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# On the Dynamics of Tumor Immune System Interactions and Combined Chemo- and Immunotherapy

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## 1 Introduction

Tumors are a family of high-mortality diseases, each different from the other, but all exhibiting a derangement of cellular proliferation that often leads to uncontrolled cell growth. Tumor cells (TCs) are characterized by a vast number of genetic and epigenetic events leading to the appearance of specific antigens (e.g., mutated proteins, under- or over-expressed normal proteins and many others) triggering reactions by both the innate and adaptive immune system (IS) [17, 27, 36]. These observations have provided a theoretical basis to the old empirical hypothesis of *immune surveillance*, i.e., that the immune system may act to eliminate tumors, only recently experimentally and epidemiologically confirmed [11]. Of course, the competitive interaction between tumor cells and the immune system involves a considerable number of events and molecules, and as such is extremely complex and the kinetics of the interplay is strongly nonlinear. Moreover, to fully describe the immuno-oncologic dynamics, one has to take into account a range of spatial phenomena. Indeed, the tumor-immune system interplay is strongly shaped by the mobility of both tumor cells and the effector cells of the immune system [25]. The outcome of this interplay is not only constituted by either tumor suppression or tumor outbreak, but there exist many intermediate scenarios. Indeed, the vast majority of theoretical immuno-oncology studies predict that a dynamic equilibrium may be established that allows the tumor to survive in a microscopic (and undetectable) dormant state [6, 8, 25]. This was largely inferred from clinical data. However, recently this theoretical prediction was directly confirmed by Koebel and coworkers [19], who were able to experimentally show, through an ad hoc mouse model, that adaptive immunity can

maintain occult cancer in an equilibrium state. It is quite intuitive that this equilibrium can be disrupted by sudden events affecting the immune system. Indeed, if disease related impairments of innate and adaptive immune systems or immuno-suppressive treatments preceding organ transplantations occur, then the tumor may restart developing. This has experimentally been shown both by mouse models and through epidemiologic studies [11, 35]. There also is a major class of causes of disruption of the equilibrium that are not related to immuno-suppression, but to adaptive processes called *immuno-editing* [11]: over a long period of time, the neoplasm may develop multiple strategies to circumvent the action of the immune system [11, 27], which may allow it to re-commence growing [8, 11] into clinically apparent tumors [19] which theoretically can reach their carrying capacity [8].

Overall, tumor-immune system interactions exhibit a multitude of dynamic properties that include multi-stability, i.e., persistence of both benign and malignant scenarios. Unmodeled outside effects such as immuno-suppressive treatments or immuno-editing may move the current state (comprising cancer and immune cells) across the boundary between these regions of attraction and in effect turn a benign situation into a malignant one. On the other hand, therapeutic interventions are made to the other effect in the form of immunotherapy [28], an interesting therapeutic approach consisting in stimulating the immune system in order to better fight, and hopefully eradicate, a cancer. Here we will only be considering generic immunostimulations, for example via cytokines. The basic idea of immunotherapy is simple and promising, but the results obtained in medical investigations are globally controversial [1, 15], even if in recent years there has been evident progress. As far as the mathematical description of tumor and immune system interaction is concerned, many works have appeared using deterministic [5]-[9], [20, 21, 25, 34, 37] or stochastic [4, 10] models, as well as models based on kinetic theories of non-linear statistical mechanics [2] introduced by Bellomo.

In this paper, we describe a metamodel of d’Onofrio for tumor-immune system interactions and then formulate treatment by cytotoxic agents and immunostimulations as an optimal control problem. Based on the biological background and the dynamic properties of the resulting system, we formulate a general mathematical objective function that expresses the underlying aim of moving initial conditions that lie in the malignant region of the state space (characterized through a macroscopic equilibrium or unbounded tumor growth) into its benign region (characterized by a microscopic equilibrium point). We then give a couple of numerical illustrations of optimal solutions for a modification of the classical model by Stepanova [34].

## 2 A Metamodel for Tumor-Immune System Interactions

In this section, a metamodel for tumor immune interactions will be developed and an analysis of the tumor free equilibrium state will be given.

## 2.1 Classical mathematical models of tumor-immune interactions

The analysis of classical finite dimensional models for tumor-immune system interactions [34, 21, 18, 37], reveals the following dynamical features:

1. the existence of a tumor free equilibrium,
2. the possibility that a tumor grows to a macroscopic size or beyond limits to  $\infty$ ,
3. the possible coexistence of small or tumor-free and large tumor-size equilibria,
4. a constant the influx of effector cells,
5. a varying proliferative profile of effector cells that depends on the tumor burden,
6. tumor-size dependent death rates of effectors, and
7. the possible existence of limit cycles.

From this rough summary, one may understand that the puzzling results obtained up to now by immunotherapy [1] may be strictly linked to the complex dynamical properties of the immune system-tumor competition. In general, it is possible that a cancer-free or microscopic equilibrium coexists with other stable equilibria or with unbounded growth, so that the success of treatment or cure very much depends on the initial conditions.

