

Y. KHEIFFEZ*, Y. KOGAN*, Z. AGUR*

**MATRIX AND COMPACT OPERATOR DESCRIPTION OF RESONANCE
AND ANTI-RESONANCE IN-CELL POPULATIONS SUBJECTED
TO PHASE-SPECIFIC DRUGS**

1. INTRODUCTION

At present cancer patients are treated by traditional as well as novel modes of anti-cancer therapy. The traditional modes include surgery, radiotherapy and classical chemotherapy, inhibiting growth of rapidly proliferating cells. The novel anti-cancer therapies involve, for example, the disruption of signal transduction pathways that are important for tumor growth, the inhibition of tumor-induced angiogenesis, or immunotherapy, which exploits tumor-specific antigens. Cancer treatment strategies employed for the majority of the patients are currently multi-modal. This multi-modality and the ongoing development of new treatment approaches, generate a fast growing number of different possible protocols for the treatment of cancer. Given the limited human and financial resources for clinical trials, optimal protocols cannot be determined empirically, that is, by trial-and-error alone, as is presently the only existing medical paradigm. Rather, a formal method is necessary for *a priori* suggesting improved drug schedules, according to criteria set by the physician. These criteria may be, for example, life expectancy of the patient, time to reach a specified disease stage, side effects, quality of life, cost of treatment, etc.

Cancer progression in a patient undergoing chemotherapy is a highly nonlinear process. As a result it is impossible to predict, on the basis of biological knowledge and intuition alone, the therapeutic results of changes in treatment schedules. Rather, such predictions must take account of the specific effects of the treatment schedule on the relevant cellular and molecular dynamics of the patient. Calculating these detailed dynamics one can predict the effects of each individual treatment scenario and, subsequently, suggest improved treatment schedules for the drugs in question.

A mathematical model that takes account of cell-cycle dynamics of tumor and host cellular dynamics suggests that intermittent delivery of cell-cycle phase-specific drugs, at intervals equivalent to the mean cell-cycle time, might minimize harmful toxicity without compromising therapeutic effects on target cells (*The Z-Method*, [1,4]). Subsequently, the explicit general formulae has been derived for the growth or decay of cell populations that are subjected to repeated pulse delivery of cell-cycle phase-specific drugs [9, 11], and an

* Institute for Medical Biomathematics, Hate'ena St. 10, POB 282, 60991, Bene-Ataroth, Israel

algorithm has been developed for calculating the required length of treatment for this protocol [10]. The existence of this "*resonance*" *phenomenon* has been further demonstrated for a general class of chemotherapy functions, thus supporting the underlying theory [18, 13, 15, 16].

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 marrow cell-cycle time, animals survive and myelo-toxicity 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 [5, 6, 17, 8].

Only periodic policies were considered in the above mentioned models. Therefore treatments were to be given at regular times $t_0 + il$, for $i = 1, \dots, n$ and a given time, l , between the onsets of consecutive treatments. It was also assumed that all treatment periods are of the same given length. Concluding from [10], if the treatment duration is shorter than the host cells life cycle, and if we choose l to be a multiple of the host cells life cycle, each treatment will strike the host cell and its descendants at the same point of the life cycle and therefore, except for the damage caused to host cells by the first treatment, no further damage will be caused by the following treatments.

For some specific types of cell-cycle-duration's distributions (normal in [4] and some other [18, 11] described later in this work) it was showed numerically ([4, 18, 11]) that resonance in cells population growth takes place when drug is supplied regularly in short pulses every τ , where τ equals the mean cell-cycle-duration or is its integer or a fractional multiple. It is shown that resonance becomes sharper as variance of the cell-cycle-duration's distribution is smaller.

In this work we show that the cell population dynamics under drug treatment can be modelled by iterative compact operator application on initial cell age-distribution. It is further shown that the model can be chosen discrete. Methods for fast estimation of population growth-rate are proposed.

2. DEFINITION OF THE PROBLEM

2.1. EFFICIENT TREATMENT CRITERIA

In this section we consider medical criteria of effective cancer treatment. As many phase-specific drugs can have cumulative toxicity and sometimes even carcinogenicity, the overall duration of the treatment, in principle, should be limited. In addition, at any moment of treatment, the number of drug-susceptible host cells that must exceed a certain level, in order not to endanger the patient's life. We consider a tumor as eliminated if the number of tumor cells drops beneath some threshold number. Thus we suppose that there are three major cancer treatment criteria: time of treatment, minimal quantity of host cells

that must survive, efficacy of treatment (minimal fraction of tumor cells that must be eliminated).

We state the problem of effective treatment search as follows: find any plausible treatment subject to the above mentioned three strict requirements, posed by medical observations, and prove that the constraints are indeed fulfilled. The approach adopted here is that the question of optimization is dispensable: if a given protocol fulfills prescribed criteria, then it seems unnecessary to search for a better one, especially if it is hard to do so. Generally, in order to analytically prove that a given treatment is optimal, it is necessary to significantly simplify the model. Such simplifications could render the model inapplicable to real-life. It also seems that numerical optimization procedures, such as in [7], cannot always guarantee that the resulting treatment will fulfill all the prescribed constraints. Indeed, the general idea of the cited work is as follows: each criterion has been assigned with some weight and in each time step the algorithm chooses the best performance. Some randomness has been introduced in order to make optimization "more global" (Monte-Carlo, annealing methods). Evidently, this method does not guarantee that the resulting treatment always satisfies the strict medical demands.

In order to develop efficient treatment strategies (as defined above) it is necessary to develop fast methods for estimating the number of host and cancer cells at any time. The present work dwells in this task.

3. MATHEMATICAL AND COMPUTATIONAL MODELS

3.1. NOTATIONS AND ASSUMPTIONS

We assume that the drug eliminates all cells during the S -phase of their cycle.

