Mathematical Models and Methods in Applied Sciences
Vol. 16, No. 7S (2006) 1155–1172

World Scientific
www.worldscientific.com

LONG-RANGE PREDICTABILITY IN MODELS OF CELL POPULATIONS SUBJECTED TO PHASE-SPECIFIC DRUGS: GROWTH-RATE APPROXIMATION USING PROPERTIES OF POSITIVE COMPACT OPERATORS

Y. KHEIFETZ*, Y. KOGAN† and Z. AGUR‡
Institute for Medical Biomathematics, Hate'ena St. 10, P.O. Box 282
Bene Ataroth, 60991, Israel
**yurih@imbm.org*
†*yuri@imbm.org*
‡*agur@imbm.org*

Received 18 January 2005
Revised 10 June 2005
Communicated by N. Bellomo and P. Maini

The aim of the present work is twofold: to develop numerical procedures for *a priori* determining whether a given cell population, having a distributed cell-cycle duration, will grow or decay when subjected to prescribed chemotherapy; to evaluate the cumulative error in the long-term predictions for such populations. We show that cell population dynamics under drug treatment can be modelled by iterative application of a compact operator on the initial cell age-distribution. We further show that this model can be approximated by iterative application of matrices on some finite-dimensional vector, containing initial conditions. Moreover, we develop a method for estimating the growth rate of cell population and show that in fully periodic treatments the estimated error does not grow as time tends to infinity. From the biomedical viewpoint this means that only fully periodic (strictly periodic) schedules can be considered for successfully predicting the long-term effect of chemotherapy. Thus, cyclic drug treatment is shown to be advantageous, not only in increasing selectivity of chemotherapy, as has been previously demonstrated, but also in increasing long-term predictability of specific treatment schedules.

Keywords: Cancer modelling; compact operators; spectral radius evaluation; population dynamics; numerical approximations; biological measurement error.

1. Introduction

Why have we made so little progress in the war against cancer? While there have been substantial achievements in the last three decades, the USA annual death toll has risen over 73% over this period. One of the major reasons for that is that investigators rely on models that are consistently bad in predicting treatment success (Fortune Magazine, March 2004).

Although the above argument refers to the poor predictability of *animal* models for human cancer, *mathematical* models of cancer suffer from a similar drawback, in that they are seldom both realistic enough and predictive enough to have long-range clinical implications.

Numerous mathematical models of cancer, which take into account different levels of tumor organization, have been developed, while multiscale modelling of multicellular systems has been critically analyzed by Bellomo *et al.*[11] The present work is related to a simplified approach in which tumor and host organism are considered as groups of cells whose growth dynamics under cell-cycle phase-specific drug treatment is studied. A mathematical theory suggests the existence of a resonance phenomenon, in which intermittent delivery of cell-cycle phase-specific drugs, at intervals equivalent to the mean cell-cycle time of host cells, can minimize harmful toxicity without compromising therapeutic effects on target cells (*Z-Method*).[1–3] Subsequently, explicit general formulae have been derived for the growth or decay of cell populations that are subjected to repeated pulse delivery of cell-cycle phase-specific drugs,[10,12] and an algorithm has been developed for calculating the required length of treatment for this protocol.[7] The existence of this resonance phenomenon has been further demonstrated for a general class of chemotherapy functions, thus supporting the underlying theory.[19,24,25,29]

The predictions of the *Z-method* have been verified in experiments in mice bearing lymphoma, treated by repeated pulse delivery of the anti-cancer drug, Ara-C, and by the anti-viral drug AZT. In these experiments it has been shown that when the rhythm of drug delivery roughly coincides with the characteristic bone-marrow cell-cycle time, animals survive and myelotoxicity is significantly reduced. The optimal spacing of repeated treatments was determined by measurements of the kinetics of cell movement through different cell-cycle phases. These experiments showed that it is feasible to control host toxicity by rational drug scheduling, based on the *Z*-method.[4,5,9,27]

Realistic models of cell population dynamics take into account distributions of cell-cycle length in the population. For some specific distributions of cell-cycle duration (normal[3] or some other[3,12,29] described below) it was shown both analytically and numerically[3,12,29] that resonance in cell population growth takes place when the drug is administered regularly every τ, where τ equals the mean cell-cycle duration or is its integer or fractional multiple. It is shown that the resonance is sharper for smaller variance in the distribution of cell-cycle duration.[3] However, the applicability to the clinic of cell population models with generally distributed cell-cycle has yet to be shown.

The main aim of the present work is to develop model-specific numerical procedures for *a priori* determining whether a given cell population, having a distributed cell-cycle duration, will grow or decay when subjected to prescribed chemotherapy. Assuming classical linear age-structured model,[12,20,26] we will show that cell population dynamics under a drug treatment can be modelled by iterative applications of compact operator on the initial cell age-distribution. We further show

that the model can be approximated by iterative applications of matrices on some finite-dimensional vector, containing initial conditions. Moreover, we will develop a method for growth-rate estimation and will show that under fully periodic treatments the estimation error does not grow as time tends to infinity. In addition, the problem of inexact initial data will also be considered and the criteria for determining whether or not this inexactness is crucial for cell population growth estimation will be developed.

2. Continuous Model

In this section the differential equation, describing cell age distribution $n(a,t)$, is integrated, and as a result a recursive formula for $r(t) = n(0,t)$ is obtained. Here a is cell age and t is time. It will be shown that the behavior of $r(t)$ determines the behavior of $N(t)$, i.e. the number of cells at time t, as t tends to infinity.

The model equations, describing cell age distribution are

$$n_t(a,t) + n_a(a,t) = -(\beta(a) + \eta(a,t))n(a,t), \quad a > 0, \quad t \in \mathbb{R}, \tag{2.1}$$

$$n(0,t) = 2\int_{\tau_b}^{\tau_m} \beta(a)n(a,t)da, \quad t > 0, \tag{2.2}$$

$$n(a,0) = n_0(a), \quad a > 0, \tag{2.3}$$

where n_a and n_t denote partial derivatives $\partial n/\partial a$ and $\partial n/\partial t$, respectively.[12,20,26] The age-specific division rate of cells is $\beta(a)$, the age-specific mortality rate (due to natural causes or to a treatment) of cells is $\eta(a,t)$, and the initial age distribution of cells is $n_0(a)$. The function $\beta(a)$ satisfies $\beta(a) = f(a)/\alpha(a)$, where $\int_{a_1}^{a_2} f(a)da$ is the probability that a cell divides between ages a_1 and a_2 and $\alpha(a) = \int_a^\infty f(\hat{a})d\hat{a}$ (the function $\alpha(a)$ gives the fraction of cells undivided by age a). In our case the support of β (the set of all points on which β has nonzero values) is a subset of $[\tau_b, \tau_m]$.

In this particular model we assume that the division and mortality rates of the population are independent of the population density. It should be noted that in general, the division rate of cell population may depend on the total cell number. This can be so in noncancerous cells populations, where β and η depend also on the total number of the cells, $N(t) = \int_0^{\tau_m} n(a,t)da$. In such cases, being out of the scope of the present paper, $\beta(N,a)$ is a decreasing and $\eta(N,a,t)$ is an increasing function of N (negative feedback regulation of overall cell number).