Summarizing and generalizing the above cited biological features and models, in [6] d'Onofrio introduced the following family of models [A]:

$$\dot{x} = x(f(x) - \phi(x)y) \quad (1)$$

$$\dot{y} = \beta(x)y - \mu(x)y + \sigma q(x) + \theta(t) \quad (2)$$

with  $x$  and  $y$  denoting the "sizes" (given by the total number, cell volumes, densities or adimensional quantities) of, respectively, tumor cells and effector cells (ECs) of the immune system.

It is assumed that  $0 < f(0) \leq +\infty$  and that  $f$  is nonincreasing,  $f'(x) \leq 0$ . In some relevant cases we shall suppose that  $\lim_{x \rightarrow 0^+} xf(x) = 0$  and that there exists a positive carrying capacity  $K$ , i.e.,  $f(K) = 0$ . Equations  $f$  of this type incorporate widely used models of tumor growth rates such as exponential, logistic, generalized logistic or Gompertzian growth models and many more (e.g., see [13, 14, 22]). The functional parameters are given by differentiable functions that satisfy the following qualitative properties:  $\phi$  is positive and decreasing,  $\phi(0) = 1$ , and  $x\phi(x) \rightarrow \ell \leq +\infty$ ;  $\beta$  is nonnegative, monotonically nondecreasing with  $\beta(0) = 0$ . In the model, it is assumed that there is a tumor-induced loss of effector cells [40] which is described by a strictly increasing function  $\mu$ . The function  $q = q(x)$  satisfies  $q(0) = 1$  and it may be nonincreasing or also initially increasing and then decreasing. Thus, we may assume that the growth of the tumor either decreases the influx of immune cells or that, on the contrary, it actually initially stimulates this influx before leading to an inhibitory pattern. In fact, for some cases of cancer it has been

observed experimentally that progression may cause generalized immunosuppression which is reflected in an assumption of the type  $q'(x) < 0$  for  $x \gg 1$ ; for example, see [32] and the references therein. Finally, the term  $\theta(t)$  is a positive function that describes the influx of effector cells from the primary organs and will also be used to model immunostimulation.

This metamodel includes, as particular cases, the ones by Stepanova [34], Kuznetsov, Makalkin, Taylor and Perelson [21] and de Vladar and Gonzazalez [37]. For instance, for the Stepanova model [34] we have that tumor growth is exponential,  $f(x) \equiv \alpha = \text{const}$  and

$$\phi(x) \equiv 1, \quad \beta(x) = \beta_1 x, \quad \mu(x) = \mu_0 + \mu_2 x^2 \quad \text{and} \quad q(x) \equiv 1. \quad (3)$$

The terms in the model by de Vladar and Gonzalez [37] are similar except that the tumor growth is Gompertzian,  $f(x) = \alpha \log(K/x)$ , [26]. In the model by Kuznetsov et al. [21], a logistic tumor growth model is used,  $f(x) = \alpha(1 - x/K)$ , and the functions are given by

$$\phi(x) \equiv 1, \quad \beta(x) = \frac{\beta_\infty x}{m + x}, \quad \mu(x) = \mu(0) + \mu_1 x, \quad \text{and} \quad q(x) \equiv 1. \quad (4)$$

## 2.2 A Generalised model [B]

While the model [A] provides a general start, to make it biologically more accurate, it needs to be expanded. A first modification involves the uptake rate of T-cells. We shall allow this function to be a nonmonotone function of the tumor burden and a nonlinear function of the number of effector cells. The latter feature is considered to take into account possible cooperative and/or competitive effects between effector cells. This leads to the following equation for the dynamics of tumor cells:

$$\dot{x} = x(f(x) - \phi(x)\pi(y))$$

where now the predation function  $\pi(y)$  no longer is linear, but is a generic strictly increasing growth function,  $\pi'(y) > 0$ . The overall functional response of tumor cells,  $U(x) = x\phi(x)$ , can be non-monotone. The other change concerns the proliferation of the cells of the immune system in response to tumors. It is reasonable to assume that the proliferation of effector cells depends on  $y$ . Apart from crowding effects, indeed, the proliferation stimulation might depend on the relative abundance of the two competing populations [12]. Taking this into account leads to equations of the form [B]:

$$\dot{x} = x(f(x) - \gamma\xi(t) - \phi(x)\pi(y)) \quad (5)$$

$$\dot{y} = \left( P(x, y) - \mu(x) - \eta\xi(t) \right) y + \sigma q(x) + \theta(t) \quad (6)$$

Here we included the possibility of the delivery of cytotoxic chemotherapy with blood profile  $\xi(t)$  that may also affect the immune system effector cells.

