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RESONANCE PHENOMENA IN CELL POPULATION CHEMOTHERAPY MODELS

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1. Introduction. Mathematical models of cell population dynamics offer a means to predict the effectiveness of chemotherapy treatments. The basic ideas of such models are to view chemotherapy as a loss function for both normal and tumor cell populations, and to design optimal treatment regimens in consideration of the parameters that distinguish normal and tumor cells.

In this paper we will focus upon the qualitative analysis of periodic chemotherapy applications. For this purpose we use an age- and size-structured model of cell population dynamics with a time periodic loss function. The normal and tumor cell populations have the same model but with different parameters. The main difference of the two populations is the longer mean cycle length of tumor cells. This difference results in a remarkable resonance effect in the presence of periodic phase-specific cell loss. A marked preferential advantage for the normal cell population occurs when the treatment period is close to the mean cycle length of normal cells. This resonance effect is apparent through a wide range of age- and size-dependent parameter values. It is evident whenever a phase-sensitive loss is impressed upon two age-structured proliferating cell populations with distinct mean division-age frequencies. This resonance phenomenon was discovered by Dibrov et al. [**13**], who studied it from a numerical point of view with age-structured models of cell population dynamics. A similar selective synchrony effect was studied by Rotenberg [**31**]. In this paper we will present examples to demonstrate that resonance phenomena are present in more refined cell population models. The general age- and size-structured model we use includes the well-known transition probability, size control, and inherited properties models of cell population dynamics. It also allows for the asymmetric division of mother cells, which some researchers believe to be a primary explanation of cell cycle variability (M. Kimmel et al. [**22**]). The use of a size-structure variable also allows a more accurate

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specification of the phase of the cell cycle sensitive to drug toxicity.

The organization of this paper is as follows: In §2 we will present a general age- and size-structured model of cell population dynamics. In §3 we will discuss the exponential growth constants that determine the behavior of the cell populations in the presence of periodic loss. In §4 we will illustrate with numerical examples resonance phenomena and optimal periodic treatment scheduling.

2. An age-size structured model of cell population dynamics. It is generally recognized that individual cells exhibit considerable variability as they transit through the cell cycle. Structured models of cell population dynamics account for this variability in age, mass, volume, RNA content, and other physical measurable properties. Such models, in various formulations, have been used extensively in the recent literature of cell population dynamics. These models originated in Bell and Anderson [**8**], Scherbaum and Rasch [**34**], Sinko and Streifer [**35**], Trucco [**39**], and Von Foerster [**42**]. Review surveys of these models are found in Alberghina et al. [**1, 2**], Bertuzzi and Gandolfi [**9**], Bertuzzi et al. [**10**], Eisen [**16**], Metz and Diekmann [**28**], Rubinow [**32**], Webb [**48**], and White [**50**]. Operator-theoretic analyses of these models are given in Arendt et al. [**4**], Arino and Kimmel [**5**], Diekmann et al. [**14**], Diekmann et al. [**15**], Greiner [**17**], Gyllenberg and Heijmans [**19**], Gyllenberg and Webb [**20**], Heijmans [**21**], Metz and Diekmann [**28**], Tucker and Zimmerman [**40**], Webb [**44, 45, 46**], and Webb and Grabosch [**49**].

A general model of age-size structured cell population dynamics is discussed in Webb [**47**]. The nonautonomous version of this model has the formulation

(1)
$$N_t(a,x,t) + N_a(a,x,t) + (g(x)N(a,x,t))_x = -b(a,x,t)N(a,x,t) - d(a,x,t)N(a,x,t), \quad a \geq 0,\ x \geq 0,\ t \geq t_0,$$

(2)
$$N(0,x,t) = 2\int_0^\infty \int_0^\infty k(x,y)b(a,y,t)N(a,y,t)\,dy\,da, \quad x \geq 0,\ t \geq t_0$$

(3)
$$N(a,x,t_0) = \psi(a,x), \qquad a \geq 0,\ x \geq 0$$

In this formulation $\int_{a_1}^{a_2}\int_{x_1}^{x_2} N(a,x,t)\,dx\,da$ is the total population of cells with age between a_1 and a_2 and size between x_1 and x_2 at time t, and ψ is the initial age-size distribution of cells at time $t = t_0$.