Our approach to solving the system (2.1)–(2.3) is close to that of Diekmann *et al.*,[13,14] except that we use a less general basic system of equations in order to achieve more explicit results. Both Diekman *et al.* and Webb[19,28,29] have analyzed the behavior and stability of the system (2.1)–(2.3), while we focus our study on the prediction capacity of the models, where tractability is traded-off by increased realism and, hence, population growth is numerically estimated. In the works of Webb it is assumed that cells can divide as of the zeroth age. In reality, this is not the case, and therefore, we replace this assumption by minimal division age

being $\tau_b > 0$. This latter assumption enables recursive evaluation of $n(a,t)$ as t increases. As a consequence, when $n(a,t)$ is given for each positive a and for each negative t and is continuous and integrable, it is possible to calculate $n(a,t)$ for any positive time and the existence and uniqueness of solution follows automatically (see (2.9), (2.11), (2.15)). When $\tau_b = 0$, the solution for $n(a,t)$ is written as a functional implicit equation and the proof of uniqueness and existence is difficult to obtain.[19,28,29]

Let us find general solutions of (2.1)–(2.3) in the form $n(a,t) = m(a, t-a)$ (it is clear that $\eta = t - a$ is a characteristic curve of the Eq. (2.1)). Let us denote $\tilde{\eta}(a,t) = \eta(a, t+a)$. Then Eqs. (2.1)–(2.3) take the following form:

$$m_a(a,\zeta) = -(\beta(a) + \tilde{\eta}(a,\zeta))m(a,\zeta), \quad a > 0, \tag{2.4}$$

where $\zeta = t - a$,

$$m(0,\zeta) = 2\int_{\tau_b}^{\infty} \beta(a)m(a,\zeta+a)da, \quad \zeta = t > 0, \tag{2.5}$$

$$m(a,-a) = n_0(a), \quad a > 0. \tag{2.6}$$

It is easy to see that

$$\begin{aligned}\int_{\tau_b}^{a} \beta(\alpha)d\alpha &= \int_{\tau_b}^{a} \frac{f(\alpha)}{\int_{\alpha}^{\tau_m} f(\nu)d\nu} d\alpha = -\int_{\tau_b}^{a} \left(\ln\left(\int_{\alpha}^{\tau_m} f(\nu)d\nu\right)\right)' d\alpha \\ &= \ln\left(\frac{\int_{\tau_b}^{\tau_m} f(\nu)d\nu}{\int_{a}^{\tau_m} f(\nu)d\nu}\right) = -\ln\left(\int_{a}^{\tau_m} f(\nu)d\nu\right),\end{aligned} \tag{2.7}$$

because $\int_{\tau_b}^{\tau_m} f(\nu)d\nu = 1$ (f is a distribution function on $[\tau_b, \tau_m]$).

Thus the general solution of (2.4) is

$$m(a,\zeta) = \begin{cases} r(\zeta)e^{-\int_0^a \tilde{\eta}(\alpha,\zeta)\,d\alpha}, & 0 \le a < \tau_b, \\ r(\zeta)\left(\int_a^{\tau_m} f(\nu)\,d\nu\right) e^{-\int_0^a \tilde{\eta}(\alpha,\zeta)\,d\alpha}, & \tau_b \le a < \tau_m, \\ 0, & \tau_m \le a, \end{cases} \tag{2.8}$$

where $r(\zeta)$ is any C^1 (continuously differentiable) function, which in each specific case is determined by given boundary conditions. Thus

$$n(a,t) = r(t-a)F(a)\Theta(a,t), \tag{2.9}$$

$$F(a) = \begin{cases} 1, & 0 \le a < \tau_b, \\ \int_a^{\tau_m} f(\nu)d\nu, & \tau_b \le a < \tau_m, \\ 0, & \tau_m \le a, \end{cases}$$

$$\Theta(a,t) = e^{-\int_0^a \tilde{\eta}(\alpha,t-\alpha)\,d\alpha}.$$

where $\Theta(a,t)$ describes treatment. For very aggressive treatment $\Theta(a,t)$ tends to 0 and in the absence of the drug $\Theta(a,t)=1$. The boundary condition (2.3) looks as

$$n_0(a) = r(-a)F(a)\Theta(a,0), \tag{2.10}$$

or

$$r(-a) = \begin{cases} \dfrac{n_0(a)}{\Theta(a,0)F(a)}, & 0 \le a < \tau_m, \\ \lim\limits_{a\to\tau_m} \dfrac{n_0(a)}{\Theta(a,0)F(a)}, & a = \tau_m. \end{cases} \tag{2.11}$$

It follows from (2.9) that

$$n(0,t) = r(t) \tag{2.12}$$

so that $r(t)$ is always finite by its biological definition. Thus the set of all admissible functions $n_0(a)$ must be such that $\lim_{a\to\tau_m} \frac{n_0(a)}{\Theta(a,0)F(a)}$ exists, making (2.11) legitimate.

Boundary condition (2.2) reads as

$$r(t) = 2\int_{\tau_b}^{\tau_m} \beta(a) r(t-a) e^{-\int_{\tau_b}^{a}\beta(\alpha)\,d\alpha}\,\Theta(a,t)da, \quad t>0. \tag{2.13}$$

From (2.7) it follows that

$$\begin{aligned} \beta(a)\,e^{-\int_{\tau_b}^{a}\beta(\alpha)\,d\alpha} &= \beta(a)\frac{\int_a^{\tau_m} f(\nu)d\nu}{\int_{\tau_b}^{\tau_m} f(\nu)d\nu} = \frac{f(a)}{\int_a^{\tau_m} f(\nu)d\nu}\cdot\frac{\int_a^{\tau_m} f(\nu)d\nu}{\int_{\tau_b}^{\tau_m} f(\nu)d\nu} \\ &= \frac{f(a)}{\int_{\tau_b}^{\tau_m} f(\nu)d\nu} = f(a)\,. \end{aligned} \tag{2.14}$$

From (2.13) and (2.14), we have

$$r(t) = 2\int_{\tau_b}^{\tau_m} f(a)\,r(t-a)\,\Theta(a,t)da. \tag{2.15}$$

In the next section we find the iterative solution of the integral equation (2.15). Theorem 1 stated in Sec. 4 uses this solution to obtain the description of the asymptotic behavior of the cell number $N(t)$.