For sake of simplicity, in this section we take  $\xi(t)$  constant and such that  $0 \leq \xi < f(0)/\gamma$ . The proliferation rate  $P = P(x, y)$  satisfies  $P(0, y) = 0$ , is strictly increasing in  $x$  and nonincreasing in  $y$ . For example, Forys et al. [12] propose the following functional relationship depending on the ratio  $x/y$ :

$$P(x, y) = \beta_\infty \frac{\left(\frac{x}{y}\right)^\alpha}{1 + \left(\frac{x}{y}\right)^\alpha} = \beta_\infty \frac{x^\alpha}{x^\alpha + y^\alpha}. \quad (7)$$

### 2.3 Equilibria and null-clines of model [B]

The equilibria of (5) and (6) are determined by the equations  $\dot{x} = 0$  and  $\dot{y} = 0$ . The equation  $\dot{x} = 0$  yields  $x = 0$  (which we will examine later), or

$$f(x) - \gamma\xi - \phi(x)\pi(y) = 0$$

which implies that  $y$  is given in the form

$$y = Y_C(x; \xi) = \pi^{-1}(y_C(x; \xi)), \quad (8)$$

with

$$y_C(x; \xi) = (f(x) - \gamma\xi)/\phi(x). \quad (9)$$

We call  $Y_C(p; \xi)$  the C null-cline and call  $y_C(p; \xi)$  the baseline C-curve. This is the curve that would be the C null-cline for the case  $\pi(y) = y$ . Note that  $\frac{\partial Y_C}{\partial \xi}(x; \xi) < 0$ , and that one can rewrite the tumor-dynamics equation in the following, technically useful form:

$$\dot{x} = U(x)(y_C(x; \xi) - \pi(y)). \quad (10)$$

Clearly, if

$$\pi(\infty) \geq \max_{x \in [0, K]} y_C(x; \xi), \quad (11)$$

then  $Y_C(x; \xi)$  is bounded; otherwise it has vertical asymptotes where  $\pi_\infty = y_C(x; \xi)$ . For sake of simplicity, we assume that (11) holds.

The equation  $\dot{y} = 0$  yields the I-nullcline  $Y_I(x; \theta, \xi)$  determined by the equation

$$P(x, y) = \mu(x) + \eta\xi - \frac{\theta + \sigma q(x)}{y}, \quad (12)$$

If  $\lim_{y \rightarrow \infty} P(x, y) = 0$ , then equation (12) has a unique solution  $y$  in an interval  $(y^*(x), \infty)$  and there exists no  $\hat{p} < \infty$  such that

$$\lim_{x \rightarrow \hat{x}} Y_I(x; \theta, \xi) = \infty. \quad (13)$$

The boundedness of  $Y_I(x)$  also holds if we relax assumptions to the less restrictive condition

$$\lim_{y \rightarrow \infty} P(x, y) < \mu(x) \quad \text{for all } x > 0. \quad (14)$$

Thus, defining the function

$$\Psi_\infty(x) = \mu(x) - \lim_{y \rightarrow \infty} P(x, y), \quad (15)$$

if  $\Psi_\infty(x)$  is strictly positive, then the I null-cline is bounded (biologically, the tumor may be classified as “lowly immunogenic” or “highly aggressive”). On the other hand, when  $\Psi_\infty(x)$  has varying signs, then the I null-cline is unbounded (and the tumor may be classified as “highly immunogenic” or “lowly aggressive”). It is easy to show that the effect of a constant immunotherapy on the I null-cline is to increase it ( $\frac{\partial Y_I}{\partial \theta}(x; \theta, \xi) > 0$ ), whereas the effect of a constant chemotherapy is to decrease it ( $\frac{\partial Y_I}{\partial \xi}(x; \theta, \xi) < 0$ ).

Single or multiple equilibria may be determined by the intersections of the null-clines in  $\mathbb{R}_+^2$ . Stability properties of these equilibria can easily be related to the properties of the functions  $Y_C(x; \xi)$  and  $Y_I(x; \theta, \xi)$ :

**Proposition 1.** *An equilibrium point  $E = (x_e(\theta, \xi), y_e(\theta, \xi))$  of the system (5) and (6) is locally asymptotically stable if*

$$Y_I'(x_e; \theta, \xi) > Y_C'(x_e(\theta, \xi); \xi) \quad \text{and} \quad U(x_e)\pi'(y_e)Y_C'(x_e; \xi) < -\frac{\partial B}{\partial y}(x_e, y_e). \quad (16)$$

## 2.4 Tumor-free equilibrium

In absence of therapy, there is a disease-free equilibrium at

$$TF = \left(0, \frac{\sigma q(0)}{\mu(0)}\right), \quad (17)$$

which for  $\sigma = 0$  degenerates to  $(0, 0)$ .

**Proposition 2.** *In the absence of immunotherapy (i.e., for  $\theta = 0$ ), if  $\sigma > 0$  and  $Y_I(0) > Y_C(0; \xi)$ , i.e., if*

$$\frac{\sigma q(0)}{\mu(0)} > \pi^{-1}(y_C(0; \xi)), \quad (18)$$

*then the tumor free equilibrium  $TF$  is locally asymptotically stable. If  $\sigma = 0$ , then the degenerate tumor free equilibrium  $TF = (0, 0)$  is always unstable with the  $y$ -axis the stable manifold.*

There are examples of observations of persistent oscillations in oncological diseases in the medical literature [16, 18, 38]. In [6], d’Onofrio studied the limit cycle dynamics present in the case of  $q(x) \geq 0$ , and (in absence of chemotherapy) in [6, 7] it was shown that a necessary condition for the presence of periodic or other closed orbits is that  $y'_C(x)$  has varying sign. These results can also be applied in the co-presence of constant chemo- and immunotherapies:

**Proposition 3.** *Suppose there exists exactly one equilibrium point  $EQ = (x_e, y_e)$  other than  $TF$ . If  $y_C(x; \xi)$  is decreasing, then there are no closed orbits. If  $EQ$  is unstable with*

$$U(x_e)\pi'(y_e)Y'_C(x_e; \xi) > -\frac{\partial B}{\partial y}(x_e, y_e; \theta, \xi),$$

*then there exists at least one locally asymptotically stable limit cycle.*

For the tumor free equilibrium  $TF$  under constant therapy  $\theta$ , there exists a value  $\theta_{LAS}(\xi) \geq 0$  such that for  $\theta > \theta_{LAS}(\xi)$  the tumor free equilibrium  $TF$  is locally asymptotically stable. It is thus reasonable to investigate if there is a second value  $\theta_{GAS}(\xi) \geq \theta_{LAS}(\xi) \geq 0$  such that for  $\theta(\xi) > \theta_{GAS}(\xi)$ , the disease-free equilibrium becomes globally asymptotically stable. Concerning this point, here we give the following proposition on the global eradicability of a tumor, under time-varying chemo- and immuno- therapies, which extends the slightly less general result in Proposition 6.1 of [7]:

**Proposition 4.** *If  $\theta(t) \geq 0$  and  $\xi(t) \geq 0$  are such that*

$$Y_I(x; \theta_{min}, \xi_{min}) > Y_C(x; \xi_{min}), \quad (19)$$

*where*

$$\theta_{min} = \min_{t \geq 0} \theta(t) \quad \text{and} \quad \xi_{min} = \min_{t \geq 0} \xi(t),$$

*then  $TF$  is globally asymptotically stable for nonnegative initial conditions, i.e., the tumor is eradicated independently of the initial tumor burden and state of the immune system.*

### 3 Optimal Control for Mathematical Models of Tumor-Immune System Interactions

In view of harmful side effects of both cytotoxic drugs and also of drugs that boost the immune system, it is not feasible to consider indefinite administrations of agents. Thus, and proceeding beyond models of constant blood profiles, the practically important question becomes how are therapeutic agents best administered. The goal is to transfer an initial condition  $(x_0, y_0)$  that lies in the region of malignant cancer growth for the uncontrolled system into the region of attraction of the stable, benign (microscopic) equilibrium point thus controlling the cancer volume. In an optimal control formulation, the aim is to achieve this goal in an efficient and effective way.

Intuitively, such a transfer requires to minimize the cancer cells  $x$  while not depleting the effector cell density  $y$  too strongly. The boundary between the benign and malignant regions consists of the stable manifolds of unstable equilibria. For most models, such as the classical version of Stepanova's model

[34] or its extension by de Vladar and Gonzalez [37], there exists a unique saddle point whose stable manifold defines this boundary, the so-called separatrix. In general, it is rather difficult to give analytic descriptions of these manifolds, but their tangent spaces are readily computed and provide a first approximation for the separatrix. This motivates to tailor a term in the mathematical objective to be minimized that induces the system to move across this boundary. The underlying system is two-dimensional and thus the saddle has a unique stable eigenvector  $\mathbf{v}_s = (B, A)^T$ . It follows from the underlying geometry that typically these coefficients are positive. Thus, by including a penalty term  $Ax(T) - By(T)$  at the final time, this not only conforms with the heuristic notion of minimizing cancer cells and maximizing effector cells, but in a very precise mathematical way justifies the chosen weights by providing an incentive for the system to move across the separatrix into the benign region.

Furthermore, side effects of the treatment need to be taken into account. The model above, in a first approximation, does not incorporate healthy cells and tissue and thus side effects are only modeled indirectly. It is assumed that chemo- and immunotherapies have a proportional effect on healthy tissue and thus in our formulation we add weighted integral terms  $\int_0^T u(t)dt$  and  $\int_0^T v(t)dt$  that measure the total amounts given of a cytotoxic agent  $u$  and an immunostimulator  $v$ , respectively. Side effects of the immune boosts are less severe, but generally cannot be ignored. Thus both integrals are included in the objective with proper weights. Alternatively, based on medical expertise, these amounts could be limited a priori and then a minimization problem subject to isoperimetric constraints

$$\int_0^T u(t)dt \leq U_{\max} \quad \text{and} \quad \int_0^T v(t)dt \leq V_{\max}$$

might be considered.

