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A lumped ODE model for metastatic cancer treatment

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ABSTRACT: In [*J Theor Biol* **203**(2) (2000):177–186], a size-structured PDE population model has been proposed for characterizing the growth (in number of cells) of metastatic tumors. Recently, such simple transport PDE models were carefully validated through laboratory experiments with tumor-bearing mice. Many efforts have been devoted to developing more efficient numerical algorithms for solving such interesting PDE models, but its computational cost remains high in the framework of optimal control for seeking optimized treatment strategy due to a huge spatial domain. In particular, the computed cell-level metastatic density from PDE model is not of direct biological interest, instead, its weighted integration (e.g., the total number of tumor cells) is of more clinical importance in practice. In this work, we reformulate such a transport PDE model into a lumped ODE model that involves a Volterra integral equation of convolution type which is independent of the control variable. Such a reformulation can significantly reduce the computational cost by only computing the lumped (or aggregated) quantity without spatial dependence. Moreover, for better practicality, we incorporate the nonlinear Pharmacokineticv and Pharmacodynamic effects of treatment into our lumped ODE model. Based on the open-source nonlinear optimal control software ICLOCS2, numerical examples are presented to illustrate some interesting findings on optimal treatment that may inspire clinical practice.

KEYWORDS: metastatic cancer, lumped model, optimal control, bang-bang control, singular control

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INTRODUCTION

Cancer is a leading cause of death worldwide. The spread of cancer tumor cells from one location to many other locations, called *metastasis*, accounts for the majority of cancer-related deaths [1]. Unfortunately, the mechanism of metastasis remains the least understood aspect of cancer biology [2–4]. Recent studies [5] on breast cancer suggest that, contrary to more traditional thinking, metastatic dissemination can occur rather early. Such early occult metastasis [6] is undetectable by the existing standard diagnosis/imaging modalities. Hence, we need alternative methodologies for quantifying and controlling such lethal metastasis as early as possible, so that tumor growth can be controlled by effective therapy at the earliest time.

Quantitative approaches based on mathematical modeling and optimal control theory have become increasingly important in cancer treatment research, see e.g. [7–11]. Such insightful mathematical models were validated by experimental data, which can augment experimental and clinical studies by deepening our understanding of mechanisms driving tumorigenesis. More importantly, they can be utilized to further optimize current cancer treatment strategies [12, 13].The use of deterministic ODE optimal control theory to optimize cancer treatment (e.g., chemotherapy) is an old topic, see for example [14, 15]. To accommodate the spatial interactions, size-structured PDE-based optimal control models for cancer treatment optimization were also studied, see for instance [16–18]. Although such PDE models can provide better capacity with higher resolution in describing more detailed system dynamics, their computational costs become significantly higher due to the invovled huge spatial domain. In addition, the optimal control or treatment is only a function of time (independent of the spatial size variable) and the clinically meaningful qualities is reconstructed by integrating the PDE solutions in space. This leads to unnecessary computational burden, especially in the framework of optimal control or treatment.

In this paper, we contribute to reformulating the size-structured PDE model [19] into a lumped ODE model through integration along the characteristic lines, so that its optimal control or treatment becomes easier to analyze and also much faster to compute. The derived optimal control based on our proposed linear lumped ODE model is shown to be bang-bang control, which matches with the conclusion obtained with PDE model [20]. Furthermore, we augment the proposed lumped ODE model with nonlinear Pharmacokineticv (PK) and Pharmacodynamic (PD) effects, which leads to a quite different control structure that often consists of a transition phase of singular control from the maximum dosage to the minimal. This suggests it can be more effective to gradually phase

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out the drug dosage in clinical practice. Although the size-structured PDE model can provide more detail information on the distribution of tumor sizes, the computation of size-independent optimal control does not necessary benefit from such detail information. Therefore, it is computationally more efficient to work with the corresponding simpler ODE model after eliminating the size variable through integration in space. This reformulation assumes the drug dosage is only time-dependent.

REVIEW OF A SIZE-STRUCTURED PDE MODEL AND ITS OPTIMAL CONTROL

In [19], the authors proposed an ODE-PDE dynamical model, which describes the colony size distribution of metastatic tumors. It consists of an ODE for the growth of the primary tumor size:

$$x_p'(t) = g(x_p(t)), \quad x_p(0) = x_0, \tag{1}$$

with $x_p(t)$ being the primary tumor size with an estimated growth rate $g(x)$, and a size-structured transport PDE for the distribution of metastatic tumors of continuous sizes:

$$\begin{cases} \bar{\rho}_t(x,t) + (g(x)\bar{\rho}(x,t))_x = 0, \quad t > 0,\ x \in (1,b), \\ g(1)\bar{\rho}(1,t) = \beta(x_p(t)) + \int_1^b \beta(x)\bar{\rho}(x,t)\,\mathrm{d}x,\ t > 0, \\ \bar{\rho}(x,0) = 0, \end{cases} \tag{2}$$

with $\bar{\rho}(x,t)$ being the metastatic density with colonization (birth) rate $\beta(x) = \mu x^\alpha, \alpha \in (0,1]$. In [19], a Gompertz growth model with $g(x) = ax\ln(b/x)$ is used, where a is growth rate constant and $b \approx 10^8$–10^{12} is the maximum tumor size (in number of cells). In [19] the authors also derived an infinity series solution of the above PDE model via the Laplace transform technique, which is however not applicable to the more general cases. As discussed in [21], the solution of PDE (2) has a singularity near $x = 1$ due to the nonlocal boundary condition with a huge spatial domain $(1, b)$, which needs careful numerical treatment if a high approximation accuracy is desired.

The optimal control (treatment) based on the above metastatic PDE model was first discussed in [22, 23], where the control (treatment) $u(t)$ is assumed to directly reduce the growth rate $g(x)$ and the combinations of chemotherapy and anti-angiogenic therapy are considered. Recently, this metastatic PDE model was validated through laboratory experiments with tumor-bearing mice [24–26] and applied to modeling of metastatic breast cancer after neoadjuvant treatment [27], which highly motivates us to further study and improve this model.

