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Optimizing Cancer Chemotherapy: from Mathematical Theories to Clinical Treatment

Zvia Agur and Yuri Kheifetz

Abstract Cancer chemotherapy is much influenced by the “dose dense” paradigm, advocating maximally possible dose density early in treatment. This paradigm is based on a controversial mathematical model, assuming Gompertz tumor growth law. Alternatively, it has been suggested that for maximizing efficacy/toxicity ratio in cancer chemotherapy, the inter-dosing intervals should be determined according to the Resonance theory. This theory asserts that cell growth is maximal when the periodicity of drug administration is an integer or fractional multiple of the characteristic periodicity of the cell population. Model analysis and *in vitro* and *in vivo* experiments, suggest that differences in cell-cycle distributions of host and cancer cells can be taken advantage of in chemotherapy by cell-cycle phase-specific drugs which use Resonance or Anti-Resonance (stochastic) drug pulsing. Mathematical proofs showing long-term prediction accuracy of cell population growth models under cell-cycle phase-specific drugs, enabled developing a heuristic optimization method for drug scheduling. Using this method in conjunction with personalized models of vascular tumor growth under chemotherapy by docetaxel and bevacizumab, an optimal combination regimen was tailored to a particular mesenchymal chondrosarcoma patient. The personalized regimen was prospectively validated, leading to increased longevity and quality of life of the patient. This patient’s model was further simulated, suggesting that the relative advantage of “Dose Dense” drug therapy depends on personal cytokinetic and angiogenic parameters.

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1 Introduction

Efficacy of cancer therapy is often unpredictable and significantly different among patients, as a result of differences in age, gender, diet, organ function, and genetic variability [13, 29]. Yet, under the current paradigm of clinical trials, new drug candidates are approved if they show statistically significant advantage, when applied by precisely the same protocol to a large patient population. Due to the high cost of such large scale population trials, only a few protocols are tested, inevitably implicating suboptimal treatment for the patient.

In trying to identify an efficacious general chemotherapy policy, Larry Norton and Richard Simon constructed a simple mathematical model for relating the efficacy of cytotoxics to the growth dynamics of the tumor. Mathematically, the Norton-Simon model can be written $N'(t) = f(N(t))(1-d(t))$, where $N(t)$ denotes the number of tumor cells at time t, $N'(t)$ is the growth rate of the tumor at time t, $d(t)$ reflects the rate of removal of cells as a result of treatment, and f is a function which describes the growth dynamics of the unperturbed tumor. Norton and Simon assumed that this growth function obeys Gompertz law, and that the rate of tumor regression induced by chemotherapy is proportional to the rate of unperturbed growth of tumor of that size. Consequently, they argued, to be more efficient, the dose rate of chemotherapy should be increased, for example by applying the maximum tolerated dose *(MTD)* and decreasing the inter-dosing intervals [18, 19].

The Norton–Simon hypothesis has been influential in oncology and much inspired the clinical investigation. It served as a basis and justification for the "dose-dense" approach to breast cancer chemotherapy, shown in many studies to achieve drops in cancer recurrence and death, as the model predicts [11].

The rationale of the "dose-dense" paradigm is rooted in the nature of the underlying Gompertz model. However, Norton and Simon never checked if the Gompertz model is valid, or if the paradigm is valid also for alternative models of tumor growth (see, for example [15, 20, 21, 28]. Can their model be validated? Can it be generalized, for example, to all vascular cancers, or all chemotherapeutic drugs? In this work we will sketch some prerequisites for the use of mathematical models of cell population dynamics for chemotherapy optimization. It will be shown, both theoretically and experimentally, that the relative advantage in dose dense therapy may depend on cytokinetic parameters of drug-susceptible host and cancer cells, and on the level of tumor angiogenesis.

We will summarize theoretical research, which shows that periodically applied chemotherapy creates a resonance effect by which cell population growth can be maximized or minimized, depending on the periodicity of the drug pulsing. Experiments supporting the validity of this *Resonance phenomenon* in real-life will be summarized and it will be shown that models of cell populations which are treated by schedules of cell cycle phase-specific (CCPS) drugs, yield reliable long range predictions. This opens the way to chemotherapy optimization by use of mathematical models of cancer progression, and, further, to the development of an optimization method by which the inter-dosing interval is timed, essentially, to minimize the toxicity/efficacy ratio of the drug.

