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# DYNAMICS AND CONTROL OF A MATHEMATICAL MODEL FOR METRONOMIC CHEMOTHERAPY

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Abstract. A 3-compartment model for metronomic chemotherapy that takes into account cancerous cells, the tumor vasculature and tumor immune-system interactions is considered as an optimal control problem. Metronomic chemotherapy is the regular, almost continuous administration of chemotherapeutic agents at low dose, possibly with small interruptions to increase the efficacy of the drugs. There exists medical evidence that such administrations of specific cytotoxic agents (e.g., cyclophosphamide) have both antiangiogenic and immune stimulatory effects. A mathematical model for angiogenic signaling formulated by Hahnfeldt et al. is combined with the classical equations for tumor immune system interactions by Stepanova to form a minimally parameterized model to capture these effects of low dose chemotherapy. The model exhibits bistable behavior with the existence of both benign and malignant locally asymptotically stable equilibrium points. In this paper, the transfer of states from the malignant into the benign regions is used as a motivation for the construction of an objective functional that induces this process and the analysis of the corresponding optimal control problem is initiated.

1. **Introduction: Administration of chemotherapeutic agents.** The administration of chemotherapeutic agents in the treatment of cancer still is an issue that has not yet been settled satisfactorily in all cases. Cancer is a widely symptomless disease that often is only detected in an advanced stage which makes it imperative to take strong action as soon as possible. As a result, so-called *MTD*-strategies that give *maximum tolerated doses* with upfront dosing are common. Such procedures indeed are the optimal solutions when mathematical models of homogeneous tumor populations are considered that consist of chemotherapeutically sensitive cells (e.g., see [26, 27, 43, 44, 45, 47]). However, if heterogeneity is taken into account (as tumors often consist of subpopulations of cells of widely varying chemotherapeutic sensitivities), this no longer need be the case (e.g., see [28, 31, 46]). In view of the existence of possible drug resistant strains, it seems to be intuitive, and also has been argued in the medical literature, that in such a case it might be a better

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strategy to maintain a level of chemotherapeutically sensitive cells to keep the more resistant and harmful strain of cells in check (*adaptive therapy*, [13]). Other strategies pursued in medical research that have shown effectiveness for certain types of cancer are so-called *chemo-switch* protocols that follow an initial MTD dose with administrations at significantly reduced dose rates [18, 35] or *metronomic* protocols that administer chemotherapeutic agents at significantly lower dose rates, almost continuously, with only short interruptions to increase the efficacy of the drugs [2, 5, 8, 22]. The rationale behind reducing dosage is that, in the absence of severe limiting toxic side effects, it will be possible to give chemotherapy over prolonged time intervals so that, because of the greatly extended time horizon, the overall effect may be improved when compared with repeated short MTD doses [20, 49]. Such strategies seem to be especially of interest in pediatric cancers.

From a treatment perspective, it is still a question of utmost importance how one can optimize the overall effects of therapy by modulating the administration schedules. This does not only include the cytotoxic effects of drugs on tumor cells, but also includes possible ancillary features that operate within a tumor's microenvironment such as antiangiogenic or pro-immune effects. Mathematical models for therapy that consider specific aspects of the tumor microenvironment have been considered, for example, in [3, 9, 11, 12, 14, 21, 30, 32]. There exists medical evidence that low-dose chemotherapy, while still having a moderate cytotoxic effect on cancerous cells in the absence of significant negative side effects, has antiangiogenic (e.g., [5, 8, 16]) and immune stimulatory effects (e.g., see [1, 2, 19, 33] and the editorial [34]) whereas high-dose chemotherapy often suppresses the immune system and thus takes out one beneficial factor of a tumor's microenvironment that could have come to the aid in fighting the tumor. In addition, the argument that low-dose chemotherapy promotes drug resistance which also led to the "kill as much as possible, as quickly as possible" paradigm is being questioned. For example, in clinical experiments it has been observed that cell cultures that were drug resistant to high concentrations responded to low-dose concentrations of the very same agent. In addition, because of the low expenses of some of the drugs used in this context (such as cyclophosphamide), such a strategy becomes an important option for cancer treatment in low-income countries and, in view of excessive health care costs, also in developed countries. Hence, and of course depending on the specific cancer and patient situation, metronomic administration schedules of chemotherapy could provide a viable alternative to classical procedures. Indeed, mathematical models that compare the long-term benefits of metronomic and MTD chemotherapy [4, 16] generally come to the conclusions that metronomic administrations fare better.

The literature on mathematical models for metronomic chemotherapy is small and this topic has not been explored extensively. In this paper, we consider a minimally parameterized 3-compartment mathematical model for metronomic chemotherapy that takes into account both the effects of chemotherapy on the cancerous cells and its effects on the two principal components of a tumor's microenvironment, the tumor vasculature and tumor immune-system interactions. This is achieved by merging a mathematical model for angiogenic signaling formulated by Hahnfeldt et al. in [17] with the classical equations for tumor immune system interactions by Stepanova [41]. The model considered here was introduced and analyzed from a dynamical systems point of view in [39]. It exhibits a wide range of dynamical behaviors that encompass a variety of medically realistic scenarios. These range from cases when low-dose metronomic chemotherapy is able to completely eradicate the

tumor (in the sense that all trajectories converge to the tumor free equilibrium point) to situations when tumor dormancy is induced (a unique, globally asymptotically stable benign equilibrium point with small positive tumor volume exists) to multi-stable situations that have both persistent benign and malignant behaviors (the typical multi-stable scenario of mathematical models for tumor-immune system interactions) to situations when tumor growth simply is dominant and the disease cannot be cured by low-dose metronomic chemotherapy. Thus, despite its simplicity, the model is able to capture the most important structural features of tumor development. From a practical point of view, the most relevant and interesting scenario is when the model exhibits bistable behavior with the existence of both benign and malignant locally asymptotically stable equilibrium points. This is the case we consider in this paper. We briefly summarize the mathematical model in Section 2 and recall the most important features of the corresponding dynamical system under constant low-dose metronomic chemotherapy [39]. In Section 3 we then formulate an optimal control problem whose objective functional is designed to transfer states from the malignant into the benign region. Since metronomic dosing aims to be almost uninterrupted, in this paper we explore the structure and optimality status of specific time-varying control structures that are called singular in optimal control.