In our recent work [20], we developed a bilinear optimal control model for treatment, where the chemotherapy drug dosage rate over time is treated as a control variable $u(t)$ that affects the mortality (death) rate. Here we assumed the drug has a uniform treatment effectiveness [28] on all tumors that are independent of the tumor's size. Based on the assumption that both the primal and metastatic tumor emit new metastases at the same colonization rate (see [19, 29, 30]), in [20] we proposed a unified size-structured PDE model. By introducing a Dirac delta density function for the primal tumor $\hat{\rho}(x,t) = \delta_{x_p(t)}(x)$, and then defining the total tumor density function $\rho(x,t) = \bar{\rho}(x,t) + \hat{\rho}(x,t)$, the model (1)–(2) can be unified into a McKendrick-Von Foerster type model [31–33]

$$\begin{cases} \rho_t(x,t) + (g(x)\rho(x,t))_x = 0, \quad 1 \leqslant x \leqslant b, 0 < t < T, \\ g(1)\rho(1,t) = \int_1^b \beta(x)\rho(x,t)\,\mathrm{d}x, \qquad t > 0, \\ \rho(x,0) = \delta_{x_0}(x), \qquad 1 \leqslant x \leqslant b, \end{cases} \tag{3}$$

where the Dirac delta initial condition $\delta_{x_0}(x)$ is from $x_p(0) = x_0$. Such a size-structured PDE model allows us to handle more general initial tumor size distribution by choosing any initial condition $\rho(x,0) = \rho_0(x)$ based on the actual observation data (e.g., from CT scans). For the efficient numerical solution of such linear PDE models with a nonlocal boundary condition, we refer to the recent contributions [34, 35] for related discussion.

Next, we consider a optimal control model for treatment. Let $w(x) > 0$ be a given weight function and define the weighted total metastases

$$M_w(t) := \int_1^b w(x)\rho(x,t)dx, \tag{4}$$

which gives the total number of tumor cells (resp. the total metastatic mass) if $w(x) = 1$ (resp., $w(x) = x$). To find the optimal treatment strategy $u(t) \in [0, \bar{u}]$, we can minimize the following objective functional of total metastases and weighted drug toxicity ($\theta \in \{0, 1\}$)

$$\min_{0 \leqslant u(t) \leqslant \bar{u}} J_\theta(\rho, u) := M_w(T) + \theta \int_0^T M_w(t)\,\mathrm{d}t + \gamma \int_0^T u(t)\,\mathrm{d}t, \tag{5}$$

where $\rho(x,t)$ satisfies the following PDE that describes the controlled growth of metastatic tumors

$$\begin{cases} \rho_t(x,t) + (g(x)\rho(x,t))_x = -u(t)\rho(x,t), \\ \qquad\qquad 1 \leqslant x \leqslant b,\ 0 < t < T, \\ g(1)\rho(1,t) = \int_1^b \beta(x)\rho(x,t)dx, \qquad t > 0, \\ \rho(x,0) = \rho_0(x), \qquad 1 \leqslant x \leqslant b. \end{cases} \tag{6}$$

Here $0 \leqslant u(t) \leqslant \bar{u}$ is the prescribed drug dosage rate bounds. The linear log-kill term $u(t)\rho(x,t)$ describes the simplest (but unrealistic) PK/PD effects of chemotherapy on the cancer, that is chemotherapy kills cancer cells at a rate proportional to their population

and the used drug dosage. In the objective functional J_θ, we assume the weight parameters $\gamma > 0$ and $\theta \geqslant 0$. If the patient only cares about the outcomes at the end of the treatment period, one may take $\theta = 0$, which allows the possible large growth of tumor during treatment and it also leads to non-uniqueness of optimal control [20]. In [20], we have derived the following first necessary optimality KKT conditions for the model (5)–(6). Notice that $u(t)$ only depends on the integration of $p(x,t)$ in space.

Theorem 1 ([20]) *A control $u \in U_{ad} := \{u \in L^\infty(0,T) : 0 \leqslant u(t) \leqslant \bar{u}\}$ with the associated state ρ is optimal for the optimal control problem (5)–(6) if and only if the corresponding Lagrange multiplier (adjoint state) p satisfies the following adjoint equation (marching backward in time)*

$$\begin{aligned} &p_t(x,t)+g(x)p_x(x,t)-u(t)p(x,t)+\beta(x)p(1,t)=\theta w(x), \\ &\qquad\qquad 1 \leqslant x \leqslant b,\ 0 < t < T, \quad (7)\\ &p(x,T) = -w(x), \qquad 1 \leqslant x \leqslant b, \end{aligned}$$

and the optimal control u is given by the variational inequality for almost every $t \in [0,T]$:

$$\left(\gamma + \int_1^b \rho(x,t)p(x,t)\,\mathrm{d}x\right)(v-u(t)) \geqslant 0,\ \forall\, v \in [0,\bar{u}]. \quad (8)$$

In [20], the authors proved that the optimal control is of bang-bang type when it is unique (i.e., $\theta = 1$). Based on a second-order accurate characteristic scheme, a projection gradient descent (PGD) algorithm is developed to iteratively solve the optimality system with a linear convergence rate. Each iteration requires forward and backward time-marching along the characteristic curves to solve the PDE for ρ and p, respectively. Such a PGD algorithm based on characteristic schemes in space has a high computational cost since it needs to iteratively solve PDEs many times with a very fine mesh. This stimulates us to reformulate the size-structured PDE model into the following Volterra integral equation model that allows more efficient numerical algorithms by eliminating the spatial variable and then reducing it into a lumped ODE model. Since the size-structured metastatic density $\rho(x,t)$ itself may not be of direct biological interest, it is clinically more meaningful to compute the biological quantities (e.g. $M_w(t)$) directly without explicitly computing $\rho(x,t)$ first.

A NEW LUMPED ODE MODEL WITH PK/PD EFFECTS

Inspired by the interesting idea in [36], we will reformulate the above PDE optimal control model into a Volterra integral equation regarding $M_w(t)$, where the control term $u(t)$ acts on $M_w(t)$ globally or collectively and there is no need to compute or approximate $\rho(x,t)$ anymore. Essentially, this procedure reduces the above PDE model to an ODE model together with a Volterra integration equation that is independent of the control term.

Reformulation of the PDE model into a linear lumped ODE model

Let $X(s)$ be the solution of $X'(s) = g(X(s))$ with initial condition $X(0) = 1$, there holds $X(\infty) = b$ if choosing $g(x) = ax\ln(b/x)$. After some tedious calculation (see Appendix for detail), the above PDE-based treatment model (5)–(6) can be reformulated into the following minimization problem

$$\min_{0\leqslant u(t)\leqslant \bar{u}} J_\theta(\rho,u) := M_w(T) + \theta\int_0^T M_w(t)\,\mathrm{d}t + \gamma\int_0^T u(t)\,\mathrm{d}t, \quad (9)$$

subject to a linear Volterra integral equation (VIE) on $M_w(t)$:

$$M_w(t) = \int_0^t \beta(X(r))\,\mathrm{e}^{U(t-r)-U(t)} M_w(t-r)\,\mathrm{d}r + \mathrm{e}^{U(0)-U(t)}F(t) \quad (10)$$

where

$$U(t) := \int_0^t u(\tau)\,\mathrm{d}\tau \quad (11)$$

is the total drug usage up to time t and $F(t)$ only depends on w, β, g, and ρ_0. In our considered case with $\rho_0(x) = \delta_1(x)$ we will have a simple expression $F(t) = w(X(t))$.

