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Fastest Time to Cancer by Loss of Tumor Suppressor Genes

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Abstract Genetic instability promotes cancer progression (by increasing the probability of cancerous mutations) as well as hinders it (by imposing a higher cell death rate for cells susceptible to cancerous mutation). With the loss of tumor suppressor gene function known to be responsible for a high percentage of breast and colorectal cancer (and a good fraction of lung cancer and other types as well), it is important to understand how genetic instability can be orchestrated toward carcinogenesis. In this context, this paper gives a complete characterization of the optimal (time-varying) cell mutation rate for the fastest time to a target cancerous cell population through the loss of both copies of a tumor suppressor gene. Similar to the (one-step) oncogene activation model previously analyzed, the optimal mutation rate of the present two-step model changes qualitatively with the convexity of the (mutation rate-dependent) cell death rate. However, the structure of the Hamiltonian for the new model differs significantly and intrinsically from that of the one-step model, and a completely new approach is needed for the solution of the present two-step problem. Considerable insight into the biology of optimal switching (between corner controls) is extracted from numerical results for cases with nonconvex death rates.

Keywords Cancer · Genetic instability · Tumor suppressor gene · Optimal control

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1 Introduction

Genetic instability induced by excessive genetic mutation as a cause for carcinogenesis has been an active research area for more than four decades starting as early as Loeb et al. (1974) with representative findings reported in review articles such as Branzei and Foiani (2010), Bristow and Hill (2008), Negrini et al. (2010), Pikor et al. (2013), Wodarz and Komarova (2005) and Wodarz and Komarova (2014). With technological advances and clinical interest, research effort in this area has further expanded in this new century as seen from Ashworth et al. (2011), Bailey and Murnane (2006), Bartek (2011), Bartkova et al. (2005), Breivik (2005), Campbell et al. (2012), Colotta et al. (2009), Corcos (2012), Deng (2006), Gorgoulis et al. (2005), Grady and Carethers (2008), Ledzewicz et al. (2013), Maslov and Vijg (2009), Michor et al. (2005), Nouspikel (2013) and Smith et al. (2003) and references cited therein. Fundamental knowledge gained from these studies include the followings:

- There are two principal sources of genetic instability: The *chromosomal instability* (CIN) associated with chromosome abnormality in cells (Cahill et al. 1999) and *microsatellite instability* (MSI) associated with an impaired mismatch repair mechanism leading to a high level of errors in stretches of DNA (known as microsatellites) (Kinzler and Vogelstein 2002; Perucho 1996). Other possible causes include telomeric abnormality (Rudolph et al. 2001; Samper et al. 2001).
- Genetic instability has two main effects on carcinogenesis (see Wodarz and Komarova 2005 for example): (1) A possible increase in the probability for a cell to experience an advantageous, malignant mutation which can increase the cell's proliferation rate and lead to cancerous growth and (2) an increased chance of unwanted deleterious changes in the cell's genome which can lead to a higher cell death rate.

Notably, new directions of research include the initiation of mathematical modeling, analysis and numerical simulations to provide a theoretical basis for the empirical and clinical findings (de Pillis and Radunskaya 2003; Pillis et al. 2007; dePillis et al. 2007; Komarova et al. 2002, 2003; Ledzewicz et al. 2013; Nowak et al. 2006; Wodarz and Komarova 2005, 2014). That genetic instability can both increase the rate of cancer progression (by increasing the probability of cancerous mutations) and decrease the rate of cancer growth (by imposing a higher cell death rate) has led to theoretical studies on how genetic instability may be orchestrated to promote carcinogenesis (as it is known to do so) in the microevolution inside the biological organism (Komarova and Wodarz 2004; Komarova 2004; Komarova et al. 2008; Wan et al. 2010). The microevolutionary forces that act on cancer cells during multistage carcinogenesis can be modeled by taking into account both beneficial and deleterious effects and formulating the question of interest from the viewpoint of cancerous cells. In that context, we are interested in the optimal level of mutation rate that makes carcinogenesis progress in the fastest way. This information is expected to provide insight into the clinical data on the change in mutation rate during the progression of breast and intestinal cancer on the one hand (Lengauer et al. 1997, 1998) and into the time available for clinical intervention on the other hand. The mathematical problem of finding the most efficient rate of genetic changes toward a target

cancer cell population was solved in Komarova and Wodarz (2004) and Komarova (2004).

With the microevolutionary pressures inevitably change as cancer progresses, a good strategy of high mutation rate at the start of the cancerous growth may be detrimental for the cancerous colony later on, favoring less mutation once a sufficiently large population of fast proliferating mutants has been produced. The observation motivated an extension of the Komarova–Wodarz model by allowing for temporal changes in the cancerous mutation rate in Komarova et al. (2008). A time-varying mutation rate has experimental support. The findings in Chin et al. (2004) suggest that the level of genetic instability in breast cancers first increases, reaches a peak and then decreases as the cancer passes through telomere crisis. Data reported in Rudolph et al. (2001) on intestinal carcinoma in mice and humans are also consistent with a similar model: Telomere dysfunction promotes CIN which drives carcinogenesis at early stages, and telomerase activation restores stability to allow further tumor progression through normal proliferation of tumor cells. The mechanism of telomerase activation and subsequent prevention of CIN is also described in Artandi and DePinho (2000) and Samper et al. (2001). It is found that short telomeres in later stages can make mice resistant to skin cancer because of an increased cell death rate (Gonzalez-Suarez et al. 2000).

Given the reality of time-varying mutation rates, we are interested in the factors that shape them as we extend the model of Komarova and Wodarz (2004) to allow for temporal nonuniformity. In Komarova et al. (2008), mathematical models for the time-dependent optimization problem were formulated for two biologically realistic cases. One (one-step) model characterizes cancerous mutation activated by an *oncogene*. A second (two-step) model corresponds to cancerous mutation initiated by the loss of both copies of a *tumor suppressor gene* (TSG) in accordance with the so-called *two-hit hypothesis* (Knudson 1971). An optimal mutation rate, which appears as an unknown function of time in these models, was sought to maximize the growth of the mutants.

The optimization problem for the first model was solved by an ad hoc iterative algorithm for a specific class of death rate for cells susceptible to malignant mutation. Below are the two main findings among those reported in Komarova et al. (2008) for the class of normalized death rates $d(u)$ whose functional dependence on the normalized mutation rate u is specified by (7) given in the next section:

- For a wide range of parameters, the most successful strategy is to keep a high rate of mutations at first and then switch to stability. This explains much of the biological data in Chin et al. (2004), Rudolph et al. (2001) and Shih et al. (2001), for example (see also Komarova and Wodarz 2004).
- It turns out that, depending on the convexity of the death rate (7), the corresponding optimal strategies are qualitatively different. If $d(u)$ is a linear or concave function of the mutation rate u, then the optimal strategy is an abrupt (discontinuous) change from maximum instability to maximum stability (known as bang–bang control in control theory). If $d(u)$ is convex, the transition is gradual and smooth.

The results of Komarova et al. (2008) for the one-step model for a death rate of the specific form (7) were justified rigorously in Wan et al. (2010). For this one-step model (in the biologically realistic region of the parameter space), it was proved mathematically that the optimal mutation rate for fastest time to cancer is (1) a bang–bang control for a death rate function (7) with $\alpha \geq 1$; and (2) a smoothly decreasing function for $0 < \alpha < 1$ until it reaches the minimum feasible rate allowed (and continues at that rate thereafter). In this sense, the strategy most advantageous for the tumor's growth is completely determined for this model and consistent with the numerical results for specific cases computed in Komarova et al. (2008). A similar complete characterization of the optimal mutation rate was also deduced in Wan et al. (2010) for a general concave function and a general strictly convex death rate function, respectively, without the restriction (7). With the theoretical results in Wan et al. (2010), efficient theory-based algorithms can be developed for computing the optimal solution once $d(u)$ is specified (Sanchez-Tapia 2015).

The one-step model is for the case of cancerous mutation induced by the activation of an oncogene. The first oncogene, *Src* (sarcoma), identified in 1970 was eventually shown to be the oncogene of a chicken retrovirus (Martin 2001). The first nucleotide sequence of v-src and related contributions (Czernilofsky et al. 1980) led to a Nobel Prize for Michael Bishop and Harold Varmus in 1989. In contrast, the first tumor suppressor gene, retinoblastoma protein (pRb) was already discovered in human retinoblastoma at the start of the nineteenth century. It has been found over the years since then that 65 % of colon cancers, 30–50 % of breast cancers and 50 % of lung cancers involve inactivation of TSG (though not all subject to the two-step process). Mutated TSG is also involved in the pathophysiology of leukemias, lymphomas, sarcomas and neurogenic tumors. Clearly, the loss of TSG functions is at least as significant to carcinogenesis as (if not more so than) the activation of an oncogene. It is therefore important that we have a good understanding of carcinogenesis associated with the loss of both copies of TSG.

Given the findings in Wan et al. (2010), it is natural to apply the same mathematical analysis for a complete characterization of the optimal mutation rate for the two-step model with the class of death rates (7). Unexpectedly, the mathematical analysis of Wan et al. (2010) failed to yield any information on the optimal mutation rate to start the growth process for the two-step model (as shown in Sect. 3 of this paper). The new analytical approach needed for the two-step model (developed herein) turns out to be substantially more complex than that for the oncogene case. The resulting theoretical findings on the optimal mutation rates also enable us to formulate appropriate computational algorithms for the determination of the optimal solution. Sample solutions for realistic value ranges in the parameter space show some surprising results that offer important insight into the biology of the optimal mutation strategy.

It should be noted that methods of optimization and optimal control have been applied to the study of issues in carcinogenesis (see de Pillis and Radunskaya 2003; Pillis et al. 2007; dePillis et al. 2007; Kirschner et al. 1997; Ledzewicz et al. 2013; Lenhart and Workman 2007; Swan 1990 for examples). However, the present problem on the fastest time to cancer requires a substantively different kind of theoretical analysis and computational approach in conjunction with the application of the maximum principle.

2 Carcinogenesis Induced by Loss of Tumor Suppressor Gene (*TSG*)

2.1 The Two-Step Model for Loss of *TSG*

We summarize in this section the two-step process that models carcinogenesis due to the loss of both copies of a tumor suppressor gene (*TSG*) that leads to mutant clonal expansion. In this two-step molecular process, the two alleles of the *TSG* are inactivated one at a time. The inactivation of just one allele does not result in any phenotypic changes. The inactivation of the second allele leads to the abnormal cell proliferation needed to overcome homeostasis. This two-step process to cancer, typical for the initiating events of familial colorectal cancer (Lengauer et al. 1998), has been modeled by a system of the three ordinary differential equations (ODE) in Komarova et al. (2008). For this model, we let $x_0(t)$ be the (normalized) population at time t of $TSG^{+/+}$ cells with both copies of the TSG intact, $x_1(t)$ be the (normalized) population of $TSG^{+/-}$ cells where one of the copies of the tumor suppressor gene has been mutated, and $x_2(t)$ be the (normalized) population of $TSG^{-/-}$ cells, where the remaining copy of the TSG has been lost. The first two cell populations are normalized by the initial normal ($TSG^{+/+}$) cell population size N just prior to the onset of cancerous mutation so that $x_0(0) = 1$ and $x_1(0) = 0$ while the cancerous cell population is normalized by the final target population size for cancer M, so that $x_2(0) = 0$ and $x_2(T) = 1$ at terminal time T. As in Komarova et al. (2008), we measure time in units of the natural growth rate constant of the $TSG^{+/+}$ cells (assumed to be the same as that of the $TSG^{+/-}$ cells).

As in the case of colorectal cancer and the adenomatous polyposis coli (APC) gene, there is a different mechanism, known as a "loss-of-chromosome" event, by which the second copy of the TSG can be turned off. This second mechanism is known to be responsible for the inactivation of a large percentage of TSG in cancers (Kinzler and Vogelstein 2002). As a result of this event, the whole chromosome corresponding to the TSG in question becomes lost or replaced by one with TSG mutated. This is a gross chromosomal change, whose (normalized) probability, $u(t)$, is our control parameter. Further discussion of this asymmetry between the first and the second inactivation events, particularly with the first allele also inactivated by a loss-of-chromosome event, can be found in Komarova and Wodarz (2004) and Komarova et al. (2008). For this two-step process, the time evolution of the three cell populations is typically modeled by the following three first-order ODE:

$$x_0' = -2\mu x_0 + x_0(1 - d(u))(1 - x_0 - x_1) \equiv g_0(x_0, x_1, x_2, u), \tag{1}$$

$$x_1' = 2\mu x_0 - (\mu + u_m u)x_1 + x_1(1 - d(u))(1 - x_0 - x_1) \equiv g_1(x_0, x_1, x_2, u), \tag{2}$$

$$x_2' = \frac{1}{\sigma}(\mu + u_m u)x_1 + x_2(1 - d(u))(a - x_0 - x_1) \equiv g_2(x_0, x_1, x_2, u), \tag{3}$$

with $(\,)' = \mathrm{d}(\,)/\mathrm{d}t$, $\sigma = M/N \gg 1$, $a \geq 2$ (usually $\gg 1$) and $0 < u_m \leq 1$ (see Komarova et al. 2008 for further discussion). These three state ODE are augmented by the following four auxiliary conditions which follow from the definitions of the three state variables $\{x_k(t)\}$:

$$x_0(0) = 1, \qquad x_1(0) = 0, \qquad x_2(0) = 0, \qquad x_2(T) = 1 \tag{4}$$

where T is the time when the cancerous mutant cell population reaches the target size M. Evidently, the length of time to target is expected to depend on the choice of mutation rate $u(t)$. The fastest time $\bar{T}$ to target is therefore an unknown constant to be determined along with the optimal mutation rate $\bar{u}(t)$.

To summarize, cells reproduce and die with time rescaled so that the rate of renewal is 1 for types x_0 and x_1. The mutants x_2 expand at rate $a \gg 1$ (in addition to the expansion rate due to the mutation of x_1). The parameter μ, $0 < \mu \ll 1$, is the (normalized) *basic mutation rate* by which an allele of *TSG* can be inactivated while the quantity $u_m u$ corresponds to the additional (normalized) mutation rate resulting from genetic instability. The nonnegative normalized *gross chromosomal change rate* has been scaled so that u is limited by the inequality constraint (see Komarova et al. 2008)

$$0 \le u \le 1. \tag{5}$$

The death rate $d(u)$ in the three state Eqs. (1)–(3) is a function for the (normalized) mutation rate u. When mutation rate is large, cells often lose chromosomes to result in a higher death rate. For this study, we stipulate

$$d(0) = 0, \quad d(1) = 1, \quad 0 \le d(u) \le 1 \quad \text{and} \quad d^{\cdot}(u) > 0 \quad (0 \le u \le 1) \tag{6}$$

where a superscripted dot denotes differentiation with respect to the argument of the function (see Komarova et al. 2008 for some results for $d(u) < 1$ in the entire range of u). In that case, it is seen from (3) $u(t) = 0$ [so that $d(u(t)) = 0$] would allow a finite cancerous cell population to break out of homeostatic control and grow exponentially. But without some mutation to produce enough cancerous cells for fast proliferation, it would take much longer time to reach the target population. The present work is to find that a time-varying optimal control $\bar{u}(t)$ for $x_2(t)$ to reach the target population in the shortest time. It turns out that the qualitative features of the optimal strategy depend only on the convexity of $d(u)$.

To develop the solution technique for a complete characterization of the optimal mutation rate for the shortest time, we first work with the following class of death rate functions

$$d(u) = 1 - (1 - u)^{\alpha} \tag{7}$$

to show how the actual optimal control depends on α. The solution technique is then modified to extend the results for the special death rate (7) to general death rate with different convexity.

2.2 The Shortest Time Problem

The optimization problem for carcinogenesis is to choose a time-varying normalized *gross chromosomal change rate u* to minimize the time T needed to drive the cancerous

mutants to the target population size with the specified growth dynamics for the three nonnegative cell populations given that all cells are of the $TSG^{+/+}$ type initially. The admissible (feasible) controlling mutation rates are restricted to the class Ω of piecewise continuously differentiable functions (with only finite jump discontinuities) on the interval $[0, T]$, denoted by *PWS*, satisfying the inequality constraint (5):

$$\Omega = \{u(t) \in PWS \,|0 \le u(t) \le 1, 0 \le t \le T\}. \tag{8}$$

This shortest time problem is conventionally recast in the standard form of choosing $u(t)$ from Ω to minimize the performance index:

$$J = \int_0^T 1 \, \mathrm{d}t, \tag{9}$$

subject to the equations of state (1)–(3), the boundary conditions (4), the inequality constraint (5) and nonnegativity constraints

$$x_k \ge 0, \qquad k = 0, 1, 2, \tag{10}$$

with $T > 0$ to be determined as a part of the solution so that we have a free end point problem.