The processes of individual cells are governed by the *growth function* g, *division function* k, *transit function* f, and *mortality function* h. These functions have the following interpretations:

The age of a cell with size x that had birth size y is $\int_y^x du/g(u)$. The size of a cell at age a with birth size y is $S(a,y)$, and the birth size of a cell with size x at age a is $s(a,x)$. The function S satisfies $S_a(a,y) = g(S(a,y))$, $S(0,y) = y$, and the function s satisfies $s_a(a,x) = -g(s(a,x))$, $s(0,x) = x$. Notice that $S(a,y) = x$ if and only if $y = s(a,x)$ if and only if $a = \int_y^x du/g(u)$. The case that $g(x) :\equiv c$ is called *linear growth* of individual cells, and the case that $g(x) :\equiv cx$ is called *exponential growth* of individual cells.

The probability that a daughter cell born from a mother cell of size x has birth size between y_1 and y_2 is $\int_{y_1}^{y_2} k(y,x)\,dy$. The function k satisfies $k(y,x) = 0$ if $y > x$, $\int_0^\infty k(y,x)\,dy = 1$, $x \geq 0$, and $k(y,x) = k(x-y,x)$, $0 \leq y \leq x$. If division is *symmetric* with both daughter cells of equal size, then $k(y,x) = \delta(y - x/2)$, where $\delta(\cdot)$ is the *dirac delta function.*

The probability that a cell with birth size y at time t survives to division at age between a_1 and a_2 is $\int_{a_1}^{a_2} f(a,y,t)\,da$. The probability that a cell born with age y at time t does not divide before age a is $\alpha(a,y,t) :\equiv \int_a^\infty f(\hat{a},y,t)\,d\hat{a}$. The *per capita rate per unit of time at time t of dividing cells of age a and size x* is $b(a,x,t) :\equiv f(a,s(a,x),t-a)/\alpha(a,s(a,x),t-a)$. The function α satisfies $\alpha(a,y,t) = \exp[-\int_0^a b(\hat{a},S(\hat{a},y),t+\hat{a})\,d\hat{a}]$ and $\alpha(0,y,t) = 1$.

The probability that a cell born with birth size y at time t dies between ages a_1 and a_2 is $\int_{a_1}^{a_2} h(a,y,t)\,da$. The probability that a cell born with size y at time t does not die before age a is $\mu(a,y,t) :\equiv \int_a^\infty h(\hat{a},y,t)\,d\hat{a}$. The *per capita death rate per unit time at time t of cells of age a and size x* is $d(a,x,t) :\equiv h(a,s(a,x),t-a)/\mu(a,s(a,x),t-a)$. The function μ satisfies $\mu(a,y,t) = \exp[-\int_0^a d(\hat{a},S(\hat{a},y),t+\hat{a})\,d\hat{a}]$ and $\mu(0,y,t) = 1$.

The use of both age- and size-structure variables in the formulation (1)–(3) incorporates such features as transition probabilities, size con-

trols, and inherited properties. This formulation includes standard age only and size only models, as well as the RNA unequal division model of Kimmel et al. [**22**] and the stochastic activator synthesis model of Alt and Tyson [**3**]. The importance of asymmetric division of mother cells into two daughter cells of unequal size is claimed in Arino and Kimmel [**5**], Gyllenberg [**18**], and Kimmel et al. [**22**].