2. **A minimally parameterized mathematical model for metronomic chemotherapy.** Metronomic chemotherapy is a relatively new concept in medicine (see also [37]) and in the absence of clear protocols and guidelines, mathematical modeling can be useful in shedding some light into adminstration schedules for the drugs. So far, however, there do not seem to exist established mathematical models on this topic that would capture the multi-dimensional effects of this treatment on the various compartments of the tumor microenvironment. In an effort to formulate such a mathematical model that also is minimally parameterized, we combine the model of tumor growth under angiogenic signaling developed by Hahnfeldt, Panigrahy, Folkman and Hlatky [17] with the classical model for tumor-immune system interactions by Stepanova [41]. This leads to the following equations:

$$\dot{p} = -\xi p \ln\left(\frac{p}{q}\right) - \theta p r, \tag{1}$$

$$\dot{q} = p - \left(\mu + d p^{\frac{2}{3}}\right) q, \tag{2}$$

$$\dot{r} = \alpha\left(p - \beta p^2\right) r + \gamma - \delta r. \tag{3}$$

Here $p$ denotes the primary *tumor volume*, $q$ the *carrying capacity of its vasculature* (measured in terms of the volume of the endothelial cells that provide the lining for the newly formed vessels and capillaries) and $r$ is a non-dimensional, normalized, order of magnitude quantity related to the activities of various types of $T$-cells activated during the immune reaction. We summarily refer to it as the *immunocompetent cell density*. All other letters in these equations denote constant coefficients. Note that, if we define $\hat{r} = \lambda r$ and rescale the parameters $\gamma$ and $\theta$ as $\hat{\gamma} = \lambda\gamma$ and $\hat{\theta} = \frac{\theta}{\lambda}$, then the solutions are unchanged. We use this 1-parameter group of scaling symmetries to normalize the set point value for $r$.

We briefly discuss the modeling premises. Equation (2) is taken from [17] and describes the interactions between the tumor and its vasculature consisting of a balance between stimulatory and inhibitory terms. Tumor-derived stimulators act

locally which is reflected in a fast clearing of these agents while inhibitors have a more systemic action. In [17], an asymptotic expansion of the solutions for the underlying consumption-diffusion equation is made that suggests specific relations between the stimulation and inhibition terms. Based on this analysis, the authors take the stimulation term proportional to the tumor volume, $bp$, with $b$ a constant mnemonically labeled for 'birth' and take the inhibition term in the form $dp^{\frac{2}{3}}q$ with $d$ labeling a tumor stimulated 'death' term. The functional relation $p^{\frac{2}{3}}q$ reflects an interaction of the carrying capacity $q$ with the tumor surface through which inhibitors need to be released. The constant $\mu$ denotes the natural rate of death for cells related to the carrying capacity and generally is small, often set to zero. The third equation, (3), summarizes the main interactions of the tumor with the immune system and is taken from Stepanova's paper [41]. Various organs such as the spleen, thymus, lymph nodes and bone marrow, each contribute to the development of immune cells in the body and the parameter $\gamma$ models a combined rate of influx of $T$-cells generated through these primary organs; $\delta$ is simply the rate of natural death of the $T$-cells. The first term in this equation models the proliferation of lymphocytes. For small tumors, it is stimulated by the tumor antigen and this effect here is taken to be proportional to the tumor volume $p$. It is argued in [41] that large tumors suppress the activity of the immune system. The reasons lie in an inadequate stimulation of the immune forces as well as a general suppression of immune lymphocytes by the tumor (see [41] and the references therein). This feature is expressed in the model through the inclusion of the term $-\beta p^2$. Thus $1/\beta$ corresponds to a threshold beyond which the immunological system becomes depressed by the growing tumor. The coefficients $\alpha$ and $\beta$ are used to calibrate these interactions and collectively describe a state-dependent net influence of the tumor on the stimulation of the immune system. The first equation, (1), models tumor growth. Following [17], here a Gompertzian growth rate has been chosen with $\xi$ a tumor growth coefficient. Other models are equally viable and have been considered in the literature. In Stepanova's original research an exponential model was used while Kuznetsov, Makalkin, Taylor and Perelson [23] use a logistic model. A Gompertzian model has also been used in the work by de Vladar and Gonzalez [48]. The qualitative structure of the dynamical properties of the underlying system, however, are not effected by the choice of the growth model (e.g., see [25]). The second term, $-\theta pr$, models the beneficial effects of the immune system reaction on the cancer volume and $\theta$ denotes the rate at which cancer cells are eliminated through the activity of $T$-cells.

The main properties of low-dose chemotherapy that we incorporate into the model are a moderate cytotoxic effect, distinctive antiangiogenic features and immune stimulatory properties. Using the linear log-kill hypothesis [40, 50], the influence of the chemotherapeutic agent on the tumor volume $p$ and its carrying capacity $q$ are modeled in the form $-\varphi_1 pu$ and $-\varphi_2 qu$, respectively. Immune stimulatory effects of metronomic chemotherapy are well documented (e.g., [19, 33]) and include both direct and indirect mechanisms. For example, it depletes Treg and inhibits MDSC (myeloid derived suppressor cells), which, as a result, downregulates immunosuppression; it also enhances dendritic cell function which leads to increased activity of the immune system. Metronomic chemotherapy stimulates the immune system further by enhancing the immunogenicity of the tumor, for example, by increasing tumor associated antigens and exposure of calreticulin and heat shock proteins [19]. At the level of modeling pursued here, and in the spirit of minimally

parameterizing the model, we therefore also use a term of the form $\varphi_3 ru$ to describe the immune stimulatory effect of chemotherapy. For a number of cytotoxic drugs (like cyclophosphamide) for which experimental data are available, low dose metronomic chemotherapy has a strong antiangiogenic effect while the cytotoxic and pro-immune effects are lower. Generally, however, these relations depend on the specific drug-tumor combination and these properties would be represented by inequality relations between the parameters $\varphi_i$. In our theoretical analysis below, however, we do not need to make any assumptions on these values. Overall, the controlled equations take the following form:

$$\dot{p} = -\xi p \ln\left(\frac{p}{q}\right) - \theta pr - \varphi_1 pu, \tag{4}$$

$$\dot{q} = bp - \left(\mu + dp^{\frac{2}{3}}\right) q - \varphi_2 qu, \tag{5}$$

$$\dot{r} = \alpha\left(p - \beta p^2\right) r + \gamma - \delta r + \varphi_3 ru. \tag{6}$$

For simplicity, we do not include a standard linear pharmacokinetic model and identify the dose rate with the concentration of the agent.

In the paper [39] we have analyzed the system (4)-(6) for a constant metronomic dosing, $u(t) = u \equiv \text{const}$, from a dynamical systems point of view and we summarize the main results in the theorem below.

