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Optimal Cell Distribution Control for Cancer Chemotherapy*

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***Abstract*—Designing an effective cancer therapy has long been of practical interest in bio-science and engineering. Thanks to today's technology, a handful of techniques are available and effective for treating cancer diseases, including chemotherapy. The main limitation of such treatments comes from the tumor heterogeneity resulting in the inefficiency of the treatment after a year or two. Hence, it is common to provide overdosed treatment in practice, which enhances the side effects and even builds up drug resistance. To tackle this issue, a representative mathematical model is developed from clinical research observations to simulate the dynamic behavior of the cancerous cell population under tumor heterogeneity. This model, in which tumor heterogeneity is marked by the cells' drug-resistance intensity, has been widely used in the areas of systems science and engineering. Our previous research has studied the resulting optimal control problem for multiple significant traits, however, it remains a challenge to discuss the drug's impact on the growth of cancer cells through the standard optimal control formulation. In other words, an optimal cell-distribution control problem is in great demand to minimize the combination of tumor volumes and drugs' side effects, which guarantees the effectiveness of the designed treatment. In this paper, we extend our previous work and combine it with the Liouville approach for distribution controls to describe the evolution of the cancerous cell population quantitatively. Several numerical examples are included to demonstrate the performance of this technique and discuss the optimal cancer chemotherapeutic treatment scenarios when a single treatment is available.**

I. Introduction

While a variety of treatment options, including surgery, radiation therapy, immunotherapy, targeted therapy, hormone therapy, and stem cell transplantation are available, chemotherapy remains the most common form of care [1]. And, its conjunction with other treatment techniques such as radiotherapy and immunotherapy [2, 3] is thought to be the most popular and efficient method for treating cancer. Cancer chemotherapy treatment has captured the attention of clinical researchers [4, 5] as well as systems science and engineering experts [6, 7], owing to its practical significance. The main challenge is that patients are reported to suffer from unavoidable and increasing side effects, which, in the long run, may even lead to cells' resistance to chemotherapeutic drugs. This is mainly because those cancerous cells are generally unstable and heterogeneous – coupled with different proliferation rates, which leads to a wide range of chemotherapeutic sensitivities as well as various phenotypes according to the Norton-Simon hypothesis [8–11]. Thus, a robust mathematical model is in great demand to describe this genetic instability phenomenon, aiming at long-time survival and nonfatal side effects, so that the overall dynamic evolution of cancerous cell distribution can be well-presented and the resulting cancer chemotherapeutic treatment can be viewed as cell-distribution control from the control engineering point of view.

To initiate such discussions, a mathematical dynamic model that quantitatively correlates tumor heterogeneity and cancerous cell growth needs to be in place. Recent studies [12, 13] have developed such a dynamic model for cell growth in solid tumors from clinical data that both tumor heterogeneity and drug effects can be quantified by drug's resistant rates, which allows for a continuum of possible traits. Later on, according to [14, 15], the model was altered to account for the various roles played by different traits within the population of cancerous cells. This was achieved by increasing cell densities and introducing mutations that led to the emergence of specific traits, which then became dominant. [5, 16]. This phenomenon could result from evolutionary mechanisms, or, the fact that resistance is achieved through pathways that use up energy which then cannot be used for proliferation [17]. If there exist sub-populations for which the activation mechanisms of certain drugs (targeted or not) do not work, eventually the therapy will fail. Intuitively, in the presence of drug-resistant strains, as the cytotoxic agent kills off the sensitive cells, the resistant ones become increasingly more dominant.