Finally, we keep the terminal time  $T$  in our problem formulation free. However, because of the existence of a tumor-free or microscopic benign equilibrium, it is possible—and this indeed is observed in simple models [23, 24]—that trajectories use the zero controls over very long time horizons. These trajectories, which improve the value of the mathematical objective without incurring any cost, provide a “free pass,” but lead to a mathematically ill-posed problem formulation as no minimum may exist in this case. Indeed, the infimum arises as the control switches to follow  $u = 0$  and  $v = 0$  when the controlled trajectory intersects the separatrix, then follows the separatrix for an infinite time to the saddle and then again leaves this saddle point along the unstable manifold, once more taking an infinite time. This indeed would be the “optimal” solution for this problem formulation, but it is not an admissible trajectory in our system. In order to avoid this scenario, we include a penalty term on the final time as well. From a biological point of view, the addition of this term induces optimal solutions to give more drugs and thus

reach the benign equilibrium point faster rather than take a very long time with a smaller amount of agents. Clearly, it is not desirable for the system to evolve along the border between benign and malignant tumor behavior and it is this term that forces the system into the benign region more quickly. In view of imprecise and mathematically unmodeled dynamics and other random perturbations, from a system theoretic perspective, the addition of this term provides desired robustness and stability properties for the underlying real system.

Summarizing, we formulate a mathematical *objective* of the following form that consists of

1. a weighted average of the penalty term  $Ax(T) - By(T)$  which induces the system to move across the separatrix from the malignant into the benign region of the state space,
2. the cumulative side effects of the chemotherapeutic agent and the immune boost taken as an indirect measure of the side effects of treatment, and
3. a small penalty term on the terminal time  $T$  that makes the problem mathematically well-posed:

$$J(u) = Ax(T) - By(T) + C \int_0^T u(t)dt + D \int_0^T v(t)dt + ST.$$

As explained earlier,  $A$  and  $B$  are positive coefficients determined by the stable eigenvector  $\mathbf{v}_s = (B, A)^T$  of the saddle and  $C$ ,  $D$  and  $S$  are positive weights. We emphasize that the latter coefficients are variables of choice and may be chosen to calibrate the response of the system. The choice of the weights aims at striking a balance between the benefit at the terminal time  $T$ ,  $Ax(T) - By(T)$ , and the overall side effects measured by the total amount of drugs given while it guarantees the existence of an optimal solution by also penalizing the free terminal time  $T$ . The integrals of the dose rates model the side effects of the therapies on the healthy tissue and if there exist clinical data as to the severity of the drugs, then this will be reflected in the choices for  $C$  and  $D$ . Naturally, also the specific type of tumor and even the stage of cancer the patient has, will enter into the calibration of these coefficients. For the case of a more advanced stage, higher side effects need to be tolerated and thus smaller values of  $C$  and  $D$  will be taken. Overall, the coefficients  $C$ ,  $D$  and  $S$  are variables of choice that can be fine tuned to calibrate the system's optimal response.

Thus, for a system with tumor-immune interactions, the following optimal control problem in Bolza form arises:

[OC] for a free terminal time  $T$ , minimize the objective

$$J(u, v) = Ax(T) - By(T) + \int_0^T (Cu(t) + Dv(t) + S) dt, \quad (20)$$

over all Lebesgue measurable functions

$$(u, v) : [0, T] \rightarrow [0, 1] \times [0, 1], \quad t \mapsto (u(t), v(t))$$

subject to the dynamics (1) and (2) respectively (5) and (6).

It is clear that for any correct modeling of the problem we must have that the states  $x$  and  $y$  remain positive for positive initial conditions  $x_0$  and  $y_0$  and arbitrary admissible controls  $u$  and  $v$ . Since  $x = 0$  is an equilibrium solution of (1) and (5), the variable  $x$  cannot cross 0 and if  $y = 0$ , then because of the influx of effector cells that is part of the positive function  $\theta(t)$ , we always have that  $\dot{y} > 0$ . Thus the region  $P = \{(x, y) : x > 0, y > 0\}$  is positively invariant and no positivity constraints need be imposed on the variables.

#### 4 Optimal Controls for a Modified Stepanova model

The structures of optimal controls no longer just depend on the qualitative features that are incorporated into the general models [A] and [B], but on the specific choices of the functional parameters such as the tumor growth model. In this section, we give two examples of the structure of optimal controls for a modified version of the classical model by Stepanova [34] when exponential tumor growth has been replaced with a Gompertzian model. Specifically, we consider the following equations:

$$\dot{x} = -\mu_C x \ln\left(\frac{x}{x_\infty}\right) - \gamma xy - \kappa_X xu \quad x(0) = x_0, \quad (21)$$

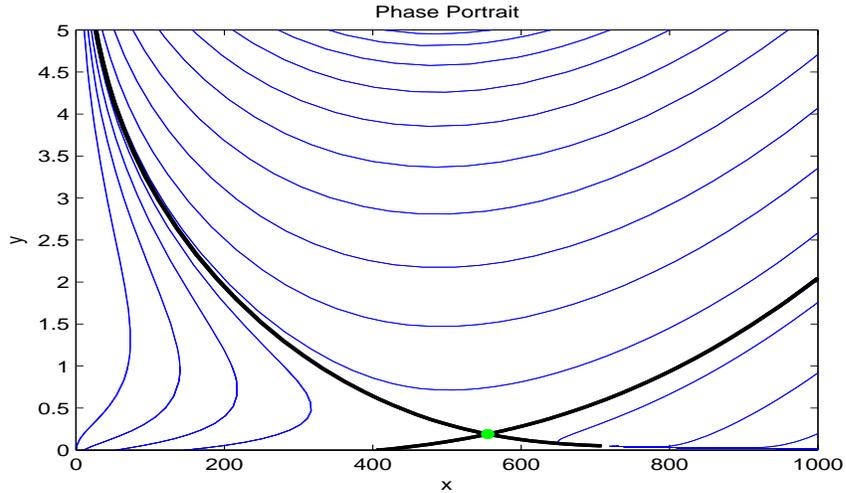
$$\dot{y} = \mu_I (x - \beta x^2) y - \delta y + \alpha + \kappa_Y yv \quad y(0) = y_0. \quad (22)$$

The controls  $u$  and  $v$  denote the blood profiles of a cytotoxic agent and a generic immune stimulation agent, respectively;  $\alpha$  is a positive constant that models a constant influx of effector cells from the primary organs.