In Webb [**47**] it is shown that the hyperbolic partial differential equation formulation (1)–(3) is equivalent to the functional equation formulation

$$D(x,t) = 2\int_0^\infty \int_0^\infty k(s(a,x),y)D(y,t-a)\frac{g(s(a,x))}{g(x)}$$

$$f(a,s(a,x),t-a)\mu(a,s(a,x),t-a)\,dy\,da, \quad x \geq 0,\ t \geq t_0 \tag{4}$$

$$D(x,t) = \psi(x,t), \quad x \geq 0,\ t < t_0 \tag{5}$$

In this formulation the number of dividing cells per unit time at time t with size between x_1 and x_2 is $\int_{x_1}^{x_2} D(x,t)\,dx$. The history of dividing cells before the initial time $t = t_0$ is given by ψ.

The *flux* $D(x,t)$ *of dividing cells at time* t satisfies

$$D(x,t) = \int_0^\infty b(a,x,t)N(a,x,t)\,da, \quad x \geq 0,\ t \geq t_0. \tag{6}$$

The number of cells being born per unit time at time t with size between x_1 and x_2 is $\int_{x_1}^{x_2} B(x,t)\,dx$. The *flux* $B(x,t)$ *of cells born at time* t satisfies

$$B(x,t) = 2\int_0^\infty k(x,u)D(u,t)\,du, \quad x \geq 0,\ -\infty < t < \infty \tag{7}$$

In the case of *symmetric division*,

$$B(x,t) = 4D(2x,t), \quad x \geq 0,\ -\infty < t < \infty. \tag{8}$$

The age-size density $N(a,x,t)$ satisfies

$$N(a,x,t) = B(s(a,x),t-a)\frac{g(s(a,x))}{g(x)}$$
$$\alpha(a,s(a,x),t-a)\mu(a,s(a,x),t-a), \quad a \geq 0,\ s \geq 0,\ t \geq t_0, \tag{9}$$

and, in the case of *symmetric division*,

$$N(a,x,t) = 4D(2s(a,x), t-a)\frac{g(s(a,x))}{g(x)} \tag{10}$$
$$\alpha(a,s(a,x),t-a)\mu(a,s(a,x),t-a), \quad a \geq 0,\ x \geq 0,\ t \geq t_0.$$

3. The exponential growth constant. In the case that $b(a,x)$ and $d(a,x)$ are independent of time, the solutions of (1)–(3) give rise to a *strongly continuous semigroup of bounded linear operators* $T(t), t \geq t_0 :\equiv 0$ given by the formula $T(t)\psi = N(\cdot,\cdot,t)$. This semigroup customarily exhibits *asynchronous exponential growth* in the sense that there exists a constant λ (the *exponential intrinsic growth constant*) and a distribution ϕ (the *exponential steady state*) such that

$$\lim_{t\to\infty} e^{-\lambda t}T(t)\psi = c\phi, \tag{11}$$

where c is a constant that depends only on ψ. In this situation, λ is the dominant real eigenvalue of the *infinitesimal generator* A of $T(t)$, $t \geq 0$. These ideas have been exploited for various structured population models in Arendt et al. [**4**], Arino and Kimmel [**5**], Diekmann et al. [**14**], Diekmann et al. [**15**], Greiner [**17**], Gyllenberg and Heijmans [**19**], Gyllenberg and Webb [**20**], Metz and Diekmann [**28**], Tucker and Zimmerman [**40**], Von Foerster [**42**], Webb [**45, 46**, and Webb and Grabosch [**49**].

In the case that $b(a,x,t)$ and $d(a,x,t)$ depend on time, the solutions of (1)–(3) give rise to a *strongly continuous evolution operator* $\mathcal{U}(t,t_0)$, $t \geq t_0 \geq 0$, given by the formula $\mathcal{U}(t,t_0)\psi = N(\cdot,\cdot,t)$. In our discussion here we consider the case that $b(a,x)$ is independent of time and $d(a,x,t)$ is periodic in time with period p. This model corresponds to a cell population undergoing periodic chemotherapy. In this situation the evolution operator typically exhibits an asymptotic behavior similar to (11). Again, there is a constant λ (the *exponential growth constant*) such that, as $t \to \infty$,

$$e^{-\lambda t}\mathcal{U}(t,0)\psi - c\phi(t) = e^{-\epsilon t}\mathcal{O}(1), \tag{12}$$