With this existing dynamic model, an ensemble optimal control problem was formulated in our previous work to explore the drugs' impact on cancer cells, within a widely chosen range of drug resistance rates, where the objective is to minimize the combination of tumor volumes and drugs' side effects [8, 18–20]. This issue presented a significant level of inherent complexity due to the fact that the best possible controls - in this case, drug dosages - for cancer chemotherapy were limited. Moreover, they needed to be effective in eradicating most of the tumor cells that had varying drug resistance rates for a long period, which only added to the complexity of the tumor's dynamics as a result of its heterogeneity. The large-scale nature of the ensemble dynamic system as well as the structural similarities of PD for each trait requires the desired control to be robust and highly effective, which may even make it unfeasible.

We previously pursued the problem by creating a model with a finite number of dimensions, which inspired us to consider the possible outcomes. Despite its simplification, the optimal control problem is still a challenge due to the limited

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availability of drugs. In other words, a few controls are permitted for a significant number of diverse cell populations. Several numerical methods have been developed to solve optimal control problems with multiple subsystems, including direct and indirect methods [21–23]. It is worth noting that the discretized nonlinear programs (NLPs) may be sensitive to their initialization and structure in these problems [24, 25]. Hence, slow convergence, low efficiency, or even instability issues may be encountered when directly implementing those existing methods. Instead, we derived the necessary conditions for the best control scenarios from geometric optimal control theory and then adopted the shooting method for searching for possible candidates. It is known that the standard shooting method is sensitive to the initial guess of the co-state and the choice of step size. To avoid inefficiency, the previously developed iterative method [26, 27] is adopted here to be combined with the standard shooting method to look for a reasonable starting estimate of the co-state.

In this paper, we first introduce the optimal distribution control formulation, and then discuss optimal treatment strategies through the Liouville approach [28] as well as taking advantage of the previously developed technique for solving the associated simplified problem. This class of optimal distribution control problems involving a partial differential equation can be related to the typical optimal ensemble control problems, which are numerically tractable through our previous approach and have been studied thoroughly. Intuitively, the optimal distribution control should be more applicable in practice and require less "control energy" because the focus is less restrictive – not only on the majority of the population system but the entire distribution of cancerous cells. Our initial step is to outline the mathematical framework, drawing on previous research [15] in cancer chemotherapy, and then establish the problem of controlling the distribution of cells, which requires resolving a partial differential equation. Afterward, we introduce a practical and computationally efficient approach to determine the optimal treatment plan without requiring optimization. The case study section includes various numerical examples, where we present different drug treatment scenarios by tracking the evolution of the cancerous cell population throughout the treatment process.

II. Dynamic Framework for Cancer Treatment

In this part, tumor growth from a mathematical perspective [14, 15], which connects tumor heterogeneity with cells' resistance rate to treatment, is presented. First, a continuum of potential characteristics (phenotype), $x \in [0,1]$ is defined, which can be used to identify sub-populations that have varying responses to particular chemotherapeutic agents. The Norton-Simon Hypothesis [10, 11] suggests that the replication rates r and natural death rates μ of cells should depend on the trait x. Secondly, the Michaelis-Menten (MM) relationship, is adopted to describe the impact of a fast-acting medication, where a saturation model is included to quantify the pharmaco-dynamic (PD) effects of the drug concentration. This saturating MM model, based on $E_{\max}$-model in pharmacology, penalizes the overdose and restricts side effects compared to the conventional Log-Kill Hypothesis. Furthermore, a long time horizon (compared to the PD reaction time) is taken into account to enable the discussion of the fast-acting treating scenario. As a result, the treatment impact can then be roughly approximated by $c(x)\frac{u(t)}{UC_{50}+u(t)}n(t,x)$, where the drug's concentration at which it has a 50% effect is denoted by UC_{50}, and the corresponding cytotoxic killing parameter is represented by c.