Let us also denote the first moment during a cell's S -phase as age zero. Let $n(a, t)$ be the age density of cells at time t . Assume that the drug is present in the organism every τ time units for a short period δ . Only the cells which enter zeroth age at time intervals $[m\tau + \delta, (m + 1)\tau - |S|]$ can survive. Such an interval will be denoted "*m-th drug-free interval*".

The distinct feature of the present model is that we consider cells at fixed age (age zero) between subsequent treatments $n(0, t), t \in [m\tau + \delta, (m+1)\tau - |S|]$, rather than cell's ages distribution for fixed time t (this resembles the distinction between Eulerian versus Lagrangian formalism in fluid mechanics).

We propose to consider two different models, based on discrete and continuous time scale respectively. The major benefit of the discrete model is its finite dimensional matrix formalism, whereas the continuous model is characterised by operator formalism. It is assumed in both cases that cell's life-span may vary from T_b to T_m with a distribution function f having a single maximum. It is further assumed that $T_b > 0$ and T_m are either positive numbers or ∞ .

3.2. MODELS' PRECISION

It should be noted that currently, experimental measurements of most of cells parameter (such as distribution function f of cell-cycle duration) have low precision. Evidently, the maximal precision of mathematical models is determined by the precision of the experimental data. For example, most existing models (e.g., [11]) assume that the distribution function $f(t)$ decays nearly exponentially to zero when t tends to ∞ . Thus, there exists t_0 , such that for any $t > t_0$ $\int_{t_0}^{\infty} f(t)dt$ and $f(t)$ are less than the resolution of the experimental measurements. In this case we may assume that $f(t) \equiv 0$ for $\forall t > t_0$ without affecting the model's precision.

3.3. CONTINUOUS MODEL

The equations, describing cell age distribution are (Appendix A)

$$n_t(a,t) + n_a(a,t) = -(\beta(a) + \eta(a,t))n(a,t), \quad a > 0, t > 0 \quad (1)$$

$$n(0,t) = 2 \int_{T_b}^{T_m} \beta(a)n(a,t)da, \quad t > 0, \quad (2)$$

$$n(a,0) = n_0(a), a > 0, \quad (3)$$

where n_a and n_t mean partial derivatives $\partial n/\partial a$ and $\partial n/\partial t$, respectively. The age specific division rate of cells is $\beta(a)$, the age specific mortality rate (due to natural and external courses) 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 of points on which β has nonzero values) is a subset of $[T_b, T_m]$.

In this particular model we assume that division and mortality rates of population growth are independent from population density. In very general case division rate of cell population can depend on the overall cell number. This event can take place in noncancerous cells populations. In this cases β and η depends also on the total quantity of he cells, $N(t) \int_0^{T_m} n(a,t)da$.

Thus in this case, which is out of the scope of the present article, $\beta(N, a)$ is a decreasing and $\eta(N, a, t)$ is an increasing functions of N (negative feedback regulation of overall cell's quantity).

Let us find general solutions of (1-3) in the form $n(a, t) = m(a, t - a)$ (it is clear that $\eta = t - a$ is a characteristic curve of the equation (1)). Let us denote $\bar{\eta}(a,t) = \eta(a,t+a)$. The equations (1-3) take the following form:

$$m_a(a, \zeta) = -(\beta(a) + \bar{\eta}(a, \zeta))m(a, \zeta), \quad a > 0, \quad (4)$$

where $\zeta = t - a$,

$$m(0, \zeta) = 2 \int_{T_b}^{\infty} \beta(a)m(a, \zeta + a)da, \quad \zeta = t > 0, \quad (5)$$

$$m(a, -a) = n_0(a), \quad a > 0. \quad (6)$$

It is easy to see that

$$\begin{aligned} \int_{T_b}^a \beta(\alpha)d\alpha &= \int_{T_b}^a \frac{f(\alpha)}{\int_{\alpha}^{T_m} f(u)du} d\alpha = - \int_{T_b}^a \left(\ln \left(\int_{\alpha}^{T_m} f(u)du \right) \right)' d\alpha = \\ &= \ln \left(\frac{\int_{T_b}^{T_m} f(u)du}{\int_a^{T_m} f(u)du} \right) = - \ln \left(\int_a^{T_m} f(u)du \right), \end{aligned} \quad (7)$$

because $\int_{T_b}^{T_m} f(u)du = 1$ (f is distribution function on $[T_b, T_m]$).

Thus the general solution of (4) is

$$m(a, \zeta) = \begin{cases} r(\zeta)e^{-\int_0^a \bar{\eta}(\alpha, \zeta)d\alpha}, & 0 \leq a < T_b \\ r(\zeta) \int_a^{T_m} f(u)du e^{-\int_0^a \bar{\eta}(\alpha, \zeta)d\alpha}, & T_b \leq a < T_m \\ 0, & T_m \leq a, \end{cases} \quad (8)$$

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

$$n(a, t) = \begin{cases} r(t-a)e^{-\int_0^a \bar{\eta}(\alpha, t-a)d\alpha}, & 0 \leq a < T_b \\ r(t-a) \int_a^{T_m} f(u)du e^{-\int_0^a \bar{\eta}(\alpha, t-a)d\alpha}, & T_b \leq a < T_m \\ 0, & T_m \leq a. \end{cases} \quad (9)$$

The boundary condition (3) looks as

$$n_0(a) = \begin{cases} r(-a)e^{-\int_0^a \bar{\eta}(\alpha, -a) d\alpha}, & 0 \leq a < T_b \\ r(-a) \int_a^{T_m} f(u) du e^{-\int_0^a \bar{\eta}(\alpha, -a) d\alpha}, & T_b \leq a < T_m \\ 0, & T_m \leq a, \end{cases} \quad (10)$$

or

$$r(-a) = \begin{cases} n_0(a) e^{\int_0^a \bar{\eta}(\alpha, -a) d\alpha}, & 0 \leq a < T_b \\ n_0(a) \frac{e^{\int_0^a \bar{\eta}(\alpha, -a) d\alpha}}{\int_a^{T_m} f(u) du}, & T_b \leq a < T_m. \end{cases} \quad (11)$$