**Theorem 2.1.** [39] *The dynamical system (4)-(6) has at most three equilibria with positive p-values,* $(p_*^{(i)}, q_*^{(i)}, r_*^{(i)})$ *for* $i = 1, 2, 3$, *with saddle-node bifurcations generically occurring at points where the graphs of the functions*

$$\Phi(p) = \xi \ln\left(\frac{\mu + \varphi_2 u + dp^{\frac{2}{3}}}{b}\right) + \varphi_1 u$$

*and*

$$\Psi(p) = -\frac{\theta\gamma}{\alpha\beta p^2 - \alpha p + \delta - \varphi_3 u}$$

*intersect tangentially. If there exists only one equilibrium point, then it is globally asymptotically stable. If there exist three equilibrium points and if these equilibria are ordered according to their tumor volumes* $p_*^{(i)}$, $p_*^{(1)} < p_*^{(2)} < p_*^{(3)}$, *then the low equilibrium point* $(p_*^{(1)}, q_*^{(1)}, r_*^{(1)})$ *and the high equilibrium point* $(p_*^{(3)}, q_*^{(3)}, r_*^{(3)})$ *are locally asymptotically stable while the intermediate equilibrium point* $(p_*^{(2)}, q_*^{(2)}, r_*^{(2)})$ *is unstable with a 2-dimensional stable manifold.*

It also follows from the results in [39] that the tumor volumes for the low equilibrium point cannot exceed $\frac{1}{2\beta}$ by much and generally are quite smaller. The low equilibrium point can therefore be interpreted as a *microscopic tumor* and we call this equilibrium point *benign* and its corresponding region of attraction the *benign region*. We recall that if $x_*$ is a locally asymptotically stable equilibrium point for a dynamical system $\dot{x} = f(x)$ defined on a region $G$ (i.e., an open and connected set), then its region of attraction, $A(x_*)$, consists of all initial conditions $x_0$ for which the corresponding solution exists for all $t \geq 0$ and converges to $x_*$ as $t \to \infty$,

$$A(x_*) = \left\{x_0 \in G : x(t; x_0) \text{ exists for all } t > 0 \text{ and } \lim_{t\to\infty} x(t; x_0) = x_*\right\}.$$

This set consists of the totality of all initial states of the system for which a low-dose metronomic chemotherapy $u(t) = u \equiv \text{const}$ is able to limit the cancer at the benign equilibrium point. Situations when this is the only equilibrium point

in the system are related to the concepts of *tumor dormancy* and *immunosurveillance* of the medical literature [42]. On the other hand, the tumor volumes for the high equilibrium point are by an order of magnitude larger than for the low equilibrium point and these can be interpreted as a *macroscopic tumor* with the high value indicating that the patient will succumb to the disease. We therefore call the high equilibrium point *malignant* and its region of attraction the *malignant region*. This region corresponds to initial conditions for which tumor growth overcomes the effects of the low dose chemotherapy, is able to evade the actions of the immune system and tumor dormancy and eventually, unless other treatment options will be pursued, becomes lethal. Naturally, reality is far more complicated than accounted for in this simplified model, and random (and otherwise) events take place that will consistently perturb the state of the system. In the case when both benign and malignant regions exist, transitions between these regions are possible (because some events simply are not covered in the model which leads to random perturbations that misplace the state of the system). Once such a temporary disturbance has passed, the system will settle down to follow the trajectories in the phase portrait. Clearly, if the malignant region is quite large, then it is easily possible under such a scenario that the state will end up in this malignant region and these models correspond to more aggressive forms of the disease. In fact, since such 'perturbations' are a constant recurrence, it is quite likely that this eventually will happen and the disease cancer will develop. Naturally, thus the boundary between the benign and malignant behaviors is the most interesting and important structure. The model (4)-(6) is Morse-Smale [15] and this boundary is formed by a 2-dimensional embedded submanifold, the stable manifold of the saddle point.

The analytical results described above are generally valid and we briefly illustrate these features for a specific set of parameter values. Biologically validated data for the separate models are given for the model of angiogenic signalling in the paper by Hahnfeldt et al. [17] for Lewis lung carcinoma implanted in mice and for the mathematical model for tumor-immune system interactions in the paper by Kuznetsov et al. [23] based on in vivo experimental data for B-lymphoma $BCL_1$ in the spleen of mice. Clearly, these parameter values cannot just be combined. The equilibrium of the model for angiogenic signaling from [17] is given by $\left(\frac{b-\mu}{d}\right)^{\frac{3}{2}}$ and is by an order of magnitude larger than the carrying capacity for the model in [23]. We therefore adjusted the values of $b$ and $d$ that determine the high equilibrium point to be in the same range as the carrying capacity for the tumor-immune system model. Also, the dynamical model for the immunocompetent density in [23] is taken of the form

$$\dot{r} = \left(\frac{\rho}{\eta + p} - \mu\right) rp + \gamma - \delta r$$

and for the parameter values from [23] we approximated the expression $\frac{\rho}{\eta+p} - \mu$ by the linear term $\alpha\,(1 - \beta p)$ employed in [41] that has the same value for $p = 0$ and the same zero. Table 1 lists the numerical values that we use for the computations shown here. Following [23], $p$ and $q$ are given in multiples of $10^6$ cells and $y$ is a dimensionless quantity that describes the immuno-competent cell density on a relative order of magnitude basis. For the given parameter values this set-point is taken to be 1. The time scale is taken relative to the tumor cell cycle in mice and and is in terms of 0.11 days [23]. But we emphasize that these values are only for numerical illustration.

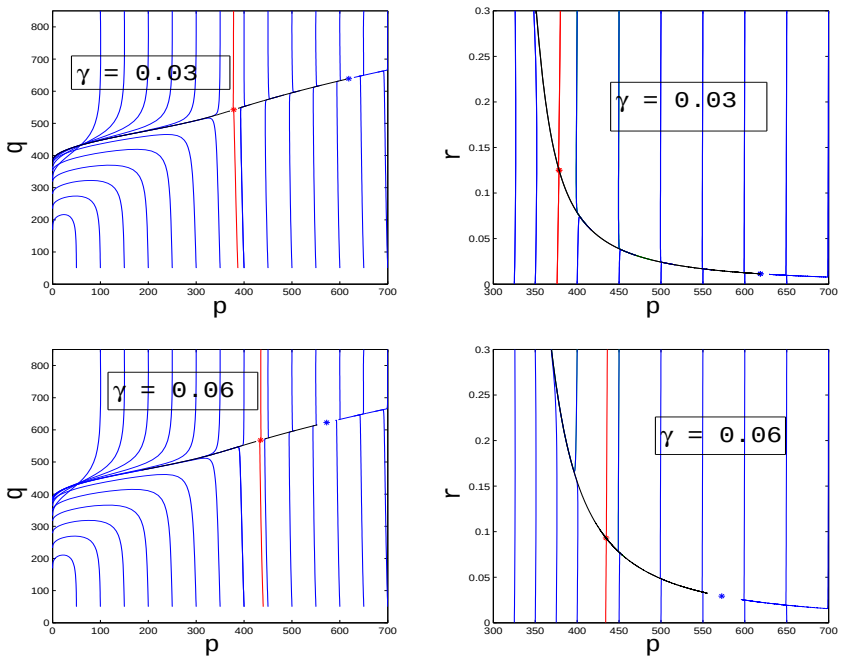


FIGURE 1. Two-dimensional projections of trajectories of the dynamical system (1)-(3) into the $(p, q)$ and $(p, r)$-planes for $\gamma = 0.03$ (top) and $\gamma = 0.06$ (bottom).