On the other hand, the cells would compete for nutritional elements in the environment to proliferate as desired, or, to be more precise, both healthy and cancerous cells would only grow with sufficient nutrients. As a consequence, larger tumors tend to have cells that more aggressively compete for limited nutrients, which slows down cell proliferation and increases the death rate when the nutrients are insufficient to fulfill normal needs for cell growth. This gives rise to the following rescaled dynamic model, assuming the rates of cell proliferation and death should depend not only on the trait x but also on the cell density $N = N(t)$ [17], which can be expanded as

$$\frac{\partial n}{\partial t}(t,x) = \Big(r(x) - \frac{\phi(x)u(t)}{1+u(t)} - \mu(x)G(N(t))\Big)n(t,x). \quad (1)$$

Notably, the notation $n(t,x)$ is used to represent the density of cancer cells with trait x at time t, while u is the variable used to refer to the concentration of the drug. Note that $n(t,x)$ denotes the population density of cancer cells with trait x at time t, and u denotes the concentration of the considered drug. It is worth pointing out that the scaling factor G should be a strictly increasing function that balances the ratio of apoptosis to growth once the cancerous cell population stabilizes. In other words, as tumor volumes increase, both cancer and healthy cells have a tendency to proliferate more slowly but die quickly due to nutrition shortage. A logistic structure that produces limiting carrying capacity [8, 14] is introduced by the model in Eq. (1) as G is defined for balancing growth and apoptosis. However, because G connects each subsystem (i.e., each drug resistance) and has the integral form of the population density $n(t,x)$, it makes the cell-population control design more challenging.

III. Optimal Distribution Control Formulation for Cancer Treatment

Using the model presented in Eq. (1), a control strategy for optimal cancerous cell-population control has been developed from a control engineering perspective. The clinical concern driving the development of this strategy is to maximize the effectiveness of treatments while minimizing the side effects of drugs. This is achieved by maintaining a low overall tumor cell population.

The main focus of this study is that the selected cancer chemotherapy drug acts ideally, killing the majority of tumor cells during the treatment, or say, reducing

the overall tumor population $N(t) = \int_0^1 n(t,x)\,dx$ over a predetermined treatment time $[0,T]$. On the other hand, the medications' toxicity and side effects, which are proportional to the concentration of the pharmaceuticals used may be approximated by the term $\int_0^T u(t)dt$. To make sure that patients are not experiencing treatment insufficiency, it is also necessary to monitor the intermediate total tumor population during the duration of the therapy, i.e., the integral term $\int_0^T N(t)\,dt$. The objective function that arises from this process has the form $J(t,N,u) = \alpha N(T) + \int_0^T (\beta N(t) + \gamma u(t))\,dt$. Combining this cost function with the dynamic model as in Eq. (1) in Section II, the optimal cancerous cell-distribution control problem can be formulated, which involves solving a partial differential equation (PDE), as follows:

Problem 1: For a fixed treatment time T, positive weights α and β, and a γ chosen specifically for the considered treatment, minimize the objective

$$J = \alpha N(T) + \int_0^T (\beta N(t) + \gamma u(t))\,dt, \tag{2}$$

with Lebesgue measurable functions $u : [0,T] \to [0, u_{\max}]$, subject to the dynamics

$$\frac{\partial n}{\partial t}(t,x) = \Big(r(x) - \frac{\phi(x)u(t)}{1+u(t)} - \mu(x)G(N(t))\Big)n(t,x),$$

where $N(t) = \int_0^1 n(t,x)\,dx, \forall t \in [0,T]$.

This class of optimum cell-population control problems is intrinsically difficult since the control job seeks to manage the dynamic behavior of the entire population of tumor cells using only a single medication. Moreover, the PDE that describes the dynamic behavior of the heterogeneous cancerous cell population, includes the term N. This double integral makes the task even more challenging and triggers the idea of first exploring the associated simplified problem.