To recapitulate, we adopt in this paper the theoretical framework where it is possible to set the rate of genetic instability, captured by the normalized cancerous mutation rate $u(t)$, to any biologically admissible value (normalized to [0, 1]) at each moment of time. Every choice of such a function determines a growth process for the cancerous cells. We shall seek the choice of $u(t)$ that allows the cancerous population to reach a given size, M, in the shortest possible time. The specified terminal population size, normalized to be 1, is called the *target*. Each possible choice of $u(t)$ steers the mutant cell population to the target at a different pace. As such, the (normalized) cancerous mutation rate controls the growth of the mutant population and $u(t)$ is the *control* (also called *strategy*) for time to target in our model. The control that steers the mutant population to the target faster than any other control is said to be the *optimal control*, denoted by $\bar{u}(t)$. In this terminology, we seek an optimal control for the mutant population to reach the target in the fastest time possible. As we shall see, $\bar{u}(t)$ is unique for our problem; hence, we can speak of "the" optimal control throughout this paper.

A meaningful qualitative comparison between two controls (strategies) is now possible: the "better" or "more advantageous" control is the one allowing the mutant cells to reach the target sooner. Thus, an "advantageous strategy" is advantageous for cancer. The optimal control or strategy is determined by way of the terminal time, T, which is the solution of the equation

$$x_2(T) = 1 \tag{11}$$

where x_2 is the solution of system (1)–(3) for the three cell populations. The terminal growth time, T, depends on all the parameters of the ODE system, including the time-dependent mutation rate, u. The optimal control, denoted by $\bar{u}$, is the one that minimizes the value of T. The simplest case of limiting admissible controls, $u(t)$, to

constant functions results in an optimization problem with a single unknown constant optimal mutation rate value, u_{op}, that depends on the parameters of the ODE system. Such a problem was solved in Komarova and Wodarz (2004). However, faster times to target is possible if we allow u to be a function of time as evident from clinical observations of Chin et al. (2004) and Rudolph et al. (2001) and the mathematical results of Wan et al. (2010) for the one-step model. More specifically, suitably higher initial values and lower subsequent values of u (than u_{op}) would facilitate faster growth. The goal of this paper is to prove that this is the case also for the two-step model and determine $\bar{u}(t)$. However, the method of solution for the one-step model, as we shall see, does not apply to the present two-step model and a completely different analysis is required to accomplish the task on hand.

2.3 Evolution of Cell Populations

To help establish the clinically observed difference in mutation rate at the two end of the time interval for the two-step model, we begin by investigating the evolution of the cell populations near the start [without the restriction (7)].

Lemma 1 *For any death rate satisfying properties stipulated in* (6)*, we have*

$$\begin{aligned} &i)\ x_0 + x_1 = 1 - \mu(\mu + u_m u(0))t^2 + O(t^3),\ (0 \le t \ll T). \\ &ii)\ x_0(t) + x_1(t) \le 1\ (0 \le t < T)\ \textit{with equality only for}\ t = 0. \end{aligned}$$

Proof From the initial conditions (4), we have $x_0(0)+x_1(0) = 1$. For $t > 0$, summing (1) and (2) gives

$$(x_0 + x_1)' = -(\mu + u_m u)x_1 + (x_0 + x_1)(1 - d(u))(1 - x_0 - x_1). \tag{12}$$

and, with $x_1(0) = 0$ (and no jump discontinuities in the mutation rate at $t = 0$),

$$\begin{aligned} \left[(x_0 + x_1)'\right]_{t=0} &= 0, \\ \left[(x_0 + x_1)''\right]_{t=0} &= \left[-(\mu + u_m u)x_1'\right]_{t=0} \\ &= \left[-(\mu + u_m u)(2\mu x_0)\right]_{t=0} = -2\mu(\mu + u_m u(0)). \end{aligned}$$

It follows that

$$x_0 + x_1 = 1 - \mu(\mu + u_m u(0))t^2 + O(t^3)$$

given $0 \le u(0) \le 1$. This proves part (*ii*) of the Lemma with

$$x_0 + x_1 < 1 \quad (0 \le t < T^*)$$

at least for some $T^* \ll T$.

If $x_0 + x_1$ should increase and approach 1, it does so from below and maximally with $u = 0$ so that $d(u) = 0$. In that case, the negative term $-(\mu + u_m u)x_1$ in (12)

eventually dominates [given the lower bound (93) for x_1 for $u = 0$ established in the Appendix of this paper] as $1 - x_0 - x_1 \to 0$ from above. It follows that $1 - x_0 - x_1$ could never reach 0. This establishes part (i) of the Lemma. □

Results obtained in Komarova et al. (2008) and Wan et al. (2010) suggest that the *upper corner control* $u(t) = 1$ plays a significant role at least near the start of the cancerous growth. Below are some results for the three cell populations for the upper corner control, to be denoted by $\left\{x_k^{(1)}(t)\right\}$, useful in later developments.

Lemma 2 *For $u = 1$, we have $(x_0^{(1)} + x_1^{(1)})' < 0$ and $x_0^{(1)} + x_1^{(1)} < 1$ for $t > 0$ with $x_1^{(1)}(t)$ attaining its unique maximum at*

$$t_M = \frac{1}{u_m - \mu} \ln\left(\frac{u_m + \mu}{2\mu}\right) > 1 \tag{13}$$

Proof For $u = 1$, (12) simplifies to

$$\left(x_0^{(1)} + x_1^{(1)}\right)' = -(\mu + u_m)x_1^{(1)} < 0$$

Together with the initial condition $x_0^{(1)}(0) + x_1^{(1)}(0) = 1$, we have $x_0^{(1)}(t) + x_1^{(1)}(t) < 1$ for $t > 0$.

It is evident from the state equations that $x_0^{(1)}(t)$ is positive and monotone decreasing, $x_2^{(1)}(t)$ is nonnegative and monotone increasing, while $x_1^{(1)}(t)$ is nonnegative with a stationary point when $2\mu x_0^{(1)} = (\mu + u_m)x_1^{(1)}$. It is straightforward to deduce from the ODE (1) and (2) for $u = 1$ and the initial conditions (4) the exact solution,

$$x_1^{(1)} = \frac{2\mu}{u_m - \mu}\left[e^{-2\mu\tau} - e^{-(\mu+u_m)\tau}\right],$$

(see the first section of the Appendix of this paper) with $x_1^{(1)}(t)$ attaining a unique maximum at the instant t_M given by (13). □

Remark 3 The same exact solutions (85) and (86) (in the Appendix of this paper) for the upper corner control may be used to determine the following three cell population sizes at $t = t_M$:

$$\begin{aligned}
x_0^{(1)}(t_M) &= \left(\frac{2\mu}{u_m + \mu}\right)^{\frac{2\mu}{u_m - \mu}} \equiv x_0^M \\
x_1^{(1)}(t_M) &= \left(\frac{2\mu}{u_m + \mu}\right)^{\frac{u_m + \mu}{u_m - \mu}} = \frac{2\mu}{u_m + \mu} x_0^M \equiv x_1^M \\
x_2^{(1)}(t_M) &= \frac{1}{\sigma}\left[1 - \frac{u_m + 3\mu}{u_m + \mu} x_0^M\right] \equiv x_2^M
\end{aligned} \tag{14}$$

with

$$x_1^M + x_0^M = \frac{u_m + 3\mu}{u_m + \mu} x_0^M < 1 - \mu. \tag{15}$$

Results obtained in Komarova et al. (2008) and Wan et al. (2010) also suggest that the *lower corner control* $u(t) = 0$ plays a significant role at least near the terminal time of the cancerous growth. Below are some results for the three cell populations for the lower corner control, to be denoted by $\left\{x_k^{(0)}(t)\right\}$, useful in later developments.

Lemma 4 *For $u = 0$, the following relations hold*

1. $(x_0^{(0)}+x_1^{(0)})' > 0$ *if* $x_0^{(0)}+x_1^{(0)} \le 1-\mu$ *and* $(x_0^{(0)}+x_1^{(0)})' < 0$ *if* $x_0^{(0)}+x_1^{(0)} = 1-\varepsilon$ *for sufficiently small positive* $\varepsilon > 0$, *and therewith* $0 < x_0^{(0)} + x_1^{(0)} < 1$ *for all* $t > 0$.
2. *The coupled system of state equations for* $x_0^{(0)}$ *and* $x_1^{(0)}$ *has two admissible fixed points: an unstable fixed point at* $(0, 0)$ *and an asymptotically stable fixed point at* $(0, 1 - \mu)$ *with* $\left(x_0^{(0)} + x_1^{(0)}\right) \to 1 - \mu$ *as* $t \to \infty$.

Proof For $u = 0$, (12) simplifies to

$$\left(x_0^{(0)} + x_1^{(0)}\right)' = -\mu x_1^{(0)} + \left(x_0^{(0)} + x_1^{(0)}\right)\left(1 - x_0^{(0)} - x_1^{(0)}\right)$$

and therewith $(x_0^{(0)} + x_1^{(0)})' > 0$ for $x_0^{(0)} + x_1^{(0)} \le 1 - \mu$. For the case $x_0^{(0)} + x_1^{(0)} = 1 - \varepsilon < 1$, the corresponding expression is

$$\left(x_0^{(0)} + x_1^{(0)}\right)' = -(\mu - \varepsilon)x_1^{(0)} + \varepsilon x_0^{(0)}$$

which would be <0 for a sufficiently small ε. These results for part (i) show that $x_0^{(0)} + x_1^{(0)}$ hovers around $1 - \mu$ for large t and $0 < x_0^{(0)} + x_1^{(0)} < 1$ for all $t > 0$.

Part (ii) of the lemma gives a more detailed characterization of the solution behavior for large time. The stated results are consequence of the systems (1) and (2) specialized with the lower corner control $u = 0$,

$$\begin{aligned}\left(x_0^{(0)}\right)' &= -2\mu x_0^{(0)} + x_0^{(0)}\left(1 - x_0^{(0)} - x_1^{(0)}\right),\\ \left(x_1^{(0)}\right)' &= 2\mu x_0^{(0)} + x_1^{(0)}\left(1 - \mu - x_0^{(0)} - x_1^{(0)}\right).\end{aligned} \tag{16}$$

It can be verified by the usual linear stability analysis that $(0, 0)$ and $(0, 1 - \mu)$ are the only critical points of the system with the indicated stability. □

3 The Hamiltonian and Adjoint Variables

3.1 The Maximum Principle

The key to the solution of our optimal control problem is the maximum principle (Bryson and Ho 1969; Gelfand and Fomin 1963; Pontryagin et al. 1962; Wan 1995) for the *Hamiltonian*:

$$\begin{aligned} H &= 1 + \lambda_0 g_0 + \lambda_1 g_1 + \lambda_2 g_2 \\ &= 1 + A(t) + \frac{u_m}{\sigma} u R(t) + [1 - d(u)]\, D(t) \end{aligned} \tag{17}$$

with

$$A(t) = -2\mu\lambda_0 x_0 + \mu\lambda_1(2x_0 - x_1) + \frac{\mu}{\sigma}\lambda_2 x_1 \tag{18}$$

$$D(t) = (1 - x_0 - x_1)P + \lambda_2 x_2(a - 1), \;\; R(t) = x_1(\lambda_2 - \sigma\lambda_1) \tag{19}$$

$$P(t) = \lambda_0 x_0 + \lambda_1 x_1 + \lambda_2 x_2 \tag{20}$$

where the three functions $\{\lambda_k\}$ are the *adjoint variables* for the problem chosen to satisfy the three adjoint ODE,

$$\lambda_k' = -\left(\lambda_0 \frac{\partial g_0}{\partial x_k} + \lambda_1 \frac{\partial g_1}{\partial x_k} + \lambda_2 \frac{\partial g_2}{\partial x_k}\right) \qquad (k = 0, 1, 2). \tag{21}$$

For the state Eqs. (1)–(3) with any control $u(t)$, these adjoint equations specialize to

$$\lambda_0' = 2\mu\,(\lambda_0 - \lambda_1) + (1 - d)\{P - \lambda_0(1 - x_0 - x_1)\} \tag{22}$$

$$\lambda_1' = -\frac{u_m u + \mu}{\sigma}\,(\lambda_2 - \sigma\lambda_1) + (1 - d)\{P - \lambda_1(1 - x_0 - x_1)\} \tag{23}$$

$$\lambda_2' = -\lambda_2(1 - d)(a - x_0 - x_1). \tag{24}$$

Recall that $u(t)$ may have finite jump discontinuities but continuously differentiable otherwise; the state and adjoint variables must therefore be continuous with piecewise smooth (PWS) derivatives. The quantities $A(t)$, $D(t)$, $P(t)$ and $R(t)$ as defined by (22)–(24) do not depend on $u(t)$ explicitly, but do so implicitly through the state and adjoint variables.

The system of three state ODE, three adjoint ODE and four prescribed auxiliary conditions are augmented by two *Euler boundary conditions* (Bryson and Ho 1969; Gelfand and Fomin 1963; Pontryagin et al. 1962; Wan 1995)

$$\lambda_0(T) = \lambda_1(T) = 0. \tag{25}$$

For the optimal solution of our minimum terminal time problem, the application of the maximum principle (Bryson and Ho 1969; Gelfand and Fomin 1963; Pontryagin et al. 1962; Wan 1995) consists of seeking

- an *optimal control* $\bar{u}(t)$ that minimizes the Hamiltonian at each instance of time over all u in Ω with the minimum [attained at $\bar{u}(t)$] denoted by $\bar{H}(t)$;
- six quantities $\{\bar{x}_i(t), \bar{\lambda}_j(t)\}$that satisfy the six differential Eqs. (1)–(3) and (21) [or (22)–(24)] and six auxiliary conditions in (4) and (25) with $u(t) = \bar{u}(t)$;
- the optimal terminal time $\bar{T}$ that satisfies the *free end* (*transversality*) *condition*

$$\left[\bar{H}(t)\right]_{t=\bar{T}} = [1 + \bar{\lambda}_2 \bar{g}_2]_{t=\bar{T}} = 0 \tag{26}$$

with

$$[\bar{g}_2]_{t=\bar{T}} = [g_2(\bar{x}_0(t), \bar{x}_1(t), \bar{x}_2(t), \bar{u}(t))]_{t=\bar{T}} = [g_2(\bar{x}_0, \bar{x}_1, 1, \bar{u})]_{t=\bar{T}};$$

after simplification by the Euler boundary conditions (25) and the terminal condition in (4), and

- at any switch point $\bar{T}_s$ of a finite jump discontinuity of the optimal control, the Hamiltonian is continuous

$$\left[\bar{H}(t)\right]_{t=\bar{T}_s-}^{t=\bar{T}_s+} = 0. \tag{27}$$

As the central feature of the maximum principle, the optimal control $\bar{u}(t)$ must minimize the Hamiltonian with

$$\begin{aligned} \bar{H}(t) &\equiv H\left(\bar{x}_0(t), \bar{x}_1(t), \bar{x}_2(t), \bar{\lambda}_0(t), \bar{\lambda}_1(t), \bar{\lambda}_2(t), \bar{u}(t)\right) \\ &\leq H\left(\bar{x}_0(t), \bar{x}_1(t), \bar{x}_2(t), \bar{\lambda}_0(t), \bar{\lambda}_1(t), \bar{\lambda}_2(t), u\right) \end{aligned} \tag{28}$$

for all $u \in \Omega$, i.e.,

$$\bar{H}(t) = \min_{u \in \Omega} \left[H(\bar{x}_0(t), \bar{x}_1(t), \bar{x}_2(t), \bar{\lambda}_0(t), \bar{\lambda}_1(t), \bar{\lambda}_2(t), u)\right] \tag{29}$$

While the process of determining the optimal control is greatly simplified by the condition (29), it is still far from straightforward for our problem as we shall see in the subsequent developments.

3.2 The Stationary Solution

Prime candidates for the optimal control $\bar{u}(t)$ [known as an "interior control" and denoted by $u_i(t)$] are the solution of the stationary condition

$$\frac{\partial H}{\partial u} = \frac{u_m}{\sigma} R(t) - D(t) d^{\cdot}(u) = 0. \tag{30}$$

The relation (30) is a necessary condition for (29) and, in principle, determines possible candidates for $\bar{u}(t)$ in terms of the state and adjoint variables. For the death rate (7) with $d^{\cdot}(u) = \alpha(1-u)^{\alpha-1}$, the relation (30) becomes

$$D(t)d^{\cdot}(u) = \alpha(1-u)^{\alpha-1}D(t) = \frac{u_m}{\sigma}R(t). \tag{31}$$

We see from (18), (19) and the initial conditions in (4) that both $R(t)$ and $D(t)$ in (30) vanish at $t = 0$. Hence, the stationary condition does not specify the control $u_i(t)$ at the initial time and the problem of finding $\bar{u}(t)$ requires a more refined analysis.