The phase portrait of the dynamical system (4)-(6) consists of the totality of all its solutions plotted in the 3-dimensional $(p, q, r)$-space. In order to better visualize its structures, Figure 1 shows two examples of 2-dimensional projections of the phase portraits into the $(p, q)$ and $(p, r)$ planes. The overlaps of trajectories seen in these figures are caused by the projections, but are not present in the 3-dimensional phase portrait. In each figure, the malignant equilibrium point is marked by a blue star and the unstable equilibrium by a red star. The benign equilibrium point has a very small tumor volume and is located almost at the origin. It is not shown in these diagrams. The red curves through the unstable equilibrium point depict corresponding sections of the 2-dimensional stability boundary between benign and malignant behaviors and its 1-dimensional unstable manifold is shown as the black curve. While keeping all other parameters constant, we show two cases for $\gamma$, $\gamma = 0.03$ and $\gamma = 0.06$. This parameter represents the constant influx of immune cells from the primary organs. The qualitative behavior of the system is identical and, more generally, the same behavior persists until a saddle-node bifurcation occurs for $\gamma_* = 0.07524$. The figures illustrate how the unstable and malignant equilibrium points move towards each other as $\gamma$ approaches $\gamma_*$. For values of $\gamma$ larger than $\gamma_*$, the benign equilibrium point is globally asymptotically stable and the immune system is strong enough to control the cancer in a form of immunosurveillance.

3. **Optimal control formulation for the combined model.** We formulate an optimal control problem to transfer an initial state that lies in the malignant region into the benign region. It is assumed that the system (1)-(3) has a bi-stable

| variable/ parameters | interpretation | numerical values used for figures | dimension | Ref. |
|---|---|---|---|---|
| $p$ | tumor volume | | $10^6$ cells | [41] |
| $q$ | carrying capacity of the vasculature | | $10^6$ cells | [17] |
| $r$ | immuno-competent cell density | | orders of magnitude non-dimensional | [41] |
| $u$ | concentration of the cytotoxic agent | | mg of dose/$10^6$ cells | |
| $\alpha$ | tumor stimulated proliferation rate of immune system | 0.0529 | non-dimensional | |
| $\beta$ | inverse threshold of tumor suppression | 0.00291 | non-dimensional | [23] |
| $\gamma$ | constant influx into immune system | 0.03/0.06 | $10^6$ cells/unit time | [23] |
| $\delta$ | death rate | 0.3743 | non-dimensional | [23] |
| $\theta$ | tumor immune system interaction rate | 0.1 | | |
| $\xi$ | tumor growth parameter | 0.0347 | cells/unit time | |
| $b$ | tumor induced stimulation parameter of vasculature | 5 | cells/unit time | |
| $d$ | tumor induced inhibition parameter of vasculature | 0.0667 | non-dimensional | |
| $\mu$ | loss of vascular support through natural causes | 0 | cell/unit time | |
| $\varphi_1$ | cytotoxic killing parameter | 0.005 | $10^6$ cells/mg of dose | |
| $\varphi_2$ | antiangiogenic elimination parameter | 0.06 | $10^6$ cells/mg of dose | |
| $\varphi_3$ | immune stimulatory parameter | 0.01 | $10^6$ cells/mg of dose | |

TABLE 1. Variables and parameter values used in numerical computations.

behavior with $z_* = (p_*^{(2)}, q_*^{(2)}, r_*^{(2)})$ the unstable intermediate equilibrium point and we denote by $N$ its 2-dimensional stable manifold. Ideally, if a formula for $N$ were available in the form $N = \{(p, q, r) : \sigma(p, q, r) = 0\}$, then one would want minimize or maximize this function at the endpoint depending on whether $\sigma$ is negative or positive in the benign region. But generally these manifolds are defined by highly transcendental relations and rarely such expressions can be determined. However, linear approximations are easily obtained since the tangent space to $N$ at the hyperbolic equilibrium point $z_*$ is spanned by the two stable eigenvectors of the Jacobian matrix at $z_*$. It thus is reasonable to include in the objective a linear penalty term at the terminal point of the form $Ap(T) + Bq(T) - Cr(T)$ where the vector $(A, B, -C)$

could be chosen either as a (properly oriented) normal vector to the tangent space to $N$ at $z_*$ or simply as the unstable eigenvector. In each case, the $p$ and $q$ components of these vector are positive while the $r$ component is negative and for this reason we label the vector as $(A, B, -C)$ with all coefficients positive. Clearly, this also makes sense since the aim is to lower the tumor volume and its carrying capacity while increasing the activities of the immune system. But rather than making arbitrary choices, here we use the underlying geometry of the uncontrolled system ($u \equiv 0$) to come up with meaningful coefficients.

The side effects of treatment are measured indirectly by the total dosage of agents given. We therefore include the control $u$ in the Lagrangian of the objective with a weight $M$. Furthermore, the existence of the benign region allows for trajectories that improve the objective value without incurring a cost and this may lead to a mathematically ill-posed structure with 'optimal' solutions defined over an infinite horizon. We therefore also include a penalty on the terminal time. This simply generates a well-posed optimal control problem for which the existence of solutions is guaranteed by standard results [10]. Overall, we therefore take the objective functional in the following Bolza format,

$$J(u) = Ap(T) + Bq(T) - Cr(T) + \int_0^T (Mu(t) + S)\, dt, \tag{7}$$

and consider the following optimal control problem:

**[M]:** For a free terminal time $T$, minimize the objective (7) over all Lebesgue measurable functions $u : [0, T] \to [0, u_{\max}]$ subject to the dynamics (4)-(6) with initial condition $(p_0, q_0, r_0)$.