Problem 2: For a fixed treatment time T, n-dimensional row vectors $\bar{\alpha}$ and $\bar{\beta}$ of positive weights and a γ chosen specifically for the considered treatment, minimize the objective

$$J(u) = \bar{\alpha}\bar{N}(T) + \int_0^T \big(\bar{\beta}\bar{N}(t) + \gamma u(t)\big)\,dt$$

over all Lebesgue measurable functions $u : [0,T] \to [0, u_{\max}]$, subject to the dynamics

$$\frac{d}{dt}\bar{N}(t) = \left(R - \frac{\Phi u(t)}{1+u(t)} - G(e\bar{N}(t))M\right)\bar{N}.$$

Given a large number of traits, i.e., $x_i \in [0,1]$, $i = 1,\ldots,n$, we simplified the tumor population $n(t,x)$ as the $\bar{N}(t)$, where $\bar{N}(t)$ is a n-dimensional vector consisting of the corresponding $n(t,x_i)$'s. Also, R, Φ, M are defined as diagonal matix of r, ϕ and M, respectively. Now, it is possible to approximate the total tumor population $N(t)$ by $e\bar{N}(t)$ where $e = (1,\ldots,1)/n \in \mathbb{R}^{1\times n}$. Accordingly, we define the weights $\bar{\alpha} = \alpha e$ and $\bar{\beta} = \beta e$. By transforming problem 1 into a multi-targeted optimal control problem 2 with finite dimensions, we can make it numerically tractable.

It is common to select parameters $\bar{\alpha}$, $\bar{\beta}$, and γ in a way that balances the focus between cancer cell populations and drug toxicity levels. From the geometric optimal control theory, the Hamiltonian $\bar{H}$ of Problem 2 is,

$$\bar{H} = \lambda^T \left(R - \frac{\Phi u(t)}{1+u(t)} - G(e\bar{N})M\right)\bar{N} + \big(\bar{\beta}\bar{N}(t) + \gamma u(t)\big), \tag{3}$$

According to Pontryagin's Maximum Principle [29, 30], the co-state variable λ satisfies the following:

$$\dot{\lambda} = -\bar{\beta} - \lambda\left(R - \frac{\Phi u}{1+u} - G(e\bar{N})M\right)\bar{N} + \lambda G'(e\bar{N})(eM\bar{N}),$$

Here, we note that $\lambda(T) = \bar{\alpha}$ and G' refers to the derivative of G. Pontryagin's Maximum Principle therefore yields the optimal control law as:

$$u = \min\left\{(\max\left[\left(\sqrt{\frac{\Psi(t)}{\gamma}} - 1\right), 0\right], u_{\max}\right\} \tag{4}$$

Here, the notation $\Psi(t) = \lambda(t)\Phi\bar{N}(t)$ is used to denote the indicator function for control u. Notably, the optimal control for Problem 2 is continuous.

Our numerical approach to obtaining the optimal control for Problem 2, which adopted the shooting method for each iteration [18, 20], is included here as a foundation to search for a possible candidate for Problem 1. Then, after solving the resulting cancerous cell population, we validate that the control u^* is indeed the optimal control for Problem 1 by checking the associated necessary conditions. A brief description of this solving procedure can be found in the following pseudo Algorithm 1. The shooting procedure, in general, is quite sensitive to the initial estimate, in this case, $\lambda(0)$. To address this shortcoming, the developed iterative approach [20, 26, 27] is included to search for a trustworthy prediction of $\lambda(0)$, to guarantee the efficiency of the aforementioned algorithm to be optimization-free and hence allow us to obtain the desired optimal cell-population control from Eq. (4). With the obtained control u^* for Problem 2, the PDE solver