By defining $\Phi(t) := \mathrm{e}^{U(t)}M_w(t)$ and noting $U(0) = 0$, the above VIE-based treatment model (9)–(10) can be further simplified as

$$\min_{0\leqslant u(t)\leqslant \bar{u}} J_\theta(U,u) := \mathrm{e}^{-U(T)}\Phi(T) + \theta\int_0^T \mathrm{e}^{-U(t)}\Phi(t)\,\mathrm{d}t + \gamma U(T), \quad (12)$$

where $\Phi(t)$ is given by the following Volterra integral equation of convolution type

$$\Phi(t) = \int_0^t \beta(X(t-r))\Phi(r)\,\mathrm{d}r + F(t). \quad (13)$$

Here $\Phi(t)$ is independent of the control $u(t)$ or $U(t)$. In addition, there is a simple ODE constraint

$$U'(t) = u(t), \quad U(0) = 0. \quad (14)$$

Due to the simplified structure, we expect the above ODE model (12)–(14) to be much cheaper to solve numerically. In fact, $\Phi(t)$ can be computed very efficiently from (13) by FFT-based techniques [37].

To find the first-order necessary optimality conditions of (12)–(14), we construct the Hamiltonian

$$\mathscr{H}(U,u,p) := \theta\, \mathrm{e}^{-U(t)}\Phi(t) + p(t)u(t),$$

where $p(t)$ is the adjoint state or Lagrange multiplier. The necessary optimality system [38, p. 233] consists of both the state equation on $U(t)$ and the adjoint equation on $p(t)$:

$$U'(t) = u(t), \quad U(0) = 0, \tag{15}$$

$$\begin{aligned} p'(t) &= -\frac{\partial \mathscr{H}}{\partial U} = \theta\, \mathrm{e}^{-U(t)}\Phi(t), \\ p(T) &= \gamma - \mathrm{e}^{-U(T)}\Phi(T), \end{aligned} \tag{16}$$

and by the Pontryagin's Minimum Principle, the optimal control $u^*(t)$ satisfies the condition

$$\begin{aligned} \mathscr{H}(U,u^*,p) &= \min_{0\leqslant u(t)\leqslant \bar{u}} \mathscr{H}(U,u,p) \\ &= \min_{0\leqslant u(t)\leqslant \bar{u}} \{\theta\, \mathrm{e}^{-U(t)}\Phi(t) + p(t)u(t)\}. \end{aligned}$$

By defining the switching function

$$\phi(t) := \frac{\partial \mathscr{H}}{\partial u} = p(t),$$

then the optimal control u^* is expected to have the following typical piece-wise structure

$$u^*(t) = \begin{cases} 0, & \text{whenever } \phi(t) > 0, \\ \text{singular}, & \text{whenever } \phi(t) = 0, \\ \bar{u}, & \text{whenever } \phi(t) < 0, \end{cases} \tag{17}$$

where the optimal control u^* is bang-bang type if $\phi(t) \neq 0$ holds almost everywhere.

Similar to the results obtained in [20], we have the following interesting conclusions:

- If $\theta = 0$, then $p'(t) = 0$ and hence $\phi(t) = p(t) = p(T) = \gamma - \mathrm{e}^{-U(T)}\Phi(T)$. By letting $\phi(t) \equiv 0$ we can obtain the optimal total drug dosage

  $$U^*(T) = \ln(\Phi(T)/\gamma),$$

  which implies the optimal (singular) control $u^*(t)$ is *not unique* as long as its satisfies the global integral relation

  $$\int_0^T u^*(\tau)\,\mathrm{d}\tau = \ln(\Phi(T)/\gamma).$$

  The same conclusion was also derived in [20] using a simple function minimization argument. We will not consider this situation further since it has no control over total metastatic mass.

- If $\theta = 1$, then $p'(t) = \mathrm{e}^{-U(t)}\Phi(t) > 0$. Hence $\phi(t) = p(t)$ is strictly increasing and it can change sign only once (from negative to positive) depending on the sign of $p(T) = \gamma - \mathrm{e}^{-U(T)}\Phi(T)$. This implies the optimal control can switch at most once from $\bar{u}$ to 0 at some time $t_1 \in [0,T]$ and hence it is unique and of bang-bang type. Clearly $0 \leqslant U(T) \leqslant T\bar{u}$. If $\gamma > 0$ is very small such that

  $$p(T) = \gamma - \mathrm{e}^{-U(T)}\Phi(T) \leqslant \gamma - \mathrm{e}^{-T\bar{u}}\Phi(T) \leqslant 0,$$

  then $p(t) < p(T) \leqslant 0$ and hence $u^*(t) = \bar{u}$ for all $t \in [0,T]$, which says the maximum dosage should be used if the drug side effect is very low. If $\gamma > 0$ is large enough such that $p(T) > 0$, then we may solve for $p(t)$ and then construct a nonlinear equation to find $t_1 \in (0,T)$ such that $p(t_1) = 0$ if it exists. We refer to [20] for the discussion on how to find t_1 numerically.

Integrate nonlinear PK/PD effects in treatment

The previous treatment model is based on a simple but unrealistic assumption that the drug's dosage $u(t)$ is identical to its concentration and effects (on death rate), which leads to a bilinear control problem that is relatively simpler to analyze and solve. For more practical use of our model, we will incorporate more realistic cell-kill hypotheses, such as the Norton–Simon hypothesis [39], in which chemotherapy kills cancer cells at a rate proportional to their growth rate, and the (sigmoid) $E_{\max}$ model [40], in which chemotherapy kills cancer cells at a saturable rate.