Remark 5 In contrast, we recall for the one-step model

$$\begin{aligned} R(0) &= [x_1(\lambda_2 - \sigma\lambda_1)]_{t=0} = \lambda_2(0) - \sigma\lambda_1(0) \\ D(0) &= [(\lambda_1 x_1 + \lambda_2 x_2)(1-x_1) + (a-1)\lambda_2 x_2]_{t=0} = 0 \end{aligned}$$

With $x_1(0) = 1$ and $q(0) = \lambda_2(0) - \sigma\lambda_1(0) < 0$ (see Komarova et al. 2008 or Lemma 12 below), minimizing $H(0)$ requires

$$u(0) = 1;$$

The situation is further complicated by the fact that even when the stationary condition

$$\left[\frac{\partial H}{\partial u}\right]_{u=u_i} = 0 \tag{32}$$

determines a well-defined $u_i(t)$ in some interval of time away from $t = 0$, the interior control may violate the inequality constraints (5) in some segment(s) of $(0, T)$. As such, $u_i(t)$ may not be admissible (and the optimal control may be one of the corner controls) in one or more subintervals of $[0, T]$. In the remaining subsections of this section, we obtain some preliminary results needed to specify the optimal control when it is not the interior control for the entire solution domain.

The following proposition is related to a well-known result for our Hamiltonian system of autonomous state and adjoint ODE with a general PWS death rate restricted only by (6).

Proposition 6 *For an optimal control $\bar{u}(t)$ (which may be the interior control $u_i(t)$, a corner control or a combination of both), the Hamiltonian (17) for the optimal control problem of our two-step model vanishes for all t in $[0, T]$, i.e., $\bar{H} \equiv [H]_{u=\bar{u}(t)} = 0$, for all t in $[0, T]$.*

Proof Except for locations of simple jump discontinuities of the control $u(t)$, we can differentiate H with respect to time to get

$$\frac{\mathrm{d}H}{\mathrm{d}t} = \frac{\partial H}{\partial u}\frac{\mathrm{d}u}{\mathrm{d}t}. \tag{33}$$

where we have made use of the Hamiltonian structure of the six relevant state and adjoint ODE to eliminate terms involving derivatives of state and adjoint variables. For $u = \bar{u}(t)$, the right-hand side of (33) vanishes since either $\bar{u}(t)$ is an interior control so that $\partial H/\partial u = 0$ or it is a corner control in which case we have $\mathrm{d}\bar{u}(t)/\mathrm{d}t = 0$. Hence,

$\bar{H}(t)$ is a constant in any interval where H is continuously differentiable. With the free end condition (26), we have $\bar{H}(t) = 0$ in the interval $(T_s, T]$ if there should be a simple jump discontinuity in $\bar{u}$ at some earlier time $T_s < T$ in the interval $(0, T)$. The switching condition (27) requires the constant $\bar{H}(T_s)$ to be the same (and equal to zero by the free end condition) on both sides of the jump in $\bar{u}(t)$. The observation allows us to extend $\bar{H}(t) = 0$ to the next switch point and finally for the entire interval $[0, T]$. □

3.3 Local Behavior of $R(t)$ and $D(t)$ for $t \ll T$

Next, we show $R(t) = O(t)$ and $D(t) = O(t^2)$ in a small interval adjacent to $t = 0$ for a general PWS death rate subject only to (6).

Proposition 7 *Prior to any switch point of the control $u(t)$, we have for some $\omega > 0$ and $\upsilon > 0$*

$$\begin{aligned} R(t) &= 2\mu q(0)t + O(t^{1+\omega}), \\ D(t) &= \frac{\mu}{\sigma}\left[(\mu + u_m u)\left\{(a-1)\lambda_2 + \sigma\lambda_0\right\}\right]_{t=0} t^2 + O\left(t^{2+\upsilon}\right) \end{aligned}$$

where $q(t) = \lambda_2 - \sigma\lambda_1$.

Proof From the expression for $R(t)$ in (18) and $x_1(0) = 0$, we have

$$\begin{aligned} R(t) &= x_1(\lambda_2 - \sigma\lambda_1) = x_1'(0)q(0)t + O(t^{1+\omega}) \\ &= 2\mu q(0)t + O\left(t^{1+\omega}\right). \end{aligned} \tag{34}$$

where we have made use of (2) to set $x_1'(0) = 2\mu$. Similarly, we have from Lemma 1 and the state Eqs. (1)–(3) along with the initial conditions $x_1(0) = x_2(0) = 0$ and $x_0(0) = 1$

$$\begin{aligned} D(t) &= P(1 - x_0 - x_1) + (a-1)\lambda_2 x_2 \\ &= -\left[P\left(x_0'' + x_1''\right) - (a-1)\lambda_2 x_2''\right]_{t=0} \frac{t^2}{2} + O(t^{2+\upsilon}) \\ &= \frac{\mu}{\sigma}\left[(\mu + u_m u)\left\{(a-1)\lambda_2 + \sigma\lambda_0\right\}\right]_{t=0} t^2 + O(t^{2+\upsilon}) \end{aligned} \tag{35}$$

where (in an interval $[0, \tilde{T})$ that does not contain a switch point) the second derivatives $x_k''(0)$, $k = 0, 1, 2$, are obtained from differentiating the state equations and evaluating the results at $t = 0$. □

Corollary 8 $[\lambda_0 - \lambda_1]_{t=0} = 1/2\mu$

Proof In view of Proposition 7 and the known initial conditions, we have $H(0) = 1 + A(0) = 1 - 2\mu\left[\lambda_0(0) - \lambda_1(0)\right]$. But from Proposition 6, we have $H(0) = 0$ for an optimal control; the corollary follows. □

As pointed out earlier, the stationary condition (30) [or (31) for a death rate in the form (7)] does not determine the interior control for our problem at least at $t = 0$ because $D(0) = 0$ and $R(0) = 0$. With Proposition 7, the interior control may be inadmissible for $t \geq 0$. To see this, we solve (31) for u to get

$$u_i(t) = 1 - \left[\frac{u_m}{\alpha\sigma}\frac{R(t)}{D(t)}\right]^{1/(\alpha-1)}.$$

While the right-hand side is well defined for $t > 0$, $u_i(t)$ becomes negative for sufficiently small (but positive) t if $\alpha > 1$ (by Proposition 7), violating the inequality constraint (5). With the interior control inadmissible, the optimal control $\bar{u}(t)$ would have to be an boundary point of the control set Ω, i.e., a *corner control*, at least in a small interval adjacent to the starting time $t = 0$. The situation is different, however, if $0 < \alpha < 1$. In that case, the interior control is well defined and admissible at least for some interval of time adjacent to the starting time. Together, these observations suggest that for a general death rate the optimal control is likely to be qualitatively different depending on the convexity of the death rate.

3.4 Global Behavior of Adjoint Variables for General Death Rate

When the stationary condition (32) does not determine the optimal control, which is the case at least in a small interval adjacent to the starting time for the death rate function (7) with $\alpha > 1$, we need to work with the more general condition (29) to minimize $H(t)$. For this purpose, we need some information on the adjoint variables, even when we cannot determine their solutions, analytically or numerically, without knowing the optimal control. We begin by noting that the two relations (17) and (24) for a *general death rate* determine the sign of $\lambda_2(t)$.

Lemma 9 *$\lambda_2(t) < 0$ and $\lambda_2'(t) \geq 0$ $(0 \leq t \leq T)$ for any admissible control $u(t)$.*

Proof From (26) and (25), we have (after omitting the bar in $\bar{T}$ and other quantities (except for $\bar{u}(t)$) for brevity henceforth)

$$\begin{aligned}\lambda_2(T) &= -\left[\frac{1}{\bar{g}_2}\right]_{t=T} \\ &= -\left[\frac{\sigma}{(\mu + u_m\bar{u})x_1 + \sigma x_2(1 - d(\bar{u}))(a - x_0 - x_1)}\right]_{t=T} < 0. \end{aligned} \tag{36}$$

with

$$\left[\lambda_2'\right]_{t=T} = -\left[\lambda_2(a - x_0 - x_1)\{1 - d(\bar{u})\}\right]_{t=T} \geq 0 \tag{37}$$

by (24). The two conditions (36) and (37) imply $\lambda_2(t) < 0$ in some neighborhood of $t = T$. The lemma follows from these local results and the ODE (24). □

Let

$$S(t) = (a-1)\lambda_2 + \sigma P,\ q(t) = \lambda_2 - \sigma\lambda_1. \tag{38}$$

with $P(t)$ as previously defined in (20). The additional properties of the state and adjoint variables below also hold for *any admissible control* and a general PWS death rate restricted only by (6):

Lemma 10

$$P'(t) = (1-d(u))\,(x_0+x_1)\,P, \tag{39}$$

$$D'(t) = \frac{\mu + u_m u}{\sigma} x_1 S,\ R'(t) = 2\mu x_0 q - (1-d)x_1 S \tag{40}$$

and

$$S'(t) = (1-d)\,[(x_0+x_1)\,\sigma P - (a-1)(a-x_0-x_1)\lambda_2] \tag{41}$$

for all t in $(0,T)$ other than the switch points of any admissible $u(t)$.

Proof For the first three relations, it is straightforward to obtain the expressions for the derivatives of the combinations of state and adjoint variables on the left-hand side of these equations from the differential equations (1)–(3) and (22)–(24).

To get (41), we use (24) and (39) to eliminate λ_2' and P', respectively, from

$$S' = \sigma P' + (a-1)\lambda_2'.$$

□

Lemma 11 *(i) $D(0) = 0$, (ii) $P(t)$ and $S(t)$ are negative in $[0,T]$ while $D(t) < 0$ for $t > 0$; (iii) $\lambda_1(0) < \lambda_0(0) < 0$ and (iv) $\lambda_1(t) < 0$ and $\lambda_0(t) < 0$ at least for some (small) interval $[0, T_\ell)$ for some $T_\ell < T$.*

Proof Part (*i*) follows from the initial cell populations (and boundedness of the adjoint variables). With $x_0 + x_1 > 0$ and $0 \le 1 - d(u) \le 1$, the solution of ODE (39) may be written as

$$P(t) = P(T)E(t;T) = \lambda_2(T)E(t;T)$$

where

$$E(t;T) = e^{-\Psi(t,T)},\ \Psi(t,T) = \int_t^T (1-d(u))\,(x_0+x_1)\,\mathrm{d}t.$$

Since $P(T) = \lambda_2(T) < 0$, $P(t)$ is therefore a negative, continuous and nonincreasing function of t for all t in $[0,T]$. This result and $\lambda_2(t) < 0$ render $S(t)$ negative for $t \ge 0$ [see also (38)] and $D(t) < 0$ for $t > 0$ [see (19)]. This proves part (*ii*). That $\lambda_0(0) < 0$ follows from $P(0) < 0$ and the initial cell populations while $\lambda_1(0) < \lambda_0(0) < 0$ is

an immediate consequence of Corollary 8 taken in the form $\lambda_1(0) = \lambda_0(0) - 1/2\mu < \lambda_0(0) < 0$. This proves part (*iii*). Part (*iv*) follows from the continuity of the adjoint variables. □

Lemma 12 *$q(t) = (\lambda_2 - \sigma\lambda_1) < 0$ for all t in $[0, T]$, $R(0) = 0$ and $R(t) < 0$ for $t > 0$.*

Proof The adjoint differential equations give the following expression for $q'(t)$:

$$q'(t) = \{(\mu + u_m u) - (1 - d)(1 - x_0 - x_1)\}\, q - (1 - d)S. \tag{42}$$

This is a linear first-order ODE for q; its solution can be written as

$$Iq = \lambda_2(T) + \int_t^T (1 - d)S(\tau)I(\tau)\mathrm{d}t$$

with the help of an integrating factor

$$I = e^{\Gamma(t)} > 0, \quad \Gamma(t) = -\int_t^T [(1 - d)(1 - x_0 - x_1) - (\mu + u_m u)]\,\mathrm{d}t.$$

The integrand for $\Gamma(t)$ is nonsingular so that $I = e^{\Gamma(t)} > 0$ for any value of u with $I(T) = 1$. Given $S(t) < 0$ from Lemma 11, $I(t)q$ is an increasing function of t, with $I(T)q(T) = q(T) = \lambda_2(T) < 0$. Hence, we have $q(t) < 0$ for all t in $[0, T]$ with $q(0) = \lambda_2(0) - \sigma\lambda_1(0) < 0$ in particular. That $R(t) < 0$ for $t > 0$ follows from (19) while $R(0) = 0$ is a consequence of $x_1(0) = 0$. □

Remark 13 While $I(t)q$ is an increasing function of t, $q(t)$ may not be. For an interval of time where $u = 1$, we have

$$q' = (\mu + u_m)q < 0$$

in view of Lemma 12. Hence, $q(t) < 0$ is a decreasing function of t in that time interval. The situation is different when $u = 0$. With

$$0 < \mu < \{1 - d(0)\}\left\{(1 - x_0 - x_1) + \frac{S}{q}\right\},$$

we have now $q' > 0$ so that $q(t) < 0$ increases with time in that case. The sign change in the right-hand side of (42) renders the determination of the optimal control more delicate than the one-step model. The following results will be useful on the discussion of this issue in subsequent developments.

Lemma 14 *Let $z(t) = D(t)/R(t)$. For a general PWS death rate subject only to the requirements in (6), we have*

$$(i)\ z(0) = 0 \ \text{ and } \ z(t) > 0 \ \text{ for } \ t > 0.$$
$$(ii)\ z'(t) > 0 \ \text{ for } \ t \geq 0.$$

Proof Part (i) follows from the Taylor polynomials of $D(t)$ and $R(t)$ in Proposition 7 and the negativity of these quantities by Proposition 11. The former gives

$$z(t) = \frac{\mu + u_m u(0)}{2\sigma} \frac{S(0)}{q(0)} t \left\{1 + O(t^\omega)\right\}$$

near the starting time for some $\omega > 0$ so that $\lim_{t\to 0} z(t) = 0$ while the latter ensure $z(t) > 0$ for $t > 0$.

For part (ii), we differentiate $z(t)$ and use Lemma 10 to eliminate $R'(t)$ and $D'(t)$ to get

$$z'(t) = \left\{ \frac{\mu + u_m u}{\sigma} + \frac{D}{R}(1-d) \right\} \frac{S}{q} - 2\mu x_0 \frac{D}{x_1^2 q}. \tag{43}$$

As $t \to 0$, the limiting behavior of $D(t)$, $R(t)$, $S(t)$ and $q(t)$ [see Proposition 7 and (38)] leads to

$$\lim_{t\to 0} z'(t) = \frac{\mu + u_m u(0)}{2\sigma} \frac{S(0)}{q(0)} > 0.$$

Continuity of state and adjoint variables requires $z'(t) > 0$ for some finite interval $[0, T_p)$ prior to any switching of the mutation rate $u(t)$. For $t \geq T_p$, we rewrite the expression (43) for $z'(t)$ as

$$z'(t) = \frac{z}{u_m} \left\{ \left[d^{\cdot}(u)(\mu + u_m u) + u_m(1-d) \right] x_1 \frac{S}{q} - 2\mu x_0 u_m \right\}$$

With the lower bounds for x_1 established in the "Appendix", we have $x_1 = O(2\mu x_0)$ (and possibly larger) for $t \geq \min[T_\ell, T_p] \equiv T_{\min}$ and therewith

$$\begin{aligned} z'(t) &= \frac{x_1 z}{u_m} \left\{ \left[d^{\cdot}(u)(\mu + u_m u) + u_m(1-d) \right] \frac{S}{q} - \frac{2\mu x_0 u_m}{x_1}) \right\} \\ &= \frac{z x_1}{u_m} \left[d^{\cdot}(u)(\mu + u_m u) + u_m(1-d) \right] \frac{S}{q} \left\{ 1 + O\left(\frac{u_m}{a}\right) \right\} \end{aligned} \tag{44}$$

given $0 < u_m \leq 1$, $d^{\cdot}(u) > 0$ and the growth rate constant a of cancerous cell population is large compared to that of the normal cells (normalized to be 1) so that $S/q = O(a)$. With $S/q > 0$ by Lemmas 11 and 12, the second half of the part (ii) is proved. □

Remark 15 Strictly speaking, $z'(t) > 0$ for $t \geq T_p$ is proved asymptotically for a sufficiently large (which it usually is). However, we know $\lambda_2(t) < 0$ for all t and, by part iii) of Lemma 11, $\lambda_1(t) < \lambda_0(t) < 0$ at least for an interval $[0, T_\ell)$ (as it is desirable to have more of all three types of cells at least at the early stage of carcinogenesis). With $\lambda_1(t) < \lambda_0(t) < 0$ for $t = O(T_{\min})$, then

$$z'(t) \geq \frac{x_1 z}{u_m}\left\{\left[d^{\cdot}(u)(\mu + u_m u) + u_m(1-d)\right]\frac{\lambda_2\,(a-1+\sigma x_2)}{\lambda_2} - \frac{2\mu x_0 u_m}{x_1}\right\}$$
$$= \frac{x_1 z}{u_m}\left\{\left[d^{\cdot}(u)(\mu + u_m u) + u_m(1-d)\right](a-1+\sigma x_2) - \frac{2\mu x_0 u_m}{x_1}\right\} > 0 \tag{45}$$

given $2\mu x_0 u_m/x_1 = O(1)$, $a \gg 1$ and $\sigma \gg 1$. For t considerably larger than $T_{\min}$, (when it may be more advantageous for the cancerous cell population to grow by natural proliferation than by mutation of the other cell types so that $\lambda_1(t)$ and $\lambda_0(t)$ may turn positive), $|\lambda_1(t)|$ and $|\lambda_0(t)|$ would be much smaller than $|\lambda_2(t)|$ since both must tend to zero as $t \to T$ as required by the Euler boundary conditions (25). It follows that the $\lambda_2(t)$ term in both S and q remains dominant and (45) again holds for the normal range of the growth rate constant a (typically >2) without appealing to asymptoticity. Also, when it is more advantageous for $x_2(t)$ to grow by natural proliferation, the $TSG^{+/-}$ and $TSG^{+/+}$ cell populations would be of comparable magnitude [keeping in mind Lemma 4 requiring that $(x_0, x_1) \to (0, 1-\mu)$, the asymptotically stable critical point of (1) and (2) with $u = 0$]. In that case, $2\mu x_0 u_m/x_1 = O(2\mu)$ which is small compared to the S/q term so that $z'(t) > 0$ again without appealing to asymptoticity.