The uncontrolled system (i.e., for  $u = 0$  and  $v = 0$ ), has two locally asymptotically stable equilibria, one microscopic, the other macroscopic, with the regions of attraction separated by the stable manifold of an intermediate saddle point. These dynamic properties persist under full dose immunotherapy if no chemotherapy is used and thus, for some initial conditions, immunotherapy alone is not sufficient to eliminate the cancer. Figure 1 shows the phase portraits for the parameter values given in Table 1 for a constant full dose control  $v \equiv 1$  and  $u \equiv 0$ . The stable manifold of the saddle at  $(x_s, y_s) = (555.1, 0.191)$  still separates a region where the immune system aided by the immune boost can eliminate the cancer (the  $y$ -values of the system approach  $+\infty$  while  $x$  converges to 0 from the right) from a region where the cancer eventually will dominate and trajectories converge to the asymptotically stable malignant equilibrium point  $(x_m, y_m) = (715.6, 0.048)$ . Any initial condition that lies to

variable/ parameters	interpretation	numerical value	dimension	Ref.
$x$	tumor volume		$10^6$ cells	[34]
$x_0$	initial value for $x$	600	$10^6$ cells	
$y$	immuno-competent cell density		non-dimensional	[34]
$y_0$	initial value for $y$	0.10	non-dimensional	
$\alpha$	rate of influx	0.1181	1/day	[21]
$\beta$	inverse threshold for tumor suppression	0.00264	non-dimensional	[21]
$\gamma$	interaction rate	1	$10^7$ cells/day	[21]
$\delta$	death rate	0.37451	1/day	[21]
$\mu_C$	tumor growth parameter	0.5599	$10^7$ cells/day	
$\mu_I$	tumor stimulated proliferation rate	0.00484	1/day	
$x_\infty$	fixed carrying capacity	780	$10^6$ cells	
$\kappa$	chemotherapeutic killing parameter	1	$10^7$ cells/day	

**Table 1.** Numerical values for the variables and parameter used in computations.



**Fig. 1.** Phase portrait of the controlled system (21) and (22) for  $u = 0$  and  $v = 1$ .

the right of the stable manifold of the saddle cannot be transferred into the benign region with immunotherapy alone.

Necessary conditions for optimality of the controls  $u$  and  $v$  are given by the *Pontryagin maximum principle* (for some recent texts, see [3, 30]). For a 2-dimensional row-vector  $\lambda = (\lambda_1, \lambda_2)$ , define the Hamiltonian  $H = H(\lambda, x, y, u, v)$  as

$$H = (Cu + Dv + S) + \lambda_1 \left( -\mu_C x \ln \left( \frac{x}{x_\infty} \right) - \gamma xy - \kappa_X xu \right) + \lambda_2 \left( \mu_I (x - \beta x^2) y - \delta y + \alpha + \kappa_Y yv \right). \quad (23)$$

If  $(u_*, v_*)$  is an optimal control defined over an interval  $[0, T]$  with corresponding trajectory  $z_* = (x_*, y_*)^T$ , then, by the Pontryagin maximum principle, there exists an absolutely continuous covector  $\lambda = (\lambda_1, \lambda_2)$  defined on  $[0, T]$ , such that the following conditions hold:

(a)  $\lambda_1$  and  $\lambda_2$  satisfy the adjoint equations

$$\dot{\lambda}_1 = -\frac{\partial H}{\partial x} = \lambda_1 \left( \mu_C \left( 1 + \ln \left( \frac{x}{x_\infty} \right) \right) + \gamma y + u \kappa_X \right) - \lambda_2 \mu_I (1 - 2\beta x) y \quad (24)$$

$$\dot{\lambda}_2 = -\frac{\partial H}{\partial y} = \lambda_1 \gamma x - \lambda_2 \left( \mu_I (x - \beta x^2) - \delta + \kappa_Y v \right) \quad (25)$$

with terminal conditions  $\lambda_1(T) = A$  and  $\lambda_2(T) = -B$ , and

(b) for almost every time  $t \in [0, T]$ , the optimal controls  $(u_*(t), v_*(t))$  minimize the Hamiltonian  $H$  along  $(\lambda(t), x_*(t), y_*(t))$  over the control set  $[0, 1] \times [0, 1]$  with minimum value given by 0.