3. Iterative Solution for $r(t)$

The solution for $r(t)$ can be obtained recursively from $r(t)$ for negative t using (2.15) as follows. Let

$$r_n(s) = r(s+n\tau_b), \quad \text{for all } s\in[0,\tau_b],\ n\in\mathbb{Z}. \tag{3.1}$$

Taking into account that $\operatorname{supp}(f)\subseteq[\tau_b,\tau_m]$ and $s<\tau_b$ we have

$$\begin{aligned} r_n(s) &= 2\int_{\tau_b}^{\tau_m} f(a)\,r(s+n\tau_b-a)\,\Theta(a,s+n\tau_b)da \\ &= 2\int_{s}^{\tau_m+s} f(a)\,r(s+n\tau_b-a)\,\Theta(a,s+n\tau_b)da \end{aligned}$$

$$= \sum_{j=0}^{M} 2 \int_{s+j\tau_b}^{s+(j+1)\tau_b} f(a)\, r(s+n\tau_b-a)\, \Theta(a, s+n\tau_b) da$$

$$= \{\text{variables change}: \quad \nu = a-(s+j\tau_b)\}$$

$$= \sum_{j=0}^{M} 2 \int_{0}^{\tau_b} f(\nu+s+j\tau_b)\, r_{n-j-1}(\tau_b-\nu)\, \Theta(\nu+s+j\tau_b, s+n\tau_b) d\nu$$

$$= \sum_{j=0}^{M} \int_{0}^{\tau_b} E_{j,n}(\nu, s)\, r_{n-j-1}(\tau_b-\nu) d\nu = \sum_{j=0}^{M} T_{j,n}\, r_{n-j-1}(s), \tag{3.2}$$

where $E_{j,n}(\nu, s) = 2 f(\nu + s + j\tau_b)\, \Theta(\nu + s + j\tau_b, s + n\tau_b)$ and $T_{j,n} g(s) = \int_0^{\tau_b} E_{j,n}(\nu, s)\, g(\tau_b - \nu)\, d\nu$ for any $g \in L^2_{[0,\tau_b]}$; $M = \left[\frac{\tau_m}{\tau_b}\right] + 1$, is either finite or infinite. In this paper we consider the finite case, i.e. $\tau_m < \infty$. Equations (3.2) define recursively $\{r_n(t)\}_{n=1}^{\infty}$, provided that $r_{-M}(t), \ldots, r_0(t)$ are known.

4. Operator Formalism

In this section we consider the stability of the growth rate of the solution $r(t)$ as t tends to infinity as well as the accuracy of the proposed finite-dimensional approximations. The following definitions are very important for further discussion:

Definition 1. Let H be the set $(L^2_{[0,\tau_b]})^{M+1}$ with a following inner product: $\langle x, y\rangle = \sum_{j=1}^{M+1} \langle x_j, y_j\rangle$, where $\langle x_j, y_j\rangle$ is an inner product of components in $L^2_{[0,\tau_b]}$.

Clearly, H with this inner product constitutes Hilbert space. Now we define partial order relation on H, as follows:

Definition 2. For any x in H we say that x is (strictly) positive if each of its components is a (strictly) positive function and denote this by $x \geq 0$ ($x > 0$). For any x, y in H we say that $x \geq y$ ($x > y$) if $x - y \geq 0$ ($x - y > 0$).

Definition 3. Let H_+ and H_{++} be subsets of H, containing all $(M+1)$-dimensional vectors, whose elements are non-negative and strictly positive functions, respectively. We call operator K on H positive (strictly positive) if $K(H_+) \subseteq H_+$ (if $K(H_{++}) \subseteq H_{++}$), and write $K \geq 0$ ($K > 0$) to denote that K is positive (strictly positive). For any two operators S_1 and S_2 on H we say that $S_1 \geq S_2$ ($S_1 > S_2$) if $S_1 - S_2 \geq 0$ (if $S_1 - S_2 > 0$).

Let us denote

$$T_n = \begin{pmatrix} 0 & \mathrm{Id} & 0 & \dots & 0 \\ 0 & 0 & \mathrm{Id} & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \dots & \mathrm{Id} \\ T_{M,n} & T_{M-1,n} & T_{M-2,n} & \dots & T_{0,n} \end{pmatrix}, \quad v_n(t) = \begin{pmatrix} r_{n-M}(t) \\ r_{n-M+1}(t) \\ \vdots \\ r_{n-1}(t) \\ r_n(t) \end{pmatrix}. \quad (4.1)$$

Thus Eq. (3.2) can be rewritten in the following form:

$$v_n = T_n \cdot v_{n-1}, \quad (4.2)$$

and the initial conditions are given by v_0. Clearly $\{T_n\}_{n=1}^{\infty}$ is a sequence of compact operators from H to H. In the case of cyclic treatment there is a minimal $\hat{p} > 0$, such that $\Theta(a,t) = \Theta(a,t+\hat{p})$ for any $a > 0$ and any $t > t_0$. Two possibilities exist: (a) $\hat{p}/\tau_b$ is rational; (b) $\hat{p}/\tau_b$ is irrational; In the second case we can take $\tau_b' = \tau_b - \Delta$, for Δ arbitrary small positive number such that $\hat{p}/\tau_b'$ is rational. Since $\mathrm{supp}(f) \in [\tau_b, \tau_m) \subseteq [\tau_b', \tau_m)$ we can safely put $\tau_b := \tau_b'$. Thus in any case we suppose, without loss of generality, that $\hat{p}/\tau_b$ is rational, i.e. $\hat{p}/\tau_b = P/P'$, where P and P' are natural numbers and P/P' is irreducible. Thus $\Theta(a,t) = \Theta(a,t+P\tau_b)$ for any $a > 0$, $t > t_0$, and P is the minimal positive integer with this property. From this it easily follows that $\{T_n\}_{n=1}^{\infty}$ is a periodic sequence of operators with the minimal positive period P. Let us define operator, whose spectral properties are crucial for population growth rate determination, as will be shown later:

$$T = T_1 \cdot T_2 \cdot \ldots \cdot T_P. \quad (4.3)$$

This implies immediately that T is a compact operator on H and for every initial vector $v_0 \in H$ we have P sequences $\{T^m v_0\}_{m=0}^{\infty}$, $\{T^m \cdot T_1 v_0\}_{m=0}^{\infty}$, $\ldots$, $\{T^m \cdot T_1 \cdot \ldots \cdot T_{P-1} v_0\}_{m=0}^{\infty}$ and obtain a sequence of vectors of functions $\left\{\left(r_n(t), r_{n+1}(t), \ldots, r_{n-M}(t)\right)\right\}_{n=1}^{\infty}$ in the following way: $r_n(t) = T^m \cdot T_1 \cdot \ldots \cdot T_i v_0$, for any natural n, represented as $n = mP + i$, $0 \le i < P$. This means that the behavior of $r(t)$ in infinity is determined by $\{T^m\}_{m=1}^{\infty}$. The following theorem gives an estimation of the treated cell population growth through the spectral radius of the operator T.

Theorem 1. *For any* $s \in [0, \tau_b]$

$$\limsup_{n\to\infty} N_n(s)^{\frac{1}{\left[\frac{n}{P}\right]}} \le \rho(T) \quad (4.4)$$

is always true and

$$\lim_{n\to\infty} N_n(s)^{\frac{1}{\left[\frac{n}{P}\right]}} = \rho(T) \quad (4.5)$$

is true in generic case, which is in complete analogy to (3.1),

$$N_n(s) = N(s + n\tau_b), \quad \forall s \in [0, \tau_b], \quad \forall n \in \mathbb{Z}. \quad (4.6)$$

The proof of Theorem 1 is given in Appendix A.1. From this theorem it follows immediately that the value of the spectral radius $\rho(T)$ fully characterizes population growth or decay: the population grows exponentially if $\rho(T) > 1$ and decays if $\rho(T) < 1$. These rates are bounded by $\rho(T)$ and tend to it for almost all initial conditions, which are represented by non-negative functions. In the following section of this paper the problem of effective approximation of $\rho(T)$ is discussed.