Remark 16 If $\lambda_1(t) > 0$ and/or $\lambda_0(t) > 0$ at some later stage (when it is more advantageous for the cancerous cell population to grow by natural proliferation than by mutation of the other cell types), then the magnitudes, $|\lambda_1(t)|$ and $|\lambda_0(t)|$, of these "shadow cell prices" would be considerably smaller than $|\lambda_2(t)|$ since both adjoint variables must be zero at terminal time (by the Euler boundary conditions). As such, the $\lambda_2(t)$ terms in both S and q remain dominant and (45) again holds for the normal range of the growth rate constant a (typically >2) without the asymptotic restriction.

Remark 17 For strictly convex death rates, we have

$$d^{\cdot}(u) < \frac{1-d(u)}{1-u}. \tag{46}$$

The relation (44) may be simplified somewhat to

$$z'(t) \geq \frac{x_1 z d^{\cdot}(u)}{u_m}(\mu + u_m)\frac{S}{q}\left\{1 + O\left(\frac{u_m}{a}\right)\right\} > 0$$

for $t \geq T_p$.

4 Some Features of $\bar{u}(t)$ for General Death Rate

4.1 Optimal Control Does Not Start with a Lower Corner Control

We are now in a position to state the first characterization of the optimal control $\bar{u}(t)$ for a general death rate restricted only by (6) [and not by (7)]:

Proposition 18 *The optimal control $\bar{u}(t)$ is not the lower corner control $u(t) = 0$ in $0 \le t < T_1$ at least for some $T_1 \ll T$.*

Proof By Propositions 6 and 7, we have

$$H(0) = 1 + A(0) = 0$$

and, for a sufficiently small positive t, say $0 \le t < T_1$,

$$\begin{aligned} H(t) &= A'(0)t + \frac{u_m}{\sigma}u(0)R'(0)t + O(t^2) \\ &= A'(0)t + 2\mu q(0)\frac{u_m}{\sigma}u(0)t + O(t^2). \end{aligned}$$

Given $q(0) < 0$ by Lemma 12, $H(t)$ is not minimized by the lower corner control $u(0) = 0$ as the upper corner control renders $H(t)$ more negative in $[0, T_1)$ and is therefore superior. Hence, the Maximum Principle rules out the lower corner control at least in $[0, T_1)$ for a sufficiently small T_1. □

Remark 19 It should be noted that the optimal control is not necessarily the upper corner control in $[0, T_1)$ as the interior solution, $u_i(t)$, if it exists and is admissible, would be superior.

4.2 Optimal Control Does Not End in an Upper Corner Control

At the terminal time T, we have $\lambda_0(T) = \lambda_1(T) = 0$ and therewith

$$H(t = T) = \begin{cases} 1 + \frac{1}{\sigma}\lambda_2(T)\{\mu x_1(T) + \sigma[a - x_0(T) - x_1(T)]\} & (u(T) = 0) \\ 1 + \frac{1}{\sigma}\lambda_2(T)x_1(T)(\mu + u_m) & (u(T) = 1) \end{cases}. \tag{47}$$

Relevant biological parameter value ranges are $a \ge 2$, $\sigma \gg 1$, $u_m \lesssim 1$ and $\mu \ll 1$. In view of $0 < x_0 + x_1 \le 1$ by Lemma 1 and therewith $0 \le x_k \le 1$ [see (10)], we have $\sigma(a - 1) > u_m \ge u_m x_1(t)$ for any admissible solution so that

$$[H(t = T)]_{u=0} < [H(t = T)]_{u=1} \tag{48}$$

given $\lambda_2(t) < 0$ in $[0, T]$ by Lemma 9. We have thus proved the following proposition:

Proposition 20 *An optimal control is not an upper corner control for all t in an interval $(T_0, T]$ for some $T_0 < T$, i.e., $\bar{u}(t) < 1$ for $T_0 < t \le T$.*

Proof The proposition follows from (48) and the continuity of state and adjoint variables. □

Remark 21 Note that the optimal control may or may not end with a lower corner control since an interior control, if it exists and is admissible, would be superior.

4.3 Optimal Control for the Shortest Time to Cancer

In obtaining the various results in the previous sections, we have so far made use of only the properties of $d(u)$ stipulated in (6) and (5) but not any specific functional form [such as (7)] for the death rate. In the remaining sections of this paper, we show how the optimal control for our shortest time problem depends qualitatively on the convexity of $d(u)$. More specifically, we establish that

- the unique optimal mutation rate $\bar{u}(t)$ is a bang–bang control if $d(u)$ is a concave or linear function of u, and
- the unique optimal mutation rate is generally a monotone decreasing interior control $\bar{u}(t) = u_i(t) > 0$ but may start with an upper corner control adjacent to $t = 0$ and end with a lower corner control adjacent to the terminal time with continuous transition at either switch.

Because the structure of the Hamiltonian for the two-step model is qualitatively different from that of the one-step model, the method of analysis employed in Wan et al. (2010) is not applicable and a completely new approach is developed for the solution of the present problem. The new solution technique is first introduced through the special class of death rates (7) in the next three sections and then extended the results obtained to the general death rates subsequently.

5 Concave Death Rates ($\alpha > 1$)

5.1 A Corner Control Adjacent to End Points

In the next three sections, we determine the optimal control $\bar{u}(t)$ for the special class of death rates of the form (7). In this first section, we consider the strictly concave case of $\alpha > 1$. For this case, we actually can say more about the optimal control beyond the fact that it cannot be determined by (30) [or (31)].

Proposition 22 *For $\alpha > 1$, any optimal solution for a minimum terminal time must start with an upper corner control in some finite interval $[0, T_1)$, i.e., $\bar{u}(t) = 1$ for t in $[0, T_1)$ for some T_1 in $(0, T)$.*

Proof With $D(t)$ and $R(t)$ not depending on u explicitly, we make use of (29) and solve the stationary condition (31) for $u(t)$ to get the interior control

$$u_i(t) = 1 - \left[\frac{u_m}{\alpha\sigma}\frac{R(t)}{D(t)}\right]^{\eta} \left(\eta = \frac{1}{\alpha - 1} > 0\right) \tag{49}$$

With $D(t)/R(t) \to 0$ as $t \to 0$, the interior control is negative and therefore not admissible at least for some interval $[0, T_1)$ for some positive T_1. By Proposition 18, the optimal control $\bar{u}(t)$ must be the upper corner control, with $T_1 < T$ given Proposition 20. □

For $t > T_1$ where $u_i(t)$ is well defined and feasible, we have the following negative result on the interior control:

Proposition 23 *For $\alpha > 1$, the interior control $u_i(t)$ is maximizing in $[T_1, T]$, $0 < T_1 < T$.*

Proof From Lemma 10, we see that both $D(t)$ and $R(t)$ are continuously differentiable. Consequently, we can differentiate the Hamiltonian twice with respect to time for the case of an interior control to get

$$\frac{\mathrm{d}^2 H}{\mathrm{d}t^2} = \frac{\partial^2 H}{\partial u^2}\left(\frac{\mathrm{d}u}{\mathrm{d}t}\right)^2 = -D(t)d^{\,\cdot\cdot}(u)\left(\frac{\mathrm{d}u}{\mathrm{d}t}\right)^2. \tag{50}$$

after making use of the Hamiltonian structure of the state and adjoint equations to eliminate terms involving derivatives of the state and adjoint variables. With $\lambda_2(t) < 0$ (by Lemma 9) and $P(t) < 0$ (by Lemma 11), we have from (19)

$$D(t) = (1 - x_0 - x_1)P(t) + \lambda_2 x_2(a - 1) < 0, \quad (t > 0) \tag{51}$$

keeping in mind Lemma 1. It follows from this and $d^{\,\cdot\cdot}(u_i) = -\alpha(\alpha-1)(1-u_i)^{\alpha-2} < 0$ for $\alpha > 1$ that

$$\left[\frac{\mathrm{d}^2 H}{\mathrm{d}t^2}\right]_{u=u_i(t)} < 0 \quad (t > 0). \tag{52}$$

As such, the interior control, whenever it is well defined by (49) and admissible, maximizes the Hamiltonian and therefore is not optimal for minimum terminal time. □

As a consequence of Proposition 23, we can now conclude that the optimal control adjacent to the terminal time must be the lower corner control:

Proposition 24 *For $\alpha > 1$, any optimal control for the two-step model must end with a lower corner control in some finite interval $(T_0, T]$, i.e., $\bar{u}(t) = 0$ for t in $(T_0, T]$ for some T_0 in $(0, T)$.*

Proof Since we can only choose between the two corner controls, Proposition 20 eliminates the upper corner control as a candidate for optimal mutation rate in some interval $(T_0, T]$. It follows that the optimal mutation rate must end with the lower corner control in $(T_0, T]$ for some $T_0 < T$. That $T_0 > 0$ is an immediate consequence of Proposition 18 ruling out the lower corner control for some interval $[0, T_1)$. Hence, T_0 cannot be less than T_1. □

5.2 The Optimal Mutation Rate is Bang–Bang

With Propositions 24 and 22, we know that the optimal control must be the lower corner control in the interval $(T_0, T]$ and must be the upper corner control in $[0, T_1)$ with $0 < T_1 \leq T_0 < T$. In principle, it is possible to have more (than one) switches between corner controls in T_1 and T_0 (keeping in mind that the interior control is maximizing), we show presently that there can only be one switch in the interval $(0, T)$ (so that $T_1 = T_0 \equiv T_s$ with the only switch point denoted by T_s).

Proposition 25 *For a death rate* (7) *with* $\alpha > 1$, *the optimal control for our two-step model has one and only one-switch point* T_s *switching from the upper to the lower corner control in the interval* $(0, T)$.

Proof With the first switch (from $\bar{u}(t) = 1$ to $\bar{u}(t) = 0$) at $T_1 > 0$, suppose there is a second switch (from $\bar{u} = 0$ to $\bar{u} = 1$) at $t = T_2$. [We note parenthetically that, given Propositions 23 and 24, there must be at least one other switch at T_3 $(> T_2 > T_1)$ to the last lower corner control.] Let a superscript $^{(1)}$ again denotes the upper corner solution and $^{(0)}$ the lower corner solution. It is clear from the relevant ODE for the two corner controls that

$$\frac{\mathrm{d}x_2^{(1)}}{\mathrm{d}t} = \frac{u_m + \mu}{\sigma} x_1^{(1)} < \frac{\mu}{\sigma} x_1^{(0)} + x_2^{(0)} \left(a - x_0^{(0)} - x_1^{(0)} \right) = \frac{\mathrm{d}x_2^{(0)}}{\mathrm{d}t}$$

in some subinterval of (T_1, T_2), given that the lower corner control is optimal there. The situation is even less favorable for growth rate of cancerous cells with the upper corner control in the $t > T_2$ range given the relative growth rates for the two corner solutions have not changed structurally while $x_0^{(0)}$ and $x_1^{(0)}$ grow faster than $x_0^{(1)}$ and $x_1^{(1)}$ and thereby provide more fuel for mutation into more cancerous cells. Hence, a switch from the lower to upper corner control at T_2 (or any later time) is not optimal leaving us with $T_1 = T_0 \equiv T_s$. □

Altogether, we have the following complete characterization of the optimal mutation rate for a death rate (7) with $\alpha > 1$.

Theorem 26 *For* $\alpha > 1$, *the optimal mutation rate for fastest time to cancer for our two-step model is the bang–bang control*

$$\bar{u}(t) = \begin{cases} 1 & [0 \le t < T_s) \\ 0 & (T_s < t \le T] \end{cases} \tag{53}$$

with its one-switch point determined by the switching condition (27) *which may be taken to be* $H(T_s) = 0$ *in light of Proposition* 6.

Proof The proposition follows from Propositions 22, 24, 23 and 25. □

5.3 Determination of Switch Point

5.3.1 A Simple Iterative Numerical Scheme

With $\bar{H}(t)$ being continuous and vanishing on both sides of a switch point, we have from (17) $D(T_s) = u_m R(T_s)/\sigma$. Our task is to find the unique root of this equation. However, both $D(t)$ and $R(t)$ involve all the state and adjoint variables, we must solve for these six unknowns, the unknown switch point T_s and the unknown terminal time T simultaneously. An iterative solution scheme was designed in Komarova et al. (2008) to compute the solution for the present class of problems for both the one-step and two-step models without knowing the optimal control being bang–bang. Now that we

know the optimal control for a death rate (7) with $\alpha > 1$ must be bang–bang (switching from the upper corner control to the lower corner control), a more efficient solution scheme is possible.

One such scheme would be the following iterative algorithm:

- Start with an initial guess $T_s^{(0)}$ for the switch point (which should be somewhat less than the crossover point T_c of cancerous cell growth to target by each of the two corner control alone to be discussed in the next section). The three state ODE for the cell populations with the upper corner control $u = 1$,

$$x_0' = -2\mu x_0, \quad x_1' = 2\mu x_0 - (\mu + u_m u)x_1, \quad x_2' = \frac{1}{\sigma}(\mu + u_m u)x_1, \quad (54)$$

  together with the three initial conditions in (4) are solved in the interval $[0, T_s^{(0)}]$. The exact solution of this IVP is immediate and is given in the "Appendix".
- Given the continuity of the state variables, the solution of the IVP above at $T_s^{(0)}$ provides the initial conditions for a new IVP for the same three state ODE but now with $u = 0$. With the condition $x_2(T^{(0)}) = 1$, this second IVP determines an approximate terminal time $T^{(0)}$.
- If $T^{(k)}$ resulting from the kth iterate $T_s^{(k)}$ is not optimal, we modify $T_s^{(k)}$ to $T_s^{(k+1)}$ and continue the process until a minimum terminal time is found up to an acceptable tolerance.

More on this approach will be discussed in Sanchez-Tapia (2015). We report here only that for $\sigma = 10$, $\mu = 0.1$, $u_m = 1$ and $a = 2$, the iterative scheme above gives an optimal switch time of $T_s = 1.4125\ldots$ and a fastest terminal time of $T = 5.3986\ldots$ which is substantially lower than the approximate fastest time of $5.68\ldots$ obtained in Komarova et al. (2008) by an existing code for the discrete SQP algorithm (Gill et al. 2005). (It is noted that the inaccuracy is due to the ad hoc process for discretization of the continuous optimal control problem and not to any inadequacy of the SQP algorithm.) Changing only $a = 2$ to $a = 5$ leads to an optimal switch time of $T_s = 0.41415\ldots$ and a fastest terminal time of $T = 1.9817\ldots$

5.3.2 Some Bounds for the Switch Time

For an efficient implementation of the iterative scheme described in the previous section, it is desirable to have a good initial guess or a narrow range for the switch point T_s. Below are some bounds that either offer insight into the optimal solution or are actually useful as an initial guess.

Crossover of Corner Solutions An obvious upper bound for the switch time would be the crossover time T_c when the upper and lower corner solutions for the IVP problem for state Eqs. (1)–(3) have the same cancerous mutant population, i.e., $x_2^{(0)}(T_c) = x_2^{(1)}(T_c)$. While the determination of T_c by the exact solutions or numerical integration is straightforward, the use of T_c as a first approximation for T_s is too conservative. The rapid growth of the mutants in the case of a lower corner control would have made up for the associated smaller mutant population from an earlier switch time.

Crossover of Corner Cancerous Growth Rates A less conservative choice would be the time T_g when the two corner growth rates for mutants are equal:

$$\left[\mathrm{d}x_2^{(1)}/\mathrm{d}t\right]_{t=T_g} = \left[\frac{u_m+\mu}{\sigma}x_1^{(1)}\right]_{t=T_g} = \left[\frac{\mu}{\sigma}x_1^{(0)} + x_2^{(0)}(a - x_0^{(0)} - x_1^{(0)})\right]_{t=T_g}$$
$$= \left[\mathrm{d}x_2^{(0)}/\mathrm{d}t\right]_{t=T_g}.$$

For $\mu = 0.1$, $u_m = 1$, $a = 2$ and $\sigma = 10$, we have $T_g = 2.215\ldots$ compared to $T_c = 3.267\ldots$.