Finally, we will briefly report a particular application of the optimization method for treatment personalization. In this case, chemotherapy of a cancer patient was successfully optimized using a personalized mathematical model of tumor growth. The combined method was prospectively validated and it was suggested that the relative advantage of dose-dense periodic chemotherapy mainly depends on personal angiogenic and cytokinetic parameters.

2 Universal Resonance Phenomenon Suggests a New Method for Cancer Chemotherapy

Models of population dynamics, under various distributions of environmentally-inflicted loss processes, suggest that population persistence depends on the level of synchronization of the environmental and population processes. Population growth is maximized when the periodicity of environmental disturbances is an integer or fractional multiple of the characteristic periodicity of the population. This *Resonance Phenomenon* is observed in as diverse models as those of mussel growth under harsh weather regimes in the intertidal zone of the sea, or in models of measles epidemics in human populations under vaccination. The internal periodicity caused by some population characteristics and the external periodicity inflicted by environmental forces may be unique to each case, but the resonances created by these relationships are a universal phenomenon [1, 2, 6, 25].

The universality of the Resonance Phenomenon offers an attractive possibility for the control of the cancer disease. Thus, it was shown, both theoretically and experimentally, that the period of drug dosing can be determined so as to create resonances which maximize the growth of host drug-susceptible cells and, at the same time, minimize the growth of the malignant cells.

First, the generality of the Resonance Phenomenon for different host cell populations was investigated in a much simplified model of a cancer patient. The patient's model assumed that both tumor and target host tissues are collections of cells that vary only in cell-cycle parameters; the spatial arrangement of these cells was ignored. In this way, the complex physiological and pathological dynamics of an oncology patient under chemotherapy was reduced into one essential variable, namely, the ratio between tumor growth and that of the host target tissues under different chemotherapy regimens of CCPS drugs.

Two types of treatments were considered : (i) drug efficacy is stepwise "infinite," i.e. all cells in the vulnerable cycle-phases are instantly eliminated during the fixed period in which the drug is effective, while no cells are affected during the drug-free interval [5]; (ii) drug efficacy is "finite" and drug decay kinetics is considered [10]. The previous case, a limit of the latter one, can be considered as a reasonable approximation to reality. Assuming stochastic inter-dosing intervals, this model successfully shows a clear advantage for population growth when the period of the loss process coincides with an inherent population reproduction period.

In [10], the resonance effect was examined under improved realism of the drug's pharmacokinetics (PK). A probabilistic model was constructed, which assumes (i) a

constant cell-cycle duration, (ii) a constant drug-sensitive cycle-phase, (iii) S-phase drug susceptibility and (iv) negative exponential drug elimination. This is a major departure from the previous model, where a dichotomous, "all or none" drug effect was assumed. Analysis of this model provides explicit formulae for the growth or decay of the tumor cell population. Notably, it is shown that the resonance phenomenon is preserved even when model complexity is increased.

In the cases discussed above the models are probabilistic. In contrast, in [12], a systems of deterministic differential equations is used to analyze similar dynamics. The authors show that when the mean cell-cycle times of normal and tumor cells differ considerably, optimal drug schedules can significantly improve therapeutic efficacy, when drug periodicity is close to the mean cell-cycle time of the normal population and is practically independent of the tumor cell-cycle parameters. In this case, optimal treatment regimen heavily depends on precise estimation of the mean cell cycle duration of both cancer and host cells.

In [30], chronotherapy is discussed in structured models of tumor cell population growth, where drug treatment corresponds to a loss of cells in a periodic on-off schedule. Treatment is specific to the structure variable, so that only cells in a certain range of this variable are eliminated. The author demonstrates that resonances occur at a treatment period, p, being at, or near, integral or fractional multiples of the median age of cell division.

A rigorous mathematical analysis of the Resonance Phenomenon in periodic chemotherapy scheduling is presented in [31]. Here, realism is traded-off by rigor, and for model simplification it is assumed that cell cycle has a constant length and that treatment eliminates cells only at the time of cell division (to distinguish from the S-Phase killing, as in the model described in [5]. Moreover, differential equations model is used rather than probabilistic approach in [10].

