] H. Moradi, G. Vossoughi, and H. Salarieh, *Optimal robust control of drug delivery in cancer chemotherapy: A comparison between three control approaches*, Comput. Methods Programs Biomed., 112 (2013), pp. 69–83.

[21] J. D. Murray, *Mathematical Biology* I: *An Introduction*, 3rd ed., Interdiscip. Appl. Math. 17, Springer, New York, 2002.

[22] J. D. Murray, *Mathematical Biology* II: *Spatial Models and Biomedical Applications*, 3rd ed., Interdiscip. Appl. Math. 18, Springer, New York, 2003.

[23] G. Powathil, M. Kohandel, S. Sivaloganathan, A. Oza, and M. Milosevic, *Mathematical modeling of brain tumors: Effects of radiotherapy and chemotherapy*, Phys. Med. Biol., 52 (2007), pp. 3291–3306.

[24] S. Reichelt, *Two-Scale Homogenization of Systems of Nonlinear Parabolic Equations*, Ph. D. thesis, Weierstrass Institute for Applied Analysis and Stochastics, Berlin, Germany, 2015.

[25] R. Rockne, E. Alvord, J. Rockhill, and K. Swanson, *A mathematical model for brain tumor response to radiation therapy*, J. Math. Biol., 58 (2009), pp. 561–578.

[26] R. Rockne, J. Rockhill, M. Mrugala, A. Spence, I. Kalet, K. Hendrickson, A. Lai, T. Cloughesy, E. Alvord, Jr., and K. Swanson, *Predicting the efficacy of radiotherapy in individual glioblastoma patients in vivo: A mathematical modeling approach*, Phys. Med.

Biol., 55 (2010), pp. 3271–3285.

[27] C. Rorden, *MRIcron*, date added 2014-09-05, date modified 2020-07-29, https://www.nitrc.org/projects/mricron, 2020.

[28] K. Swanson, R. Rostomily, and E. Alvord, Jr., *A mathematical modelling tool for predicting survival of individual patients following resection of glioblastoma: A proof of principle*, British J. Cancer, 98 (2008), pp. 113–119.

[29] K. R. Swanson, E. C. Alvord, Jr., and J. Murray, *Quantifying efficacy of chemotherapy of brain tumors with homogeneous and heterogeneous drug delivery*, Acta Biotheoret., 50 (2002), pp. 223–237.

[30] K. R. Swanson, E. C. Alvord, Jr., and J. Murray, *A quantitative model for differential motility of gliomas in grey and white matter*, Cell Proliferation, 33 (2000), pp. 317–329.

[31] K. R. Swanson, C. Bridge, J. Murray, and E. C. Alvord, Jr., *Virtual and real brain tumors: Using mathematical modeling to quantify glioma growth and invasion*, J. Neurological Sci., 216 (2003), pp. 1–10.

[32] P. Tracqui, G. Cruywagen, D. Woodward, G. Bartoo, J. Murray, and E. Alvord, Jr., *A mathematical model of glioma growth: The effect of chemotherapy on spatio-temporal growth*, Cell Proliferation, 28 (1995), pp. 17–31.