Maximum $x_1^{(1)}$ Still another possible initial guess is the time t_M when $x_1^{(1)}$ attains its unique maximum. It has the advantage of having an explicit expression in terms of μ and u_m given by (13). For $\mu = 0.1$ and $u_m = 1$, we have $t_M = 1.894\ldots < T_g < T_c$ while the optimal switch point is $\bar{T}_s = 1.4125\ldots$ The corresponding terminal times for t_M and T_g are

$$[T]_{T_s = T_g} = 5.5540\ldots > [T]_{T_s = t_M} = 5.460\ldots > [T]_{T_s = \bar{T}_s.} = 5.3986\ldots$$

So, for this example, t_M provides a better upper bound for the optimal switch point $\bar{T}_s$ compared to T_g (or T_c). However, the reliability of t_M may vary since it does not depend on a or σ and therefore does not take into account the important proliferation of mutants by their fast natural growth rate. This is seen from the case with $a = 5$ (instead of $a = 2$) for which $\bar{T}_s = 0.4135\ldots$ with $[T]_{T_s=\bar{T}_s} = 1.9506\ldots$ while $[T]_{T_s=t_M} = 2.6251\ldots$ The corresponding T_g is $0.7915\ldots$ which is closer but still considerably later than the optimal switch time (though the resulting terminal time $[T]_{T_s=T_g} = 2.0895\ldots$ is much closer to the optimal T).

The reason why the actual switch point is typically earlier than the three different special times mentioned above is the more aggressive growth rate of the mutant cells compared to the gain through the mutation of $x_1^{(1)}(t)$, cells with only one copy of tumor suppressor gene. Even if $x_1^{(1)}(t) < x_1^{(1)}(t_M)$ for t less than (but close to) t_M (hence with slightly less of the x_1 cells available to start the lower corner solution), the faster growth rate of the mutant cells may more than make up for that shortfall to reach the target mutant population in the same time interval $(T_s, T]$ or faster.

A Lower Bound As long as natural proliferation is faster, the lower corner solution is more effective eventually. This suggests consideration of the threshold T_t when the proliferation rate of the mutant cells equals the gain through the mutation of $x_1^{(1)}(t)$ and use

$$\left[\mathrm{d}x_2^{(1)}/\mathrm{d}t\right]_{t=T_t} = \left[\frac{u_m+\mu}{\sigma}x_1^{(1)}\right]_{t=T_t} = \left[\frac{\mu}{\sigma}x_1^{(1)} + x_2^{(1)}(a - x_0^{(1)} - x_1^{(1)})\right]_{t=T_t}$$

or

$$\left[x_2^{(1)}(a - x_0^{(1)} - x_1^{(1)}) - \frac{u_m}{\sigma}x_1^{(1)}\right]_{t=T_t} = 0 \tag{55}$$

for determining the threshold T_t, by the exact solution for $\left\{x_k^{(1)}\right\}$ in the "Appendix" or by numerical integration.

For $a = 5$, $\mu = 0.1$, $u_m = 1$ and $\sigma = 10$, the threshold condition (55) gives $T_t = 0.41415\ldots$ with $[T]_{T_s = T_t} = 1.98177\ldots$ which is indistinguishable (at least for the number of digits calculated) from the optimal switch point $\bar{T}_s$ obtained by the iterative scheme of the previous section. We note, however, that T_t is not the actual switch point or an upper bound. For $a = 2$ (while keeping the other three parameters unchanged), we have $T_t = 1.2630\ldots$ with $[T]_{T_s = T_t} = 5.4060\ldots$. The actual optimal switch time is found by the iterative scheme of the previous section to be $\bar{T}_s = 1.4125\ldots$ which is larger.

There is a simple explanation why T_t is only a lower bound for the optimal switch point $\bar{T}_s$. Though the condition (55) is satisfied showing that natural growth rate for the mutant population $x_2^{(1)}$ has caught up with (and equal to) the gain rate from the mutation of the $x_1^{(1)}$ population at T_t, that parity may be lost after the switch to a lower control. With the switch to the lower corner control, the two populations x_0 and x_1 begin to rise more rapidly with their sum tending to $1 - \mu$ because of the addition of the logistic growth terms. Correspondingly, the natural proliferation rate of x_2 is reduced somewhat through the factor $a - x_0 - x_1$ in the third state Eq. (3). As such, the parity between the two modes of gaining mutant cells at the threshold T_t may be lost (for a short time after T_t), much less so for $a \gg 1$ and more so if $a = O(1)$. The latter scenario requires a later switch time than T_t to get a larger x_1 at the switch to balance the change in logistic growth rate after the switch to a lower corner control as shown for the $a = 2$ case. The precise condition specifying the optimal switch time is given by (27) [to be given in terms of $D(t)$ and $R(t)$ later in (56)].

The observations on the various bounds are summarized in the following proposition useful for bracketing the two starting iterates in the application of the iterative numerical solution scheme:

Proposition 27 *The threshold value T_t defined by the condition (55) provides a lower bound for the optimal switch point $\bar{T}_s$ while the smaller of T_g and t_M provides an upper bound.*

Remark 28 The iterative solution scheme has been applied for several sets of parameter values. It was found that T_t constitutes a tight lower bound, often very close to the optimal switch point. Similar to t_M, its determination only involves the upper corner control problem (for which we have an explicit exact solution). It is more effective for larger a, i.e., for more aggressive cancerous proliferation rate.

6 Linear Death Rates ($\alpha = 1$)

6.1 Nonexistence of Singular Solution

For the linear death rate case ($\alpha = 1$) with $d(u) = u$, the stationary condition requires

$$\frac{u_m}{\sigma} R(t) = D(t) \tag{56}$$

Known as the *singular solution* of the problem, the condition (56) does not involve the control explicitly and therefore does not identify directly an interior control $u_i(T)$ as a possible candidate for the optimal control $\bar{u}(t)$. The path to the optimal control for our two-step model is simplified considerably by the following nonexistence theorem;

Proposition 29 *For the two-step model with a linear death rate $d(u) = u$, the relation (56) is not satisfied for any finite interval of time; consequently, there is no singular solution for our problem.*

Proof Rewrite (56) as

$$z(t) = \frac{u_m}{\sigma} \tag{57}$$

with $z(t) = D(t)/R(t)$ as previously defined in conjunction with Lemma 14. Differentiate both sides of (57) to get

$$z'(t) = 0.$$

But this contradicts Lemma 14 which requires $z'(t) > 0$ for all $t \geq 0$. The proposition is proved. □

6.2 The Optimal Control is Bang–Bang

In the absence of a stationary (singular) solution, we are left with a choice of two corner controls. Proposition 18 requires the optimal mutation to start with an upper corner control and Proposition 20 requires it to end with a lower corner control. Similar to the $\alpha > 1$ case, the optimal mutation is shown presently to be a one-switch bang–bang control:

Proposition 30 *For $\alpha = 1$ so that $d(u) = u$, the optimal mutation rate $\bar{u}(t)$ for fastest time to cancer of our two-step model is the bang–bang control*

$$\bar{u}(t) = \begin{cases} 1 & (0 \leq t < T_s) \\ 0 & (T_s < t \leq T) \end{cases}. \tag{58}$$

Proof While it is possible to have any odd number of switches between the two corner controls (ending in the lower corner control adjacent to the terminal time), Proposition 25 applies to the present problem since (in the absence of a stationary solution) the argument in its proof does not depend on the form of the death rate. □

Remark 31 For $\alpha = 1$, the only switch point T_s for the optimal (bang–bang) control and the fastest time to target can be determined by the iterative algorithm described in the previous section. In the next subsection, we obtain an upper bound for the optimal terminal time to cancer whenever the optimal mutation rate is bang–bang. Such a finite upper bound effectively demonstrates the existence of a finite fastest time to target cancerous population.

6.3 An Upper Bound for T and Another Lower Bound for T_s

For the purpose of obtaining an upper bound for the terminal time of our problem, we specialize the exact solutions and bounds for the cell populations obtained in the "Appendix". For a growth program that starts with an upper corner control and switch to a lower corner control at T_s, the exact time evolution of the three cell population is given in (85)–(86) for $0 \le t \le T_s$. For $t > T_s$ where the control is lower corner, we have the following bounds for the corresponding cell populations:

$$
\begin{aligned}
e^{-\mu(t+T_s)} \le x_0^{(0)} &\le 1 - 2\mu \\
\left[x_1^{(1)}\right]_{t=T_s} + 2\mu \left\{e^{-2\mu T_s} - e^{-\mu(t+T_s)}\right\} \le x_1^{(0)} &\le x_1^{(p)} \lesssim 1 + \mu \\
x_2^{(0)} \ge \frac{1}{\sigma}\left[1 - \frac{u_m + \mu}{u_m - \mu} e^{-2\mu T_s}\right] e^{(a-1)\tau}
\end{aligned}
$$

with $x_1^{(p)}$ as defined in (96) and with the superscript "(0)" indicating a quantity defined for $t > T_s$ (with $\bar{u}(t) = 0$ there) and

$$
\begin{aligned}
&\tau = t - T_s, \quad \left[x_0^{(1)}\right]_{t=T_s} = e^{-2\mu T_s}, \\
&\left[x_1^{(1)}\right]_{t=T_s} = \frac{2\mu}{u_m - \mu}\left[e^{-2\mu T_s} - e^{-(\mu+u_m)T_s}\right]
\end{aligned}
$$

by continuity. We note that the upper bound for $x_1^{(0)}$ is unrealistic since $x_0^{(0)} + x_1^{(0)} < 1$ (by Lemma 1) and $x_0^{(0)} \ge 0$. However, $x_1^{(p)} \lesssim 1 + \mu$ is only an (overly conservative) upper bound and does not contradict other more realistic results for cell populations (such as Lemma 1).

With the optimal control consisting of only one switch from upper corner to lower corner control at the optimal switch point T_s, the terminal time to target cancerous population is determined by $x_2(T) = 1$. Our results for upper and lower bounds for the switch point suggest $2\mu T_s \ll 1$ and therewith

$$
\left[x_2^{(0)}\right]_{t=T} \ge \frac{1}{\sigma}\left[1 - \frac{u_m + \mu}{u_m - \mu} e^{-2\mu T_s}\right] e^{(a-1)\tau_T}, \quad \tau_T = T - T_s
$$

or

$$
e^{(a-1)\tau_T} \lesssim \frac{\sigma\,(u_m - \mu)}{2\mu\,[(u_m + \mu)\,T_s - 1]}.
$$

The relation above gives an upper bound T^* for the optimal terminal time $\bar{T}$ with

$$
\bar{T} \le T^* = T_s + \frac{1}{a-1} \ln\left(\frac{\sigma\,(u_m - \mu)}{2\mu\,[(u_m + \mu)\,T_s - 1]}\right) \tag{59}
$$

While the optimal switch point $\bar{T}_s$ is an unknown and to be determined simultaneously with $\bar{T}$, we do have several upper and lower bounds for $\bar{T}_s$ (given in the last section on the $\alpha > 1$ case. For the typical set of parameter values used in Komarova et al. (2008) ($a = 2,\ \mu = 0.1,\ \sigma = 10$ and $u_m = 1$), using $t_M = 1.894\ldots$ for t_s results in the following approximate bound for the terminal time:

$$\bar{T} \leq \left[T^*\right]_{T_s=t_M} \simeq 5.6206\ldots$$

The approximate T^* is only 4 % off the exact solution of $\bar{T} = 5.3986\ldots$ for this example. For the higher cancerous cell growth rate constant $a = 5$ (with the other three parameter values unchanged), the corresponding T^* from the same t_M (which does not depend on a),

$$\bar{T} \leq \left[T^*\right]_{T_s=T_t} \simeq 2.8258...,$$

is much less accurate, about 40 % higher than the exact solution $\bar{T} = 1.98177\ldots$

The less than rosy result for $a = 5$ may be turned into a more positive one by asking for the least informative bound possible from applications of (59). The answer is of course $T^* = \infty$ attained by taking $T_s = 1/(u_m + \mu)$. For $T_s < 1/(u_m + \mu)$, T^* would no longer be real. We have therefore the following lower bound for the switch point T_s:

Proposition 32

$$\bar{T}_s > \frac{1}{u_m + \mu}.$$

7 Convex Death Rates ($\alpha < 1$)

7.1 Existence of a Minimizing Interior Control

For death rates of the form (7) with $\alpha < 1$, for which

$$d^{\cdot}(u) = \alpha(1-u)^{\alpha-1} > 0 \quad \text{and} \quad d^{\cdot\cdot}(u) = \alpha(1-\alpha)(1-u)^{\alpha-2} > 0 \tag{60}$$

for $0 \leq u < 1$, the stationary condition (30) leads to the interior control

$$u_i(t) = 1 - [\delta(t)]^{\beta} \tag{61}$$

where

$$\delta(t) = \frac{\alpha\sigma}{u_m}\frac{D(t)}{R(t)} = \frac{\alpha\sigma}{u_m} z(t), \quad \beta = \frac{1}{1-\alpha} > 1. \tag{62}$$

With $z(t)$ known to be nonnegative from Lemma 14, the expression (61) for $u_i(t)$ is a well-defined real-valued function for $t \geq 0$ with:

$$\lim_{t\to 0+} u_i(t) = 1. \tag{63}$$

Furthermore, $u_i(t)$ is an admissible control at least for some interval adjacent to the starting time:

Proposition 33 *For a death rate* (7) *with* $0 < \alpha < 1$, *a real-valued interior control* $u_i(t)$ *for our two-step model exists for all* t *in* $[0, T]$ *with (i)* $u_i(0) = 1$, *(ii)* $u_i'(0) = 0$, *(iii)* $u_i'(t) < 0$ *for all* t *in* $(0, T]$ *and (iv)* $0 < u_i(t) < 1$ *in* $(0, T_0)$ *for some* $T_0 > 0$.

Proof We already have part (*i*) from (63). For the other parts, we differentiate (61) with respect to time to get

$$u_i'(t) = -\beta\,[\delta(t)]^{\beta-1}\,\frac{\alpha\sigma}{u_m} z'(t).$$

Parts (*ii*) and (*iii*) follow given $z'(t) > 0$ by Lemma 14, $\delta(0) = 0$ and $\delta(t) > 0$ for $t > 0$. With $u_i(t)$ monotone decreasing from $u_i(0) = 1$, part *iv*) follows. □

By the convexity property $d^{\cdot\cdot}(u) > 0$, $u_i(t)$ minimizes the Hamiltonian wherever it is admissible in the interval $[0, T]$.

Proposition 34 *For a death rate* (7) *with* $0 < \alpha < 1$, *the interior control for our two-step model is the optimal control whenever it is admissible.*

Proof For the well-defined real interior control (61), we have as in (50)

$$\frac{\mathrm{d}^2 H}{\mathrm{d}t^2} = \frac{\partial^2 H}{\partial u^2}\left(\frac{\mathrm{d}u}{\mathrm{d}t}\right)^2 = -D(t)d^{\cdot\cdot}(u)\left(\frac{\mathrm{d}u}{\mathrm{d}t}\right)^2, \tag{64}$$

given that the ODE for the state and adjoint variables form a Hamiltonian system. Since $d^{\cdot\cdot}(u) > 0$ for $0 < \alpha < 1$ and $D(t) < 0$ for $t > 0$ by Lemma 11, we have

$$\left[\frac{\partial^2 H}{\partial u^2}\right]_{u=u_i} = -d^{\cdot\cdot}(u_i)D(t)\left[u_i'(t)\right]^2 > 0,\ (t > 0)$$

As such, the unique well-defined interior control minimizes the Hamiltonian of our problem. Hence, we have $\bar{u}(t) = u_i(t)$ whenever the interior control is admissible. □

7.2 Admissibility of Interior Control

With $u_i(0) = 1$ and $u_i(t)$ monotone decreasing with increasing t, at least for some interval adjacent to the starting time, the interior control may well be well defined and admissible for the entire time duration $[0, T]$ required to reach the target cancerous cell population. However, approximate numerical solutions computed in Komarova et al. (2008) show that for some combination of system parameter values the interior

control vanishes at some $T_0 < T$. For a theoretical validation of these observations, we note that the interior control simplifies considerably at the terminal time T to

$$u_i(T) = \left[1 - \left(\frac{\sigma\alpha}{u_m}\frac{a - x_0 - x_1}{x_1}\right)^{1/(1-\alpha)}\right]_{t=T} \tag{65}$$

given $x_2(T) = 1$ and the Euler boundary conditions $\lambda_0(T) = \lambda_1(T) = 0$. With $0 \le x_1 \le x_0 + x_1 \le 1$ for all $t \ge 0$, we arrive at the following upper bound for $u_i(T)$:

$$u_i(T) < 1 - \left[\frac{\sigma\alpha}{u_m}(a-1)\right]^{1/(1-\alpha)}.$$

It follows that $u_i(T) < 0$ for $\sigma\alpha(a-1) > 1 \ge u_m$. This would be the case for the biologically realistic parameter value combinations of $\{u_m = 1,\ \sigma = 10,\ \alpha = 0.2,\ a = 2\}$ and $\{u_m = 1,\ \sigma = 4,\ \alpha = 0.1,\ a = 4\}$, leading to the following proposition on the inadmissibility of the interior control:

Proposition 35 *For the two-step model, $u_i(t) < 0$ in $(T_0^*, T]$ for some $T_0^* > 0$ if*

$$\sigma\alpha(a-1) > u_m. \tag{66}$$

Proof With (66), we have $u_i(T) < 0$. By the continuity of the various state and adjoint variables, we conclude that $u_i(t) < 0$ in $(T_0^*, T]$ for some $T_0^* < T$. T_0^* must be positive in view of Proposition 33. □

With (66), $u_i(t)$ is not admissible in $(T_0^*, T]$ for some $T_0^* > 0$. By Proposition 20, the optimal control must be the lower corner control in that interval. The sufficient condition for the inadmissibility of the interior control suggests that the interval $(T_0^*, T]$ would be larger for a larger value of "a" or "σ." Clearly, with a higher growth rate constant for the cancerous cell population, it would be more advantageous for $x_2(t)$ to grow by natural proliferation sooner. The preference for natural proliferation when the target cancerous cell population is larger (relative to the original normal cell population), i.e., large σ, is less obvious. Evidently, the gain in mutants at any instant would be a smaller and smaller fraction of the target cancerous cell population for larger and larger σ.