2.1 Laboratory Experiments Verifying the Resonance Phenomenon

A series of laboratory experiments was conducted for testing the clinical validity of the Resonance phenomenon. To this end, the effect of drug pulsing rhythm on cell proliferation was examined both *in vitro*, *in vivo* and *ex vivo*. The *in vitro* experiments tested the dependence of cell population growth on the inter-dosing interval *per se*. Thus, short pulses of Cytosine Arabinoside (ara-C) – an S-Phase-specific cancer drug, were applied to several sets of cells. Experimental results show that, regardless of the total drug dose or the experimental procedures, drug schedules whose periodicity was an integer multiple of the average population cell-cycle time showed significantly higher growth rate, as evaluated by rates of DNA synthesis [5]. In the *in vivo* murine experiments ara-C was applied to lymphoma-bearing mice, treated by short drug pulses of different distributions of the inter-dosing intervals, including stochastically determined periodicity; the total dose and total treatment duration were kept constant. Toxicity was evaluated by spleen weight, by peripheral blood measurements and by the proportion of bone-marrow cells in the S-Phase gate of the DNA content distributions. Results support theory in showing that an Anti-

Resonance regimen, namely random duration of the inter-dosing intervals, inflicts higher cytotoxicity than a regimen of constant inter-dosing intervals. The results also show that minimal myelotoxicity is exerted when the inter-dosing interval is a multiple of the inter-mitotic time of bone-marrow stem and progenitor cells, thus supporting model predictions [4]. To verify that this approach is feasible using methods that are available in clinical practice, Ubezio and colleagues [27] determined the optimal intervals between treatments, by measuring the effects of single-dose ara-C on proliferation kinetics of murine bone-marrow cells. Results showed that ara-C is toxic to S-Phase cells, causing an arrest at the G1/S boundary of the cell-cycle for about $4 - 6hr$, following which cells transit through the S-Phase in a nearly synchronized manner. Further results suggest that an optimal window for a second ara-C dose, designed to preserve the bone-marrow proliferating pool, would be optimally administered at 14–16*hr* (for $5mg/kg$) and 12–14*hr* (for $1mg/kg$) following the first ara-C dosing. This is so because in these time windows most of the surviving cells are found in the less susceptible cycle phases (G1 and G2/M). In contrast, a time periods of 7–11*hr* is expected to impose maximal toxicity to the bone-marrow, since at that time surviving cells will be transiting into the susceptible S-Phase of the cell-cycle [27]. In order to verify that, indeed, the optimal dosing period in murine chemotherapy is 14*hr*, it was first shown in bone-marrow aspirates of ara-C-injected mice, that cell kinetics following 2 or 3 ara-C dosings remained similar to that observed after a single dosing. It was further shown that, as predicted, cell-cycle kinetics was less affected when using the optimal dosing period. Indeed, when a second dose was administered after 7*hr* or 14*hr* period much less toxicity was inflicted than after a 10*hr* period, and a third dose of 14*hr* period had a considerable smaller effect on the percent of proliferating cells in the bone-marrow than any of the second dosings. Subsequently, toxicity to healthy mice by different ara-C protocols was evaluated by measuring mice survival. Thus, 4/5 mice died as a result of treatment with 4 ara-C doses given at 10*hr* intervals. Reducing the number of doses to 3 did not decrease mortality. In contrast, increasing dosing intervals to 14*hr* dramatically improved survival since 5/5 mice survived 3 ara-C doses, given at 14*hr* intervals. The next step was to examine the above scheme in tumor bearing mice. Mice were inoculated with 38C–13B lymphoma cells and treatment was initiated 3 days later. Results show that a regimen of $4 \times 14hr$ applications was not only less toxic, but it also delayed tumor progression, nearly doubling survival time, as compared to the untreated control. The protocol of 16*hr* dosing interval had similar results to the 14*hr* protocol, defining thus the width of the bone-marrow preserving time-window. In contrast, all untreated mice in the control group died within 14 days due to tumor progression, whereas the treatment with random drug application was highly toxic causing 100% death within 7 days [27].

2.2 Long-Range Predictability in Models of Cell Populations Subjected to Cell Cycle Phase-Specific Drugs

Can one *a priori* use mathematical modelling to predict whether a given cell population of distributed cell-cycle duration will be effectively eliminated by prescribed chemotherapy schedules administered according to the the suggested method? In this section we show analytically that the answer is positive, thus paving the way for the development of heuristic optimization methods for chemotherapeutic drugs, which may be applicable for prolonged treatments.