Pharmacokinetic (PK) models [41] delineate the time evolution of a drug's concentration in the blood plasma, i.e., *what the body does to the drug*. Pharmacodynamic (PD) models describe the effects that the drug concentrations have on the tumor cells, i.e., *what the drug does to the body*. Given a time-varying continuous drug dose rate $u(t) \in [0,\bar{u}]$, the drug concentration $c(t)$ in the bloodstream can be described by a simple 1-compartment linear ODE model

$$c'(t) = u(t) - \sigma c(t), \qquad c(0) = 0, \tag{18}$$

where $\sigma > 0$ is the clearance rate of the drug from the body that reduces the drug concentration. This leads to the following concentration solution formula and its upper bound

$$\begin{aligned} c(t) &= \mathrm{e}^{-\sigma t}\int_0^t u(\tau)\,\mathrm{e}^{\sigma\tau}\,\mathrm{d}\tau \\ &\leqslant \bar{u}\,\mathrm{e}^{-\sigma t}\int_0^t \mathrm{e}^{\sigma\tau}\,\mathrm{d}\tau = \bar{u}\frac{1-\mathrm{e}^{-\sigma t}}{\sigma} \leqslant \bar{u}/\sigma =: c_{\max}. \end{aligned}$$

In [42], the authors proposed a bilinear ODE model (which reduces to the above model if $\eta = 0$)

$$\begin{aligned} c'(t) &= u(t)-(\sigma+\eta u(t))c(t) \\ &= (1-\eta c(t))u(t)-\sigma c(t), \quad c(0) \quad = 0, \end{aligned} \tag{19}$$

where the free parameter η is assumed to satisfy $(\sigma+\eta\bar{u})>0$. The added nonzero parameter η allows the concentrations to build up to the maximum level at a rate different from how fast the drug is cleared by the system after the drug has been stopped. In the case of $\eta>0$, there holds

$$\begin{aligned} c(t) &= \mathrm{e}^{-\sigma t-\eta\int_0^t u(\tau)\,\mathrm{d}\tau}\int_0^t \left(u(\tau)\,\mathrm{e}^{\sigma\tau+\eta\int_0^\tau u(z)\,\mathrm{d}z}\right)\mathrm{d}\tau \\ &< \frac{\bar{u}}{\sigma+\eta\bar{u}} = \frac{1}{\sigma/\bar{u}+\eta} =: c_{\max} < \min\{\bar{u}/\sigma, 1/\eta\}, \end{aligned} \tag{20}$$

which implies the drug concentration saturates at $1/\eta$ regardless of the maximum drug dosage $\bar{u}$. In particular, if $\eta>0$ then it follows from (20) that $c(t)<1/\eta$ or equivalently $(1-\eta c(t))>0$.

The effectiveness of a chemotherapy drug, denoted by s, is often modeled as a function of the drug concentration c according to the Michaelis-Menten ($E_{\max}$) type pharmacodynamic model

$$s(c) := E_{\max}\frac{c}{EC_{50}+c}, \tag{21}$$

where $E_{\max}$ denotes the maximum effect and EC_{50} is the concentration at which half of the maximum effect $E_{\max}$ is realized. Such type of $E_{\max}$ model or its sigmoidal variants can approximate the actual effectiveness at both lower and higher levels of concentrations more accurately than the simple linear log-kill model with merely $s(c)=c$. In general, we may only assume s to be strictly increasing (i.e., $s'(c)>0$) and it satisfies $s(0)=0$ meaning no drug effect with zero drug concentration. We refer to [43] for more discussion on the properties of various PK/PD models.

Abstractly, the nonlinear function $s(c(t))$ represents the PK/PD effects of the treatment, and the drug concentration $c(t)$ depends nonlinearly on the drug dosage rate $u(t)$. Define the integrating factor (of accumulative drug effectiveness)

$$V(t) = \int_0^t s(c(\tau))\,\mathrm{d}\tau. \tag{22}$$

Combining such PK/PD effects, we propose an ODE treatment model of the following form

$$\begin{aligned} \min_{0\leqslant u(t)\leqslant\bar{u}} J_\theta(V,c,u) &:= \mathrm{e}^{-V(T)}\Phi(T) \\ &+\theta\int_0^T \mathrm{e}^{-V(t)}\Phi(t)\,\mathrm{d}t+\gamma\int_0^T u(t)\,\mathrm{d}t, \end{aligned} \tag{23}$$

subject to the nonlinear ODE system (with $\sigma>0$ and $s'(c)>0$)

$$V'(t) = s(c(t)), \quad V(0)=0, \tag{24}$$

$$c'(t) = u(t)-(\sigma+\eta u(t))c(t), \qquad c(0)=0, \tag{25}$$

where $\Phi(t) := \mathrm{e}^{V(t)}M_w(t)$ is the solution of the similar VIE (independent of u,V,c)

$$\Phi(t) = \int_0^t \beta(X(t-r))\Phi(r)\,\mathrm{d}r + F(t) \tag{26}$$

Obviously, if $s(c(t))=u(t)$ then this model reduces to the previous model by noting $V(t)=U(t)$.

To find the first-order necessary optimality conditions, we construct the following Hamiltonian

$$\begin{aligned} &\mathscr{H}(V,c,u,p_1,p_2) := \theta e^{-V(t)}\Phi(t) \\ &+\gamma u(t)+p_1(t)s(c(t))+p_2(t)(u(t)-(\sigma+\eta u(t))c(t)), \end{aligned}$$

where $p_1(t)$ and $p_2(t)$ are the adjoint-states or Lagrange multipliers. Clearly, we have

$$\frac{\partial^2\mathscr{H}}{\partial u^2} = 0,$$

which indicates the following necessary optimality condition may not be sufficient. The necessary optimality system [38, p. 233] consists of the system state equations and the adjoint equations

$$V'(t) = s(c(t)), \quad V(0)=0, \tag{27}$$

$$c'(t) = u(t)-(\sigma+\eta u(t))c(t), \quad c(0)=0, \tag{28}$$

$$\begin{aligned} &p_1'(t) = -\frac{\partial\mathscr{H}}{\partial V} = \theta\,\mathrm{e}^{-V(t)}\Phi(t), \\ &p_1(T) = -\mathrm{e}^{-V(T)}\Phi(T); \end{aligned} \tag{29}$$

$$\begin{aligned} p_2'(t) &= -\frac{\partial\mathscr{H}}{\partial c} \\ &= -p_1(t)s'(c(t))+p_2(t)(\sigma+\eta u(t)),\ p_2(T)=0. \end{aligned} \tag{30}$$

By Pontryagin's Minimum Principle, the optimal control u^* satisfies

$$\mathscr{H}(V,c,u^*,p_1,p_2) = \min_{0\leqslant u(t)\leqslant\bar{u}}\mathscr{H}(V,c,u,p_1,p_2).$$