5. Numerical Approximation for $r(t)$ and Applications

We propose a finite-dimensional approximation to $\{r_n\}_{n=1}^{\infty}$ as follows. Let N be a large natural number. Let $h = \frac{\tau_b}{N}$ $x_i = ih$, $i = 0, \ldots, N$. Then we define the following two sequences of functions on $[0, \tau_b]$:

$$
\begin{aligned}
&\hat{r}_n^u(s) = \hat{r}_n^l(s) = r_n(s), \quad \text{for } s \in [0, \tau_b], \ n \in \{-M, \ldots, 0\}, \\
&\hat{r}_n^u(s) = \sum_{j=0}^{M} \int_0^{\tau_b} E_{j,n}^u(\nu, s)\, \hat{r}_{n-j-1}^u(\nu) d\nu = \sum_{j=0}^{M} T_{j,n}^u\, \hat{r}_{n-j-1}^u(s), \\
&\hat{r}_n^l(s) = \sum_{j=0}^{M} \int_0^{\tau_b} E_{j,n}^l(\nu, s)\, \hat{r}_{n-j-1}^l(\nu)\, d\nu \\
&\qquad = \sum_{j=0}^{M} T_{j,n}^l\, \hat{r}_{n-j-1}^l(s), \quad \text{for } s \in [0, \tau_b], \ n > 0,
\end{aligned}
\tag{5.1}
$$

where

$$
\begin{aligned}
E_{j,n}^u(\nu, s) &= \sum_{i,l=0}^{N} \sup\{E_{j,n}(\nu, s) \mid (\nu, s) \in \Omega_{i,l}\} \chi_{\Omega_{i,l}}(\nu, s), \\
E_{j,n}^l(\nu, s) &= \sum_{i,l=0}^{N} \inf\{E_{j,n}(\nu, s) \mid (\nu, s) \in \Omega_{i,l}\} \chi_{\Omega_{i,l}}(\nu, s), \\
\Omega_{i,l} &= [x_i, x_{i+1}) \times [x_l, x_{l+1}), \\
\chi_A(\nu, s) &= \begin{cases} 1, & \text{if } (\nu, s) \in A, \text{ for any set } A, \\ 0 & \text{otherwise,} \end{cases} \\
T_{j,n}^u g(s) &= \int_0^{\tau_b} E_{j,n}^u(\nu, s)\, g(\nu) d\nu, \\
T_{j,n}^l g(s) &= \int_0^{\tau_b} E_{j,n}^l(\nu, s)\, g(\nu) d\nu, \quad \forall g \in L^2_{[0,\tau_b]}.
\end{aligned}
$$

In both cases we approximate $E_{j,n}(\nu, s)$ with step functions, bounding it from above (superscript "u") or from below (superscript "l"). It follows recursively that $\{\hat{r}_n^l(s)\}_{n=1}^{\infty}$ and $\{\hat{r}_n^u(s)\}_{n=1}^{\infty}$ are also step functions, constant on each of $\{[x_l, x_{l+1})\}_{l=1}^{N}$ and they constitute lower and upper boundaries of $\{r_n(s)\}_{n=1}^{\infty}$. The set of such functions is isometric with $\mathbb{C}^N$, having Euclidean norm. The isometry

can be taken as follows: every step function g is transformed to N-dimensional vector $\{f(x_i)\sqrt{h}\}_{i=1}^{N}$.

Let us denote the subspace of H, containing all $(M+1)$-dimensional vectors of step functions, which are constant on each of $\{[x_l, x_{l+1})\}_{l=1}^{N}$, as H_N. It is obvious that H_N is isometric to $\mathbb{C}^{N(M+1)}$. In complete analogy to (4.2) operators T_n^l and T_n^u can be defined. Let

$$\begin{aligned} T^l &= T_1^l \cdot T_2^l \cdot \cdots \cdot T_P^l, \\ T^u &= T_1^u \cdot T_2^u \cdot \cdots \cdot T_P^u. \end{aligned} \tag{5.2}$$

It is obvious that $T^l(H) \subseteq H_N$ and $T^u(H) \subseteq H_N$. Thus all eigenvectors of T^l and T^u are contained in H_N. Keeping in mind isometry of H with $C^{N(M+1)}$, we can treat T^l and T^u as finite-dimensional matrices in order to find their spectral radii. Different effective algorithms have been developed for this purpose.[23] The following theorem, whose proof is given in Appendix A.2, shows how $\rho(T)$ can be estimated using $\rho(T^l)$ and $\rho(T^u)$.

Theorem 2. *For any ε, if $\|T^l - T^u\| < \varepsilon$ in operator norm, then*

$$\rho(T^l) \le \rho(T) \le \rho(T^u), \tag{5.3}$$

$$|\rho(T^l) - \rho(T^u)| < \varepsilon. \tag{5.4}$$

The proof of Theorem 2 is provided in Appendix A.2. From Theorem 1 follows a property, associated with fully periodic treatments: when subjected to fully periodic drug treatments, the behavior of a cell population at large t is determined by the spectral radius of some operator T. This means that the inexactness in the evaluation of cell population dynamics is determined by the inexactness of the population growth rate estimation at any time. Thus, the error in the initial data will lead to a bounded error in the evaluation of the population growth-rate for large t. Theorem 5.3 enables one to evaluate this error as follows: we assume that the distribution function f and the chemotherapy determining function $\Theta(a,t)$ are Riemann integrable. Thus, for any $\varepsilon > 0$ it is possible to find a natural number N, determining the equal partition of $[0, \tau_b]$, as discussed before, such that $\|T^u - T^l\| < \varepsilon$. By (5.4) $\rho(T^u) - \rho(T^l) < \varepsilon$ and by (5.3) $\rho(T^l) \le \rho(T) \le \rho(T^u)$, from which will follow that $\rho(T)$ differs from $\rho(T^u)$ and $\rho(T^l)$ by less than ε.

One of the problems any predictive mathematical model has to cope with is the inexactness of the biological data. In the present model, if we know f up to some accuracy, the following question arises: given a cyclic drug treatment, is the inexactness in the biological input data crucial for our prediction ability of population growth or extinction?

Let $f_1(a) < f(a) < f_2(a)$ for each $a \in [\tau_b, \tau_m]$. Let ${}_1T$ and ${}_2T$ be the respective operators on H. Then by Proposition A.2.1, presented in the Appendix, it follows that $\rho({}_1T) \le \rho(T) \le \rho({}_2T)$. Given any $\varepsilon > 0$, we can evaluate $\rho({}_1T)$ and $\rho({}_2T)$ with accuracy less than ε. In the generic case $\rho(T) \neq 1$. Thus we can assume that for sufficiently small ε the interval $(\rho(T) - \varepsilon, \rho(T) + \varepsilon)$ is either from the left or

from the right of 1, from which follows that both $\rho({}_1T)$ and $\rho({}_2T)$ are greater or less than 1, or $\rho({}_1T) < 1 < \rho({}_2T)$. In the first case the population increases; in the second it decreases and in the third case the provided data for f are not sufficient.