In [16], numerical procedures are developed and estimated, for determining the growth rate of a cell population having distributed cell cycles under a prescribed chemotherapy protocol. It was shown that the cumulative error in estimating cells proliferation rate stays bounded and does not accumulate with time, if the considered treatment regimen is periodic. It was also proved that this rate is almost independent (with unity probability) from initial distribution of the ages in the cell population.

Let $n(a,t)$ denote the cell age density, a denote a cell age and t denote a time. It will be shown that the behavior of $r(t) = n(0,t)$ determines the behavior of $N(t)$, that is, the number of cells at time t, as t tends to infinity.

The model equations, describing cell age distribution dynamics are

$$n_t(a,t) + n_a(a,t) = -(\beta(a) + \eta(a,t))n(a,t), \qquad a > 0,\ t > 0, \tag{1}$$

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

$$n(a,0) = n_0(a), \qquad a > 0, \tag{3}$$

where n_a and n_t denote partial derivatives $\partial n/\partial a$ and $\partial n/\partial t$, respectively [12, 17, 26, 30, 31]. 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 $\alpha(a) = \int_a^{\infty} f(\widehat{a})d\widehat{a}$ (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 $[\tau_b, \tau_m]$.

In this model it was assumed that the division and mortality rates of the population are independent of the population density. Note, however, that in other cases, 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, $N(t)$ is given by integrating $n(a,t)$ from 0 to infinity. In such cases, being 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 cells number).

The differential equation (1) is integrated, and the following formula for $r(t) = n(0,t)$ is obtained:

$$r(t) = 2\int_{\tau_b}^{\tau_m} f(a)\, r(t-a)\, \Theta(a,t)\, da. \tag{4}$$

Here, $\Theta(a,t) = e^{-\int_0^a \widetilde{\eta}(\alpha,t-a)\, d\alpha}$ stands for treatment activity, where $\widetilde{\eta}(a,t) = \eta(a,t+a)$. For a very aggressive treatment $\Theta(a,t)$ tends to 0, and in the absence of the drug and in the absence of a natural loss we have $\Theta(a,t) = 1$. $f(a)$ is a probability density function of cell division at the age a with support $[\tau_b, \tau_M]$, $\tau_b > 0$.

It is shown in [16] that in the generic case, the growth rate of the total cell population, $N(t)$, is similar to $r(t)$, for t large enough.

Let $r_n(s) = r(s + n\,\tau_b)$ for $s \in (0, \tau_b)$ and $n \in \mathbb{Z}$. The fact that $\tau_b > 0$ converts (4) to recursive formula:

$$r_n(s) = \sum_{j=0}^{M} \int_0^{\tau_b} E_{j,n}(u,s)\, r_{n-j-1}(\tau_b - u)\, du = \sum_{j=0}^{M} T_{j,n}\, r_{n-j-1}(s), \tag{5}$$

where $M = [\frac{\tau_m - \tau_b}{\tau_b}] + 1$, $E_{j,n}(v,s) = 2f(v + s + j\,\tau_b)\, \Theta(v + s + j\,\tau_b, s + n\,\tau_b)$ and $T_{j,n}g(s) = \int_0^{\tau_b} E_{j,n}(u,s)\, g(\tau_b - u)\, du$ for any $g \in L^2_{[0,\tau_b]}$. (5) define recursively $\{r_n(t)\}_{n=0}^{\infty}$, provided that $r_{-M}(t), \ldots, r_0(t)$ are known.

The integration kernel $E_{j,n}(u,s)$ has been approximated in [16] by step functions, $E^u_{j,n}(u,s)$ and $E^l_{j,n}(u,s)$ bounding it from above (superscript "u") and from below (superscript "l"), defining $\{r_n(t)^u\}$ and $\{r_n(t)^l\}$ as the upper and lower approximations for $\{r_n(t)\}$.

Let H be a set $(L^2_{[0,\tau_b]})^{M+2}$ with a following inner product: $< v, w >= \sum_{j=1}^{M+2} < v_j, w_j >$, where $< v_j, w_j >$ is an inner product in L^2. It is clear that H with this inner product constitutes Hilbert space. Thus Eq. (5) can be re-written in the following form:

$$\begin{pmatrix} r_{n-M-1}(t) \\ r_{n-M}(t) \\ \ldots \\ r_n(t) \end{pmatrix} = \begin{pmatrix} 0 & Id & 0 & \ldots & 0 \\ & & \ldots & & \\ 0 & \ldots & 0 & \ldots & Id \\ 0 & T_{M,n} & T_{M-1,n} & \ldots & T_{0,n} \end{pmatrix} \begin{pmatrix} r_{n-M-2}(t) \\ r_{n-M-1}(t) \\ \ldots \\ r_{n-1}(t) \end{pmatrix}. \tag{6}$$