for some $\epsilon > 0$ where c is a constant that depends only on ψ and $\phi(t)$ is periodic in t with period p. The (period-dependent) *exponential growth*

constant λ has the property that $e^{\lambda p}$ is the dominant real eigenvalue of the operator $\mathcal{U}(p,0)$:

$$\mathcal{U}(p,0)\psi = e^{\lambda p}\psi, \quad \psi \neq 0, \tag{13}$$

$$\phi(t) :\equiv e^{-\lambda t}\mathcal{U}(t,0)\psi, \quad t \geq 0. \tag{14}$$

An analysis of this problem is provided by Diekmann et al. [**15**] for a size-structured cell population model. For the chemotherapy interpretation of this model, the *exponential growth constant* λ determines the growth ($\lambda > 0$) or decay ($\lambda < 0$) of the populations and, hence, the effectiveness of the treatment schedule.

For computational purposes it is useful to have an alternate formulation of the eigenvalue problem (13):

THEOREM . *For each* $p > 0$, $\mathcal{U}(p,0)\psi = e^{\lambda p}\psi$ *if and only if*

$$\psi(a,x) = 2\int_0^\infty \int_0^\infty k(s(a,x),u)\psi(a+\hat{a}, S(a,u))q(a,x,u,\hat{a})\, d\hat{a}\, du, \tag{15}$$
$$0 \leq a \leq p, \ x \geq 0$$

$$\psi(a+p,x) = e^{-\lambda p}\psi(a, s(p,x))r(a,x), \quad a \geq 0, \ x \geq 0, \tag{16}$$

where

$$\begin{aligned} q(a,x,u,\hat{a}) :=& \frac{f(\hat{a}, s(\hat{a},u))g(S(a,u))\mu(\hat{a}, s(\hat{a},u), p-a-\hat{a})}{g(u)\alpha(a+\hat{a}, s(\hat{a},u))\mu(a+\hat{a}, s(\hat{a},u), p-a-\hat{a})} \\ &\times \frac{g(s(a,x))\alpha(a, s(a,x))\mu(a, s(a,x), p-a)}{g(x)} \end{aligned} \tag{17}$$

$$r(a,x) := \frac{g(s(p,x))\alpha(a+p, s(a+p,x))\mu(a+p, s(a+p,x), -a)}{g(x)\alpha(a, s(a+p,x))\mu(a, s(a+p,x), -a)}. \tag{18}$$

PROOF. Let ψ satisfy (13). Then $N(a,x,p) = e^{\lambda p}\psi(a,x)$, and (9) implies

$$e^{\lambda p}\psi(a,x) = B(s(a,x), p-a)\frac{g(s(a,x))}{g(x)}\alpha(a, s(a,x))\mu(a, s(a,x), p-a), \tag{19}$$
$$a \geq 0, \ x \geq 0.$$

Let $z = s(a,x)$, $t = p - a$ so that $x = S(a,z) = S(p-t,z)$ and (19) implies

(20)
$$B(z,t) = \frac{e^{\lambda p}\psi(p-t,S(p-t,z))g(S(p-t,z))}{g(z)\alpha(p-t,z)\mu(p-t,z,t)}, \quad z \geq 0,\ -\infty < t \leq p.$$

From (6), (7), and (9), we obtain

(21)
$$\begin{aligned} B(\hat{x},\hat{t}) &= 2\int_0^\infty \int_0^\infty k(\hat{x},u)b(\hat{a},u)N(\hat{a},u,\hat{t})\,d\hat{a}\,du \\ &= 2\int_0^\infty \int_0^\infty k(\hat{x},u)b(\hat{a},u)B(s(\hat{a},u),\hat{t}-\hat{a})\frac{g(s(\hat{a},u))}{g(u)} \\ &\qquad \cdot \alpha(\hat{a},s(\hat{a},u))\mu(\hat{a},s(\hat{a},u),\hat{t}-\hat{a})\,d\hat{a}\,du \\ &= 2\int_0^\infty \int_0^\infty k(\hat{x},u)B(s(\hat{a},u),\hat{t}-\hat{a})\frac{g(s(\hat{a},u))}{g(u)} \\ &\qquad \cdot f(\hat{a},s(\hat{a},u))\mu(\hat{a},s(\hat{a},u),\hat{t}-\hat{a})\,d\hat{a}\,du, \\ &\qquad \hat{x} \geq 0,\ \hat{t} \geq 0 \end{aligned}$$