It follows from (9) that

$$n(0, t) = r(t). \quad (12)$$

Boundary condition (2) reads as

$$r(t) = 2 \int_{T_b}^{T_m} \beta(a) r(t-a) e^{-\int_{T_b}^a \beta(\alpha) d\alpha} e^{-\int_0^a \bar{\eta}(\alpha, t-a) d\alpha} da, \quad t > 0. \quad (13)$$

From (7) follows that

$$\begin{aligned} \beta(a) e^{-\int_{T_b}^a \beta(\alpha) d\alpha} &= \beta(a) \frac{\int_a^{T_m} f(u) du}{\int_{T_b}^{T_m} f(u) du} = \\ &= \frac{f(a)}{\int_a^{T_m} f(u) du} \cdot \frac{\int_a^{T_m} f(u) du}{\int_{T_b}^{T_m} f(u) du} = \frac{f(a)}{\int_{T_b}^{T_m} f(u) du} = f(a). \end{aligned} \quad (14)$$

From (13) and (14) follows that

$$r(t) = 2 \int_{T_b}^{T_m} f(a) r(t-a) e^{-\int_0^a \bar{\eta}(\alpha, t-a) d\alpha} da. \quad (15)$$

Now we restrict ourselves to less general and slightly different model. We assume an extreme discontinuous case in which mortality is caused to all cells instantly by the applied

drug and only during the drug applications. This model is close to reality, indeed, the drug's efficiency is high and the time of drug solution in blood is relatively short.

It was also assumed that rate of population growth is independent from population density. Thus cells, entering phase S less than $|S|$ (S -phase duration) before treatment die inevitably and thus can be considered as dying in the age 0 without any consequences to the model. These facts leads to the following equation for r :

$$r(t) = 2\theta(t) \int_{T_b}^{T_m} f(a)r(t-a)da, \quad (16)$$

where $\theta(t)$ has only two values 0 (for all t less than $|S|$ before treatment or during the treatment) and 1 in all other cases. Thus $\theta(t)$ represents the drug action on cell population.

General solution of $n(a, t)$ looks as

$$n(a, t) = \begin{cases} r(t-a), & 0 \leq a < T_b \\ r(t-a) \int_a^{T_m} f(u)du, & T_b \leq a < T_m \\ 0, & T_m \leq a. \end{cases} \quad (17)$$

Note that from (12) follows that $r(t)$ is a cell's density at age 0 at time t . In order to determine $n(a, t)$ it is necessary and sufficient to determine $r(t)$. In our model cell population dynamics is described completely by $n(0, t)$ and this is Eulerian formalism, as mentioned before.

Equation (11) determines $r(t)$ for negative t , equation (16) (and equation (15) in general case) defines $r(t)$ recursively for positive t . Indeed, the right-hand side of (16) is either zero or contains $r(t-a)$, where $0 < T_b < a < T_m$. Let us define the following partition of \mathbb{R} :

$$R = \bigcup_{n=0}^{\infty} J_n, \quad J_0 = (-T_m, 0], \quad J_n = [(n-1)T_b, nT_b], \quad \forall n \geq 1, \quad (18)$$

then $r(t)$ on J_0 is defined by (11) and for every $n > 0$ $r(t)$ on J_n is found by substitution of $r(t)$, defined on J_0, \dots, J_{n-1} to (15) or to (16). Let us assume that T_m is finite and let us define

$$M = \left[\frac{T_m - T_b}{T_b} \right]. \quad (19)$$

From (16) and from the fact that $support(f) \subseteq [T_b, T_m]$ follows that for any $t \in [0, T_b]$

$$\begin{aligned}
 r(t + nT_b) &= 2\theta(t + nT_b) \int_{t+nT_b-T_m}^{t+nT_b-T_b} f(t + nT_b - u)r(u)du = \\
 &= 2\theta(t + nT_b) \int_{T_b(n-M-1)}^{T_b n} f(t + nT_b - u)r(u)du = \\
 &= 2\theta(t + nT_b) \sum_{i=0}^M \int_{T_b(n-M-1)}^{T_b(n-i)} f(t + nT_b - u)r(u)du = \\
 &= 2\theta(t + nT_b) \sum_{i=0}^M \int_0^{T_b} f(t + (i+1)T_b - v)r(v + (n-i-1)T_b)dv.
 \end{aligned} \tag{20}$$

Let us define

$$r_j(t) = r(t + jT_b), \quad \forall j \in Z, \forall t \in [0, T_b] \tag{21}$$

From (20) and (21) follows that

$$\begin{aligned}
 r_n(t) &= 2\theta(t + nT_b) \sum_{i=0}^M \int_0^{T_b} f(t + (i+1)T_b - v)r_{n-i-1}(v)dv = \\
 &= 2\theta(t + nT_b) \sum_{i=0}^M T_i(r_{n-i-1}) \quad \forall n \in Z,
 \end{aligned} \tag{22}$$

where T_i is a linear integral operator defined as

$$\begin{aligned}
 T_i g(t) &= \int_0^{T_b} f(t + (i+1)T_b - v)g(v)dv = \\
 &= \int_0^{T_b} f^i(t-v)g(v)dv \quad i \in \{0, 1, \dots, n\}, g \in L^1,
 \end{aligned} \tag{23}$$

where $f^i(x) \equiv f(x + (i+1)T_b)$. In more convenient form (22) can be presented as

$$\begin{pmatrix} r_n(t) \\ r_{n-1}(t) \\ \dots \\ r_{n-M}(t) \end{pmatrix} = 2\theta(t + nT_b) \begin{pmatrix} T_0 T_1 \dots T_M \\ Id \ 0 \dots 0 \\ \dots \\ 0 \dots 0 \ Id \end{pmatrix} \begin{pmatrix} r_{n-1}(t) \\ r_{n-2}(t) \\ \dots \\ r_{n-M-1}(t) \end{pmatrix}, \tag{24}$$

i.e. $r_n(t), \dots, r_{n-M}(t)$ are evaluated through $r_{n-1}(t), \dots, r_{n-M-1}(t)$. (2) gives r_j for negative j .