Let us denote

$$T_n = \begin{pmatrix} 0 & Id & 0 & \ldots & 0 \\ & & \ldots & & \\ 0 & \ldots & 0 & \ldots & Id \\ 0 & T_{M,n} & T_{M-1,n} & \ldots & T_{0,n} \end{pmatrix}. \tag{7}$$

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 $t > t_0$. It was easily shown in [16] that $\Theta(a,t) = \Theta(a, t + P\tau_b)$ for any $a > 0$, $t > t_0$ and P is the minimal natural number with this property. From this it easily

follows that $\{T_n\}_{n=0}^{\infty}$ is a periodic sequence of operators with the minimal period P. Then $T = T_1 T_2 \dots T_P$ is a compact operator on H and for every initial vector $v_0 \in H$ we have P sequences $\{T^m v_0\}_{m=0}^{\infty}, \{T^m T_1 v_0\}_{m=0}^{\infty}, \dots, \{T^m T_0 \dots T_{P-1} v_0\}_{m=0}^{\infty}$ and obtain sequence of vectors of functions $\{(r_n(t), r_{n+1}(t), \dots, r_{n+M}(t))\}_{n=1}^{\infty}$ in the following way: for any natural n $r_n(t) = T^m T_0 \dots T_i v_0$, where $n = mP + i$, $0 \le i < P$. This means that behavior of $r(t)$ in infinity is determined by $\{T^m\}_{m=1}^{\infty}$ and in particular by $\lim_{n\to\infty} \sup_{g\in H} \frac{||T^n g||}{||g||} = \lim_{n\to\infty} ||T^n||$. From elementary course in Banach spaces [22] follows that $\lim_{n\to\infty} \sqrt[n]{||T^n||} = \rho(T)$, $\rho(T)$ is a spectral radius of T. Thus the problem is reduced to the evaluation of $\rho(T)$.

If $\{T_n\}_{n=0}^{\infty}$ has a period P, then given N and equal partition of $[0, \tau_b]$, $\{T_n^l\}_{n=0}^{\infty}$ and $\{T_n^u\}_{n=0}^{\infty}$ have also period P. Let $T^l = T_1^l T_2^l \dots T_P^l$ and $T^u = T_1^u T_2^u \dots T_P^u$. These are obviously finite rank operators. Thus the behavior of $\hat{r}^l(t)$ and $\hat{r}^u(t)$ is determined by $\rho(T^l)$ and $\rho(T^u)$ respectively. $\rho(T^l)$ and $\rho(T^u)$ can be readily calculated. This is because these operators are of finite rank and can be identified with finite dimensional matrices by means of isometry of $\mathbb{C}^N$ with the space of step functions with equal partition of $[0, \tau_b]$ to N equal subintervals, as described earlier.

The following propositions have been established:

Proposition 1. *If* $\rho(T) < 1$ *then* $\lim_{n\to\infty} ||T^n v|| = 0$.
If $\rho(T) > 1$ *then* $\lim_{n\to\infty} ||T^n v|| = \infty, \quad \forall v \in H$.

Proposition 2. *For any nonnegative compact operator K on H, the spectral radius* $\rho(K)$ *is an eigenvalue of K with at least one eigenfunction* $x \ge 0$.

Proposition 3. *For any nonnegative compact operator K on H and for almost every* $v \in H_+$, $\lim_{n\to\infty} ||K^n v||^{\frac{1}{n}} = \rho(K)$.

where H_+ denotes the subspace of H, containing vectors with nonnegative elements.

We summarize the results as follows: The value of the spectral radius $\rho(T)$ fully characterizes population growth or decay. The population exponentially grows 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 nonnegative functions).

The following proposition states that order is preserved by a map, which is defined on the set of all bounded nonnegative operators on H, and assigns its spectral radius for any such operator. This means that if $A_1 \le T \le A_2$, where A_1, A_2 and T are bounded operators on H, and if $\rho(A_1)$, $\rho(A_2)$ are known, then $\rho(T) \in [\rho(A_1), \rho(A_2)]$. This fact in conjunction with results of Proposition 5 below gives a quantitative estimation of $\rho(T)$ through $\rho(A_1)$ and $\rho(A_2)$, in the case that $\rho(T)$ is compact and $\rho(A_1)$ with $\rho(A_2)$ are operators of finite rank.