Set $\hat{x} = s(a,x), \hat{t} = p - a$; (19) and (21) imply

(22)
$$\begin{aligned} \psi(a,x) &= e^{-\lambda p}B(\hat{x},\hat{t})\frac{g(s(a,x))}{g(x)}\alpha(a,s(a,x))\mu(a,s(a,x),p-a) \\ &= 2e^{-\lambda p}\int_0^\infty \int_0^\infty k(\hat{x},u)B(s(\hat{a},u),p-a-\hat{a})\frac{g(s(\hat{a},u))}{g(u)} \\ &\qquad \cdot f(\hat{a},s(\hat{a},u))\mu(\hat{a},s(\hat{a},u),p-a-\hat{a})\,d\hat{a}\,du \\ &\qquad \cdot \frac{g(s(\hat{a},x))}{g(x)}\alpha(s(a,x))\mu(a,s(a,x),p-a), \\ &\qquad 0 \leq a \leq p,\ x \geq 0. \end{aligned}$$

Set $z = s(\hat{a},u), t = p - a - \hat{a}$ so that $S(p-t,z) = S(a+\hat{a},s(\hat{a},u)) = S(a,u)$ and (20) and (22) imply (15).

Next, $N(a,x,0) = \psi(a,x)$, and (9) implies

(23)
$$\psi(a,x) = B(s(a,x),-a)\frac{g(s(a,x))}{g(x)}\alpha(a,s(a,x))\mu(a,s(a,x),-a),$$
$$a \geq 0,\ x \geq 0.$$

Set $z = s(a,x), t = -a$ so that $S(a+p,z) = S(a+p,s(a,x)) = S(p,x)$ and (20) and (23) imply

(24)
$$\psi(a,x) = \frac{e^{\lambda p}\psi(a+p,S(p,x))g(S(p,x))\alpha(a,s(a,x))\mu(a,s(a,x),-a)}{\alpha(a+p,s(a,x))\mu(a+p,s(a,x),-a)g(x)},$$

$$a \geq 0,\ x \geq 0,$$

which implies (16).

Similar calculations show that (15) and (16) imply $N(a,x,p) = e^{\lambda p}\psi(a,x)$. □

4. Periodic chemotherapy regimens and resonance. A number of researchers have treated mathematical modelling of chemotherapy, including Aroesty et al. [**6**], Aroesty et al. [**7**], Bertuzzi et al. [**10**], Chuang and Lloyd [**11**], Dibrov et al. [**12**], Dibrov et al. [**13**], Eisen [**16**], Lincoln et al. [**26**], Nicolini et al. [**29**], Rigney [**30**], Rubinow and Lebowitz [**33**], Swan [**36, 37**], Tannock [**38**], Wille and Scott [**51**], Zietz [**52**], and Zietz and Nicolini [**53**]. The objective of these studies is to exploit the differences between normal and tumor cell populations. One difference that occurs frequently is that tumor cells have longer mean cycle times. For periodic treatment protocols the *exponential growth constant* λ (as in (12)) determines the asymptotic behavior of solutions of both normal and malignant models. Since both normal and malignant cells are destroyed by the cytotoxic agent, the goal is to optimize the period of treatment in terms of highest normal cell population growth and lowest malignant cell population growth.