6. Discussion

In the present work we have analyzed an age-structured growth model of cancer cells treated by chemotherapy. The model is presented in terms of PDE with boundary conditions for population density function. Under a reasonable assumption of existence of minimal and maximal possible values of cell-cycle length, we obtained an iterative solution of the equation. We showed that under a strictly cyclic treatment the asymptotic behavior of the cell number $N(t)$ is similar to that of $r(t)$, i.e. the density of cells of age 0 at time t. The iterative equation for $r(t)$ was presented using operator formalism on Banach space of vectors of real functions. The solution is given by iterative application of the compact operator T on the vector of initial conditions. Theorem 1 shows that the asymptotic behavior of population size is determined by the spectral radius $\rho(T)$. Thus, we turned to the problem of evaluating the spectral radius of compact operator. To this end, we propose finite-dimensional approximation of $N(t)$ and $r(t)$ with step functions, bounding them from above and from below. This approximation is based on partitioning the time axis into intervals of length τ_b/N, and on considering the space of functions which are constant on each of these intervals. We have shown that this approximation induces approximation of T by operators T^u and T^l bounding it from above and below. These operators act on $(M+1)$ N-dimensional space of vectors of piecewise constant functions that approximate the original real-valued functions. We show that by choosing finite-dimensional approximations, close enough to T, we can evaluate $\rho(T)$ with arbitrarily small error. The precision of this approximation depends on N. We propose the following algorithm: given the equation, approximate $\rho(T)$ to the desired precision, so that the interval $[\rho(T^l), \rho(T^u)]$ lies entirely below or above 1 (this is the generic case). Then $\rho(T)$ lies within this interval, and the asymptotic behavior of $N(t)$ is known. Note that in the case $\rho(T) = 1$, the algorithm does not give a solution to the problem and, indeed, in this case the asymptotic behavior of $N(t)$ is unknown — it can be bounded or grow subexponentially, e.g., in a polynomial fashion. Since this case is not generic, its consideration has little practical importance.

We also discuss the problem of inexactness of the biological measurements, i.e. when the parameters of the equation are given up to some error. In this case we assume that $T_1 \leq T \leq T_2$ (in operator sense). We can evaluate $\rho(T)$ as lying within the interval $[\rho(T_1), \rho(T_2)]$, or in the finite-dimensional approximation, as lying within the interval $[\rho(T_1^l), \rho(T_2^u)]$. If no approximation can locate this interval strictly below or above 1, we can state that the biological data are not exact enough for inferring the asymptotic behavior of $N(t)$. We also stress that only a strictly periodic treatment allows such estimations as above, since in this case the evaluation

error of population growth rate does not accumulate due to the periodicity of the solution. Such a predictability is the advantage of periodic regimens over non-periodic ones.

7. Perspectives

A number of generalizations can be added to the model. First and foremost, cell populations whose growth rate depends on population density need to be considered. In addition, populations can consist of several subpopulations that differ in cell age distribution functions, so that selection during the treatment can take place. Drug diffusion and spatial heterogeneity can also be taken into account. In practice, the treatment cannot be ideally cyclic, so stochastic deviations in drug application can be introduced into the model. The putative effect on cell population dynamics of cell-cycle arrest, caused by some phase-specific drugs, should also be explored.

In the Appendix we present proofs of Theorems 1 and 2. These proofs employ results on positive and compact operators. For a more profound survey of this subject see Refs. 15–17.

Appendix A

A.1. *Proof of Theorem* 1

In order to prove Theorem 1 several important results from operator theory are presented. Let us bear in mind the following elementary fact in operator theory: if X is a Banach space, $v \in X$ and A is a bounded operator on X, then

$$\|Av\| \leq \|A\| \, \|v\|, \tag{A.1}$$

$$\rho(A) = \lim_{n \to \infty} \|A^n\|^{\frac{1}{n}}. \tag{A.2}$$

The following proposition with its proof can be found in Ref. 22.

Proposition A.1.1. *For any positive compact operator K on H, the spectrul rudius $\rho(K)$ is an eigenvalue of K with at least one eigenfunction $x \geq 0$.*

Proposition A.1.2. *For any positive compact operator K on H and for any $v \in H$, $\lim_{n\to\infty} \|K^n v\|^{\frac{1}{n}} \leq \rho(K)$, and for almost every $v \in H_+$, $\lim_{n\to\infty} \|K^n v\|^{\frac{1}{n}} = \rho(K)$.*

Proof of Proposition A.1.2. The first part of this proposition can be obtained trivially from (A.1) and (A.2) as follows: $\|K^n v\|^{\frac{1}{n}} \leq \|K^n\|^{\frac{1}{n}} \|v\|^{\frac{1}{n}} \to \rho(K)$. In order to prove the second part, it is sufficient to prove that the set $\{v \mid \lim_{n\to\infty} \|K^n v\|^{\frac{1}{n}} = \rho(K)\}$ contains a subset, which is open and dense in H_+. Let H_{+++} be a set of strictly positive functions in H_+, such that their infimum is also positive. It is clear that H_{+++} is open and dense in H_+. Let e_T be a unit vector in H_+, which is an eigenvector of $\rho(T)$ (from Proposition A.1.1 we know that e_T exists). Let W be a subspace of H_{+++} of all the vectors having nonzero product with e_T, such that for each $w \in W$ there exists a small $\delta_w > 0$, such that $w - \delta_w e_T \in H_{+++}$. It is

clear that W contains open and dense sets in H_{+++} and thus in H_+. Then for any $w \in W$

$$K^n w = K^n \delta_w e_T + K^n(w - \delta_w e_T) > K^n \delta_w e_T = \delta_w \rho(K)^n e_T,$$
$$\text{thus } \|K^n w\| \geq \delta_w \rho(K)^n \quad \text{or} \quad \|K^n w\|^{\frac{1}{n}} \geq \delta_w^{\frac{1}{n}} \rho(K). \tag{A.3}$$

As n tends to infinity the last inequality in (A.3) looks as $\lim_{n\to\infty} \|K^n w\|^{\frac{1}{n}} \geq \rho(K)$. Taking into account that $\|K^n w\|^{\frac{1}{n}} \leq \|K^n\|^{\frac{1}{n}} |w|^{\frac{1}{n}} \to \rho(K)$ we immediately obtain $\lim_{n\to\infty} \|K^n w\|^{\frac{1}{n}} = \rho(K)$. This completes the proof of Proposition A.1.2. □

Proof of Theorem 1. By definition of total cell number at time t, $N(t)$ and in complete analogy to (3.2), (A.4) we get:

$$\begin{aligned} N_n(s) &= \int_0^{T_m} n(a, s + n\tau_b)da \\ &= \sum_{j=-1}^{M-1} \int_{j\,T_b}^{(j+1)\,T_b} r(s + n\tau_b - a)\Theta(a, s + n\tau_b)F(a)da \\ &= \sum_{j=-1}^{M} \int_0^{\tau_b} F(\nu + s + j\tau_b)\, r_{n-j-1}(\tau_b - \nu)\, \Theta(\nu + s + j\tau_b, s + n\,\tau_b)d\nu \\ &= \sum_{j=-1}^{M} \int_0^{\tau_b} \tilde{E}_{j,n}(\nu, s)\, r_{n-j-1}(\tau_b - u)d\nu \\ &= \sum_{j=-1}^{M} \tilde{T}_{j,n} r_{n-j-1}(s), \quad \forall n \in \mathbb{N}, \end{aligned} \tag{A.4}$$

where

$$\tilde{E}_{j,n}(\nu, s) = F(\nu + s + j\tau_b)\, \Theta(\nu + s + j\tau_b, s + n\tau_b),$$
$$\tilde{T}_{j,n} g(s) = \int_0^{\tau_b} \tilde{E}_{j,n}(\nu, s)\, g(\tau_b - \nu)d\nu, \quad g \in L^2_{[0,\tau_b]}.$$