Proposition 4. *Given* S_1, S_2 *being any bounded nonnegative operators on H, such that* $S_1 \ge S_2$, *their spectral radiuses satisfy similar inequality:* $\rho(S_1) \ge \rho(S_2)$.

The following proposition is significant as it directly estimates the radius of any given compact operator through the spectral radius of finite rank operator close to it.

Proposition 5. *Assume that K is a compact operator on separable Hilbert space H, $\rho(K) > 0$ and A is a finite rank operator, such that $||K - A|| < \varepsilon$ in operator norm for some $\varepsilon > 0$. If $\varepsilon < \rho(K)$, then*

$$\rho(K) < \rho(A) + \varepsilon \left(3 + \frac{||K||}{\rho(K)}\right). \tag{8}$$

From Proposition 1 follows a property, which is 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 equal to 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. From Propositions 1, 4, 5 and from the approximation of compact operator by finite rank operators developed above, it follows that the spectral radius is a continuous function on the set of operators, whose spectrum is nontrivial. This guarantees the stability of the population growth rate under fully periodic treatment.

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 any $a \in [\tau_b, \tau_m]$. Let ${}_1T$ and ${}_2T$ be the respective operators on H. Then by Proposition 5 it follows that $\rho({}_1T) \leq \rho(T) \leq \rho({}_2T)$. Given any $\varepsilon > 0$, we can evaluate $\rho({}_1T)$ and $\rho({}_2T)$ with accuracy less than ε. In the generic case $\rho({}_1T) \neq 1$ and $\rho({}_2T) \neq 1$. Thus, for sufficiently small ε we will know wether both $\rho({}_1T)$ and $\rho({}_2T)$ are larger 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.

3 Optimizing Chemotherapy Regimens

3.1 Simple Optimization Methods for Minimizing Toxicity/Efficacy Ratio in Chemotherapy

Having guaranteed the long range predictability of models with periodic drug dosing, one could develop methods for predicting the optimality of prescribed schedules, when both efficacy to the cancer and toxicity to the patient are concurrently considered [5].

First, a simple optimization problem was defined, as follows: minimize the ratio between the average elimination time of the malignant population and that of the limiting host population, employing a newly defined efficacy coefficient, Z, such that

$$Z = 1 - T_M/T_H,$$

where T_M and T_H denote the mean elimination time of the malignant and the host cells, respectively. The efficacy coefficient, Z tends to unity for treatments that rapidly eliminate the cancer and bear little toxicity for host cells, it will be close to zero for indiscriminating treatments, and will be less than zero for treatments that cause severe damage to the host but have little effect on the cancer. The efficacy coefficient, Z was calculated over large schedule and parameter spaces,for a different formalism of the optimization problem.

In [7], the mathematical properties of the suggested method are analyzed by applying $\{\phi n\}$ series, where $0 < \phi < 1$ and $\{\phi n\}$ is the fraction part of ϕn. Using continued fractions a fast algorithm is put forward for computing the required treatment duration and the desired number of drug applications for eliminating the tumor under the suggested method. Note that this algorithm relies on a model that assumes deterministic temporal cell-cycle parameters and a "bang-bang" (all or none) drug effect.

3.1.1 A Heuristic Method for Personalizing Clinical Cancer Therapy – an Independent Support for the Resonance Phenomenon

For complying with the many constraints of modern clinical oncology strategies, a heuristic method for personalizing drug schedules was developed [8]. The method is based on simulations of the patient's pharmacodynamics (PD) in models for cancer and host cell dynamics, so that the number of cells that are susceptible to drug at every moment of therapy is calculated. Local search heuristics are then employed for finding the optimal solution, as clinically prescribed.The suggested method does not depend on the exact assumptions of the model, thus enabling its use in complex mathematical descriptions of the biomedical scenario.

The main constituents of the method are two procedures that simulate the growth of cells during treatment and when no treatment is given. For simplicity, logistic growth is assumed for the host cells, while the growth of the cancer cells is taken as exponential.

This model has been employed for examining how to improve regimens of high-dose chemotherapy (HDC), currently believed to be one of the most effective strategies for obtaining higher anti-tumor efficacy for breast cancer. In particular, a high-dose $(210mg/m^2)$ $3hr$ infusion of Paclitaxel (half-life: $10-12hr$) is routinely used in the adjuvant setting for high-risk patients after mastectomy. Under these regimens dose-limiting myelosuppression is common [23] so that autologous bone-marrow transplantation becomes mandatory.