By defining the switching function (notice $\gamma>0$ and $(1-\eta c(t))>0$ from the bound (20))

$$\phi(t) := \frac{\partial\mathscr{H}}{\partial u} = \gamma+p_2(t)(1-\eta c(t)),$$

the optimal control u^* is expected to have the following typical piece-wise structure

$$u^*(t) = \begin{cases} 0, & \text{whenever } \phi(t)>0, \\ \text{singular}, & \text{whenever } \phi(t)=0, \\ \bar{u}, & \text{whenever } \phi(t)<0. \end{cases} \tag{31}$$

Due to non-linearity of the above necessary optimality system (27)–(30), it becomes too intricate to derive the analytical expression of the optimal control; see [38, p. 300] for further discussion on how to analytically find singular control under rather simplified cases. We will explore the characteristics of the optimal control based on the numerical experiments with the MATLAB-based open software package ICLOCS2. We remark that there are many other high-standard ODE-based optimal control softwares, such as GPOPS-II [44], which are based on pseudospectral methods.

NUMERICAL RESULTS

In this section, we will present several numerical examples to illustrate our proposed lumped ODE model with nonlinear PK/PD effects in treatment. We used the MATLAB-based Imperial College London Optimal Control Software (ICLOCS2, http://www.ee.ic.ac.uk/ICLOCS/default.htm) for numerically solving our ODE optimal control problem. ICLOCS2 will transcribe the optimal control problems into nonlinear programming problems that are solved by the well-known Interior Point OPTimizer (IPOPT) [45]. We choose $\beta(x) = \mu x^{\alpha}, g(x) = ax\ln(b/x)$, $\theta = 1$ and $w(x) = x$ in our numerical examples, and denote $M(t) = M_w(t)$ for simplicity. As used in [20], we will test three different cases of model parameters:

(A) (Toy case) $a = 1$, $b = e$, $\mu = 1$, $\alpha = 1$, $\bar{u} = 2$, $T = 10$, $\gamma = 0.1$;

(B) (Preclinical case) $a = 0.08$, $b = 6\times10^8$, $\mu = 10^{-5}$, $\alpha = 2/3$, $\bar{u} = 2$, $T = 15$, $\gamma = 0.1$;

(C) (Clinical case) $a = 0.0084$, $b = 6.25\times10^8$, $\mu = 10^{-3}$, $\alpha = 2/3$, $\bar{u} = 1/2$, $T = 30$, $\gamma = 0.1$.

We will only consider the typical case with $\rho_0(x) = \delta_1(x)$ such that $F(t) = w(X(t)) = X(t)$. Since $\Phi(t)$ is independent of the control u and state variables, we can evaluate $\Phi(t)$ numerically offline before or during the optimization procedure. Fig. 1 shows the expected exponential growth of numerically computed $\Phi(t)$ of different model parameters, which are efficiently computed by FFT techniques as described in [36, 37]. Notice that $\Phi(t)$ in different cases has a different growth rate.

The linear case without PD/PK effects

In the first example, we consider the linear lumped ODE model without the nonlinear PD/PK effects, which corresponds to the linear optimality system (15)–(16). Fig. 2 compares the dynamics of metastatic mass $M(t)$ and the corresponding optimal drug dosage $u(t)$ for the three different sets of model parameters, respectively. As expected from our discussion, the optimal drug dosage $u(t)$ in all cases are bang-bang control switching from the maximum dosage $\bar{u}$ to zero only once. Such obtained optimal bang-bang control structures in our lumped ODE model are compatible to the results in [20] based on the transport PDE model. Hence, there is no need to solve the expensive transport PDE model from the viewpoint of practical use.

The nonlinear case with PD/PK effects

In the second example, we consider the lumped ODE model with nonlinear PD/PK effects, which corresponds to the nonlinear optimality system (27)–(30). Here we first fix parameters $E_{\max} = 6$, $EC_{50} = 0.5$ and then test different combination of parameters $\eta = 0, 2$, $\sigma = 0.4, 4$. Notice that the max drug concentration $c_{\max}$ is decreasing as the clearance rate σ gets larger. Fig. 3 and Fig. 4 illustrate the dynamics of metastatic mass $M(t)$ and the corresponding optimal drug dosage $u(t)$ with $\eta = 0, 2$ and $\sigma = 0.4, 4$, respectively. Except for the case of $\eta = 0$ and $\sigma = 0.4$, all the optimal control $u(t)$ displays similar pattern of three pieces: starts a period of maximum drug dosage, then a transition phase of singular control, and finally no drug in the last stage. The length of the singular control segment seems to depend on the value of σ and η.

When $\eta = 0$, for a small clearance rate $\sigma = 0.4$, the overall optimal control pattern is closer to the typical bang-bang control since the drug concentration decreases very slowly, but when $\eta = 2$ we do observe a very prolonged very low drug dosage following the maximum dosage. This interesting observation matches the recommendation of a low-dose, continuous, metronomic administration scheme over a more classical maximum tolerated dose schedule [23].

If the drug has a larger clearance rate σ, it remains in the body for a shorter period and at a lower concentration. Therefore, adopting a regimen with a longer period of maximum drug dosage followed by a maintenance phase of lower drug dosage could help maintain adequate drug levels in the body to control metastatic growth effectively. The smooth transition pattern agrees with the clinical practice of phasing out the maximum drug dosage gradually, which is in contrast to the previous bang-bang control without PD/PK effects.

Finally, we study the effects of the PD parameters $E_{\max}$ and EC_{50}. In particular, we fix the parameters $\eta = 0$ and $\sigma = 0.4$ and then vary the PD parameters $E_{\max}$ and EC_{50}. It is observed from Fig. 5 that the optimal control decreases with increasing $E_{\max}$ and increases with increasing EC_{50}, respectively. Recall that $E_{\max}$ represents the maximum effect of the drug, and EC_{50} is the drug concentration at which half of the maximum effect (i.e., $E_{\max}/2$) is achieved. A higher $E_{\max}$ indicates a more effective drug, thereby requiring a lower dosage. Conversely, a higher EC_{50} means that a higher drug concentration is needed to effectively control the metastatic growth, leading to a higher optimal drug dosage.