Algorithm 1 Numerical Distribution Control Method

TASK 1 - Obtaining control candidate u for Problem 2
Require: $\bar{N}(t) > 0$, $\forall t \in [0,T]$
  Begin by selecting an estimated value $\lambda(0)$, along with a step size s and a threshold value $\varepsilon > 0$
  while $\|\lambda(T) - \bar{\alpha}\| > \varepsilon$ **do**
    calculate $\bar{N}$ and λ at each time
    $\lambda(0) \Leftarrow \lambda(0) - s\Big(\frac{\delta\lambda(T)}{\delta\lambda(0)}\Big)^{-1}(\lambda(T) - \bar{\alpha})$
  end while
TASK 2 - Check the obtained control u^* for Problem 1
Require: u^* from TASK 1, and boundary values (i.e., $\bar{N}(0,x)$)
  Plug into the PDE Toolbox in MATLAB
  Check that u^* is indeed a good optimal control candidate for Problem 1 through the first-order necessary condition
Validate: Optimality of u^*
  Check the associated Riccati-like equation

in MATLAB is introduced to solve the dynamic equation (1) to obtain the corresponding evolution of the cancerous cell population. The first-order condition for optimality is automatically guaranteed by our solving procedure, hence it suffices to check the second-order sufficient condition i.e., the associated Riccati-like equation for the optimality of this large-scale system:

$$\begin{aligned} \dot{s} + sH_{\lambda^T N} + H_{N\lambda^T} s + H_{NN} - (sH_{\lambda^T u} + H_{Nu}) \\ H_{uu}^{-1}(sH_{\lambda^T u} + H_{Nu})^T \equiv 0 \end{aligned} \tag{5}$$

where $s = s(t), t \in [0,T]$, H is the Hamiltonian associated with Problem 1 that is defined similarly as in Eq. (3) and $H_{xy} = \frac{\partial^2 H}{\partial x \partial y}$ for variables x and y. The obtained treatment scenario is a strong local minimum once the associated Riccati-like equation has a solution over the full therapy horizon.

IV. Numerical Examples

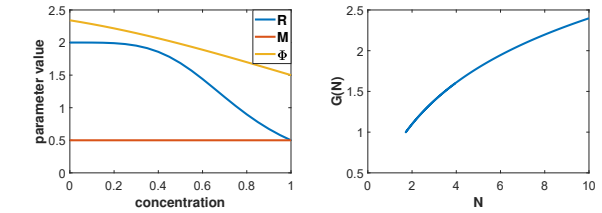
A selection of cancer chemotherapy treatment scenarios, with a single chemotherapeutic treatment available, are numerically generated and examined in this section. Through these examples, we demonstrate the robustness of this aforementioned method and further validate the applicability of the introduced mathematical model. Our interpretations of the numerical scenarios are included to illustrate how our technique of the control attained can be used to manage the optimal distribution of cancer cells.

A. Case 1

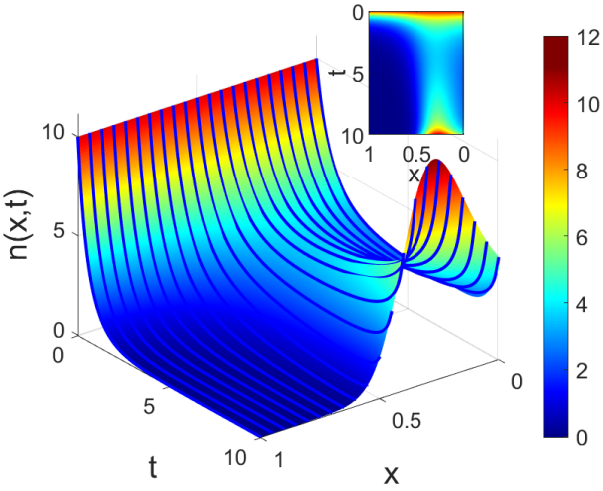
Fig. 1 gives an example of optimal dose strategy with a single drug when $r(x) = \frac{2}{1+3x^4}$, $\varphi(x) = -\sin(x-1)+1.5$, $\delta(x) = 0.5$, as shown in Fig. 1(a). The objective function parameters are $\alpha = 5$, $\beta = 400$ and $\gamma = 10000$, and $u_{\max} = 3$ to limit the drug toxicity. The scaling factor $G(\tau) = \log(1+\tau)$, as shown in Fig. 1(b), is an increasing function and balances the impact of the chosen growth and apoptosis rates.