Using the mathematical algorithms in [8], the killing effect on cancer cells and on host bone-marrow cells was calculated for several treatment schedules of a Paclitaxel-like HDC by a CCPS drug. Subsequently, a comparison has been made between schedules of a single dosing of the drug, and those of a fractionated dosing with the same or a smaller total drug dose. In these calculations it was assumed that cells in the $G1$ and $G2/M$ phases of the cell-cycle are more susceptible to the drug than S-phase cells [24], and that breast cancer cell cycle lasts $40hr$, while that of bone-marrow cells is roughly $24hr$. The computations show that by splitting the dose

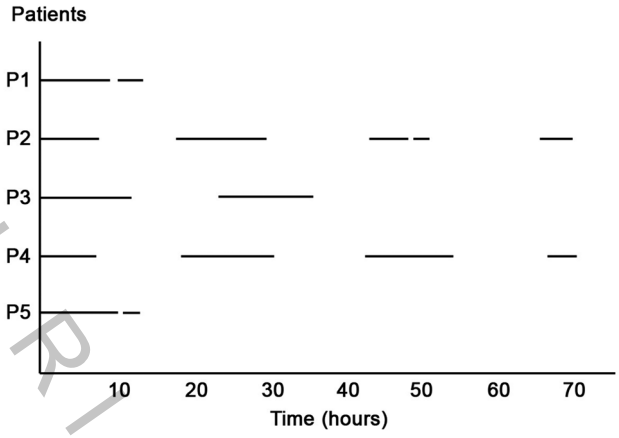

Fig. 1. Optimal treatment regimen for five patients, having different putative cancer indications, P1-P5. The patients are assumed to be similar in all; cell cycle and susceptible phase duration of the drug susceptible host cells being 24*hr* and 10*hr*, respectively. The patients vary with respect to the cancer cell cycle parameters; cell cycle duration (16*hr* (P1, P3), 28*hr* (P2, P4), 20*hr* (P5), and duration of the drug susceptible phase (10*hr* (P1, P2), 6*hr* (P3, P4), 14*hr*(P5)

in a specific manner some advantages are possible for increasing the survival/killing ratio of the host and breast cancer cells. It was shown that a HDC treatment regimen, in which a Paclitaxel-like drug exerts a very high cell kill (50%/*hr*) during 10*hr*, reduces tumor size to 0.148 of its initial size. However, this treatment causes more damage than cure, as the bone-marrow cell population is reduced even more significantly, to 0.137 of its initial size. This drug effect is reversed when the dosing is fractionated, so as to resonate with the susceptible bone marrow cell-cycle. Under these circumstances toxicity to normal cells is reduced while cancer cell kill is maintained, as expected by the Resonance Theory.

It is important to note that the heuristic optimization method put forward in [8] does not demand any *a priori* treatment periodicity. Nevertheless, its results show that, theoretically, a periodic treatment is optimal over a large range of biologically realistic system parameters. More specifically, two general classes of optimal cancer drug schedules are identified, depending on the temporal cycle parameters of the host and cancer cells. One class comprises one-time intensive treatments, while the other comprises treatments characterized by series of quasi-periodic non-intensive pulsing. We see, then, the Resonance Phenomenon emerging again in an independent model, this time under a more complex optimization method (Fig. 1).

4 From Theory to the Clinic

Mesenchymal Chondrosarcoma (MCS) is a rare malignant disease. One MCS patient was diagnosed with mediastinal located MCS at age 45. Shortly after the resec-

tion of the primary tumor, multiple bilateral pulmonary nodules were discovered. The patient underwent aggressive chemotherapy, but disease progression was not arrested, and additional liver and bone metastases appeared. The patient also developed severe myelosuppression with pancytopenia due to toxic side-effects of the prolonged chemotherapy.

4.1 *Integrating* in Silico *and* in Vivo *Models for Treatment Personalization*

To determine the best possible treatment for the MCS patient, tumor fragments, taken from his lung metastases, were implanted in mice (denoted tumorgrafts), and different pharmacotherapy regimens were applied to the animals.