A *controlled trajectory*  $((x, y), (u, v))$ , consisting of admissible controls  $(u, v)$  and corresponding solution  $(x, y)$  of the initial value problem (21) and (22), for which there exists a multiplier  $\lambda$  such that the conditions of the maximum principle are satisfied is called an *extremal* (pair) and the triple  $((x, y), (u, v), \lambda)$  is an *extremal lift* (to the cotangent bundle). More generally, in an optimal control problem there is another constant multiplier  $\lambda_0$  associated with the objective, but in our case it can always be normalized to  $\lambda_0 = 1$  and we already have anticipated this in our formulation.

By condition (b), the optimal controls  $u_*(t)$  and  $v_*(t)$  minimize the Hamiltonian  $H$  along the extremal  $(\lambda(t), x_*(t), y_*(t))$  over the control set  $[0, 1] \times [0, 1]$  a.e. on  $[0, T]$ . Since  $H$  is linear in the controls and the control set is a rectangle, these minimizations decouple and can be carried out separately. Defining the *switching function*  $\Phi_1 = \Phi_1(t)$  for  $u$  as

$$\Phi_1(t) = C + \langle \lambda(t), g_1(z_*(t)) \rangle = C - \lambda_1(t) \kappa_X x_*(t), \quad (26)$$

it follows that

$$u_*(t) = \begin{cases} 0 & \text{if } \Phi_1(t) > 0, \\ 1 & \text{if } \Phi_1(t) < 0, \end{cases} \quad (27)$$

and with  $\Phi_2 = \Phi_2(t)$  the switching function for  $v$ ,

$$\Phi_2(t) = D + \langle \lambda(t), g_2(z_*(t)) \rangle = D + \lambda_2 \kappa_Y y_*(t), \quad (28)$$

the optimal control  $v_*$  satisfies

$$v_*(t) = \begin{cases} 0 & \text{if } \Phi_2(t) > 0, \\ 1 & \text{if } \Phi_2(t) < 0. \end{cases} \quad (29)$$

We refer to the constant controls given by the extreme values 0 and 1 as *bang* controls. The minimum conditions by themselves do not determine the controls at times when the switching functions vanish,  $\Phi_i(\tau) = 0$ . But if the time-derivative  $\dot{\Phi}_i(\tau)$  does not vanish, then at such a time the control switches between its extreme values with the order depending on the sign of  $\dot{\Phi}(\tau)$ . Thus also the name of bang-bang controls. In the other extreme, if  $\Phi(t) \equiv 0$  on an open interval  $I$ , then all derivatives of  $\Phi(t)$  must vanish as well and typically this does allow to compute the control. Controls of the second kind are called *singular* [3, 30]. In principle, in a multi-input case, as it is considered here, it is even possible that both controls are singular at the same time and in this case the controls are called totally singular. Overall, optimal controls need to be synthesized from these classes of candidates.

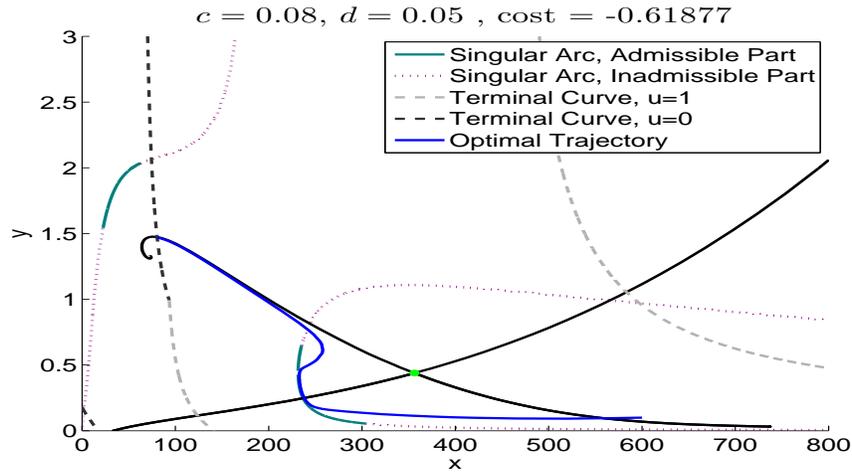
In the papers [24] and [31] we have undertaken an extensive analysis of the local optimality of singular controls. For the monotherapy problem with chemotherapy as the only control, singular controls satisfy the Legendre-Clebsch condition, a second-order necessary condition for optimality, in its strengthened form away from the strip  $\{(x, y) : \frac{1}{4\beta} \leq x \leq \frac{1}{2\beta}\}$  and indeed are locally optimal. Explicit formulas for the singular control and corresponding singular arcs are given in [24] and using these formulas, optimal controls have been computed numerically using GPOPS, a Gauss hp-adaptive pseudospectral method [29]. Below in Figure 2 we give a numerical illustration for this case.