In the next section we shall see that functions $r_n(t)$ may be represented as vectors in R^N for some big N , and operators T_i may be represented as matrices with any accuracy

(depending on N). $\theta(t + nT_b)$ should be represented as a matrix Θ_n of dimension $N \cdot M \times N$, such that

$$\Theta_n(i + kM, j) = \begin{cases} 0, & i \neq j \\ 1 & i = j \text{ and there is no drug in } \frac{i}{N} + kN \\ 0 & i = j \text{ and there drug in } \frac{i}{N} + kN, \end{cases} \quad (25)$$

where $k = 0, 1, \dots, M-1$. Thus (24) may be presented as linear equation. The population properties depend upon consequential application of the matrix

$$A_n = \Theta_n \begin{pmatrix} T_0 T_1 \dots T_M \\ Id \ 0 \dots 0 \\ \dots \\ 0 \dots 0 \ Id \end{pmatrix} \text{ on vector which contains initial conditions.}$$

If the treatment is cyclic, and cycle size is equal to a divisor of MT_b than Θ_n is independent from n and the population dynamics is described by iteration of matrix $A \equiv A_n$. In this case the population properties depend on spectral properties of A , as is shown bellow. In what follows we discuss this particular case.

3.4. DISCRETE TIME FORMULATION

In this section we describe discrete time formalism, i.e. finite dimensional vectors are used instead continuous functions.

Let N be a big natural number, let $t_i = iT_b/n$, $i \in Z$. Any continuous function $g(t)$ in $[0, T_b]$ can be approximated by a vector $g \in R^N$, where $g_i = g(t_i)$. Then operator T_k in (23) may be approximated with any accuracy by operator ${}_k A : R^N \rightarrow R^N$ as follows

$${}_k A(g)_j = 2 \sum_{i=0}^{N-1} \frac{f_{j-i}^k}{N} g_i \quad (26)$$

where g is an N -dimensional vector ($g_i = g(t_i)$), $f_{j-i}^k = f^k(t_j - t_i)$. Thus the matrix ${}_k A$ in (26) is defined as follows:

$${}_k A_{s,t} = \frac{f_{s-t}^k}{N} \quad s, t \in \{1, \dots, N\}. \quad (27)$$

It is clear that the matrix ${}_k A$ has the following properties: ${}_k A_{ij} \geq 0$ for any $i, j \in \{1, \dots, N\}$ and ${}_k A_{ij} = {}_k A_{i+1, j+1}$ for any i, j for which the last equality is defined. The equation (23) may be formulated in discrete form as follows:

$$T_k(g)(t_j) = \sum_{i=0}^{N-1} f^k(t_j - t_i)g(t_i) / N. \quad (28)$$

It is proved in Appendix B that accuracy grows as N is chosen bigger.

3.5. DISTRIBUTION FUNCTION F

According to Dibrov et al ([11]), the cell-cycle-length distribution function is of the form

$$f(a) = \frac{k^m (a - T_b)^{m-1}}{(m-1)!} e^{-k(a-T_b)} \theta(a - T_b), \quad (29)$$

where

$$\theta(t) = \begin{cases} 1, & t \geq 0 \\ 0, & t < 0. \end{cases}$$

We assume that in the case of cancer cells m is larger and k is smaller than that of normal cells, so that the distribution function f of cancer cells has larger variance and its maximum is shifted to the right. We assume, as mentioned earlier, that T_b is the same for the cancer and the normal cell populations. In any case f has a single maximum and tends exponentially to 0 for large a . Thus, given any accuracy ε , it is possible to assume that $f(a) \equiv 0$ for $t > T_m$ where T_m depends on ε , k and m .

3.6. CELL-POPULATION GROWTH RATE AND SPECTRAL PROPERTIES OF OPERATOR T

In this part we use matrix and operator formalism, developed in the previous sections in order to investigate the dynamics of cell populations that are subjected to regular phase-specific drug treatment. The main questions are as follows:

1. Do qualitative differences in the population dynamics exist between the cases of constant and distributed life-cycle durations?
2. Will the given population grow or decay in the course of treatment?

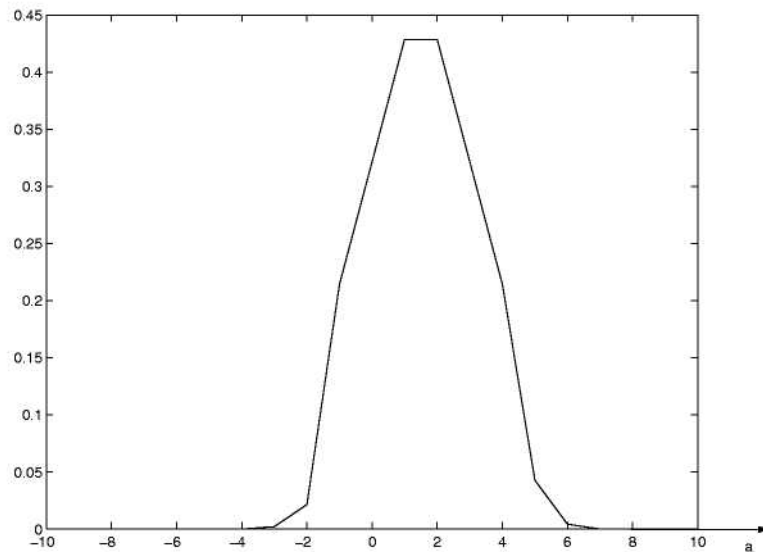


Fig. 1. A graph of $f(a - T_b)$

3. Will population growth-rate and age-distribution tend to some constant values after sufficiently many iterations? If so, how are these values related to the operator's properties?
4. What is the "resonance phenomenon" from the mathematical point of view?