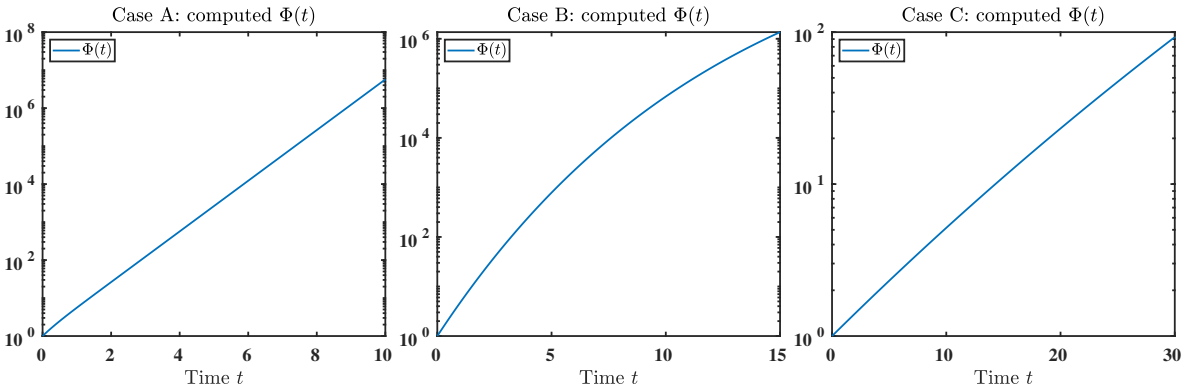

Fig. 1 Computed $\Phi(t)$ with model parameters from left to right: Case A, Case B, and Case C.

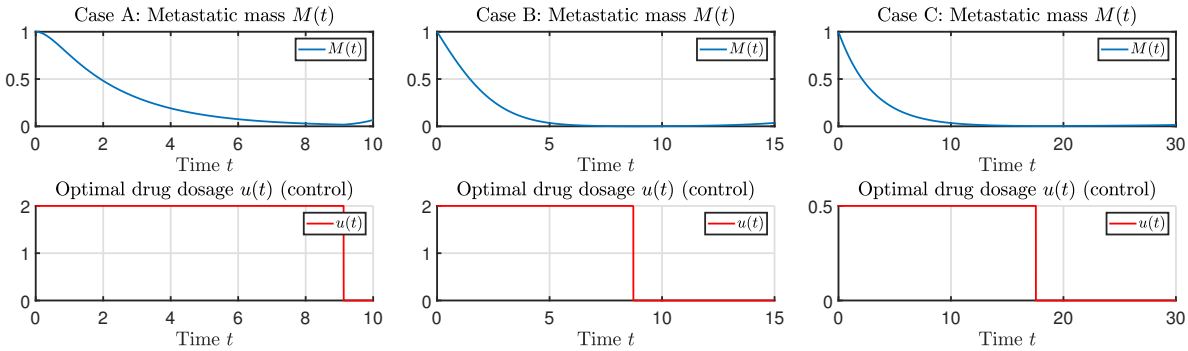

Fig. 2 J_1 model without PD/PK effects: dynamics of metastatic mass under the optimal drug dosage. The model parameters from left to right: Case A, Case B, and Case C.

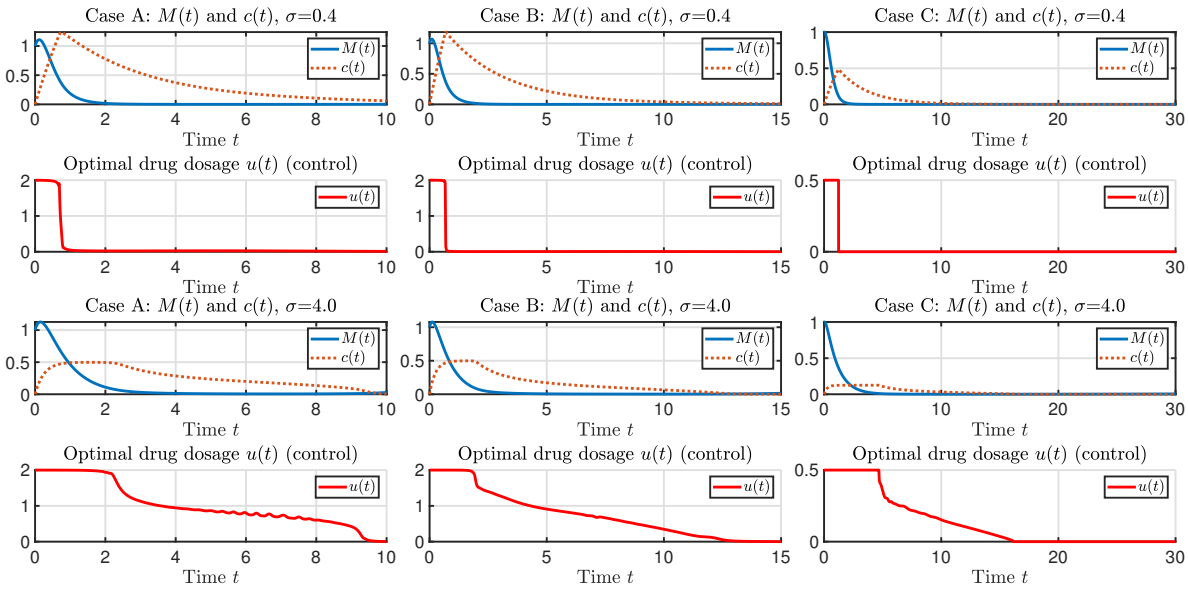

Fig. 3 J_1 model with $\eta = 0$: dynamics of metastatic mass and drug concentration under the optimal drug dosage (with $\sigma = 0.4$ (top) and $\sigma = 4$ (bottom)). The model parameters from left to right: Case A, Case B, and Case C.