**Scenario 1: chemotherapy only.** We used the numerical values given in Table 1 and the following coefficients in the objective:

$$A = 0.00192, \quad B = 1, \quad C = 0.08, \quad D = 0, \quad S = 0.05.$$

Singular controls are only admissible along the specific curves in the state space shown as solid green segments in Figure 2. The tumor volume is measured in multiples of  $10^6$  while the immunocompetent cell densities are on a scale relative to 1. The optimal trajectory starting at  $(x_0, y_0) = (600, 0.1)$  initially administers cytotoxic agents at full dose until the corresponding trajectory (i.e., the response of the system) hits an admissible singular arc. At this time, the optimal control switches to a singular control and the trajectory follows the singular arc across the separatrix. Then, at a certain time  $\tau$  the administration of chemotherapy ceases, i.e., the system follows the uncontrolled

trajectory ( $u = 0$ ) towards the benign equilibrium point. The optimal final time  $T$  is realized when the objective becomes minimized along this trajectory. Overall, a concatenation sequence for the control of the form  $1s0$  results with the 1 indicating therapy at maximum dose, the  $s$  denoting a time-varying profile that follows a singular control and the 0 denoting no chemotherapy. Figure 2 shows the resulting controlled trajectory with the initial and terminal conditions labeled as  $w_0$  and  $w_T$ , respectively, and the consecutive switching points denoted by  $w_1$ ,  $w_2$  and  $w_3$ .

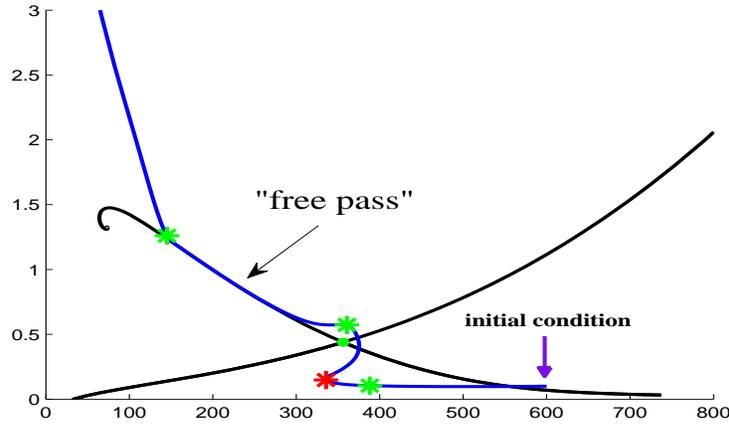


**Fig. 2.** Example of an optimal controlled trajectory of the form  $1s0$  for the problem with chemotherapy only.

**Scenario 2: chemotherapy combined with immune boost.** Figure 3 gives the analogous phase portrait of an optimal controlled trajectory for a case when the immune boost  $v$  is included in the model. Again, the parameters used were the ones given in Table 1 and here the coefficients in the objective are

$$A = 0.00192, \quad B = 1, \quad C = 0.025, \quad D = 0.005, \quad S = 0.0005.$$

We have chosen the coefficients so that the side effects of chemotherapy are more severe than those of the immune boost. Thus, naturally one expects that the immune boost will play a significant role in this scenario. However, the initial condition still lies in the malignant region for the controls  $u \equiv 0$  and  $v \equiv 1$  and thus a constant immune boost in itself is not able to control the cancer volume. Thus, and although the cost is high, initially full dose chemotherapy must be given to move the state out of the region of attraction of this malignant equilibrium into the region where an immune boost can control



**Fig. 3.** Optimal controlled trajectory in Scenario 2. The stars indicate the points when switchings in the optimal controls occur (red asterisks for switchings in the chemotherapy, green asterisks for switchings in the immunotherapy). The curve gives the response of the system to the optimal controls.

the cancer volume. Once there, chemotherapy turns off (the red asterisk along the trajectory) and the immune boost (which starts at the first green asterisk counting from the initial condition) moves the state of the system into the benign region. Then, as in scenario 1, the uncontrolled trajectory (“free pass”) becomes the most cost-effective strategy (only paying a small penalty for the time spent along it) until, because of the low cost of the immune boost, it becomes once again beneficial to give an immune boost as the cancer volume becomes small.

Naturally, the structure of optimal controls depends on the coefficients selected for the objective. If the weights for the side effects of chemotherapy become less severe, then chemotherapy overall has the better effect and it remains the dominant therapy with the control structure similar to the one in the monotherapy case with chemotherapy only (e.g., see [31]). In fact, this is the typical scenario for a broad range of parameters and there exists only a rather small window of parameters when true interactions between the tumor immune system occur. Around this region, the underlying system is quite sensitive to parameters.

## 5 Conclusion

We outlined a metamodel for tumor-immune system interactions that incorporates various classical models from the literature (e.g., [34, 21, 37]) and

becomes the basis for the problem of finding optimal procedures for administering cancer treatments. Mathematically, the problem to cure the patient becomes the problem to transfer the system from an initial condition in the malignant region of the state space through therapy into a benign region. In this paper, combinations of a chemotherapeutic agent and an immune boost are applied to achieve this goal in an optimal way in the sense of scheduling the dosages and their sequencing. Methods of optimal control are used to solve the problem and some examples of solutions are presented for a specific case of the metamodels presented, a modified version of the classical model by Stepanova. These solutions indicate chemotherapy will always be needed first to bring down a large tumor volume before the actions of the immune system can become effective.

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