Numerical studies of periodic chemotherapy treatment have been carried out by Dibrov et al. [**13**] for certain age-structured cell population models. The results in Dibrov et al. [**13**] are designed with parameters corresponding to leukemia chemotherapy. In Dibrov et al. [**13**] the numerical studies revealed the resonance phenomenon that has important implications for periodic treatment scheduling. The cytotoxic agent is assumed to act in a specific phase of the cell cycle for both populations (usually the S-phase). Leukemic cells typically have much longer mean cycle times than normal cells (hemopoietic stem cells). The studies in Dibrov et al. [**13**] demonstrate that, because of resonance, the optimal period of treatment is approximately equal to the mean cycle

length of normal cells (usually somewhat less, since the typical gamma distribution of dividing cells is left-skewed about the mean).

The explanation of this resonance phenomenon is discussed in Dibrov et al. [**13**]. The intuitive idea is that, with the first application of the periodic treatment, there is a loss of both normal and tumor cells by the phase-specific cytotoxic agent. If the period of treatment is close to the mean cycle length of normal cells, then fewer normal cells are destroyed with successive applications than would otherwise be destroyed for some other choice of the period. The reason is that the population of normal cells in the sensitive phase becomes emptier with successive applications when the period of application approximates normal cell mean cycle length. For the tumor cell population this preferential effect does not occur since its mean cycle length is much larger. An analogy due to Rotenberg [**31**] is very useful in understanding this resonance phenomenon. Imagine a circular turntable with grains of sand spread on it. The turntable revolves with fixed period p. The grains of sand correspond to normal cells and a single revolution corresponds to the mean cycle time of normal cells. As the turntable revolves, an arm periodically reaches down and removes some grains of sand through a sector of the turntable. This removal corresponds to the loss of cells due to a phase-specific treatment. After the first removal there is an empty slice on the turntable. If the arm falls with the same period p, then it will fall back on the already empty sector with successive applications. This choice of the period minimizes the loss of normal cells. Now imagine a second turntable corresponding to the population of tumor cells revolving with a different period p'. If the arm falls upon it with period p, then the preferential effect does not occur and the tumor cells suffer a greater loss.

In the examples below, this resonance phenomenon is illustrated for age-size structured models of cell population dynamics. In these examples it is assumed that the *growth function* is $g(x) = 1$ (*linear growth*), the *division function* is $k(y, x) = \delta(y - x/2)$ (*symmetric division*), and the *transit function* $f(a, y)$ is

$$f(a,y) = \begin{cases} 0, & \text{if } 0 \le a \le \tau(y), \\ c^2(a-\tau(y))\exp(-c(a-\tau(y))), & \text{if } \tau(y) < a. \end{cases} \tag{25}$$

This choice of the *transit function* yields a so-called *transition probability model*. The cell cycle is divided into an A-phase and a B-phase.

Each cell passes through on A-phase of variable duration governed by a transition probability for two random events that occur in any order with probability c per unit time (the choice of two events is made for simplicity). Each cell must also pass through a B-phase of fixed duration $\tau(y)$ dependent upon its birth size y. The resulting transit function $f(a, y)$ is a displaced gamma distribution, which gives a typical experimentally observed distribution of cell cycle lengths.

The *per capita loss rate* $d(a, x, t)$ *of cells of age* a *and size* x *at time* t is 0 for $t < 0$, is defined periodically in t with period p for $t \geq 0$ and, for $0 \leq t \leq p$, is

$$d(a,x,t) = \begin{cases} 0, & \text{if } 0 \leq t < p^*, \\ 1, & \text{if } p^* \leq t \leq p \text{ and } a \geq a_1 \text{ and } x \geq x_1, \\ 0, & \text{if } p^* \leq t \leq p \text{ and } a < a_1 \text{ or } x < x_1. \end{cases} \tag{26}$$

This loss function corresponds to a periodic on-off destruction of cells. The parameter p^* controls the intensity of the treatment. The parameters a_1 and x_1 control the phase sensitive to the cytotoxic agent.