The answer to the first question is affirmative: in the case of constant life-cycle duration, τ' , if $\tau \neq \tau'$ then cell population will be inevitably eliminated ([18, 13, 7]) and the time of elimination is bounded by $(\tau^2 / |\tau - \tau'|)$, as may be easily inferred from the above cited papers. In the case of varying cell-cycle duration, even if the mean cell-cycle duration, τ' has a different periodicity than that of drug treatment, the population may grow with each iteration. Matrix formalism can illustrate this event: let $f(a), a \in \mathbb{Z}$ be defined in the table and in Fig.1 (its support is $\{-3, \dots, 5\}$). The expectation $\sum_{n=-\infty}^{n=\infty} f(n)$ equals to 1.5423, i.e.

the distribution is shifted strongly to the right and this expectation is a deviation of the mean cycle duration from the treatment period. This fact, inevitably, leads to population extinction in the constant cycle duration model. In contrast, for 10×10 matrix the eigenvalue of maximal absolute value is 1.1515. This means, that in the case where the initial discrete time-distribution of cells at the age 0 equals to the eigenvector, corresponding to the maximal eigenvalue, the population will increase by 1.1515 following each treatment cycle.

N	-3	-2	-1	0	1	2	3	4	5	6
$f(n)$	0.002	0.021	0.214	0.322	0.429	0.429	0.322	0.214	0.043	0.004

In order to answer the second and third questions we use the following statements from matrix theory:

- [i] If all elements of a matrix A are nonnegative, then there is a real nonnegative eigenvalue of A , which equals its spectral radius. We call it *maximal eigenvalue of A* . This theorem may be found in ([14]).
- [ii] In generic case, the discrete time-distribution of cells tends to some superposition of eigenvectors of the eigenvalues of A with the absolute values being equal to the spectral radius of A . The population growth rate tends to this spectral radius, as the number of steps increases (Appendix C).
- [iii] If the matrix A has a single eigenvalue, which is equal to its spectral radius, and if this eigenvalue has one corresponding dimensional space of eigenvectors, then the process described in [ii] is exponential (Appendix C). This was also the case in 50 computer simulations we have performed for checking this result. We have yet to understand whether or not this is a generic case.

It is clear from the above discussion that after many generations of cyclic treatment, with cycle size being equal to a divisor of $M T_b$, the population growth rate generically approaches the spectral radius of the matrix (operator) describing it. It is easy to numerically compute the spectral radius of any matrix (see [14]). Therefore, it follows that it is possible to evaluate the growth rate of the population after many iterations for any cell-cycle-duration distribution function f , and a regular treatment by a phase-specific drug: it is necessary to perform a discrete approximation with appropriate accuracy and subsequently, to calculate the spectral radius of the resulting matrix.

3.7. SUMMARY OF MATHEMATICAL RESULTS

The above results are summarized as follows:

1. Analytical solution of differential equations, describing cell-age-distribution (whose growth is independent of cell density) dynamics under drug treatment, has been obtained. Euler formulation has been used (in analogy to fluid mechanics), i.e. distributions of the zeroth age in time, rather than the age distribution for fixed time has been studied.
2. Under regular drug treatment this solution has been represented as iterative application of compact integral operator on the distribution of the zeroth aged cells in the initial time interval.
3. Finite dimensional approximation has been developed and its accuracy has been estimated.
4. It has been shown that the finite dimensional operators from (3) have a real positive eigenvalue, equal to their spectral radius. The eigenvectors, corresponding to this eigenvalue, correspond to distributions whose growth rate is maximal. The cell population growth-rate tends to the spectral radius as number of iterations increases. In the generic case, any initial distribution tends to some linear combination of of eigenvalues' eigenvectors with the absolute values equalling the operator's spectral radius. This process is exponential in the case of only one eigenvalue having maximal absolute value, and in the case of the space of its eigenvectors being one dimensional.
5. The resonance (antiresonance) phenomenon is stated mathematically: the resonance (antiresonance) is the existence of maximum (minimum) in the dependence of the

operator's spectral radius on the relation between the age-distribution function f and the treatment period, τ . Numerically it has been shown that the spectral radius increases as τ' (mean cell cycle duration) approaches τ and the variation of f decreases. We have yet to prove this result analytically.

4. PERSPECTIVES

As stated above, the maximal rate of population growth during each drug-free interval tends (after a large number of treatments) to the spectral radius of the matrix A . Our future investigation will focus on the influence of the cell-cycle distribution on the spectral properties of the matrix A . In particular we will investigate how the variance in cell-cycle duration and the deviation of the treatment cycle from the mean cell-cycle influence the spectral radius of the matrix A (in the case of a cyclic treatment). Non-cyclic treatments are studied at present as well as cell populations whose growth rates depend on cell density. We also investigate the dynamics of heterogeneous cell tissues, in which cells from different regions have different distributions of cell-cycle-duration. This is particular relevant to cancer tissues with inhomogeneous nutrition of different tumor parts.