7.3 The Optimal Mutation Rate

The extent of the admissibility of $u_i(t)$ for $t < T_0^*$ is answered by the next proposition.

Proposition 36 *Let T_0 be the first zero of $u_i(t)$, so that $u_i(T_0) = 0$ and $u_i(t) > 0$ for $t < T_0$. Then, for a strictly convex death rate of the form (7) (with $0 < \alpha < 1$), the optimal mutation rate $\bar{u}(t)$ for our two-step model is the continuous and PWS control*

$$\bar{u}(t) = \begin{cases} u_i(t) & (0 \le t \le T_0) \\ 0 & (T_0 \le t \le T) \end{cases}. \tag{67}$$

Proof With $u_i(T_0) = 0$ and $u_i'(t) < 0$ for all $t \ge T_0$ (by Proposition 33), we have $u_i(t) < 0$ for all t in $(T_0, T]$; hence, the interior control is not admissible for $t > T_0$. By Proposition 20, the optimal mutation rate must be as given by (67). □

7.4 Approximate Location of the Zero of $u_i(t)$

With (65), we see that the optimal mutation rate $\bar{u}(t)$ is the interior control $u_i(t)$ for the entire solution domain $[0, T]$ if

$$\frac{\sigma\alpha}{u_m}\left[\frac{a - x_0 - x_1}{x_1}\right]_{t=T} \le 1. \tag{68}$$

In that case, the three state ODE (1)–(3), three adjoint ODE (22)–(24), the four boundary condition (4), the two Euler boundary conditions (25) and the transversality condition (26) together determine the optimal solution. With some re-arrangements, such a problem can be solved by any of the available mathematical software for two-point boundary value problems with error estimates.

Unfortunately, the cell populations $x_0(T)$ and $x_1(T)$ are not known without the solution of the problem. The obvious upper bound of the expression on the left side of (68),

$$\frac{\sigma\alpha}{u_m}\left[\frac{a - x_0 - x_1}{x_1}\right]_{t=T} < \frac{\sigma\alpha}{u_m}\frac{a}{x_1(T)},$$

still contains the unknown $x_1(T)$ with an obvious lower bound $2\mu e^{-2\mu T}$ too conservative for our purpose. With the optimal control vanishing for $t \ge T_0$, it would seem reasonable to expect

$$x_1(T) \ge x_1^M = x_1^{(1)}(t_M) = \left(\frac{2\mu}{u_m + \mu}\right)^{\frac{u_m+\mu}{u_m-\mu}}.$$

In that case, we may get some insight into the location of $\bar{T}_s$ by taking $x_1(T) > 2\mu$ [given $\mu \ll u_m = O(1)$]. For the biologically realistic parameter values $\alpha = 0.05$, $a = 2$, $u_m = 1$, $\sigma = 2$ and $\mu = 0.1$, we have

$$\frac{\sigma\alpha}{u_m}\left[\frac{a - x_0 - x_1}{x_1}\right]_{t=T} < \frac{\sigma\alpha}{u_m}\frac{a}{x_1(T)} < 1 \tag{69}$$

so that $T_0 > T$ on the basis of the assumption $x_1(T) > 2\mu$. While the assumed lower bound for $x_1(T)$ gives a possible location for T_0, it is still necessarily to verify whether the interior control is nonnegative for the entire interval $[0, T]$ even if (69) is met. Methods of solution for determining $\bar{u}(t)$ (including the unknown T_0) as given by

(67) in the absence of an ironclad assurance of $T_0 > T$ will be discussed in Sanchez-Tapia (2015).

8 General Death Rates

In this section, we extend the findings for death rates of the form (7) to general death rates (of appropriate convexity) having the properties stipulated in (6). We denote by P_d^2 the class of twice continuously differentiable function $d(u)$ satisfying (6):

$$P_d^2 = \left\{ d(u)\, \epsilon C^2 \,|d(0) = 0,\ d(1) = 1,\ 0 \le d(u) \le 1, d^{\cdot}(u) > 0\ (0 \le u < 1) \right\}. \tag{70}$$

8.1 Death Rate Strictly Concave in the Mutation Rate

Consider first P_d^2 death rates that are *strictly concave* so that $d(u)$ satisfies the inequality

$$d^{\cdot\cdot}(u) < 0\ \ (0 \le u \le 1)\,. \tag{71}$$

The following key result is an immediate consequence of (71):

Proposition 37 *For a P_d^2 death rate that is strictly concave, the corresponding interior control for our two-step model. $u_i(t)$, whenever admissible, maximizes the Hamiltonian and is therefore not optimal.*

Proof From (50), we have for an interior control

$$\frac{\mathrm{d}^2 H}{\mathrm{d}t^2} = \frac{\partial^2 H}{\partial u^2}\left(\frac{\mathrm{d}u}{\mathrm{d}t}\right)^2 = -d^{\cdot\cdot}(u) D(t)\left(\frac{\mathrm{d}u}{\mathrm{d}t}\right)^2 < 0 \quad (t > 0)$$

given Lemma 11 and the concavity condition (71). Hence, any admissible interior control is maximizing and therefore not optimal for the minimum time problem. □

Proposition 37 requires the optimal control to be a corner control. Proposition 18 and 20 [which do not depend on the specific form (7) for $d(u)$] then require the optimal control to start with an upper corner control $\bar{u}(t) = 1$ in some interval $[0, T_1)$ and to end in a lower corner control in some interval $(T_0, T]$ with $T_1 \le T_0$. In principle, we may have more switches between the corner controls inside the interval (T_1, T_0). The following proposition rules out that possibility requiring $T_1 = T_0 \equiv T_s$ and thereby completely specifies the optimal mutation rate for strictly concave P_d^2 death rates:

Proposition 38 *For a P_d^2 death rate that is strictly concave, the optimal mutation rate for the fastest time to target for our two-step model is the following bang–bang control for some switch point T_s:*

$$\bar{u}(t) = \begin{cases} 1 & [0 \le t < T_s) \\ 0 & (T_s < t \le T] \end{cases}. \tag{72}$$

Proof The proof for Proposition 26 applies since it actually does not depend on the form of the death rate function. □

8.2 Death Rates Strictly Convex in Mutation Rate

8.2.1 Interior Control Minimizes Hamiltonian

The situation is quite different for strictly convex P_d^2 death rates characterized by

$$d^{\cdot\cdot}(u) > 0 \quad (0 \le u \le 1). \tag{73}$$

It follows from (73) that the positive $d^{\cdot}(u)$ itself is also monotone increasing and (see Wan 1995)

$$\alpha < d^{\cdot}(u) < \frac{1 - d(u)}{1 - u} \quad (0 \le u < 1). \tag{74}$$

In that case, the stationary condition (30), written as

$$0 < d^{\cdot}(u) = \frac{u_m}{\sigma} \frac{R(t)}{D(t)} \equiv w(t), \tag{75}$$

is invertible to give a unique real-valued interior control $U_i(w(t)) \equiv u_i(t)$. We have immediately the following important conclusion:

Proposition 39 *For a strictly convex P_d^2 death rate, the unique interior control $u_i(t)$ of our two-step model minimizes the Hamiltonian for the problem and is therefore optimal whenever it is admissible.*

8.2.2 Interior Control is Monotone Decreasing in Time

Recall from Propositions 11 and 12 that both $R(t)$ and $D(t)$ are negative for $t > 0$ and their local behavior given by Proposition 7 holds in some interval $[0, T_1)$. With $R(t)$ decreasing at a slower rate than $D(t)$ in that interval, the positive ratio $R(t)/D(t)$ decreases monotonically with time at least for all $t < T_1$. In that case, $u_i(t) = U_i(w(t))$ is a decreasing function of t with $u_i'(t) < 0$ for $0 \le t < T_1$. We wish to extend this result to the entire time interval $[0, T]$ (where Proposition 7 may not be applicable).

To accomplish this, we rewrite the stationary condition (75) in terms of $z(t) = D(t)/R(t)$ previously introduced in connection with Lemma 14,

$$0 < d^{\cdot}(u) = \frac{u_m}{\sigma} \frac{R(t)}{D(t)} = \frac{u_m}{\sigma z(t)},$$

and differentiate both sides of (75) with respect to t to obtain

$$d^{\cdot\cdot}(u) u_i'(t) = -\frac{u_m z'(t)}{\sigma [z(t)]^2}$$

Since the death rate function is strictly convex, we have $d^{\cdot\cdot}(u) > 0$. With Lemma 14 assuring us $z'(t) > 0$, we have proved the following proposition:

Proposition 40 *For any P_d^2 death rate that is strictly convex, the interior control for our two-step model is a monotone decreasing function of time for $t \geq 0$, i.e., $u_i'(t) < 0$ for all t in $[0, T]$.*

8.2.3 Admissibility of the Interior Control Adjacent to Starting Time

In the special case of (7) with $0 < \alpha < 1$, the interior control $u_i(t)$ for the two-step model is always admissible adjacent to the initial time but may become negative prior to the terminal time (and hence not admissible). For our more general class of strictly convex death rates, the situation is complicated by the additional possibility that $u_i(t)$ may exceed the upper bound. The actual admissibility of the interior control near $t = 0$ is shown presently to depend on the value u_∞ of the mutation rate u for which $d(u)$ becomes unbounded,

$$\lim_{u \to u_\infty} d(u) = \infty. \tag{76}$$

Note that with the restrictions imposed on P_d^2 death rates specified in (70), we must have $1 \leq u_\infty \leq \infty$. Strict convexity of $d(u)$ requires its slope to satisfy

$$d^{\cdot}(u) > d^{\cdot}(0) \equiv \alpha_0 > 0. \tag{77}$$

Proposition 41 *For a strictly convex P_d^2 death rate, we have (i) $u_i(\hat{T}) = 1$ for some $0 \leq \hat{T} < T$, (ii) $u_i(t) > 1$ for all $t < \hat{T}$ and (iii) $u_i(t) < 1$ for all $t > \hat{T}$.*

Proof For strictly convex $d^{\cdot}(u)$ death rates, we have $d^{\cdot\cdot}(u) > 0$ so that $d^{\cdot}(u)$ is itself a monotone increasing function [see (73)]. It follows that

$$0 < \alpha_0 = d^{\cdot}(0) < d^{\cdot}(u) < d^{\cdot}(u_\infty) \tag{78}$$

for $0 \leq u < u_\infty \leq \infty$ (keeping in mind $u_\infty \geq 1$ for P_d^2 death rates). Then, the inverse of (75), $U_i(w)$, is a monotone increasing (strictly concave) function of w and bounded above by u_∞. With $w(t) = u_m / [\sigma z(t)]$ a monotone decreasing function of time from $t = 0$ and

$$\lim_{t \to 0} d^{\cdot}(u_i(t)) = \lim_{t \to 0} w(t) = \lim_{t \to 0} \frac{u_m}{\sigma} \frac{R(t)}{D(t)} = \infty,$$

the inverse function $u_i(t)$ is a monotone decreasing function of t starting from $t = 0$. If $u_\infty > 1$, then $u_i(t) > 1$ for $[0, \hat{T})$ for some $\hat{T} > 0$ with $u_i(\hat{T}) = 1$ and $u_i(t) < 1$ for $t > \hat{T}$. □

Corollary 42 *If $u_\infty > 1$, the optimal control starts with the upper corner control for the interval $[0, \hat{T}]$, i.e., $\bar{u}(t) = 1$ in $[0, \hat{T}]$.*

Proof Since $u_i(t) > 1$ for $0 \le t < \hat{T}$, it is not admissible in that interval. By Lemma 18, the optimal control must be the upper corner control there. □

8.2.4 The Optimal Control Configuration

For the actual configuration of the optimal control, we need to know when the interior control remains admissible in $(\hat{T}, T]$. We saw from Proposition 41 how the admissibility of $u_i(t)$ adjacent to $t = 0$ depends on u_∞. We now show how the admissibility of $u_i(t)$ adjacent to terminal time T depends of the initial slope $\alpha_0 = d'(0)$.

Lemma 43 *If $d(u)$ is a strictly convex P_d^2 death rate and $u_m/(\sigma z(T)) > \alpha_0$, then $u_i(t)$ is admissible in the interval $(\hat{T}, T]$ with the threshold $\hat{T}$ defined in Proposition 41 (which may be 0 as in the special case of (7) with $\alpha < 1$) with $0 < u_i(t) < 1$ there.*

Proof The Lemma follows from $u_i'(t) < 0$. From $d'(u(T)) = u_m/(\sigma z(T)) > \alpha_0$ follows $u_i(T) > 0$ and hence $0 < u_i(t) < 1$ in that interval. □

Remark 44 The lemma above holds also for $u_m/(\sigma z(T)) = \alpha_0$ with $u_i(T) = 0$ in that case.

For the complementary case of $u_m/(\sigma z(T)) < \alpha_0$, we have $u_i(T) < 0$. As such $u_i(t)$ is not admissible for the problem in an interval $(T_0, T]$ for some positive $T_0 < T$ with $u_i(T_0) = 0$ and $\bar{u}(t) = 0$ in that interval. Note that T_0 is necessarily positive since the lower corner control is not optimal in some interval $[0, T_1)$ adjacent to the starting time by Lemma 18.

In the interval $[0, T_0)$, we have $u_i(t) > 0$ and monotone decreasing as a function of t with $\bar{u}(t) = u_i(t)$ in $[0, T_0)$ if $u_i(t) \le 1$ in that interval. If $u_i(\hat{T}) = 1$ for some $\hat{T} > 0$, then the upper constraint in (5) requires $\bar{u}(t) = 1$ for all t in $[0, \hat{T}]$. These observations are summarized in the following proposition:

Proposition 45 *For a strictly convex P_d^2 death rate and $u_m R(T)/\sigma D(T) < \alpha_0$, the optimal mutation rate $\bar{u}(t)$ for fastest time to target for our two-step model is*

$$\bar{u}(t) = \begin{cases} 1 & (0 \le t < \hat{T}) \\ u_i(t) & (\hat{T} \le t \le T_0) \\ 0 & (T_0 \le t \le T) \end{cases}$$

with $u_i(T_0) = 0$ and $u_i(\hat{T}) = 1$ if $\hat{T} > 0$.

Remark 46 Note that $\bar{u}(t) = u_i(t)$ for all t in $[0, T_0)$ only if

$$\lim_{u \to 1-} d'(u) = \infty.$$

This was the case when $d(u)$ is of the form (7) with $0 < \alpha < 1$.