It is clear that $0 \leq \tilde{E}_{j,n}(\nu, s) \leq 1$ for all natural j, n, and $s, \nu \in [0, \tau_b]$. Thus

$$\begin{aligned} N_n(s) &\leq \sum_{j=-1}^{M} \int_0^{\tau_b} r_{n-j-1}(\tau_b - \nu)d\nu \\ &= \sum_{j=-1}^{M} \int_0^{\tau_b} r_{n-j-1}(\nu)d\nu \\ &\leq \sum_{j=-1}^{M} \tau_b \|r_{n-j-1}\| \end{aligned} \tag{A.5}$$

$$\left\{\text{because of the addition of non-negative term } \tau_b\left(\|r_{n-M}\| + \sum_{j=-1}^{M-1} \|r_{n-j-1}\|\right)\right\}$$

$$\leq \tau_b \left(\|r_n\| + \|r_{n-M}\| + 2 \sum_{j=-1}^{M-1} \|r_{n-j-1}\| \right)$$
$$\leq \tau_b M_1 (\|v_n\| + \|v_{n-1}\|), \tag{A.6}$$

for any $s \in [0, \tau_b]$, $n \in \mathbb{N}$. Here M_1 is a constant, for which $\|\alpha\|_1 \leq M_1 \|\alpha\|_2$ for any vector $\alpha \in \mathbb{C}^{M+1}$ (such M_1 exists because every two norms on finite-dimensional Banach spaces are equivalent). Cauchy–Schwartz inequality has been used in (A.6). The last inequality in (A.6) is based on the fact that for any real numbers $a_1, \ldots, a_k$ the following inequality always takes place:

$$\sqrt{a_1^2 + \cdots + a_k^2} \leq |a_1| + \cdots + |a_k|.$$

It should be noted that in this paper the notation of norm of any object relates to the space, where the object is situated, for example in (A.6) $\|r_i\|$ means norm of r_i in $L^2_{[0,\tau_b]}$ and $\|v_i\|$ means norm of v_i in H for any relevant index i.

From Proposition A.1.2 we know that $\lim_{n\to\infty} \|v_n\|^{\frac{1}{\lceil \frac{n}{P} \rceil}} \leq \rho(T)$ (and equals to it in generic case). Thus

$$\limsup_{n\to\infty} N_n(s)^{\frac{1}{\lceil \frac{n}{P} \rceil}} \leq \rho(T) \tag{A.7}$$

for any $s \in [0, \tau_b]$. Let $\tilde{T}_n$ be the operator from $H \times H$ to $L^2_{[0,\tau_b]}$, defined as

$$\tilde{T}_n = ((0, \ldots, 0, \tilde{T}_{M,n}), (\tilde{T}_{M-1,n}, \ldots, \tilde{T}_{0,n}, \tilde{T}_{-1,n})). \tag{A.8}$$

Thus

$$N_n = \tilde{T}_n(v_{n-1}, v_n). \tag{A.9}$$

Bear in mind the notations of Proposition A.1.2: e_T is a unit vector in H_+ which is an eigenvector of $\rho(T)$, let W be a subspace of H_{+++} of all the vectors of H having nonzero product with e_T, such that for each $w \in W$ there exists a small $\delta_w > 0$, such that $w - \delta_w e_T \in H_{+++}$. It has been shown that W is open and dense in H_+. Let us denote by

$$\begin{aligned} r_n^*(s) &= T_n \cdot \cdots \cdot T_1 e_T(s), \\ r^*(n\tau_b + s) &= r_n^*(s), \\ N_n^*(s) &= \tilde{T}_n(r_{n-1}^*(s), r_n^*(s)), \\ N^*(n\tau_b + s) &= N_n^*(s). \end{aligned} \tag{A.10}$$

$r^*(t)$ and $N^*(t)$ are $r(t)$ and $N(t)$ respectively for initial conditions of $r(t)$, determined by e_T (i.e. $\tau_{1-j} = (e_T)_{M+1-j}$, $j = 1, \ldots, M+1$),

Let

$$\theta_r = T_{n-1} \cdot \cdots \cdot T_{n-r-1}, \quad r = 0, 1, \ldots, P-1. \tag{A.11}$$

Thus in generic case, taking $v_0 \in W$, determining initial conditions for $r(t)$, as has been mentioned before, we have

$$\begin{aligned} N_n(s) &= \tilde{T}_n(T_{n-1}\cdot\cdots\cdot T_1 v_0(s), T_{n-1}\cdot\cdots\cdot T_1 v_0(s)) \\ &\geq \delta_{v_0}^2 \tilde{T}_n(T_{n-1}\cdot\cdots\cdot T_1 e_T(s), T_{n-1}\cdot\cdots\cdot T_1 e_T(s)) \\ &= \delta_{v_0}^2 \tilde{T}_n\left(\theta_{j_{n-1}}\cdot T^{\left[\frac{n-1}{P}\right]} e_T(s), \theta_{j_n}\cdot T^{\left[\frac{n}{P}\right]} e_T(s)\right) \\ &= \delta_{v_0}\rho(T)^{\left[\frac{n-1}{P}\right]+\left[\frac{n}{P}\right]} \tilde{T}_n(\theta_{j_{n-1}} e_T(s), \theta_{j_n} e_T(s)), \end{aligned} \tag{A.12}$$

for any $s \in [0, \tau_b]$. Here $j_n = n - \left[\frac{n}{P}\right] P$.

Proposition A.1.3. *There exists $\varepsilon^* > 0$ such that $\tilde{T}_n(\theta_{j_{n-1}} e_T(s), \theta_{j_n} e_T(s)) > \varepsilon^*$ for any $s \in [0, \tau_b]$ and any natural n.*

Proof of Proposition A.1.3. Suppose that this is not true. Then there are sequences $\{n_k\}_{k=1}^{\infty}$ of natural numbers and $\{s_k\}_{k=1}^{\infty}$ in $[0, \tau_b]$, such that

$$\tilde{T}_{n_k}(\theta_{j_{n_k-1}} e_T(s_k), \theta_{j_{n_k}} e_T(s_k)) \xrightarrow{k\to\infty} 0. \tag{A.13}$$

It is easy to see that $\{\tilde{T}_n(\theta_{j_{n-1}} e_T, \theta_{j_n} e_T)\}_{n=1}^{\infty}$ is a periodic sequence of functions with period P of functions. Thus, without loss of generality, we can assume that there is $l_0 \in \{0, 1, \ldots, P-1\}$, such that $\tilde{T}_{n_k}(\theta_{j_{n_k}-1} e_T, \theta_{j_{n_k}} e_T) \equiv \tilde{T}_{l_0}(\theta_{j_{l_0}} e_T, \theta_{j_{l_0}-1} e_T)$. From this, (A.13) and the fact that $[0, \tau_b]$ is a compact set, it follows that there is $s^* \in [0, \tau_b]$, which is a density point of $\tilde{T}_{l_0}(\theta_{j_{l_0}} e_T, \theta_{j_{l_0}-1} e_T)$. It is obvious that $N^*(l_0\tau_b + s^*) = N_{l_0}^*(s^*) = \tilde{T}_{l_0}(\theta_{j_{l_0}} e_T(s^*), \theta_{j_{l_0}-1} e_T(s^*)) = 0$. If $N^*(t^*) = 0$ for some time t^* then $N^*(t) \equiv 0$ and $r^*(t) \equiv 0$ for any $t > t^*$, because $N^*(t)$ is the total number of cells at time t and $r(t) = n(0, t)$, density of cells at time t and at zeroth age. Thus $r_n^*(s) \equiv 0$ for any $n > l_0\tau_b$ and any $s \in [0, \tau_b]$. From this it follows that $T^n e_T \equiv 0$ for all $n > l_0 + M + 1$, and this contradicts to the fact that e_M is eigenvector of T relative to $\rho(T)$, which is positive. This proves Proposition A.1.3. □