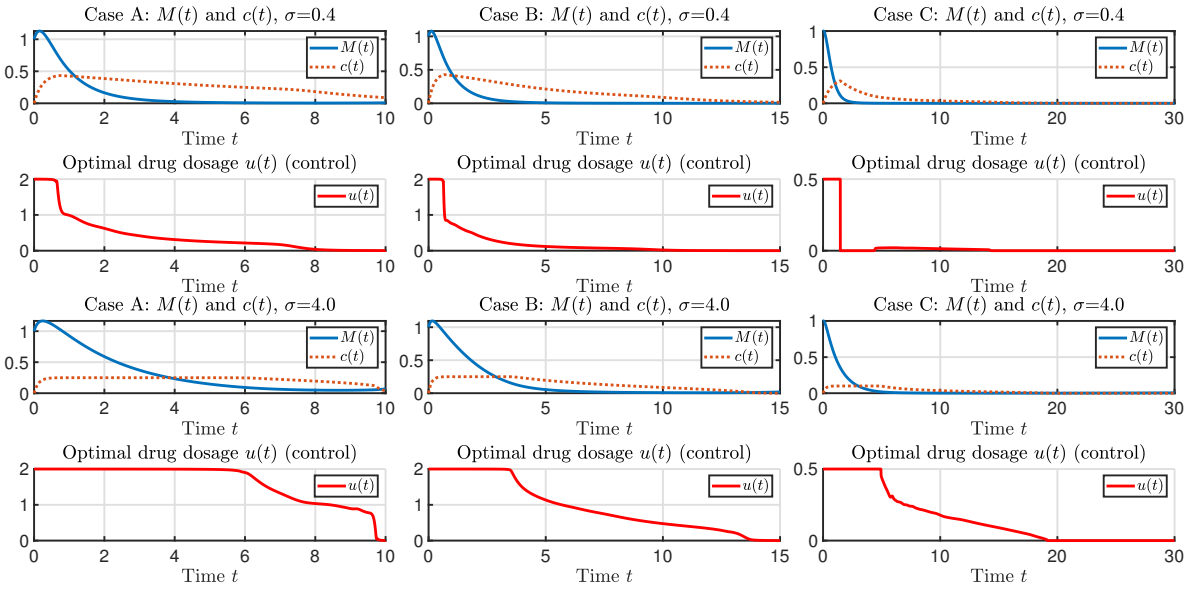

Fig. 4 J_1 model with $\eta = 2$: dynamics of metastatic mass and drug concentration under the optimal drug dosage (with $\sigma = 0.4$ (top) and $\sigma = 4$ (bottom)). The model parameters from left to right: Case A, Case B, and Case C.

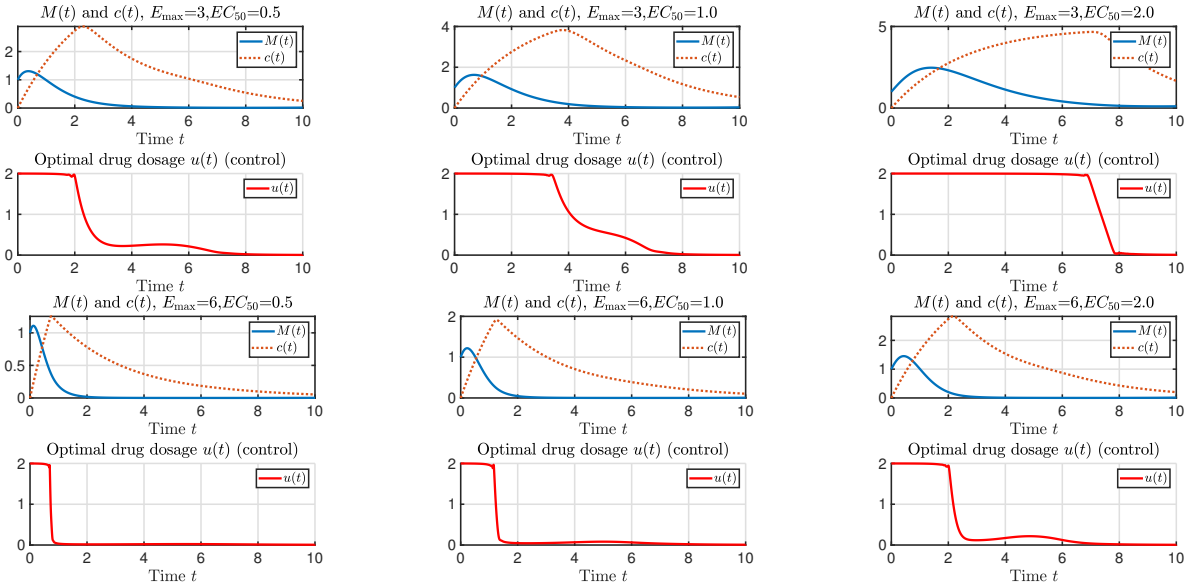

Fig. 5 J_1 model (Case A) with $\eta = 0$ and $\sigma = 0.4$: dynamics of metastatic mass and drug concentration under the optimal drug dosage (top to bottom: $E_{\max} = 3, 6$, left to right $EC_{50} = 0.5, 1, 2$.

In summary, the nonlinear PD/PK effects indeed dramatically change the bang-bang control patterns of optimal drug dosage as observed in the previous linear lumped ODE models.

CONCLUSION

In this paper, we proposed a lumped ODE model through the integral reformulation of a size-structured transport PDE model for describing metastatic tumor growth. With the standard optimal control theory, we can easily obtain similar conclusions as derived from the size-structured PDE model in our previous work. With this lumped ODE model, the nonlinear PK and PD effects of treatment are also integrated for better practicality. Different possible optimal control (treatment) strategies are demonstrated through numerical examples with the state-of-the-art optimal control software ICLOCS2. From the point of view of clinical practice, such a simple lumped ODE model is advantageous to the size-structured PDE model since it is mathemati-

cally simpler to analyze and computationally faster to optimize. Our provided simulation results indicate that the optimal drug dosage is monotonically dependent on the related PK/PD parameters. Specifically, the optimal control $u(t)$ decreases as $E_{\max}$ increases and it increases as EC_{50}, η, and σ increases. The rigorous proof of this observed monotonicity property remains an open problem.

Appendix A. The derivation of Volterra integral equation (13)

Given $f(x)$ (e.g., $f(x)=w(x)$), define

$$M_f(t) := \int_1^b f(x)\rho(x,t)\,\mathrm{d}x. \tag{32}$$

Let $x = X(s)$ be the solution of $X'(s) = g(X(s))$ with initial condition $X(0) = 1$. We then have $X(\infty) = b$ and

$$\begin{aligned} M_f(t) &= \int_0^\infty f(X(s))g(X(s))\rho(X(s),t)\,\mathrm{d}s \\ &= \int_0^\infty f(X(s))v(s,t)\,\mathrm{d}s, \end{aligned} \tag{33}$$

where $v(s,t) := g(X(s))\rho(X(s),t)$. The transport PDE in (6)

$$\partial_t\rho + \partial_x(g\rho) = -u\rho$$

can be written as

$$\begin{aligned} &\partial_t v(s,t) = g(X(s))\partial_t\rho(X(s),t) \\ &= -g(X(s))\partial_x[g(X(s))\rho(X(s),t)] - u(t)g(X(s))\rho(X(s),t) \\ &= -\partial_s v(s,t) - u(t)v(s,t). \end{aligned}$$