Fig. 1(c) illustrates the evolution of the resulting cancerous cell distribution during the treating period $t \in [0,10]$, with the inset figure illustrating the same idea in the colormap. Also, Fig. 1(c) includes the trajectories of the discretized scheme traits for Problem 2, which matches the solution manifold for Problem 1 perfectly. Matching trajectories indicate that the solution to Problem 2 can be directly extended to Problem 1. Obtained by our numerical method, as in Algorithm 1, Fig. 1(d) gives the resulting local optimal control from Eq. (4), i.e., the optimal drug concentration applied to the patient. In particular, the initial (blue) and terminal (red) tumor cell distributions are specifically depicted in Fig. 1(e), from which we can see that the bulk of the cancerous cell population has been eliminated throughout the treatment, with the administered medication resulting in the time-varying drug concentration as in Fig. 1(d). However, as shown in Fig. 1(e), this medication may eventually lose its ability to control cancerous cells whose resistance level x's is near 0.3.

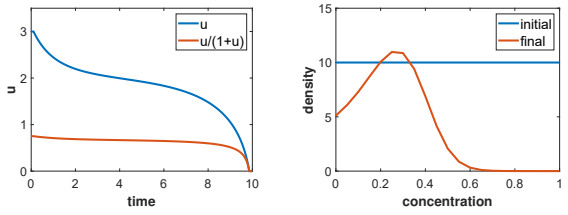
Fig. 1(c) in particular highlights the significant chemotherapeutic impact during the treatment in terms of the decrease of the cancer cell population. However, the final population increase indicates the insufficiency of the drug concentration, as seen in Fig. 1(d), which should be due to the partial dose of drug toxicity throughout the treatment. It is worth pointing out that this concentration, whose actual impact (i.e., $\frac{u}{1+u}$) roughly resembles full dosage, does not reach the full dose during the entire treatment time. One possible explanation is that the parameter arrangement shown in Fig. 1(a), which determines the dynamics, as in Eq.1, guarantees the capability of the introduced treatment.



(a) The pharmacodynamic model (b) The G function



(c) The evolution of cancerous cell distribution



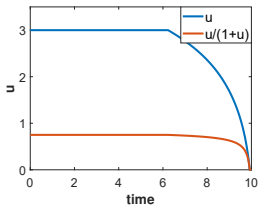
(d) The optimal control law (e) The initial and terminal cancerous distributions

Fig. 1. An example of the optimal dose strategy. (a) The pharmaco-dynamic model in Michaelis-Menten type. (b) The rescaling G function. (c) The resulting evolution of the cancerous cell distribution from $t \in [0,10]$ obtained by the control in (d), with trajectories of discretization scheme from Problem 2 and also the inset figure illustrating the color projection on tx-plane. (d) A numerically computed extremal control for the effectiveness function $\varphi(x) = -\sin(x-1)+1.5$ as in (a), $u_{\max} = 3$, weights $\alpha = (5,\ldots,5)$, $\beta = 80\alpha$, and $\gamma = 10000$ and therapy horizon $T = 10$. (e) The initial and terminal cancerous distributions, which can also be seen in (c).

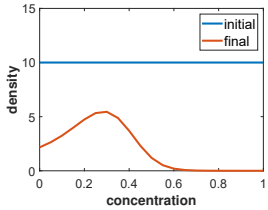
B. Case 2

Another example, as included in Fig. 2, is numerically created to illustrate the chemotherapeutic impact with reduced