We proceed with the proof of Theorem 1 as follows: from Proposition A.1.3 and (A.12) it follows immediately that

$$N_n(s) \geq \delta_w \rho(T)^{\left[\frac{n}{P}\right]} \varepsilon^*, \quad \forall s \in [0, \tau_b], \quad \text{or} \tag{A.14}$$

$$N_n(s)^{\frac{1}{\left[\frac{n}{P}\right]}} \geq (\delta_w \varepsilon^*)^{\frac{1}{\left[\frac{n}{P}\right]}} \rho(T), \quad \forall s \in [0, \tau_b], \tag{A.15}$$

in the generic case. From (A.7) and (A.14) follows that in the generic case the following limit exists for every $s \in [0, \tau_b]$:

$$\lim_{n\to\infty} \|N_n\|^{\frac{1}{\left[\frac{n}{P}\right]}} = \rho(T). \tag{A.16}$$

□

A.2. *Proof of Theorem 2*

From the definition of T, T^l and T^u, it is clear that they are positive operators. The following proposition is a classical result[16] in the theory of positive operators.

Proposition A.2.1. *Given S_1, S_2 being any bounded positive operators on H, such that $S_1 \geq S_2$, their spectral radii satisfy similar inequality: $\rho(S_1) \geq \rho(S_2)$.*

It has a practical significance: it states that the order is preserved by the map, which is defined on the set of all bounded positive operators on H, and assigns to any such operator its spectral radius. It is clear that (5.3) in Theorem 2 follows immediately from Proposition A.2.1.

In order to prove (5.4) in Theorem 2 we use the following proposition.

Proposition A.2.2. *Assume that S_1 and S_2 are operators on $\mathbb{C}^N$, such that $\|S_1 - S_2\| < \varepsilon$ in operator norm, then*

$$|\rho(S_1) - \rho(S_2)| < \varepsilon. \tag{A.17}$$

In order to prove this proposition let us prove the following two lemmas.

Lemma A.2.1. *Assume that A_1 and A_2 are operators on $\mathbb{C}^N$, such that $\|A_1 - A_2\| < \varepsilon$ in operator norm, and A_1 has N different eigenvalues $\lambda_1, \ldots, \lambda_n$, then*

$$\rho(A_2) < \rho(A_1) + \varepsilon. \tag{A.18}$$

Proof of Lemma A.2.1. It is possible to choose an orthonormal basis $\{e_1, \ldots, e_N\}$ of $\mathbb{C}^N$ as a set of eigenvectors of A_1, $\{\lambda_1, \ldots, \lambda_n\}$ respectively. Assume that λ is an eigenvalue of A_2, such that $|\lambda| = \rho(A_2)$. Then

$$A_2 w = \lambda w \tag{A.19}$$

for some vector $w \in \mathbb{C}^N$, $\|w\| = 1$. Thus

$$\|A_1 w - \lambda w\| = \|A_1 w - A_2 w\| = \|(A_1 - A_2)w\| < \varepsilon, \tag{A.20}$$

from which it follows immediately that

$$\sqrt{\sum_{j=1}^{N} |(\lambda_j - \lambda)\, w_j|^2} < \varepsilon, \tag{A.21}$$

where $w_j = \langle w, e_j \rangle$, $j = 1, \ldots, N$. Now assume that $|\lambda_j - \lambda| > \varepsilon$ for each $j \in \{1, \ldots, N\}$. Then

$$\sqrt{\sum_{j=1}^{N} |(\lambda_j - \lambda)\, w_j|^2} > \varepsilon \sqrt{\sum_{j=1}^{N} |w_j|^2} = \varepsilon, \tag{A.22}$$

which contradicts (A.21). Thus there exists $j_0 \in 1, \ldots, N$ such that

$$|\lambda_{j_0} - \lambda| \leq \varepsilon, \tag{A.23}$$

from which we immediately get (A.18). □

Lemma A.2.2. *For every $\varepsilon > 0$ and every operator S on N-dimensional $\mathbb{C}^N$ there exists S_ε, an operator on $\mathbb{C}^N$, such that $\|S_\varepsilon - S\| < \varepsilon$, the distance between spectra of S and S_ε is less than ε (i.e. for each eigenvalue of S exists eigenvalue of S_ε such that distance between them is less than ε, and vice versa), $S_\varepsilon|_{\mathrm{span}\{e_1,\ldots,e_N\}}$ is an isomorphism, S_ε has N different eigenvalues.*

Proof of Lemma A.2.2. Let $\{e_1,\ldots,e_N\}$ be an orthonormal basis of $\mathbb{C}^N$. Let U be an automorphism of $\mathbb{C}^N$, such that USU^{-1} has a Jordan form:

$$B \equiv USU^{-1} = \begin{pmatrix} B_1 & 0 & & \ldots & 0 \\ 0 & B_2 & 0 & \ldots & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \ldots & B_{N_1-1} & 0 \\ 0 & & \ldots & 0 & B_{N_1} \end{pmatrix}, \tag{A.24}$$

where each B_j is either complex number μ_j or s_j-dimensional Jordan block

$$B_j = \begin{pmatrix} \mu_j & 1 & 0 & \ldots & 0 & 0 \\ 0 & \mu_j & 1 & \ldots & 0 & 0 \\ \vdots & \vdots & \vdots & \ldots & \vdots & \vdots \\ 0 & 0 & 0 & \ldots & \mu_j & 1 \\ 0 & 0 & 0 & \ldots & 0 & \mu_j \end{pmatrix}, \tag{A.25}$$

in the case that $s_j > 1$. Here $j = 1,\ldots,N_1$, and $\mu_1,\ldots,\mu_{N_1}$ are the eigenvalues of B. Let $\delta > 0$ be a small number. Let us construct the matrix B^δ, as follows: B^δ is different from B on nondiagonal elements only, with the difference always less than δ in absolute value. Every N diagonal elements $\lambda_1^\delta,\ldots,\lambda_N^\delta$ are pairwise different. It is easy to see that it is always possible to construct such B^δ. The eigenvalues of B^δ are exactly $\lambda_1^\delta,\ldots,\lambda_N^\delta$, because its characteristic polynomial is $p(x) = \prod_{i=1}^N (\lambda_i^\delta - x)$.