We write the state as $z = (p, q, r)^T$ and introduce the drift and control vector fields $f$ and $g$,

$$f(z) = \begin{pmatrix} -\xi p \ln\left(\frac{p}{q}\right) - \theta pr \\ bp - (\mu + dp^{\frac{2}{3}})q \\ \alpha(p - \beta p^2)r + \gamma - \delta r \end{pmatrix} \qquad \text{and} \qquad g(z) = \begin{pmatrix} -\varphi_1 p \\ -\varphi_2 q \\ \varphi_3 r \end{pmatrix},$$

so that the dynamics takes the form

$$\dot{z} = f(z) + ug(z). \tag{8}$$

Furthermore, we define the *Hamiltonian* of the control problem, $H = H(\lambda, z, u)$, as

$$H = Mu + S + \langle \lambda, f(z) + ug(z) \rangle \tag{9}$$

where $\lambda = (\lambda_1, \lambda_2, \lambda_3)$ is a 3-dimensional row vector, $\lambda \in \left(\mathbb{R}^3\right)^*$. Explicitly,

$$\begin{aligned} H = Mu + S + \lambda_1 \left(-\xi p \ln\left(\frac{p}{q}\right) - \theta pr - \varphi_1 up\right) \\ + \lambda_2 \left(bp - (\mu + dp^{\frac{2}{3}})q - \varphi_2 uq\right) + \lambda_3 \left(\alpha(p - \beta p^2)r + \gamma - \delta r + \varphi_3 ur\right). \end{aligned} \tag{10}$$

First-order necessary conditions for optimality of a control $u_*$ are given by the Pontryagin maximum principle [36] (for some recent references, see [6, 7, 38]): If $u_*$ is an optimal control defined over an interval $[0, T]$ with corresponding trajectory

$z_* = (p_*, q_*, r_*)^T$, then there exists an absolutely continuous covector $\lambda$ defined on $[0,T]$, $\lambda : [0,T] \to \left(\mathbb{R}^3\right)^*$, that satisfies the adjoint equations

$$\dot{\lambda_1} = -\frac{\partial H}{\partial p} = \lambda_1 \left(\xi \left(1 + \ln\left(\frac{p}{q}\right)\right) + \theta r + \varphi_1 u_*\right) - \lambda_2 \left(b - \frac{2}{3} dq p^{-\frac{1}{3}}\right) - \lambda_3 \left(\alpha(1 - 2\beta p) r\right), \tag{11}$$

$$\dot{\lambda_2} = -\frac{\partial H}{\partial q} = -\lambda_1 \xi \frac{p}{q} + \lambda_2(\mu + d p^{\frac{2}{3}} + \varphi_2 u_*), \tag{12}$$

$$\dot{\lambda_3} = -\frac{\partial H}{\partial r} = \lambda_1 \theta p - \lambda_3 \left(\alpha(p - \beta p^2) - \delta + \varphi_3 u_*\right), \tag{13}$$

with terminal condition $\lambda(T) = (A, B, -C)$ such that for almost every time $t \in [0,T]$ the optimal control $u_*(t)$ minimizes the Hamiltonian over the control set $[0, u_{\max}]$ along $(\lambda(t), z_*(t))$ with minimal value given by 0. Note that the adjoint equations can succinctly be expressed in the form

$$\dot{\lambda}(t) = -\lambda(t)(Df(z_*(t)) + u_*(t) Dg(z_*(t))) \tag{14}$$

since the Lagrangian term of the objective does not depend on the state variables $p, q$ and $r$.

The key condition of the maximum principle is the minimization property. Since the Hamiltonian $H$ is linear in $u$ and the control set is a compact interval, it follows that the optimal control $u_*$ satisfies the following property:

$$u_*(t) = \begin{cases} 0 & \text{if} \quad M + \langle \lambda(t), g(z_*(t)) \rangle > 0, \\ u_{\max} & \text{if} \quad M + \langle \lambda(t), g(z_*(t)) \rangle < 0. \end{cases} \tag{15}$$

In principle, the minimization property allows for any control value $u \in [0, u_{\max}]$ to be optimal if $M + \langle \lambda(t), g(z_*(t)) \rangle = 0$. The function

$$\Phi(t) = M + \langle \lambda(t), g(z_*(t)) \rangle = M - \varphi_1 \lambda_1(t) p_*(t) - \varphi_2 \lambda_2(t) q_*(t) + \varphi_3 \lambda_3(t) r_*(t) \tag{16}$$

is called the *switching function* of the optimal control problem [M]. For, if $\Phi(\tau) = 0$, but the derivative $\dot{\Phi}(\tau)$ does not vanish, then the function $\Phi$ changes sign at time $\tau$ and the optimal control switches between the values 0 and $u_{\max}$: from 0 to $u_{\max}$ if $\dot{\Phi}(\tau) < 0$ and from $u_{\max}$ to 0 if $\dot{\Phi}(\tau) > 0$. A junction of this type is called a *bang-bang* switch and the constant controls $u \equiv 0$ and $u \equiv u_{\max}$ are called *bang* controls. However, in general, little more is known about the zero set $\mathcal{Z} = \{t \in [0,T] : \Phi(t) = 0\}$ than that it is a closed set. But there is one case in which the situation simplifies considerably, namely when a switching function vanishes over an open interval $I$. In this case all derivatives of $\Phi$ need to vanish as well and, aside from degenerate situations, this enables the computation of the control on this interval. Controls of this kind are called *singular*. Strictly speaking, to be singular is not just a property of the control, but also depends on the multiplier $\lambda$ defining the switching function.

**Definition 3.1. (Singular controls and extremals)** Let $\Gamma$ be an extremal lift for the problem [M] consisting of a controlled trajectory $(z_*, u_*)$ defined over the interval $[0,T]$ with corresponding adjoint vector $\lambda : [0,T] \to (\mathbb{R}^3)^*$ such that the conditions of the maximum principle are satisfied. The extremal lift $\Gamma$ is said to be singular on an open interval $I \subset [0,T]$ if the switching function $\Phi$ vanishes identically on $I$. We say the control $u_*$ is singular on $I$ and call the corresponding portion of the trajectory $z_*$ a singular arc.

This classical terminology is somewhat unfortunate in that it would seem to indicate that this type of controls are an aberration while nothing could be further from the truth. The terminology has its historical origin in the simple observation that the switching function can be expressed as

$$\Phi(t) = \frac{\partial H}{\partial u}(\lambda(t), z_*(t), u_*(t))$$

and thus, formally, the condition $\Phi(t) = 0$ is the first-order necessary condition for the Hamiltonian to have a minimum in the interior of the corresponding control interval. For a general (multi-input) optimal control problem, extremal lifts are called singular, respectively nonsingular, over an open interval $I$ if the first-order necessary condition

$$\frac{\partial H}{\partial u}(\lambda(t), z_*(t), u_*(t)) = 0$$

is satisfied for $t \in I$ and if the matrix of the second-order partial derivatives,

$$\frac{\partial^2 H}{\partial u^2}(\lambda(t), z_*(t), u_*(t)),$$

is singular, respectively nonsingular, on $I$. For the control-affine problem [M], this quantity is identically zero and thus portions of an optimal control that take values in the interior of the control set are automatically singular. While the terminology is a bit misleading, *singular controls* nevertheless *are the most natural candidates for optimality.* They provide what has also been called *turnpikes* for the control problem with switchings between bang controls making the transitions to and from these structures or simply arising only when singular controls are inadmissible or simply do not exist.