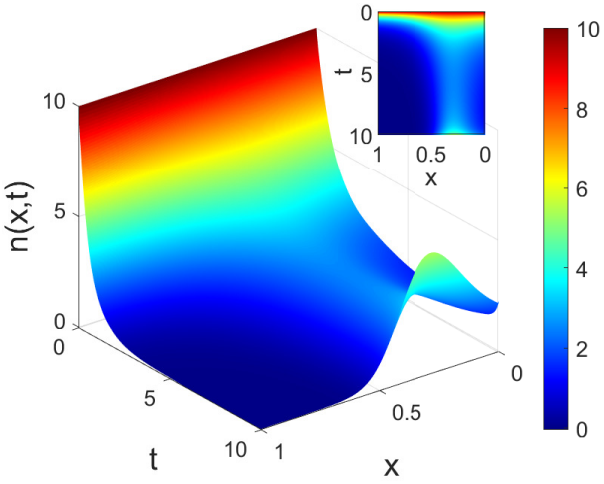
$\gamma = 3000$ while other parameters remain the same. Fig. 2(a) shows the optimal control, obtained by our method, and Fig. 2(c) describes the corresponding evolution of the cancerous cell distribution, with the color projection on the tx-plane shown in the inset figure.



(a) The optimal control law



(b) The evolution of cancerous cell distribution

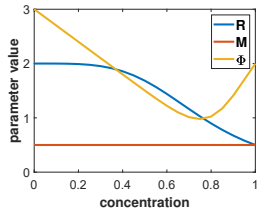


(c) The evolution of cancerous cell distribution

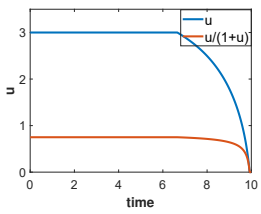
Fig. 2. A numerical example when $\gamma = 3000$ and all other parameters are the same as in Fig. fig:singleopt. (a) A numerically computed extremal control for the effectiveness function $\phi(x) = -\sin(x-1)+1.5$ as in 1(a), $u_{\max} = 3$, weights $\alpha = (5,\ldots,5)$, $\beta = 80\alpha$, $\gamma = 3000$ and therapy horizon $T = 10$. (b) Initial and terminal distributions which can also be seen in (c). (c) The resulting evolution of the cancerous cell distribution from $t \in [0,10]$ obtained by the control in (a), with the inset figure illustrating the color projection on tx-plane.

Our analysis suggests that the control strategy developed for Problem 2 is a good candidate for that of Problem 1, since the majority of the cancerous cell population has been limited by this drug concentration scenario. Note that there is a switching time in optimal control which causes the drug to switch from full dose to intermediate values. A reduction in optimal control protocol was determined starting in year 6, which is visible by the switching point in Fig. 2(a), whereas the pattern of overall treating impact (red curve) remains similar to Case 1.

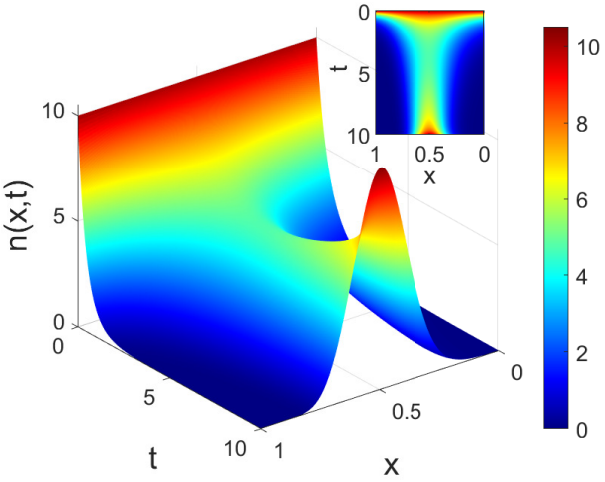
By reducing γ, the drug's side effect on the body is less penalized, and hence higher drug concentration u can be achieved to strengthen the overall treating power, as is demonstrated in Fig. 2(a). Fig. 2(c) displays that a significant proportion of the tumor cells are killed out by the treatment, and more importantly, the increase of the tumor cells towards the end of the treatment is considerably small. Due to the improved actual impact compared to that of Fig. 1(c), this peak is considerably suppressed compared to the preceding scenario. The resulting drug concentration shown in Fig. 2(a) (red) with the sudden drop happening towards the end of the therapy directly results in the resurgence of the population distribution as in Fig. 2(c).