A general mathematical model for angiogenesis-dependent solid tumor growth was used for model simulations, replicating the experiments performed in the tumorgrafts, for predicting the MCS dynamics in the control and treated animals [9]. PK/pharmacodynamics (PD) models of potential drugs were constructed, using publicly available data. In addition, qualitative chemosensitivity tests of several cytotoxic drugs were performed on tumor cells from the patient's biopsy. Incorporating the data of these chemosensitivity tests into the calculations allowed a certain level of personalization of the general PK/PD models.

The mathematical model of the MCS tumorgrafts was successfully validated in mice with the average accuracy of 87%. Subsequently, gene expression analysis of key proteins in the grafted tumors and in the MCS patient was performed in order to adjust the model to describe the tumor dynamics in the patient. The resulting personalized model of the patient's disease was then used to perform patient-specific predictions of various anti-cancer treatments.

Guided by the results of the personalized in silico/in vivo combined model, the clinicians administered the MCS patient once-weekly regimen of docetaxel (DOC). Previously, this regimen was found least toxic to hematopoiesis, e.g., [3]. Eventually, the patient had a dramatic response to therapy with an immediate substantial recovery of all 3 blood elements (hemoglobin, white blood cells and platelet count). Soft tissue disease in the lungs and liver remained stable and the patient enjoyed a period of good quality of life, ending only after pulmonary progression of his disease to which he finally succumbed [14].

4.2 *The Rate of Angiogenesis Determines the Optimal Inter-Dose Interval of Chemotherapy*

The simulations of the human MCS model for DOC delivery every 7, 14, 21 or 28 days (keeping the same average weekly dose), showed that once weekly regimen is more efficacious than all other tested alternatives. However, suggesting this DOC administration regimen may be problematic in some patients. Therefore, it would be useful to identify the patients that are more likely to benefit from the weekly chemotherapy schedules.

Cytotoxic agents, such as DOC, disturb the dynamic equilibrium between the growing tumor mass and the vessel bed that supports it, by direct killing of tumor cells. The mathematical model for angiogenesis-dependent tumor growth takes account of the cascade of compensating events which is triggered as a consequence of chemotherapy administration.

To assess tumor recovery from the cytotoxic drug shock, let us define tumor growth inhibition (TGI) in terms of the tumor volume before and after the treatment: TGI has a value of zero if the volume of the treated tumor equals to that in the control, untreated, tumor at the given time point. Larger TGI values indicate bigger inhibition, while negative TGI values indicate the situation where the treated tumor is bigger (in terms of living cells volume) than the untreated one: in other words, negative TGI values mean that the treatment was harmful, rather than beneficial.

In the human MCS model simulations [14], TGI values 7 days after a single DOC administration was 46%. As time goes on, this residual cytotoxic effect decreases to the value of 10% at day 21 – a difference of 36%. Thus, if the second DOC dose is delivered on day 21, after a substantial tumor recovery, the overall efficacy of the treatment would be small, compared to once-weekly regimens.

Moreover, if the human MCS model is simulated with VEGF secretion rate reduced by a factor of two, compared to its original value, the predicted decrease in TGI from day 7 to day 21 is only 29% (39% and 10%, respectively), indicating slower recovery from drug-induced tumor inhibition. In contrast, if the rate of new vessel formation is doubled, as compared to that calculated for the real MCS patient, the difference in the extent of tumor inhibition by DOC dose, between day 7 and day 21, increases to 92%; 69% TGI in day 7 versus −22% in day 21. This growth is made possible due to the extensive formation of blood vessels, triggered by the chemotherapy [14].

These results imply that for patients having less intensive angiogenesis, the less dense (for example tri-weekly) regimens would be approximately as efficacious as the weekly one, thus providing the clinicians more treatment alternatives [14].

5 Conclusion

The work reviewed in this chapter shows both theoretically and experimentally, that the advantage of dose-dense chemotherapy is not universal, but rather, depends on the patient's cytokinetic and angiogenic parameters and the length of the inter-dosing interval itself.

We believe that the above-reported treatment personalization study marks a transition point in the status of mathematical modelling in biomedicine. This is one of the first times that a mathematical model generates quantitative predictions that are prospectively validated in the clinic.

In general, the modelling procedures reviewed here and their experimental verification provide solid grounds for the use of rigorous biomathematical models in drug development and in the clinic. Clearly, this is an uphill struggle, which requires

patience and endurance. However, we believe that in the long run decision-making in medicine will be primarily based on biomathematical modelling.

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