5. APPENDIX

5.1. DERIVATION OF CELL AGE DENSITY EQUATION

In this section differential equations for cell population dynamics are derived (these equations appear in many different works ([18],[11]) with no derivation). In age-structured cell population models individual cells are distinguished by cell age a . The *age-density* of cells at time t is $n(a,t)$. The total population of cells at time t is $\int_0^\infty n(a,t) da$. The equations for the untreated tumor cell population are

$$n_t(a,t) + n_a(a,t) = -(\beta(a) + \eta(a,t))n(a,t), \quad a > 0, t > 0, \quad (30)$$

$$n(0,t) = 2 \int_0^\infty \beta(a)n(a,t)da, \quad t > 0, \quad (31)$$

$$n(0,t) = n_0(a), \quad a > 0. \quad (32)$$

The age specific division rate of cells is $\beta(a)$, the mortality rate 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 .

Comments Let us denote the number of cells at the ages ranging from a to b at the time as $N(a, b, t)$. It is obvious that

$$N(a, b, t) = \int_a^b n(\alpha, t) d\alpha. \quad (33)$$

Differentiating (33) relative to t we obtain

$$N_t(a, b, t) = \int_a^b n_t(\alpha, t) d\alpha. \quad (34)$$

On the other hands, let us consider the changes in the number of cells at the ages ranging from a to b during short time interval Δt , $b > a > 0$:

$$N(a, b, t + \Delta t) - N(a, b, t) \approx \Delta t(n(a, t) - n(b, t)) - \Delta t \int_a^b (\beta(\alpha) + \eta(\alpha, t)) n(\alpha, t) d\alpha. \quad (35)$$

Indeed, during interval Δt approximately $\Delta t n(a, t)$ cells enter the age interval and $\Delta t n(b, t)$ exit it in natural way. When the cell dies or divides (offsprings are always in the age 0) it exits the age interval $[a, b]$. Variation of $\eta(\alpha, t)$ is assumed to be of order Δt , so it contribute to variation of $\Delta t \int_a^b \eta(\alpha, t) n(\alpha, t) d\alpha$ with term of order $(\Delta t)^2$ that is omitted.

Dividing both sides of (35) with Δt and tending Δt to 0 we get

$$N_t(a, b, t) = n(a, t) - n(b, t) - \int_a^b (\beta(\alpha) + \eta(\alpha, t)) n(\alpha, t) d\alpha, \forall b > a > 0, t > 0. \quad (36)$$

Equating right hand sides of (34) and (36) we get

$$\int_a^b n_t(a, t) d\alpha = n(a, t) - n(b, t) - \int_a^b (\beta(\alpha) + \eta(\alpha, t)) n(\alpha, t) d\alpha, \forall b > a > 0, t > 0. \quad (37)$$

Dividing (37) by $b - a$, tending b to a we get (30).

The expression (31) is obtained in the following way: all new cells (age 0) come from cells from all ages proportional to age density. Every mature cell gives two cells of the age 0.

5.2. DISCRETE CASE

In this appendix we show that (22) and (24) can be approximated in a discrete form to any accuracy.

Lemma 1 Assume that for some $\varepsilon > 0$, some $k \in \{0, \dots, M\}$ there exists δ , so that from $|t_1 - t_2| < \delta$ for follows $\forall t_1, t_2 \in [0, T_b] |f^k(t_1) - f^k(t_2)| < \varepsilon$ Then for any $g \in L^1$ and any $k \in \{0, \dots, M\}$ from $|t_1 - t_2| < \delta \forall t_1, t_2 \in [0, T_b]$ follows $|T_k(g)(t_1) - T_k(g)(t_2)| < \varepsilon \|g\|_1$

Proof

$$\begin{aligned} & \forall t_1, t_2 \in [0, T_b], |t_1 - t_2| < \delta: \\ & |T_k(g)(t_1) - T_k(g)(t_2)| \leq \int_0^{T_b} |f^k(t_1 - u) - f^k(t_2 - u)g(u)| du \leq \varepsilon \|g\|_1. \end{aligned} \quad (38)$$

Definition For any given $\varepsilon > 0$ let us denote by $W_{\delta, \varepsilon}$ a subspace of $L^1([0, T_b])$ such that for any $h \in W_{\delta, \varepsilon}$ from $|t_1 - t_2| < \delta$ for $\forall t_1, t_2 \in [-T_b, T_b]$ follows $|h(t_1) - h(t_2)| < \varepsilon$

Lemma 1 states that if $f^k \in W_{\delta, \varepsilon}$ then $T_k(g) \in W_{\delta, \varepsilon \|g\|_1}$ for any $g \in L^1[0, T_b]$. For any given $\varepsilon > 0$ let N be a natural number such that $f \in W_{\frac{1}{N}, \varepsilon}$ (f^k is continuous on compact interval $[-T_b, T_b]$, so it is easy to see that for any $\varepsilon > 0$ there exists such N). Let

$$t_j = \frac{j}{N}, \quad j = 0, 1, \dots, N. \quad (39)$$

Then for any $g \in W_1$ $g \in W_{\frac{1}{N}, \varepsilon \|g\|_1}$, and for any $j \in \{0, \dots, N\}$ we have

$$\begin{aligned} & \left| T_k(g)(t_j) - \sum_{i=0}^{N-1} f^k(t_j - t_i)g(t_i) / N \right| = \\ & \left| \int_0^{T_b} f^k(t_j - u)g(u)du - \sum_{i=0}^{N-1} f^k(t_j - t_i)g(t_i) / N \right| = \\ & = \left| \sum_{i=0}^{N-1} \left(\int_{i/N}^{(i+1)/N} f^k(t_j - u)g(u)du - f^k(t_j - t_i)g(t_i) / N \right) \right| = \\ & = \left| \sum_{i=0}^{N-1} \int_{i/N}^{(i+1)/N} (f^k(t_j - u)g(u) - f^k(t_j - t_i)g(t_i)) du \right| = \\ & = \left| \sum_{i=0}^{N-1} \int_{i/N}^{(i+1)/N} (f^k(t_j - u)g(u) - \right. \\ & \left. - f^k(t_j - t_i)g(u) + f^k(t_j - t_i)g(u) - f^k(t_j - t_i)g(t_i)) du \right| \leq \\ & \leq \left| \sum_{i=0}^{N-1} \int_{i/N}^{(i+1)/N} g(u)(f^k(t_j - u) - f^k(t_j - t_i)) du \right| + \end{aligned}$$

$$+ \left| \sum_{i=0}^{N-1} \int_{i/N}^{(i+1)/N} f^k(t_j - t_i)(g(u) - g(t_i)) du \right| \leq$$