If the control $u$ is singular on an interval $I$, then all derivatives of the switching function vanish. These derivatives can be written compactly using Lie brackets of vector fields. Recall that the Lie bracket of two continuously differentiable vector fields $f : \mathbb{R}^n \to \mathbb{R}^n$ and $g : \mathbb{R}^n \to \mathbb{R}^n$ is the vector field $[f, g] : \mathbb{R}^n \to \mathbb{R}^n$ given by $[f, g](z) = Dg(z)f(z) - Df(z)g(z)$. If $h : \mathbb{R}^n \to \mathbb{R}^n$ is a continuously differentiable vector field and $\Psi(t) = \langle \lambda(t), h(z(t)) \rangle$ where $z$ a solution to the system equation (8) corresponding to the control $u$ and $\lambda$ a solution to the corresponding adjoint equation (14), then a straightforward computation (e.g., see [6, 7, 38]) verifies that

$$\dot{\Psi}(t) = \langle \lambda(t), [f + ug, h]\, z(t) \rangle\,. \tag{17}$$

In particular, if an optimal control $u_*$ is singular on an open interval $I$, then it follows that

$$\dot{\Phi}(t) = \langle \lambda(t), [f, g](z_*(t)) \rangle \equiv 0$$

with the Lie bracket given by

$$[f, g](z) = \begin{pmatrix} -(\varphi_1 - \varphi_2)\xi p + \varphi_3 \theta p r \\ (\varphi_1 - \varphi_2) b p - \frac{2}{3}\varphi_1 d p^{\frac{2}{3}} q \\ \varphi_1 \alpha (p - 2\beta p^2) r + \varphi_3 \gamma \end{pmatrix}.$$

Along an optimal controlled trajectory for problem [M] the Hamiltonian function $H$ vanishes identically and thus along a singular extremal we also have that

$$H = \langle \lambda(t), f(z_*(t)) \rangle + S \equiv 0.$$

Except for a 2-dimensional surface where the vector fields $f$, $g$ and $[f,g]$ are linearly independent, the conditions $\Phi(t) \equiv 0$, $\dot{\Phi}(t) \equiv 0$ and $H \equiv 0$ determine the multiplier $\lambda$ and we have the following result:

**Proposition 1.** *If an optimal control $u_*$ is singular on an open interval $I$, then, away from the surface*

$$\mathcal{L} = \{z = (p,q,r) : \det(f(z), g(z), [f,g](z)) = 0\}$$

*the associated multiplier $\lambda(t)$ is the unique solution of the equation*

$$\lambda(t)\,(f(z_*(t)), g(z_*(t)), [f,g](z_*(t)) = (-S, -M, 0). \tag{18}$$

Hence, away from the set $\mathcal{L}$, equation (18) determines the multiplier $\lambda$ along a singular extremal as a feedback function of $z$, $\lambda = \lambda_{\text{sing}}(z)$. Singular controls are then computed by solving the equation for the second derivative of the switching function, $\ddot{\Phi}(t) \equiv 0$, for the control. It follows from equation (17) that

$$\ddot{\Phi}(t) = \langle \lambda(t), [f + ug, [f,g]](z(t)) \rangle$$

and thus the singular control is given by the feedback function

$$u_{\text{sing}}(z) = -\frac{\langle \lambda_{\text{sing}}(z), [f,[f,g]](z) \rangle}{\langle \lambda_{\text{sing}}(z), [g,[f,g]](z) \rangle}. \tag{19}$$

We can express the second-order Lie brackets $[f,[f,g]]$ and $[g,[f,g]]$ as linear combinations of the basis $f$, $g$ and $[f,g]$ in the form

$$[f,[f,g]](z) = \rho_1(z) f(z) + \rho_2(z) g(z) + \rho_3(z)[f,g](z)$$

and

$$[g,[f,g](z) = \omega_1(z) f(z) + \omega_2(z) g(z) + \omega_3(z)[f,g](z).$$

Hence, along a singular arc we have that

$$\langle \lambda_{\text{sing}}(z), [f,[f,g]](z) \rangle = -\rho_1(z) S - \rho_2(z) M$$

and

$$\langle \lambda_{\text{sing}}(z), [g,[f,g]](z) \rangle = -\omega_1(z) S - \omega_2(z) M$$

so that the singular control is given as

$$u_{\text{sing}}(z) = -\frac{\rho_1(z) S + \rho_2(z) M}{\omega_1(z) S + \omega_2(z) M}. \tag{20}$$

Note that, if the emphasis is put on quick actions, i.e., $S \gg M$, then $u_{\text{sing}}(z) \simeq -\rho_1(z)/\omega_1(z)$ while $u_{\text{sing}}(z) \simeq -\rho_2(z)/\omega_2(z)$ if $M \gg S$.

Singular controls can be both minimizing or maximizing and the Legendre-Clebsch condition, a necessary condition for optimality of singular extremals, allows to distinguish between these cases. For a minimization problem it requires that

$$\langle \lambda_{\text{sing}}(z), [g,[f,g]](z) \rangle = -\omega_1(z) S - \omega_2(z) M \leq 0.$$

Since this is the denominator in the formula for the singular control, we have the following result:

**Proposition 2.** *Away from the surface $\mathcal{L}$, the smooth vector field*

$$\mathcal{S} = f(z) + u_{\text{sing}}(z) g(z)$$

*defined by the singular feedback control (20) is a candidate for optimality in the region where the strengthened Legendre-Clebsch condition is satisfied, i.e., where*

$$\omega_1(z) S + \omega_2(z) M > 0.$$

Thus, besides the constant bang controls $u \equiv 0$ and $u \equiv u_{\max}$, that correspond to no or full dose treatments, there exists a third feedback control, $u_{\text{sing}}(z)$, defined on the region

$$\mathcal{D}_{\text{sing}} = \{z \notin \mathcal{L} : \omega_1(z)S + \omega_2(z)M > 0,\ 0 < u_{\text{sing}}(z) < u_{\max}\},$$

which describes time-varying dosages at intermediate values and is a third prime candidate for optimality.