In the examples below, the growth constants λ_N and λ_T (as in (12)) are computed for the normal and tumor cell populations, respectively, as a function of the period p. For each period p, the value of the intensity parameter $p^* = p^*(p)$ is determined so that $\lambda_N = 0$. The corresponding value of λ_T is then computed for this value of p^*. For these examples λ_T is graphed as a function of p for the particular choices of the *transit functions* f and the *loss functions* d.

EXAMPLE 1. In this example there is no size dependence. The *transit function* $f_N(a)$ for normal cells is as in (25) with $c = .5$ and $\tau(y) = 4.0$, and the *transit function* $f_T(a)$ for tumor cells is as (25) with $c = .16667$ and $\tau(y) = 12.0$. These gamma probability distribution functions for the normal and tumor cell populations (without the loss function) yield mean cell cycle length $M_N = 8$ hours and $M_T = 24$ hours, respectively. The coefficient of cell cycle length variation is $V_N = V_T = .35355$ for both. In the absence of cell loss, the intrinsic growth constants (as in (11)) for the normal and tumor cell populations are $\lambda_N = .0903$ and $\lambda_T = .0301$, respectively (see Webb [**48**]). The *loss function* $d_N(a, t)$ for normal cells is as in (26) with $a_1 = 4.0$, $x_1 = 0$, and the *loss function* $d_T(a, t)$ for tumor cells is as in (26) with $a_1 = 12.0$, $x_1 = 0$. For these

loss functions, $\mu(a,t)$ is given for $a \geq 0$, $-\infty < t \leq p$, and $0 \leq a+t \leq p$ by

$$\mu(a,t) = \begin{cases} e^{-1\cdot(a-a_1)}, & \text{if } p^* < a_1 + t \text{ and } a_1 < a, \\ e^{-1\cdot(a-p^*+t)}, & \text{if } a_1 + t \leq p^* \leq a + t, \\ 1, & \text{if } p^* \leq a + t \text{ and } a \leq a_1, \\ 1, & \text{if } a + t < p^*. \end{cases}$$

Figure 1 shows the curve λ_T as a function of period p. The optimal period of treatment is $p \cong 6$ hours. Figure 2 shows the intensity $(p - p^*)/p$ (where $p^* = p^*(p)$ such that $\lambda_N = 0$) as a function of the period p. Figures 3 and 4 show the age-distribution of dividing cells in the exponential steady state for the normal and tumor cell populations with no cell loss (as in (11)).

EXAMPLE 2. In this example the *transit functions* $f_N(a,y)$ and $f_T(a,y)$ do depend on size. For normal cells, $f_N(a,y)$ is as in (25) with $c = .5$ and $\tau(y) = 4 + .1y$, and, for tumor cells, $f_T(a,y)$ is as in (25) with $c = .166667$ and $\tau(y) = 12 + .2y$. The *intrinsic growth constants* (as in (11)) in the absence of cell loss are $\lambda_N = .0812$ and $\lambda_T = .0240$ for the normal and tumor cell populations, respectively. The *loss functions* for this example are the same as in Example 1. Figure 5 shows the graph of λ_T when the loss function has period p and intensity parameter p^*. Figure 6 shows the intensity $(p - p^*)/p$ (where $p^* = p^*(p)$ such that $\lambda_N = 0$) as a function of p. Figures 7 and 8 show the age-distribution of dividing cells in the *exponential steady state* (as in (11)) for the normal and tumor cell populations, respectively, with no cell loss. The optimal period of treatment occurs at $p \cong 7.0$ hours.

EXAMPLE 3. In this example the *transit* functions $f_N(a)$ and $f_T(a)$ are the same as in Example 1. The *loss functions* $d_N(x,t)$ and $d_T(x,t)$ as in (26)) have $a_1 = 0$, $x_1 = 8.0$ for normal cells and $a_1 = 0$ and $x_1 = 16.0$ for tumor cells. For these *loss functions*, $\mu(a,y,t)$ is given

FIGURE 1. Intrinsic growth constant of tumor cell population.

FIGURE 2. Intensity of chemotherapy treatment.

FIGURE 3. Age distribution of dividing cells —normal cell population.