(using the fact that f^k is always nonnegative)

$$\leq \varepsilon \|g\|_1 + 4\varepsilon \|g\|_1 \sum_{i=0}^{N-1} \frac{f^k(t_j - t_i)}{N} = \varepsilon \|g\|_1 \left(1 + 2 \sum_{i=0}^{N-1} \frac{f^k(t_j - t_i)}{N} \right). \quad (40)$$

From the fact that

$$\lim_{N \rightarrow \infty} \sum_{i=0}^{N-1} \frac{f^k(t_j - t_i)}{N} = \int_0^D f^k(t_j - u) du \leq \int_{-\infty}^{\infty} f^k(t_j - u) du = 1,$$

follows that for N big enough $\sum_{i=0}^{N-1} \frac{f^k(t_j - t_i)}{N} \leq 1.5$ and using (40) we obtain

$$\left| T_k(g)(t_j) - \sum_{i=0}^{N-1} f^k(t_j - t_i) g(t_i) / N \right| \leq 4\varepsilon \|g\|_1 \quad (41)$$

The inequality 41 means that given any accuracy, any number G and any function g in $L^1[0, T_b]$ there exists natural number N , such that for any point t_j , $j \in \{0, \dots, N\}$, defined in 39, $T_k(g)(t_j)$ can be approximated with $\sum_{i=0}^{N-1} f^k(t_j - t_i) g(t_i) / N$, provided that $\|g\|_1 \leq G$. In tumor treatment simulation we consider only the cases that quantities of hosts and tumor cells are bounded. Thus G is prescribed in each model by biological conditions.

5.3. DEPENDANCE OF THE OF POPULATION GROWTH-RATE ON THE SPECTRAL RADIUS OF THE MATRIX A

Let us consider any matrix A iteratively applied on some vector \vec{v} . In this section we would like to answer two following questions:

- Does the limit $\lim_{m \rightarrow \infty} \frac{\|A^{m+1}\vec{v}\|}{\|A^m\vec{v}\|}$ exist and what is its value?
- Does the limit $\lim_{m \rightarrow \infty} \frac{A^m\vec{v}}{\|A^m\vec{v}\|}$ exist and what is its value?

In the case that if is an eigenvector of A relative to eigenvalue λ the answers to the above questions are trivial: $\frac{A^{m+1}\vec{v}}{A^m\vec{v}} \equiv \lambda\vec{v}$ and $\frac{A^m\vec{v}}{\|A^m\vec{v}\|} \equiv \frac{\vec{v}}{\|\vec{v}\|}$. In order to answer the above

questions let us work in the coordinates, in which A has Jordanian form.

The following lemma can be easily proved by induction:

Lemma Assume that $n \times n$ matrix B has the form of Jordan block, i.e. $B(i,i) = \lambda$, $B(i,i+1) = 1$ and $B(i,j) = 0$ for $j \neq i, i+1$. Let $\{e_i\}_{i=1}^n$ be standard basis of R^n . Then for any natural m and for any $k \leq n$.

$$B^m e_k = \sum_{j=0}^{\min(k-1,m)} \binom{m}{j} \lambda^{m-j} e_{k-j} \quad (42)$$

For $m \gg k$ and for $j \leq k$ it follows that $\binom{m}{j} = \frac{m!}{j!(m-j)!} \simeq \frac{m^j}{j!}$. Thus

$$B^m e_k \simeq \lambda^{m-k+1} \frac{m^{k-1}}{(k-1)!} e_1 + O(m^{k-2}) \quad (43)$$

for big m . Thus for any $\vec{v} = \sum_{j=1}^n a_j e_j$

$$\begin{aligned} B^m \vec{v} &= \sum_{k=1}^n m^{k-1} a_k \left(\frac{\lambda^{m-k+1}}{(k-1)!} O(1) e_1 + O(1/m) \right) = \\ &= \lambda^m \sum_{k=1}^n m^{k-1} a_k \left(\frac{1}{\lambda^{k-1} (k-1)!} O(1) e_1 + O(1/m) \right) = \end{aligned}$$

in the case that $k_0 \leq n$ is the largest index such that $a_{k_0} \neq 0$

$$= m^{k_0-1} \lambda^m \left(\frac{1}{\lambda^{k_0-1} (k_0-1)!} O(1) a_{k_0} e_1 + O(1/m) \right). \quad (44)$$

This means that for $\vec{v} \neq 0$ $\lim_{m \rightarrow \infty} \frac{\|B^{m+1} \vec{v}\|}{\|B^m \vec{v}\|} = \lambda$ and $\lim_{m \rightarrow \infty} \frac{B^m \vec{v}}{\|B^m \vec{v}\|} = e_1$. Any matrix can be represented

in Jordan form by passage to some coordinates. So, without loss of generality we assume that A has Jordan form, than $A = A_1 \otimes \dots \otimes A_s$, where A_j are Jordan blocks with eigenvalues λ_j of dimension $n_j \times n_j$, $j = 1, \dots, s$. Let $\rho(A)$ denotes the sector radius of A . Let us assume,

without loss of generality, that $\rho(A) = |\lambda_1| = |\lambda_2| = \dots = |\lambda_t| > |\lambda_{t+1}| \geq$