(a) The pharmacodynamic model



(b) The optimal control law



(c) The evolution of cancerous cell distribution

Fig. 3. The treatment scenario with $\phi(x) = 3 - \frac{3x}{1+2x^{10}}$. (a) The pharmacodynamic model in M-M type, $\phi(x) = 3 - \frac{3x}{1+2x^{10}}$ is for the drugs' concentration. (b) A numerically computed extremal control for the effectiveness function ϕ as in (a), $u_{\max} = 3$, weights $\alpha = (5,\ldots,5)$, $\beta = 80\alpha$, $\gamma = 3000$ and therapy horizon $T = 10$. (c) The resulting evolution of the cancerous cell distribution from $t \in [0,10]$ obtained by the control in (b), with the inset figure illustrating the color projection on tx-plane.

C. Case 3

Fig. 3 illustrates another treatment scenario with cytotoxic parameter $\phi(x) = 3 - \frac{3x}{1+2x^{10}}$ which acts differently for $x \in [0.1]$ compared to other cases, while all the other parameters remain the same as those in Fig. 2. The resulting optimal treatment scenario, as depicted in Fig. 3(b), is similar to the one in Fig. 2(a). This could be due to the fact that the drug is greatly toxic (i.e., the corresponding γ is relatively small). The resulting final cancerous distribution has a different pattern compared to those in Fig. 1 and 2. In particular, the location of the peak in the final distribution has been shifted to more resistant cells, i.e. it goes forward from 0.3 to around 0.5, as shown in Fig. 3(c), due to the change in ϕ. Moreover, the higher the concentration of the treatment, the higher the impact on the body within the drug's toxicity tolerance, and as a result the lower the cancer cell population over time. This new concentration pattern

determines that this scenario cannot kill better than Case 2. The large amplitude of the highest peak is a result of changing ϕ. This amplitude means that this drug is not really active in treating in comparison to Case 2 and this suggests that a certain pattern of concentration is of great interest.

Furthermore, the Riccati-like equation, as in (5), has a finite solution s for all 3 cases above. And the proportions of objective values of the above three numerical cases are included thoroughly in Tab. 1. J_{N_T}, $J_{sum(N)}$, and $J_{sum(u)}$, represent the costs for a terminal cell population, total cancer cell population, and drug side effects, respectively, as defined in Eq. (2). The drug side effect in the third case is controlled well as its related cost value proportion shows a lower value than the others while its final tumor population is in a worse situation than Case 2. Among all cases, Case 2 is the most successful in killing the tumor cells at the end of the therapy as its related portion (J_{N_T}) takes the lowest value.

	$J_{N_T}(‰)$	$J_{sum(N)}(\%)$	$J_{sum(u)}(\%)$
Case 1	0.10	54.14	45.75
Case 2	0.08	67.41	32.51
Case 3	0.09	72.89	27.01

Tab.1. Ratios of cost values

V. Conclusions

Our paper focuses on the use of a mathematical model to explore optimal distributional control problems in cancer chemotherapeutic treatment, specifically in the context of tumor heterogeneity. It begins by formulating the optimal cancerous cell population control problem, which involves a partial differential equation, and then connects it with a simplified model consisting of finite traits in consideration. A numerical method is provided to search for the optimal solution, combining our previous approach for the high-dimensional optimal control problems and the Liouville approach from the distribution evolution perspective. We also present a few numerical cases to demonstrate the applicability of this method and further discuss the cause and effects of the considered treating scenarios. We hope this optimal cell-population control formulation can provide a guideline for treating cancer diseases in practice and further enable explorations for cancer treatment with multiple treatment techniques.

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