FIGURE 4. Age distribution of dividing cells —tumor cell population.

FIGURE 5. Intrinsic growth constant of tumor cell population.

FIGURE 6. Intensity of chemotherapy treatment.

FIGURE 7. Age distribution of dividing cells —normal cell population.

FIGURE 8. Age distribution of dividing cells —tumor cell population.

for $a \geq 0$, $y \geq 0$, $-\infty < t \leq p$, and $0 \leq a + t \leq p$ by

$$\mu(a,y,t) = \begin{cases} 1, & \text{if } a + t < p^*, \\ 1, & \text{if } p^* \leq a + t \text{ and } a + y < x_1, \\ e^{-1\cdot(a - x_1 + y)}, & \text{if } p^* \leq a + t \text{ and } p^* - x_1 + y < t \text{ and} \\ & x_1 \leq a + y \text{ and } y < x_1, \\ e^{-1\cdot(a - p^* + t)}, & \text{if } p^* \leq a + t \text{ and } t \leq p^* - x_1 + y \text{ and} \\ & y < x_1, \\ e^{-1\cdot(a - p^* + t)}, & \text{if } p^* \leq a + t \text{ and } t \leq p^* \text{ and } x_1 \leq y, \\ e^{-1\cdot a}, & \text{if } p^* < t \text{ and } x_1 \leq y. \end{cases}$$

Figure 9 shows λ_T as a function of p and Figure 10 shows $(p - p^*)/p$ as a function of p. The age-distribution of dividing cells in the exponential steady state for the normal cell population with no cell loss is the same as in Example 1. The optimal period of treatment is $p \cong 6$ hours, as in Example 1.

EXAMPLE 4. In this example the *transit functions* $f_N(a,y)$ and $f_T(a,y)$ are the same as in Example 2. The *loss functions* $d_N(x,t)$ and $d_T(x,t)$ are the same as in Example 3. Figure 11 shows λ_T as a function of p and Figure 12 shows $(p - p^*)/p$ as a function of p. The age-distribution of dividing cells in the exponential steady state for the normal cell population with no cell loss is the same as in Example 2. The optimal period of treatment is $p \cong 6.5$ hours, as in Example 2.

The computation of the growth constants λ_N and λ_T in these examples involves the discretization of the integral equation eigenvalue problem (15) and (17). In this case (*linear growth* and *symmetric division*) (15) and (16) reduce to

(27)
$$\psi(a,x) = 4\int_0^{2(x-a)} \psi(a + \hat{a}, 2x - a)q(a,x,\hat{a})\, d\hat{a}, \quad 0 \leq a \leq p, a \leq x,$$

(28) $$\psi(a + p, x) = e^{-\lambda p}\psi(a, x - p)r(a,x), \quad 0 \leq a \leq x - p,$$

where

$$q(a,x,\hat{a}) = \frac{f(\hat{a}, 2x - 2a - \hat{a})\mu(\hat{a}, 2x - 2a - \hat{a}, p - a - \hat{a})\alpha(a, x - a)\mu(a, x - a, p - a)}{\alpha(a + \hat{a}, 2x - 2a - \hat{a})\mu(a + \hat{a}, 2x - 2a - \hat{a}, p - a - \hat{a})}$$

FIGURE 9. Intrinsic growth constant of tumor cell population.

FIGURE 10. Intensity of chemotherapy treatment.

FIGURE 11. Intrinsic growth constant of tumor cell population.

FIGURE 12. Intensity of chemotherapy treatment.

$$r(a,x) = \frac{\alpha(a+p, x-a-p)\mu(a+p, x-a-p, -a)}{\alpha(a, x-a-p)\mu(a, x-a-p, -a)}$$

The discretized problem becomes a large matrix eigenvalue problem. The matrices are sparse, but have no regular form (because of the unusual interdependence of size x and age a in (27) and (28)). The programs for these computations were run on the CRAY X/MP-48 at the National Center for Supercomputing Applications at the University of Illinois.

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