Explicit formulas for the functions $\rho_i$ and $\omega_i$ can be given, but they are inconclusive about the signs of these functions. In fact, the vector field $[f,[f,g]]$ consists of full and lengthy expressions that do not offer much insight although $[g,[f,g]]$ reduces to the following simple form:

$$[g,[f,g]](z) = \begin{pmatrix} \varphi_3^2\theta pr \\ -(\varphi_1-\varphi_2)^2 bp + \frac{4}{9}\varphi_1^2 d p^{\frac{2}{3}} q \\ -\varphi_1^2\alpha(1-4\beta p)pr - \varphi_3^2\gamma \end{pmatrix}.$$

However, numerical computations of these vector fields and the associated singular control (20) are easily done and below we give some illustrations of these quantities. In Table 2 we list the weights that we used in the objective (7) and the initial condition used. The coefficients $A$, $B$ and $C$ are derived from a properly oriented unstable eigenvector at the unstable equilibrium point.

| coefficient | interpretation | numerical value used in computations |
|---|---|---|
| | weight for the | |
| $A$ | tumor volume | 0.9068 |
| $B$ | carrying capacity | 0.4216 |
| $C$ | immunocompetent cell density | 0.0029 |
| | at the endpoint | |
| $M$ | penalty on the total amount of drugs used | 1 |
| $S$ | penalty on the total time | 0.01 |
| | initial values for the | |
| $p_0$ | tumor volume | 200 |
| $q_0$ | carrying capacity | 300 |
| $r_0$ | immuno-competent cell density | 0.1 |

TABLE 2. Values of the weights in the objective (7) used in the numerical computations.

Figure 2 shows slices of the graphs of the feedback functions $\langle \lambda_{\text{sing}}(z), [f,[f,g]](z)\rangle$ and $\langle \lambda_{\text{sing}}(z), [g,[f,g]](z)\rangle$ (the Legendre-Clebsch condition) for the values $r = 0.2$ and $r = 0.5$ and the parameter values from Table 1 with the one change that $\gamma = 0.1$. Note that the overall shape of the graphs is very much alike and shows that these functions do not have a high sensitivity to low values of $r$. The graphs of the corresponding singular control $u_{\text{sing}}(z)$ are shown in Fig. 3. The values of the singular control are small—and this would agree with a model for metronomic chemotherapy— when the carrying capacity is in the range $q \in [100, 250]$ and the tumor volumes are comparable to these values. But the singular control takes very

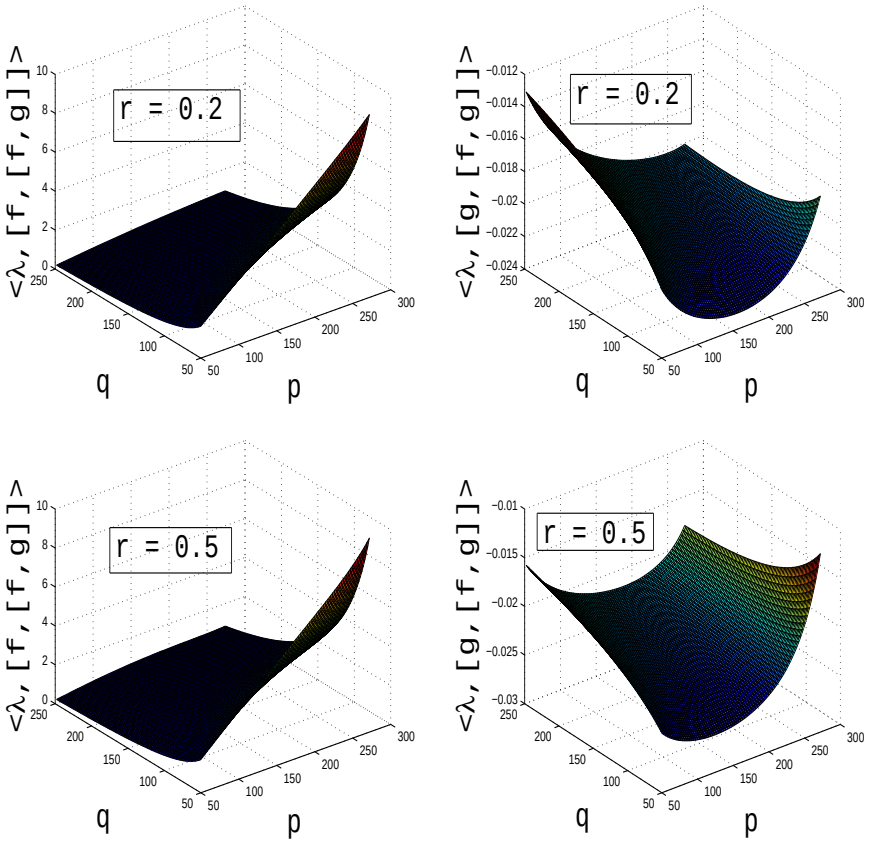


FIGURE 2. Slices of the graphs of the feedback functions $\langle \lambda_{\text{sing}}(z), [f,[f,g]](z)\rangle$ (left) and $\langle \lambda_{\text{sing}}(z), [g,[f,g]](z)\rangle$ (right) for constant values $r = 0.2$ (top) and $r = 0.5$ (bottom) and the parameters given in Tables 1 and 2.

large values for states with high tumor volume and low carrying capacity. However, such states do not correspond to medically realistic situations and thus are not of interest for the underlying problem. In Fig. 4 we show the evolution of a sample controlled trajectory for a singular control in time from the initial condition $(p_0, q_0, r_0) = (200, 300, 0.1)$.

Similarly, Fig. 5 shows slices of the graphs of the functions $\langle \lambda_{\text{sing}}(z), [f,[f,g]](z)\rangle$ and $\langle \lambda_{\text{sing}}(z), [g,[f,g]](z)\rangle$ for high tumor volumes $p$ and corresponding values $q$ in the range $(p, q) \in [350, 500] \times [350, 500]$. In this case, $\langle \lambda_{\text{sing}}(z), [g,[f,g]](z)\rangle$ is negative, i.e., the Legendre-Clebsch condition is satisfied, but $\langle \lambda_{\text{sing}}(z), [f,[f,g]](z)\rangle$ is negative as well and this generates negative and thus inadmissible values for the singular control (see equation (19)). As a result, the optimal dose rate will be maximal in this set. Thus, it is expected that for initial conditions in the malignant region the control will start with a brief maximum dose rate chemotherapy and then, once the system moves into the benign region, lower dose rate singular controls will be used to eradicate the tumor.

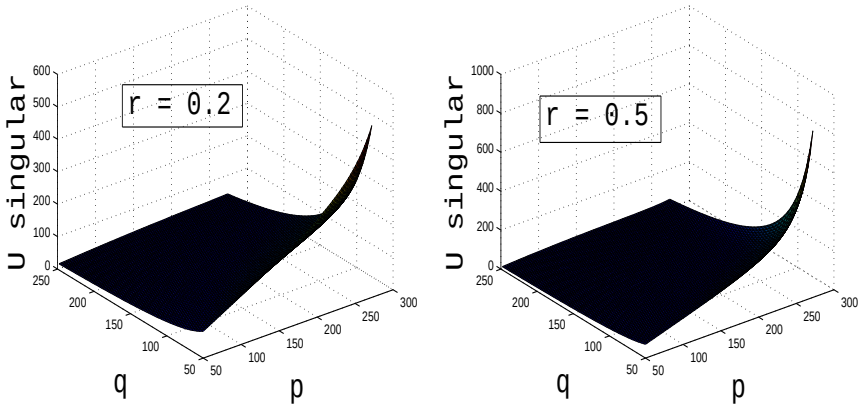


FIGURE 3. Graphs of the singular feedback control $u_{\text{sing}}(z)$ restricted to the slices $r = 0.2$ and $r = 0.5$.