For any given automorphism U of C^N the transformation $C \to U^{-1}CU$ is continuous (on the space of all matrices on C^N). Thus, we can easily choose $\delta_\varepsilon < \varepsilon$ such that $\|U^{-1}B^{\delta_\varepsilon}U - S = \| \le \varepsilon$. Let us define S_ε on H as $U^{-1}B^{\delta_\varepsilon}U$. Clearly S_ε satisfies all the demands of the lemma. □

Now we proceed to prove Proposition A.2.2, as follows hereafter.

If both S_1 and S_2 have distinct eigenvalues, then we apply Lemma A.2.1 twice, interchanging the roles of S_1 and S_2 and obtain (A.17). Otherwise, given any $\delta > 0$, using Lemma A.2.2 we find S_1^δ and S_2^δ, operators on $\mathbb{C}^N$, both have N different eigenvalues and satisfy $\|S_1 - S_1^\delta\| < \delta$, $\|S_2 - S_1^\delta\| < \delta$, $|\rho(S_1) - \rho(S_1^{\delta)}| < \delta$, $|\rho(S_2) - \rho(S_2^\delta)| < \delta$. In the case that S_1 or S_2 already has N distinct eigenvalues (without

loss of generality, S_1), we take $S_1^\delta = S_1$. From the triangle inequality it follows that

$$\|S_1^\delta - S_2^\delta\| \leq \varepsilon + 2\delta, \tag{A.26}$$

from which and from the case that both matrices have N different eigenvalues, follows

$$|\rho(S_1^\delta) - \rho(S_2^\delta)| \leq \varepsilon + 2\delta. \tag{A.27}$$

From the triangle inequality and from (A.27) follows that

$$\begin{aligned} |\rho(S_1) - \rho(S_2)| &\leq |\rho(S_1) - \rho(S_1^\delta)| + |\rho(S_1^\delta) - \rho(S_2^\delta)| + |\rho(S_2^\delta) - \rho(S_2)| \\ &< \delta + \varepsilon + 2\delta + \delta = \varepsilon + 4\delta, \end{aligned} \tag{A.28}$$

which is true for any $\delta > 0$. In the limit $\delta \to 0$ (A.28) becomes (A.17). □

Acknowledgments

The work was supported by the 6th European Commission program, MRTN-CT-204-503661, on "Using mathematical and computer simulation to improve cancer therapy". We would like to express our gratitude to the referee for providing valuable comments and drawing our attention to important references.

References

1. Z. Agur, Randomness, synchrony and population persistence, *J. Theor. Biol.* **112** (1985) 677–693.
2. Z. Agur, The effect of drug schedule on responsiveness to chemotherapy, *Ann. N.Y. Acad. Sci.* **504** (1986) 274–277.
3. Z. Agur, R. Arnon and B. Schechter, Reduction of cytotoxicity to normal tissues by new regimes of cell-cycle phase-specific drugs, *Math. Biosci.* **92** (1988) 1–15.
4. Z. Agur, R. Arnon, B. Sandak and B. Schechter, Zidovudine toxicity to murine bone marrow may be affected by the exact frequency of drug administration, *Exp. Hematol.* **19** (1991) 364–368.
5. Z. Agur, R. Arnon and B. Schechter, Effect of the dosing interval on survival and myelotoxicity in mice treated by Cytosine arabinoside, *Eur. J. Cancer* **28A** (1992) 1085–1090.
6. Z. Agur and J. L. Deneubourg, The effect of environmental disturbances on the dynamics of marine intertidal populations, *Theor. Popul. Biol.* **27** (1985) 75–90.
7. Z. Agur and Y. Dvir, Use of knowledge on $\{\phi_n\}$ series for predicting optimal chemotherapy treatment, *Random & Comput. Dyn.* **2** (1994) 279–286.
8. Z. Agur, R. Hassin and S. Levy, Optimizing chemotherapy scheduling using local search heuristics, submitted.
9. Z. Agur, G. Tagliabue, B. Schechter and P. Ubezio, AZT effect on the bone marrow — A new perspective on the Concorde Trials, *J. Biol. Sys.* **3** (1995) 241–251.
10. L. Cojocaru and Z. Agur, A theoretical analysis of interval drug dosing for cell-cycle-phase-specific drugs, *Math. Biosci.* **109** (1992) 85–97.
11. N. Bellomo, A. Bellouquid and M. Delitala, Mathematical topics on the modelling complex multicellular systems and tumor immune cells competition, *Math. Mod. Meth. Appl. Sci.* **14** (2004) 1683–1733.

12. B. Dibrov, A. Zhabotinsky, Y. Neyfakh, M. Orlova and L. Churikova, Mathematical model of cancer chemotherapy. Periodic schedules of phase-specific cytotoxic-agent administration increasing to selectivity of therapy, *Math. Biosci.* **73** (1985) 1–31.
13. O. Diekmann, H. J. A. M. Hejmans and H. R. Theme, On the stability of the cell-size distribution, *J. Math. Biol.* **19** (1984) 227–248.
14. O. Diekmann, H. J. A. M. Hejmans and H. R. Theme, On the stability of the cell-size distribution II: Time periodic developmental rates, *Comp. Math. Appl.* **12A** (1986) 419–512.
15. T. Kato, *Perturbation Theory for Linear Operators*, 2nd Edn. (Springer-Verlag, 1976).
16. I. Marek, Frobenius theory of positive operators. Comparison theorems, *SIAM J. Appl. Math.* **19** (1970) 607–628.
17. I. Marek and K. Zitny, Two-sided bounds for the spectral radius of a positive linear map, *ZAMM* **64** (1984) 457–461.
18. R. Hoffman *et al.*, *Hematology, Basic Principles and Practice*, 3rd edn. (Churchill Livingstone, 2000).
19. M. Johnson and G. F. Webb, Resonances in age structured cell population models of periodic chemotherapy, *Int. J. Appl. Sci. Comput.* **3** (1996) 57–67.
20. J. D. Murray, *Mathematical Biology*, 2nd edn. (Springer-Verlag, 1993).
21. F. Riesz and B. Sz.-Nagy, *Functional Analysis*, 2nd edn. (Frederick Ungar Publisher, 1965).
22. H. H. Schaefer, *Banach Lattices and Positive Operators* (Springer-Verlag, 1970).
23. D. Serre, *Matrices, Theory and Applications* (Springer-Verlag, 2002).
24. A. Swierniak, Cell cycle as an object of control, *J. Biol. Syst.* **3** (1995) 41–54.
25. A. Swierniak, Optimal control problems arising in cell-cycle-specific cancer chemotherapy, *Cell Prolif.* **29** (1996) 117–139.
26. J. R. Thompson and B. W. Brown, *Cancer Modelling* (Marcel Dekker, 1987).
27. P. Ubezio, G. Tagliabue, B. Schechter and Z. Agur, Increasing 1-b-D-Arabinofuranosylcytosine efficacy by scheduled dosing intervals based on direct measurement of bone marrow cell kinetics, *Cancer Res.* **54** (1994) 6446–6451.
28. G. F. Webb, Convexity of the growth bound of C_0-semigroups of operators, in *Semigroups of Linear and Nonlinear Operators and Applications*, eds. G. R. Goldstein and J. A. Goldstein (Kluwer, 1993), pp. 259–270.
29. G. F. Webb, Resonance phenomena in cell population chemotherapy models, *Rocky Mountain J. Math.* **20** (1990) 1195–1216.