Solving this equation along the characteristic line yields

$$v(s,t) = \begin{cases} v(0,t-s)\,\mathrm{e}^{U(t-s)-U(t)}, & s \leqslant t, \\ v(s-t,0)\,\mathrm{e}^{U(0)-U(t)}, & s \geqslant t, \end{cases} \tag{34}$$

where $U(t) = \int_0^t u(r)\,\mathrm{d}r$ is an antiderivative of $u(t)$. The boundary condition is

$$\begin{aligned} v(0,t) = g(1)\rho(1,t) &= \int_1^b \beta(x)\rho(x,t)\,\mathrm{d}x \\ &= \int_0^\infty \beta(X(s))v(s,t)\,\mathrm{d}s, \end{aligned} \tag{35}$$

and the initial condition is

$$v(s,0) = g(X(s))\rho(X(s),0) =: v_0(s). \tag{36}$$

A combination of (34), (35) and (36) yields

$$\begin{aligned} &\int_0^\infty f(X(s))v(s,t)\,\mathrm{d}s \\ &= \int_0^t f(X(s))\,\mathrm{e}^{U(t-s)-U(t)} \int_0^\infty \beta(X(r))v(r,t-s)\,\mathrm{d}r\,\mathrm{d}s \\ &\qquad + \int_0^\infty f(X(s+t))\,\mathrm{e}^{U(0)-U(t)}v_0(s)\,\mathrm{d}s. \end{aligned} \tag{37}$$

Especially, by choosing $f = \beta$ and $t = t-s$, we have

$$\begin{aligned} &\int_0^\infty \beta(X(r))v(r,t-s)\,\mathrm{d}r \\ &= \int_0^{t-s} \beta(X(z))\,\mathrm{e}^{U(t-s-z)-U(t-s)} \int_0^\infty \beta(X(r))v(r,t-s-z)\,\mathrm{d}r\,\mathrm{d}z \\ &\qquad + \int_0^\infty \beta(X(z+t-s))\,\mathrm{e}^{U(0)-U(t-s)}v_0(z)\,\mathrm{d}z. \end{aligned} \tag{38}$$

Substituting (38) into (37) gives

$$\begin{aligned} &\int_0^\infty f(X(s))v(s,t)\,\mathrm{d}s = \int_0^t f(X(s))\,\mathrm{e}^{U(t-s)-U(t)} \times \\ &\int_0^{t-s} \beta(X(z))\,\mathrm{e}^{U(t-s-z)-U(t-s)} \int_0^\infty \beta(X(r))v(r,t-s-z)\,\mathrm{d}r\,\mathrm{d}z\,\mathrm{d}s \\ &+ \int_0^t f(X(s))\,\mathrm{e}^{U(t-s)-U(t)} \int_0^\infty \beta(X(z+t-s))\,\mathrm{e}^{U(0)-U(t-s)}v_0(z)\,\mathrm{d}z\,\mathrm{d}s \\ &\qquad + \int_0^\infty f(X(s+t))\,\mathrm{e}^{U(0)-U(t)}v_0(s)\,\mathrm{d}s. \end{aligned}$$

On account of (37), the first integral on the right-hand side becomes

$$\begin{aligned} &\int_0^t \beta(X(z))\,\mathrm{e}^{U(t-z)-U(t)} \int_0^{t-z} f(X(s))\,\mathrm{e}^{U(t-z-s)-U(t-z)} \times \\ &\qquad \int_0^\infty \beta(X(r))v(r,t-z-s)\,\mathrm{d}r\,\mathrm{d}s\,\mathrm{d}z \\ &= \int_0^t \beta(X(z))\,\mathrm{e}^{U(t-z)-U(t)} \int_0^\infty f(X(s))v(s,t-z)\,\mathrm{d}s\,\mathrm{d}z \\ &- \int_0^t \beta(X(z))\,\mathrm{e}^{U(t-z)-U(t)} \int_0^\infty f(X(s+t-z))\,\mathrm{e}^{U(0)-U(t-z)}v_0(s)\,\mathrm{d}s\,\mathrm{d}z. \end{aligned}$$

Coupling the above two equations yields

$$\begin{aligned}
&\int_0^\infty f(X(s))v(s,t)\,\mathrm{d}s \\
&= \int_0^t \beta(X(z))\,\mathrm{e}^{U(t-z)-U(t)} \int_0^\infty f(X(s))v(s,t-z)\,\mathrm{d}s\,\mathrm{d}z \\
&- \mathrm{e}^{U(0)-U(t)} \int_0^t \beta(X(z)) \int_0^\infty f(X(s+t-z))v_0(s)\,\mathrm{d}s\,\mathrm{d}z \\
&+ \mathrm{e}^{U(0)-U(t)} \int_0^t f(X(z)) \int_0^\infty \beta(X(s+t-z))v_0(s)\,\mathrm{d}s\,\mathrm{d}z \\
&+ \mathrm{e}^{U(0)-U(t)} \int_0^\infty f(X(s+t))v_0(s)\,\mathrm{d}s.
\end{aligned}$$

In view of (32), the above equation can be written as the integral equation

$$M_f(t) = \int_0^t \beta(X(r))\,\mathrm{e}^{U(t-r)-U(t)} M_f(t-r)\,\mathrm{d}r + \mathrm{e}^{U(0)-U(t)} F(t), \quad (39)$$

where

$$F(t) := \int_0^\infty \Big\{ f(X(s+t)) + \int_0^t \big[f(X(z))\beta(X(s+t-z)) - \beta(X(z)) f(X(s+t-z)) \big]\,\mathrm{d}z \Big\} v_0(s)\,\mathrm{d}s \quad (40)$$

depends only on the initial condition, time t and the functions f, β, and g. From the definition of $U(t)$, we have $U(0) = 0$. If we define $\Phi(t) = \mathrm{e}^{U(t)} M_f(t)$, then the equation (39) becomes

$$\begin{aligned}
\Phi(t) &= \int_0^t \beta(X(r))\Phi(t-r)dr + F(t) \\
&= \int_0^t \beta(X(t-r))\Phi(r)dr + F(t), \quad (41)
\end{aligned}$$

which is independent of the control $u(t)$. For the special case when the initial profile is a delta function $\rho(x,0) = \delta_1(x)$, we obtain $F(t) = f(X(t))$, which is the weighted size of the primary cell. The kernel function $\beta(X(r))$ combines tumor growth rate (g) and colonization rate (β).

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