8.2.5 A Sufficient Condition for $T_0 < T$

The functions R and D that appear in the admissibility criteria of the last two subsections depend on the state and adjoint variables and are generally not known until we have the solution of our problem. However, the expressions for these two quantities simplify at the terminal time. With only their ratio in (75), the terminal slope $d^{\cdot}(u_i(T))$ is given by

$$w(T) = d^{\cdot}(u_i(T)) = \frac{u_m}{\sigma}\frac{R(T)}{D(T)} = \frac{u_m}{\sigma}\frac{x_1(T)}{a - x_0(T) - x_1(T)}.$$

While we also do not know $x_0(T)$ and $x_1(T)$ without the solution of our problem, the constraints on $x_1(t)$ [see (10)] and $x_0(t) + x_1(t)$ (see Lemmas 1 and 4) provide the needed ingredients for an upper bound for $d^{\cdot}(u_i(T))$ that limits the admissibility of the interior control:

Proposition 47 *If $\sigma(a-1) > u_m/\alpha_0$, where $\alpha_0 = d^{\cdot}(0)$ then $u_i(t) < 0$ for some interval $(T_0, T]$, with T_0 being the first zero of the interior control.*

Proof With

$$d^{\cdot}(u_i(T)) = \frac{u_m}{\sigma}\frac{x_1(T)}{a - x_0(T) - x_1(T)} \leq \frac{u_m}{\sigma(a-1)} < \alpha_0 = d^{\cdot}(0),$$

the strict convexity of $d(u)$ (and hence $d^{\cdot}(u)$ being monotone increasing) requires $u_i(T) < 0$. By the continuity of the death rate function and the interior control, we have $u_i(t) < 0$ for some interval $(T_0, T]$ adjacent to T where, by Propositions 40 and 45, T_0 is the first positive zero of the interior control. □

9 The Biology of Switching

The principal objective of this paper is to understand how the competing effects of mutation may be orchestrated to be in favor of carcinogenesis and to quantify this favoring process for the case of dysfunctional TSG. More specifically, we provide through the two-step model a complete characterization of the optimal mutation rate for the fastest time to cancer and how this rate depends on the convexity of the death rate as a function of the mutation rate. The overall project, however, is also concerned with several other related issues. One of these is to formulate an appropriate algorithm for computing the actual optimal mutation rate, especially for the strictly convex case when the lower constraint on the optimal control is binding prior to the terminal time. The brute force iterative scheme used in Komarova et al. (2008) for determining the optimal rate in the absence of any information about its nature or properties was not effective for strictly convex death rates of the two-step model. An effective algorithm has been developed in Sanchez-Tapia (2015) to accomplish this task and applied successfully. Another is to investigate the effects of noise on the optimal solutions. Considerable progress has also been made in Sanchez-Tapia (2015) on this problem including the

Table 1 Dependence of switch and terminal time on (normalized) basic mutation rate μ for concave cases with $u_m = 1,\ a = 2,\ d_m = 1$

μ	(*a*) $\sigma = 2$				(*b*) $\sigma = 10$			
	Oncogene		*TSG*		Oncogene		*TSG*	
	T_s	T	T_s	T	T_s	T	T_s	T
10^{-1}	0.6563	1.5713	1.4009	3.8764	0.895	2.7809	1.413	5.3986
10^{-2}	0.7451	1.6802	1.5744	6.3931	1.031	2.9238	1.574	8.0004
10^{-5}	0.7561	1.6935	1.5936	13.334	1.048	2.9734	1.592	14.943
10^{-7}	0.7561	1.6935	1.5936	17.938	1.050	2.9734	1.593	19.548

extension of the results of Komarova and Wodarz (2004) through a novel application of the Liouville equation in classical dynamical systems and statistical mechanics to allow for noise affecting the optimal mutation rate. These and more will be reported in Sanchez-Tapia (2015) and future publications. Here, we limit our discussion to some insight into the biology that determines the switch time of the bang–bang control for nonconvex death rate cases as suggested by the numerical solutions.

Since the optimal mutation rate is known to be (one switch) bang–bang, the important information for nonconvex death rate cases is the switch time T_s of the mutation rate (from upper to lower corner control) and the associated time to target T. In Table 1, the optimal T_s and T are shown for both one-step model and two-step model with $u_m = 1,\ a = 2$ and $d_m = 1$. The set (a) is for four values of μ with $\sigma = 2$ while the set (b) is for the same four values of μ with $\sigma = 10$, The corresponding results with the value of $a = 5$ are given in Table 2. The range of μ in all cases is from the CIN-type mutation rate of 10^{-7}/s to the MIS-type mutation rate of 0.01–0.1/s (Komarova and Wodarz 2004).

In each of the four combinations of σ and a , the results shown certainly confirm what is expected intuitively:

- For the same combination of σ and a, it would take the two-step model longer to get to the target cancerous population given that two mutations are needed to lose both copies of TSG (compared to one mutation to activate an oncogene) in order to get from a normal cell to a cancerous cell.
- For a fixed a, it would take cancerous mutants of each model longer to get to a larger target cancerous population, i.e., as σ increases.

Less obvious, however, is the asymptotic behavior of the switch time and the time to target as basic mutation rate μ becomes much smaller than the (normalized) maximum cancerous mutation rate u_m, i.e., $\mu \ll u_m = 1$, with

- T_s and T tending to their respective asymptotic value as $\mu/u_m \to 0$,

Evidently, for $\mu/u_m = O(10^{-2})$ and smaller, the trade-off between the two corner controls is unaffected by the basic mutation rate μ.

More interesting, however, is the biology responsible for the switch time and its asymptotic behavior. It has been proved earlier that a high mutation rate is needed at

Table 2 Dependence of switch and terminal time on (normalized) basic mutation rate μ for concave cases with $u_m = 1,\ a = 5,\ d_m = 1$

μ	(*a*) $\sigma = 2$				(*b*) $\sigma = 10$			
	Oncogene		*TSG*		Oncogene		*TSG*	
	T_s	T	T_s	T	T_s	T	T_s	T
10^{-1}	0.210	0.73360	0.410	1.58188	0.220	1.11835	0.410	1.98173
10^{-2}	0.230	0.77165	0.455	2.20387	0.245	1.16194	0.460	2.60616
10^{-5}	0.235	0.77622	0.465	3.93662	0.250	1.16719	0.465	4.33902
10^{-7}	0.235	0.77623	0.465	5.08796	0.250	1.16720	0.465	5.49032

Table 3 Threshold for switching in two-step model for concave cases $(u_m = 1,\ a = 2,\ d_m = 1)$

μ	(*a*) $\sigma = 2$				(*b*) $\sigma = 10$			
	$x_1(T_s)/\mu$	$x_2(T_s)/\mu$	$x_2'(T_s)/\mu$		$x_1(T_s)/\mu$	$x_2(T_s)/\mu$	$x_2'(T_s)/\mu$	
			$u = 1$	$u = 0$			$u = 1$	$u = 0$
10^{-1}	1.203	0.620	0.662	0.757	1.205	0.1256	0.133	0.153
10^{-2}	1.546	0.777	0.781	0.797	1.546	0.1554	0.156	0.159
10^{-5}	1.593	0.797	0.797	0.797	1.593	0.1591	0.159	0.159
10^{-7}	1.594	0.796	0.797	0.797	1.593	0.1593	0.159	0.159

the start for faster production of the exceedingly low advantageous mutants but, once a sufficiently large population of fast proliferating mutants is accumulated, becomes detrimental to the longevity of the fast (naturally) proliferating mutants. For the question of when to switch, we report in Tables 3 and 4 four pieces of information for the optimal bang–bang solution for each of the same four combinations of parameter values as Tables 1 and 2: (1) the normalized precancerous mutant (with only one copy of TSG) population at the switch time $x_1(T_s)$ responsible for the production of cancerous mutants; (2) the normalized cancerous mutant population at the switch time $x_2(T_s)$; (3) the rate of growth of the cancerous cell population at switch time by maximum mutation rate ($u = 1$); and (4) the rate of growth of the cancerous cell population at switch time without cancerous mutation ($u = 0$). (Note that $\{x_k(t)\}$ are continuous at T_s while $\{x_k'(t)\}$ are not). From these results, we learn the following less obvious facts:

- $x_1(T_s)/\mu$ and $x_2(T_s)/\mu$ tend to an asymptotic value as $\mu/u_m \to 0$.
- At switch time, the growth rate of x_2 with the lower corner control is generally not less than the corresponding growth rate with the upper corner control and essentially indistinguishable from the latter when $\mu/u_m \ll 1$, say $\mu/u_m = O(10^{-3})$ or smaller.

It appears that switch from upper to lower corner control takes place when there are sufficient cancerous mutants so that the population growth rate for the latter caught up with that for the upper corner. An exception to the second observation is when the

Table 4 Threshold for switching in two-step model for concave cases ($u_m = 1,\ a = 5,\ d_m = 1$)

μ	(a) $\sigma = 2$				(b) $\sigma = 10$			
	$x_1(T_s)/\mu$	$x_2(T_s)/\mu$	$x_2'(T_s)/\mu$		$x_1(T_s)/\mu$	$x_2(T_s)/\mu$	$x_2'(T_s)/\mu$	
			$u = 1$	$u = 0$			$u = 1$	$u = 0$
10^{-1}	0.6317	0.0778	0.347	0.344	0.6317	0.0156	0.695	0.688
10^{-2}	0.7260	0.0899	0.367	0.364	0.7322	0.0184	0.740	0.742
10^{-5}	0.7437	0.0931	0.372	0.373	0.7437	0.0186	0.744	0.745
10^{-7}	0.7437	0.0931	0.372	0.373	0.7437	0.0186	0.744	0.745

natural cancerous mutant growth rate is high (e.g., $a = 5$) and the target cancerous population is relatively small. In that case, the switch over may be sooner since, as noted previously in Sect. 5.3.2), the higher cancerous mutant growth rate with no mutation would more than make up for the shortfall from an earlier switch.

The observation that the switch should take place near the time determined by $[x_2']_{u=1} = [x_2']_{u=0}$ provides an estimate for T_s. From (3), we have

$$[x_2']_{u=1} = \frac{1}{\sigma}(\mu + u_m)x_1, \quad [x_2']_{u=0} = \frac{\mu}{\sigma}x_1 + x_2(a - x_0 - x_1).$$

Let T_s^* be the time of equality between the two growth rates at switch so that

$$\frac{u_m}{\sigma}x_1(T_s) = x_2(T_s)\left[a - x_0(T_s) - x_1(T_s)\right]. \tag{79}$$

If the switch point is taken to be at T_s^*, the relation (79) constitutes a nonlinear equation for T_s^*. With the various cell populations $\{x_k(T_s^*)\}$ known explicitly for both corner controls (see "Appendix") and continuous at the only switch point T_s^*, numerical solution can be found accurately by any of the available numerical software.

For $\mu \ll u_m$, a simple approximate determination of the switch time is possible. With $x_0(T_s^*) + x_1(T_s^*) \lesssim 1$ [see (85)], we may approximate the relation (79) by

$$x_2(T_s^*) = \frac{u_m}{\sigma\ (a-1)}x_1(T_s^*) \tag{80}$$

where we have for $\mu \ll u_m = 1$ [see (85) and (86)]

$$x_1(T_s^*) = \frac{2\mu}{u_m - \mu}\left[e^{-2\mu T_s^*} - e^{-(u_m+\mu)T_s^*}\right] = 2\mu\left[1 - e^{-T_s^*} + O(\mu)\right]$$
$$x_2(T_s^*) = \frac{2\mu}{\sigma}\left[T_s^* - 1 + e^{-T_s^*} + O(\mu)\right].$$

It follows that (80) becomes

$$T_s^* = \frac{a}{a-1}\left(1 - e^{-T_s^*}\right)\left[1 + O(\mu)\right]. \tag{81}$$

We summarize the development above in the following proposition:

Proposition 48 *With the optimal bang–bang control switches at the instant T_s^* when the cancerous mutant growth rate being indifferent to the choice of corner control (as suggested by the numerical solution for the optimal mutation rate), the switch point T_s^* is determined by (79) which simplifies to (81) up to terms of order $O(\mu/u_m)$. It follows that the switch point T_s^* does not depend on μ or σ for sufficiently small μ.*

The conclusions of the proposition are consistent with the numerical data of Tables 1, 2, 3 and 4 for the two-step model. Note that the conclusions do not apply to the one-step model since the evolution of the two relevant cell populations is no longer given by (85) and (86).

10 Summary and Concluding Remarks

10.1 Summary

Clinical data show that dysfunctional TSG is a prevalent cause of breast, colorectal and lung cancers (and others not so prevalently), it is important to gain some understanding of the TSG related mechanisms and processes favoring the promotion of these types of cancer. However, intrinsic differences between the biology of the activation of an oncogene and the loss of both copies of TSG render the successful method of analysis for the one-step model ineffective for the two-step model (see Sect. 3.2) and necessitate a considerably more intricate analysis in order to completely characterize the optimal mutation rates for the two-step model. This is accomplished herein first for a special class of death rate functions given in (7). More specifically, we have the following characterization of the optimal time-varying mutation rate:

- For $\alpha > 1$, the unique optimal mutation rate is shown to be a (one-switch) bang–bang control, starting with an upper corner control and ending in a lower corner control (see Proposition 26). An admissible interior control may exist for some interval(s) of time but is shown to maximize the Hamiltonian and therefore not optimal by the maximum principle.
- For $\alpha = 1$, the Hamiltonian is linear in the control and the stationary condition is independent of the control. For this case, it is shown (see Proposition 30) that (*i*) there is no singular solution for any time interval for the problem and (*ii*) the optimal control is also (one-switch) bang–bang, starting with an upper corner control and ending in a lower corner control.
- For $0 < \alpha < 1$, a unique monotone continuously decreasing interior control $u_i(t)$ exists for this case with $u_i(0) = 1$. The optimal control consists of the interior control for all t in $[0, T_0]$ with $\bar{u}(t) = u_i(t) > 0$ for $0 \le t < T_0$ and $\bar{u}(t) = 0$ for $T_0 \le t \le T$ if $T_0 < T$ (see Proposition 36).

The same characterization is then shown in Sect. 8 to apply to general twice continuously differentiable death rates with the properties stipulated in (6) and (5), designated as P_d^2 death rates. For concave P_d^2 death rates, the optimal control for fastest time to cancer is again bang–bang, similar to the special death rate (7) with $\alpha \ge 1$.

For strictly convex P_d^2 death rates, the results are somewhat more complicated than the special death rate (7) with $\alpha < 1$. Unlike the special case, the optimal control now may start with an upper corner control for a finite duration before transition continuously to the interior control at the instant $T_1 \leq T$. If $T_1 < T$, then $\bar{u}(t) = u_i(t)$ in the interval (T_1, T_0) for some $T_0 \leq T$. As in the case of (7), we have $\bar{u}(t) = 0$ for all t in $[T_0, T]$ if $T_0 < T$.

The qualitative characterization of the optimal program for the shortest time problem actually provides the needed information for computing the optimal solution. For the case of a bang–bang control, we have upper and lower bounds for the only switch point of the optimal mutation rate. They render a new iterative algorithm developed herein highly efficient as a replacement for the brute force iterative scheme used in Komarova et al. (2008) which was developed without the knowledge that the optimal control is bang–bang. We also obtain an upper bound for the terminal time which is helpful for validating the solution algorithm.

For the case of strictly convex P_d^2 death rates, we obtain an explicit upper bound on the terminal value of the interior control; it delimits the admissibility of the interior control adjacent to the terminal time. The information is needed as an appropriate solution algorithm for the problem necessarily depends on whether the interior control vanishes prior to the terminal time. The actual solution processes for both concave and convex death rates will be discussed in detail in Sanchez-Tapia (2015).

While the principal objective of our research is to understand how the competing effects of genetic instability may be orchestrated to favor carcinogenesis and to quantify this favoring process for the case of dysfunctional TSG, there are also other goals. These include the formulation of appropriate efficient theory-based algorithms for computing the actual optimal mutation rate for death rates of different convexities mentioned above. In addition, the results of Komarova and Wodarz (2004) has been extended to allow for noise that affects the optimal mutation rate. These items and more will be reported in future publications. Here, we have limited additional discussion to some insight into the biology that determines the switch time of the bang–bang control for nonconvex death rate cases gained from the numerical solutions of the problem as summarized in the previous section, highlighting a major difference between the one-step model and the two-step model. For dysfunctional TSG with all system parameter fixed, the switch time T_s is effectively the same for different target population size. The same is true for the oncogene case *only* when the natural growth rate of cancerous mutants is much larger than that of the normal cells. Another important observation is the biology that governs the switch time of the optimal bang–bang control: The switching takes place *not* sooner than the instant T_s^* when the cancerous mutant growth rate is indifferent to the choice of upper or lower bound of the mutation rate with T_s^* independent of the basic mutation rate μ (see Proposition 48).

10.2 Concluding Remarks

With considerable effort expended in the mathematical analysis and numerical computation of the optimal solution, it would seem reasonable to ask how well do the theoretical results compare with available empirical evidence and/or clinical data.

However, what we have determined from our idealized model is the optimal mutation rate for the fastest time to cancer (characterized by a target cancerous mutant population size) possible, not the time-varying mutation rate of any particular type of cancer. And as pointed out in the Introduction section, there are different kinds of mutations contributing to genetic stability in a biological host: CIN, MSI and telomeric abnormality, just to name a few. The frequencies of the different mutation rates are known to range from 10^(−7)/s to 0.1/s. At any instant in time, all can contribute to the progression of cancer in the same host with different temporal combinations giving different combined time-varying mutation rate histories. (For more thorough discussions, both experimental and theoretical, see Komarova and Wodarz 2004 as well as Wodarz and Komarova 2005, 2014) In addition, there are a number of genes known to contribute to CIN alone adding more rate variations in the progression toward cancer (see Cahill et al. 1999; Bardelli et al. 2001).