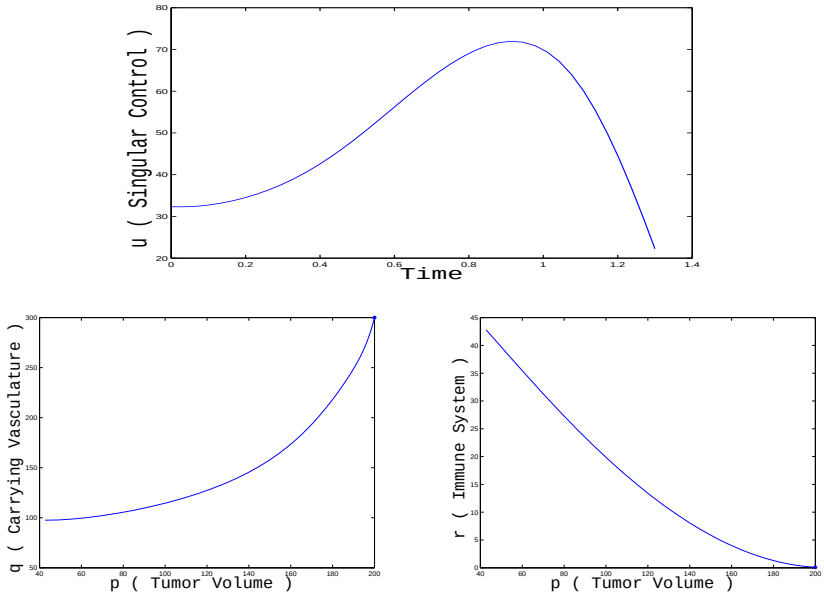


FIGURE 4. Time evolution of the singular control (top) from the initial condition $(p_0, q_0, r_0) = (200, 300, 0.1)$ and projections into the $(p, q)$ (bottom, left) and $(p, r)$ planes (bottom, right). The values of the parameters for the dynamics are from Table 1 and the weights in the objective are from Table 2.

4. **Conclusion.** In this paper, for a minimally parameterized mathematical model for metronomic chemotherapy that takes into account tumor vasculature and tumor immune system interactions and was introduced in [39], we formulated the problem of optimal drug administration as the problem of transferring an initial condition that lies in the region of attraction of a malignant equilibrium point into the region

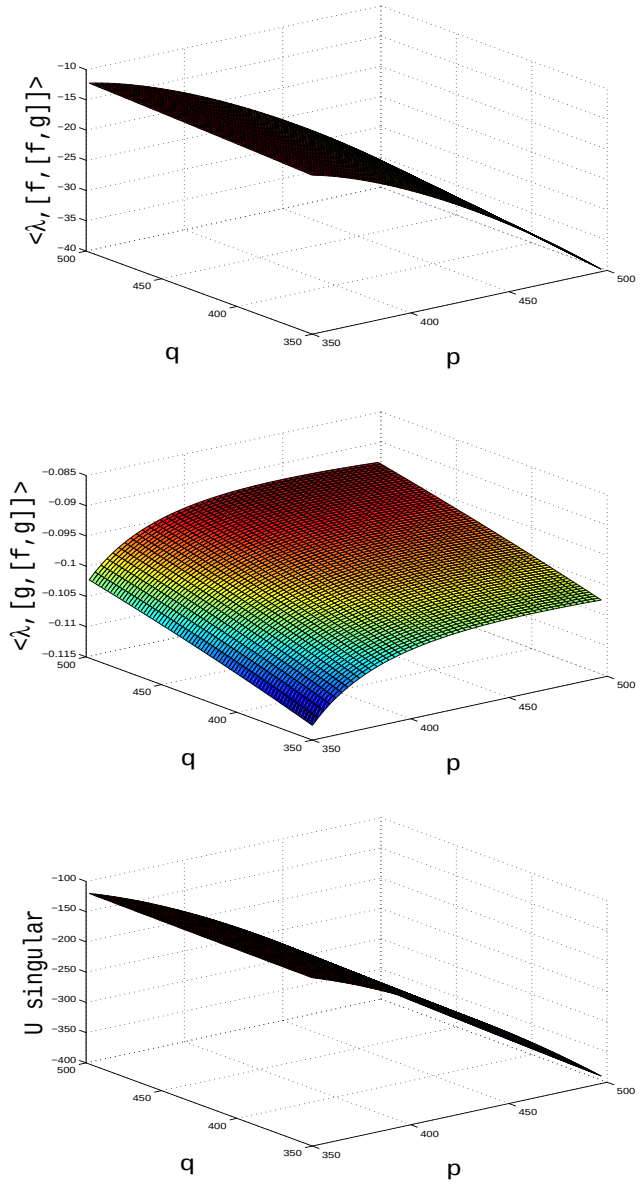


FIGURE 5. Slices of the graphs of the feedback functions $\langle \lambda_{\text{sing}}(z), [f,[f,g]](z)\rangle$ (top), $\langle \lambda_{\text{sing}}(z), [g,[f,g]](z)\rangle$ (middle) and the corresponding singular control $u_{\text{sing}}(z)$ (bottom) for $(p,q) \in [350,500]\times[350,500]$ and constant value $r = 0.5$. (The parameters are given in Tables 1 and 2). The singular control is negative and thus is inadmissible.

of attraction of a benign equilibrium point. For this problem, besides the constant controls that correspond to full dose treatment or no treatment, there exists a third main candidate for optimality given by a globally defined feedback control $u_{\text{sing}}$ determined by a singular control that takes time-varying intermediate values. We have derived an explicit analytic formula for $u_{\text{sing}}$ and illustrated its structure for some representative cases. Optimal controls will need to be synthesized from these three candidates, $u \equiv u_{\max}$, $u(z) = u_{\text{sing}}(z)$ and $u \equiv 0$ through a further analysis of the conditions of the maximum principle and this has not been done yet. Based on earlier results about optimal controls for antiangiogenic treatment for the model by Hahnfeldt et al. [29] and for the model of tumor immune system interactions by Stepanova [24, 32], it is expected that singular controls will play a major role in the solutions possibly preceded by a full-dose therapy interval if the initial tumor volume is high. These structures will be developed elsewhere. However, even this initial analysis shows the importance of singular controls that correspond to time-varying low dose protocols prevalent in metronomic chemotherapy.

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