$\dots \geq |\lambda_s|$ and $n_1 = n_2 = \dots = n_r > n_{r+1} \geq \dots \geq n_t$. Let $N = n_1 + \dots + n_s$. Given any vector $\vec{v} \in R^N$ there is probability 1 that all it's components are nonzero (generic case). From (43) it follows that

$$A^m \vec{v} = \rho(A) \left(m^{n_1-1} \left(O(1) \frac{1}{\lambda^{n_1-1} (n_1-1)!} a_1 e_1 + O(1/m) \right) + \right.$$

$$\begin{aligned}
 & m^{n_2-1} \left(O(1) \frac{1}{\lambda^{n_2-1} (n_2-1)!} a_{1+n_1} e_{1+n_1} + O(1/m) \right) + \dots \\
 & + m^{n_t-1} \left(O(1) \frac{1}{\lambda^{n_t-1} (n_t-1)!} a_{1+n_1+\dots+n_{t-1}} e_{1+\dots+n_{t-1}} + O(1/m) \right) + O \left(\frac{\lambda_{t+1}}{\rho(A)} \right)^m = \\
 & = \rho(A)^m \left(m^{n_1-1} O(1) \frac{1}{\lambda^{n_1-1} (n_1-1)!} (a_1 e_1 + a_{1+n_1} e_{1+n_1} + \dots \right. \\
 & \left. + a_{1+n_1+\dots+n_{r-1}} e_{1+\dots+n_{r-1}} + O(1/m) \right) + O \left(\frac{\lambda_{t+1}}{\rho(A)} \right)^m \quad (45)
 \end{aligned}$$

Thus in generic case it is easy to see that

$$\begin{aligned}
 & \lim_{m \rightarrow \infty} \frac{\|A^{m+1} \vec{v}\|}{\|A^m \vec{v}\|} = \rho(A) \text{ and} \\
 & \lim_{m \rightarrow \infty} \frac{B^m \vec{v}}{\|B^m \vec{v}\|} = \frac{a_1 e_1 + a_{1+n_1} e_{1+n_1} + \dots + a_{1+n_1+\dots+n_{r-1}} e_{1+\dots+n_{r-1}}}{\|a_1 e_1 + a_{1+n_1} e_{1+n_1} + \dots + a_{1+n_1+\dots+n_{r-1}} e_{1+\dots+n_{r-1}}\|} \quad (46)
 \end{aligned}$$

BIBLIOGRAPHY

- [1] Z. AGUR, "The effect of drug schedule on responsiveness to chemotherapy", *Annals N.Y. Acad. Sci.* , 504 (1986), 274-277.
- [2] Z. AGUR, *Randomness, synchrony and population persistence*, *J. theor. Biol.* (1985) 112, 677-693.
- [3] Z. AGUR, J. L. DENEUBOURG, *The effect of environmental disturbances on the dynamics of marine intertidal populations*, *Theoretical Population Biology* (1985) 27, 75-90.
- [4] Z. AGUR, R. ARNON, B. SCHECHTER, *Reduction of cytotoxicity to normal tissues by new regimes of cell-cycle phase-specific drugs*, *Mathematical Biosciences*(1988), 92, 1-15.
- [5] Z. AGUR, R. ARNON, B. SANDAK, B. SCHECHTER *Zidovudine toxicity to murine bone marrow may be affected by the exact frequency of drug administration*, *Exp. Hematol.* (1991), 19, 364-368.
- [6] Z.AGUR, R.ARNON, B.SCHECHTER, "Effect of the dosing interval on survival and myelotoxicity in mice treated by Cytosine arabinoside", *Eur. J. Cancer* (1992), 28A(6/7) 1085-1090.
- [7] Z. AGUR, R. HASSIN, S. Levy. "Optimizing chemotherapy scheduling using local search heuristics", Submitted.
- [8] Z. AGUR, G. TAGLIABUE , B. SCHECHTER, P. UBEZIO, "AZT effect on the Bone Marrow - a new perspective on the Concorde Trials", *Jour. Biol. Sys.* (1995), 3, 241-251.
- [9] L. COJOCARU, Z. AGUR. "A theoretical analysis of interval drug dosing for cell-cycle-phase-specific drugs". *Mathematical Biosciences* (1992), 109, 85-97.
- [10] Z.AGUR, Y.DVIR, "Use of knowledge on $\{\varphi_n\}$ series for predicting optimal chemotherapy treatment", *Random & Computational Dynamics*, (1994), 2, 279-286.
- [11] 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". *Mathematical Biosciences*(1985), 73, 1-31.

- [12] HOFFMAN R. et al. (eds) *Hematology, Basic Principles and Practice*, 3rd Edition Churchill Livingstone 2000.
- [13] M. JOHNSON, and G.F. WEBB, "Resonances in age structured cell population models of periodic chemotherapy", *International Journal of Applied Science and Computations*, (1996), 3, 57-67.
- [14] D. SERRE. *Matrices. Theory and applications*. 2002 Springer-Verlag New York, Inc.
- [15] A.SWIERNIAK, "Optimal control problems arising in cell-cycle-specific cancer chemotherapy", *Cell Prolif.*, (1996), 29, 117-139.
- [16] A.SWIERNIAK, "Cell cycle as an object of control", *Journal of biological systems*(1995), 3, 41-54.
- [17] P. UBEZIO , G. TAGLIABUE , B. SCHECHTER , Z. AGUR, "Increasing 1-b-D-Arabinofuranosylcytosine efficacy by scheduled dosing intervals based on direct measurement of bone marrow cell kinetics", *Cancer Res.* (1994), 54, 6446 - 6451.
- [18] G.F. WEBB, "Resonance phenomena in cell population chemotherapy models", *Rocky Mountain Journal of Mathematics* (1990) , 20, 1195-1216.