With all these factors (different genes, different abnormalities, different mutation types, etc.) contribute to each instant of a particular mutation rate time profile, even limiting to the case of dysfunctional TSG, the actual time-varying rate cannot be expected to be close to the optimal rate. An example of this expected discrepancy is the actual data for intestinal carcinoma in mice and human (Rudolph et al. 2001) and for breast cancer (Chin et al. 2004), both having a mutation rate first increases and then decreases in later stage. The optimal mutation rate, however, would start at the maximum allowable rate before eventually decrease as time progresses.

Given the expected differences between the optimal mutation rate for an idealized model and clinical data available, it is gratifying (and rather remarkable) that the order of magnitude of the optimal solution is still consistent with the rate of chromosome loss obtained by in vitro experiments using several CIN colon cancer cell lines (Lengauer et al. 1997) as previously observed in Komarova et al. (2008).

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Appendix

Cell Populations for Upper Corner Control

With the two corner controls playing a key role in the optimal solution, we note that the state equations admit an exact solution for these controls. For the upper corner control $u_1(t) = 1$, the state equations simplify to

$$\frac{\mathrm{d}x_0^{(1)}}{\mathrm{d}t} = -2\mu x_0^{(1)}, \qquad \frac{\mathrm{d}x_1^{(1)}}{\mathrm{d}t} = 2\mu x_0^{(1)} - (\mu + u_m)\, x_1^{(1)}, \quad \frac{\mathrm{d}x_2^{(1)}}{\mathrm{d}t} = \frac{u_m + \mu}{\sigma} x_1^{(1)}. \tag{82}$$

The following exact solutions for these uncoupled first-order state equations are immediate.

Lemma 49 *For $u(t) = u_1(t) \equiv 1$ and a general set of initial conditions $x_k^{(1)}(T_i) = x_k^{(i)} \geq 0,\ k = 0, 1, 2$, the exact solution of the three uncoupled first-order state Eq. (82) is*

$$x_0^{(1)} = x_0^{(i)} e^{-2\mu\tau}, \qquad x_1^{(1)} = \frac{2\mu x_0^{(i)}}{u_m - \mu}\left[e^{-2\mu\tau} - e^{-(\mu+u_m)\tau}\right] + x_1^{(i)} e^{-(\mu+u_m)\tau}, \tag{83}$$

$$\begin{aligned} x_2^{(1)} = x_2^{(i)} &+ \frac{x_1^{(i)}}{\sigma}\left\{1 - e^{-(u_m+\mu)\tau}\right\} \\ &+ \frac{x_0^{(i)}}{\sigma\,(u_m - \mu)}\left[(\mu + u_m)(1 - e^{-2\mu\tau}) - 2\mu(1 - e^{-(\mu+u_m)\tau})\right] \end{aligned} \tag{84}$$

with $\tau = t - T_i$ and a superscript "(1)" for upper corner control. The normalized mutated cell populations $x_1^{(1)}$ and $x_2^{(1)}$ are positive function of time for $\tau = t - T_i > 0$.

Remark 50 The concavity of $x_2^{(1)}(t)$ also follows from

$$\frac{\mathrm{d}^2 x_2^{(1)}}{\mathrm{d}t^2} = \frac{u_m + \mu}{\sigma}\frac{\mathrm{d}x_1^{(1)}}{\mathrm{d}t} = -\frac{(u_m + \mu)^2}{\sigma} x_1^{(1)} < 0.$$

Remark 51 For the interval adjacent to the initial time $t = T_i = 0$, the exact solutions (83) and (84) simplify by the known initial conditions to

$$x_0^{(1)} = e^{-2\mu t}, \quad x_1^{(1)} = \frac{2\mu}{u_m - \mu}\left[e^{-2\mu t} - e^{-(\mu+u_m)t}\right], \tag{85}$$

$$x_2^{(1)} = \frac{1}{\sigma}\left[1 - \frac{1}{(u_m - \mu)}\left\{(u_m + \mu)\, e^{-2\mu t} - 2\mu e^{-(\mu+u_m)t}\right\}\right]. \tag{86}$$

10.3 Cell Populations for Lower Corner Control

For the lower corner control $u_0(t) = 0$, the first two state Eqs. (1) and (2) simplify to

$$\frac{\mathrm{d}x_0^{(0)}}{\mathrm{d}t} = x_0^{(0)}\left(1 - 2\mu - x_0^{(0)} - x_1^{(0)}\right), \tag{87}$$

$$\frac{\mathrm{d}x_1^{(0)}}{\mathrm{d}t} = 2\mu x_0^{(0)} + x_1^{(0)}\left(1 - \mu - x_0^{(0)} - x_1^{(0)}\right), \tag{88}$$

They may be solved exactly (by Mathematica or Maple) allowing for the satisfaction of two initial conditions

$$x_0^{(0)}(T_s) = x_0^{(s)},\ x_1^{(0)}(T_s) = x_1^{(s)}. \tag{89}$$

Instead of writing down the exact solution, we need only the following simple bounds on $x_0^{(0)}$ and $x_1^{(0)}$ for our purposes:

$$-2\mu x_0^{(0)} \le \frac{\mathrm{d}x_0^{(0)}}{\mathrm{d}t} \le x_0^{(0)}\left(1-2\mu-x_0^{(0)}\right), \tag{90}$$

$$2\mu x_0^{(0)} - \mu x_1^{(0)} \le \frac{\mathrm{d}x_1^{(0)}}{\mathrm{d}t} \le 2\mu x_0^{(0)} + x_1^{(0)}\left(1-\mu-x_1^{(0)}\right), \tag{91}$$

given the nonnegativity of the three cell population and $0 \le x_0^{(0)} + x_1^{(0)} \le 1$ by Lemma 4. It is possible to simplify the upper bound for $dx_1^{(0)}/dt$ further by replacing the right-hand side of (91) with $2\mu x_0^{(0)} + x_1^{(0)}(1-\mu)$. We refrain from doing so to get sharper results.

Lemma 52

$$x_0^{(s)} e^{-2\mu\tau} \le x_0^{(0)} \le 1-2\mu \tag{92}$$

$$x_1^{(s)} + 2x_0^{(s)}\left\{e^{-\mu\tau} - e^{-2\mu\tau}\right\} \le x_1^{(0)} \le x_1^{(s)} \tag{93}$$

where

$$\tau = t - T_s, \quad x_k^{(s)} = x_k^{(0)}(t = T_s) \tag{94}$$

Proof The various inequalities are straightforward consequences of the inequalities (90) and (91) along with the switch conditions (89): In particular, we have

$$x_0^{(0)} \le \frac{(1-2\mu)C_0 e^{(1-2\mu)\tau}}{1+C_0 e^{(1-2\mu)\tau}} \le 1-2\mu, \quad x_1^{(0)} \le x_1^{(p)} - \frac{C_1\gamma e^{-\gamma\tau}}{1+C_1 e^{-\gamma)\tau}} \le x_1^{(p)} \lesssim 1+\mu, \tag{95}$$

where

$$C_0 = \frac{x_0^{(s)}}{1-2\mu-x_0^{(s)}} > 0, \quad C_1 = \frac{x_1^{(p)} - x_1^{(s)}}{x_1^{(s)} + x_1^{(p)} + \mu - 1} > 0, \quad \gamma = 2x_1^{(p)} + \mu - 1 > 0,$$

and

$$2x_1^{(p)} = (1-\mu) + \sqrt{1+6\mu-15\mu^2} = 2\left\{1+\mu+O(\mu^2)\right\} \lesssim 2(1+\mu), \tag{96}$$

keeping in mind $x_1^{(s)} < 1 < x_1^{(p)}$. □

Remark 53 We note that the upper bound for $x_1^{(0)}$ is unrealistic since $x_0^{(0)} + x_1^{(0)} < 1$ (by Lemma 1) and $x_0^{(0)} \ge 0$. However, $x_1^{(p)} \lesssim 1+\mu$ is only an (overly conservative) upper bound and does not contradict other more realistic results for cell populations (such as Lemma 1).

For $u = 0$, the third state Eq. (3) takes the form

$$\frac{\mathrm{d}x_2^{(0)}}{\mathrm{d}t} = \frac{\mu}{\sigma} x_1^{(0)} + x_2^{(0)}(a - x_0^{(0)} - x_1^{(0)}). \tag{97}$$

which is a linear first-order ODE for the only unknown $x_2^{(0)}$ and can be solved with the help of an integrating factor. Even without the explicit solution, we see from (97) that $x_2(t)$ increases without bound as $t \to \infty$ since $a \gg 1$.

More useful for our analysis is the following upper and lower bound for $x_2^{(0)}$:

Lemma 54 *The following inequalities hold for $u = 0$ and $x_2^{(0)}(t = T_\mathrm{s}) = x_2^{(s)}$:*

$$x_2^{(0)}(t) \geq x_2^{(s)} e^{(a-1)\tau}, \quad \tau = t - T_\mathrm{s}. \tag{98}$$

Proof With $0 \leq x_0^{(0)} + x_1^{(0)} \leq 1$ by Lemma 1, the ODE (97) implies

$$\frac{\mathrm{d}x_2^{(0)}}{\mathrm{d}t} \geq \frac{\mu}{\sigma} x_1^{(0)} + x_2^{(0)}(a - 1) \geq x_2^{(0)}(a - 1).$$

from which we get

$$x_2^{(0)}(\tau) \geq x_2^{(s)} e^{(a-1)\tau}.$$

□

References

Artandi SE, DePinho RA (2000) A critical role for telomeres in suppressing and facilitating carcinogenesis. Curr Opin Genet Dev 10(1):39–46

Ashworth A, Lord CJ, Reis-Filho JS (2011) Genetic interactions in cancer progression and treatment. Cell 145:30–38

Bailey SM, Murnane JP (2006) Telomeres, chromosome instability and cancer. Nucleic Acids Res 34(8):2408–2417

Bardelli A et al (2001) Carcinogen-specific induction of genetic instability. PNAS 98:5770–5575

Bartek J (2011) DNA damage response, genetic instability and cancer: from mechanistic insights to personalized treatment. Mol Oncol 5(4):303–307

Bartkova J et al (2005) DNA damage response as a candidate anti-cancer barrier in early human tumorigenesis. Nature 434(7035):864–870

Branzei D, Foiani M (2010) Maintaining genome stability at the replication fork. Nat Rev Mol Cell Biol 11:208–219

Breivik J (2005) The evolutionary origin of genetic instability in cancer development. Semin Cancer Biol 15(1):51–60

Bristow RG, Hill RP (2008) Hypoxia and metabolism: hypoxia, DNA repair and genetic instability. Nat Rev Cancer 8(3):180–192

Bryson A, Ho YC (1969) Applied optimal control. Ginn and Company, Waltham, MA

Cahill DP et al (1999) Genetic instability and Darwinian selection in tumours. Trends Cell Biol 9(12):57–60

Campbell CD, Chong JX, Malig M et al (2012) Estimating the human mutation rate using autozygosity in a founder population. Nat Genet 44(11):1277–1281

Corcos D (2012) Unbalanced replication as a major source of genetic instability in cancer cells. AJBR 2(3):160–169

Chin K et al (2004) In situ analyses of genome instability in breast cancer. Nat Genet 36(9):984–988
Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A (2009) Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis 30(7):1073–1081
Czernilofsky AP, Levinson AD, Varmus HE, Bishop JM, Tischer E, Goodman HM (1980) Nucleotide sequence of an avian sarcoma virus oncogene (src) and proposed amino acid sequence for gene product. Nature 287:198–203
de Pillis LG, Radunskaya AE (2003) The dynamics of an optimally controlled tumor model: a case study. Math Comput Model 37(11):1221–1244
de Pillis LG et al (2007) Chemotherapy for tumors: an analysis of the dynamics and a study of quadratic and linear optimal controls. Math Biosci 209:291–315
dePillis LG et al (2007) Seeking bang–bang solutions of mixed immuno-chemotherapy of tumors. Elec EJDE 171:1–24
Deng C-X (2006) BRCA1: cell cycle checkpoint, genetic instability, DNA damage response and cancer evolution. Nucleic Acids Res 34(5):1416–1426
Gelfand IM, Fomin SV (1963) Calculus of variations. Prentice Hall, Englewood Cliffs NJ
Gill P, Murrray W, Saunders MA (2005) SNOPT: an SQP algorithm for large-scale constrained optimization problem. SIAM Rev 47:99–131
Gonzalez-Suarez E et al (2000) Telomerase-deficient mice with short telomeres are resistant to skin tumorigenesis. Nat Genet 26(1):114–117
Gorgoulis VG et al (2005) Activation of the DNA damage checkpoint and genomic instability in human precancerous lesions. Nature 434(7035):907–913
Grady WM, Carethers JM (2008) Genomic and epigenetic instability in colorectal cancer pathogenesis. Gastroenterology 135(4):1079–1099
Kinzler K, Vogelstein B (2002) The genetic basis of human cancer, 2nd edn. The McGraw-Hill Companies Inc, New York
Kirschner D, Lenhart S, Serbin S (1997) Optimal control of the chemotherapy of HIV. J Math Biol 35(7):775–792
Knudson AG (1971) Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci 68(4):820–823
Komarova NL et al (2002) Dynamics of genetic instability in sporadic and familial colorectal cancer. Cancer Biol Ther 1(6):685–692
Komarova NL, Sengupta A, Nowak MA (2003) Mutation-selection networks of cancer initiation: tumor suppressor genes and chromosomal instability. J Theor Biol 223(4):433–450
Komarova NL, Wodarz D (2004) The optimal rate of chromosome loss for the inactivation of tumor suppressor genes in cancer. Proc Natl Acad Sci USA 101(18):7017–7021
Komarova N (2004) Does cancer solve an optimization problem? Cell Cycle 3(7):840–844
Komarova NL, Sadovsky A, Wan FYM (2008) Selective pressures for and against genetic instability in cancer: a time-dependent problem. J R Soc Interface 5:105–121
Ledzewicz U et al (2013) Optimal controls for a mathematical model of tumor-immune interactions under targeted chemotherapy with immune boost. DCDS-B 18(4):1013–1051
Lengauer C, Kinzler KW, Vogelstein B (1997) Genetic instability in colorectal cancers. Nature 386(6625):623–627
Lengauer C, Kinzler KW, Vogelstein B (1998) Genetic instabilities in human cancers. Nature 396(6712):643–649
Lenhart S, Workman JT (2007) Optimal control applied to biological models. Chapman and Hall/CRC, London
Loeb LA, Springgate CF, Battula N (1974) Errors in DNA replication as a basis for malignant changes. Cancer Res 34:2311–2321
Martin GS (2001) The hunting of the Src. Nat Rev Mol Cell Biol 2:467–475
Maslov AY, Vijg J (2009) Genome instability, cancer and aging. Biochimica et Biophysica Acta (BBA) General Subjects 1790(10):963–969
Michor F et al (2005) Can chromosomal instability initiate tumorigenesis? Semin Cancer Biol 15(1):43–49
Negrini S, Gorgoulis VG, Halazonetis TD (2010) Genomic instability—an evolving hallmark of cancer. Nat Rev Mol Cell Biol 11:220–228
Nowak MA, Michor F, Iwasa Y (2006) Genetic instability and clonal expansion. J Theor Biol 241(1):26–32
Nouspikel T (2013) Genetic instability in human embryonic stem cells: prospects and caveats. Future Oncol 9(6):867–877

Perucho M (1996) Cancer of the microsatellite mutator phenotype. Biol Chem 377:675–684
Pikor L, Thu K, Vucic E, Lam W (2013) The detection and implication of genome instability in cancer. Cancer Metastasis Rev 32(3–4):341–352
Pontryagin LS et al (1962) The mathematical theory of optimal control processes. Interscience Publishers, New York
Rudolph KL et al (2001) Telomere dysfunction and evolution of intestinal carcinoma in mice and humans. Nat Genet 28(2):155–159
Samper E, Flores JM, Blasco MA (2001) Restoration of telomerase activity rescues chromosomal instability and premature aging in $\text{Terc}^{-/-}$ mice with short telomeres. EMBO Rep 2(9):800–807
Sanchez-Tapia C (2015) Ph.D. Dissertation, Mathematics, UC Irvine
Shih IM et al (2001) Evidence that genetic instability occurs at an early stage of colorectal tumorigenesis. Cancer Res 61(3):818–822
Smith LE et al (2003) Radiation-induced genomic instability: radiation quality and dose response. Health Phys 85(1):23–29
Swan GW (1990) Role of optimal control theory in cancer chemotherapy. Math Biosci 101(2):237–284
Wan FYM (1995) Introduction to the calculus of variations and its applications. Chapman and Hall, New York
Wan FYM, Sadovsky A, Komarova NL (2010) Genetic instability in cancer: an optimal control problem. Stud Appl Math 125(1):1–10
Wodarz D, Komarova NL (2005) Computational biology of cancer: lecture notes and mathematical modeling. World Scientific, Singapore
Wodarz D, Komarova NL (2014) Dynamics of cancer: mathematical foundations of oncology. World Scientific, Singapore