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Use of Knowledge on $\{\phi n\}$ Series for Predicting Optimal Chemotherapy Treatment

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abstract. An algorithm is presented for calculating the number of drug dosings required for eliminating a neoplasia with minimal damage to the patient. The proof of the algorithm is based on knowledge about the $\{\phi n\}$ series. This algorithm relies on a model that assumes deterministic temporal cell-cycle parameters and a "bang-bang" drug effect. As such, the model can only serve for obtaining a rough estimate of prospective treatment efficacy, and further work should be invested in increasing its realism.

Introduction. Drug toxicity to the host and drug resistance in the neoplasia are still the major impediments to the success of cancer chemotherapy. A challenge for mathematical biomedicine will be to develop exact methods for predicting treatment efficacy in the individual patient. The present work is part of the effort to this end. We present a fast algorithm for estimating the duration of drug treatment required for eliminating the tumor with minimum damage to the host. Our algorithm is specific to a large class of chemotherapeutic agents, which includes the anti-HIV drug zidovudine (AZT) and many anti-cancer drugs, such as cytosine arabinoside (ara-C). These drugs, called *cell-cycle-phase-specific-drugs*, are detrimental to cells during a specific phase in the cell-cycle, usually the DNA synthesis phase (S-phase), while having

little effect on cells that are in other cell-cycle phases. The effect of such drugs on host proliferating cells can bring about bone-marrow depression and other cytotoxic side effects that are detrimental to the patient.

Employing a theory of population dynamics in perturbed environments was suggested that toxicity of cell-cycle phase-specific drugs is highly dependent on the relation between the frequency of cell-division, the inter-mitotic interval, and the frequency of drug administrations—the dosing interval [1–2]. On the basis of these results a new method has been suggested for increasing selectivity of cell-cycle-phase-specific drugs (The Z-Method; [3]). According to this method drug selectivity can be increased by manipulating the dosing interval so that a "resonance" effect is created for the host cells, minimizing their mortality, and a lack of "resonance" for the cancer cells, whose frequency of replication differs from that of the host cells. This effect can be achieved by interval drug dosing, i.e., protocols with strictly positive drug-free intervals, the dosing interval being an integer multiple of the average drug-induced inter-mitotic interval of the susceptible host cells. Based on these results a more comprehensive model has been recently provided, taking account of the detailed pharmacokinetics and pharmacodynamics of the drug, as well as of the exact distribution of cell division times. Analysis of this model yields the explicit conditions for the elimination of a given cell or viral population [4]. However, this analysis is based on the assumption that treatment duration can be unlimited, while in reality it is limited by clinical and economical constraints.

In the present work we suggest a method for estimating the optimal duration of chemotherapy treatment. Our model assumes that the temporal parameters are deterministic and that the drug dose is high enough to eliminate all cells that are exposed to the drug during their susceptible cell-cycle phase. These assumptions are made as a first approximation approach to the problem at hand. Further work is warranted for considering stochastic temporal parameters and varying drug doses.

The analysis is carried out by applying $\{\phi n\}$ series, where $0 < \phi < 1$ and $\{\phi n\}$ is the fraction part of ϕn. Using *continued fractions* we show a fast method for computing the treatment duration and the required number of drug dosings. Results on the sequence $\{\phi n\}$ and on continued fraction can be found in Swierckowski [8], Halton [6], Slater [7], van Ravenstein [9].

The model. Two types of cells are considered in our model: the limiting host population, i.e., normal cells of the host that are susceptible to the drug and whose extinction we wish to minimize (to be denoted *the host cells*), and the neoplastic cells, which we wish to eliminate by the use of the

drug (to be denoted *the abnormal cells*). The cell-cycle of both the host and the neoplastic cells can be divided into four principal phases: G_1, S, G_2 and M [5]. G_1 and G_2 are delay periods, S is the DNA synthesis period, and the M phase is the period during which the cell divides into two daughter cells. With respect to drug treatment the cell life-cycle can be divided into the susceptible phase and the resistant phase. Since for many drugs the cells are most susceptible during the S phase, we will assume here that *all* cells that are in their S-phase during the drug episode are killed, whereas all cells that are in their G_1, G_2,or their M phase are completely immune to the drug (i.e., we consider a high dose drug treatment). Let us denote the durations of the different cell-cycle phases as $T_H(G_1)$, $T_H(S)$ and so on for the host cells and $T_A(G_1)$ and so on for the abnormal cells. τ_H will be the duration of the host cell cycle so that

$$\tau_H = T_H(G_1) + T_H(S) + T_H(G_2) + T_H(M) \tag{1}$$

and a similar equation holds for the cell-cycle duration of the abnormal cells, τ_A. In the subsequent analysis the notation A or the H will be ommitted in expressions that are true both for abnormal and normal cells.

Let l be the period in which the drug is given and δ be the duration of the episode in which the drug is effective, so that the duration of the drug-free interval is $l - \delta$.

$\{\phi n\}$ series. Let t_0 be the time of treatment initiation, and let t_x be the time of birth of cell x. Let us define A_x such that $A_x = (t_x - t_0) \bmod \tau$. The interval $[c, c + r]_o$ for $0 \leq c \leq \tau$ will denote a cyclic interval, i. e. if $c + r \leq \tau$, then $A_x \epsilon [c, c + r]_o$ iff $c \leq A_x \leq c + r$. If $\tau \leq c + r < c + \tau$ then $A_x \epsilon [c, c + r]_o$ iff $c \leq A_x < \tau$ or $0 \leq A_x \leq c + r - \tau$. Otherwise if $c + r \geq \tau + c$ then $A_x \epsilon [c, c + r]_o$ for all A_x. Let n be the number of drug applications, so that the time of initiation of each drug episode is $il + t_0$, for some $0 \leq i < n$, and the time of termination of each drug episode is $il + t_0 + \delta$. Any cell that enters the S-phase during in the interval $t_0 + il - T(S)$, $t_0 + il + \delta$ is killed by the drug. Thus, if we define

$$r = T(S) + \delta, \tag{2}$$

then, clearly, a cell x is killed by the drug iff

$$A_x \epsilon [c_i, c_i + r]_o. \tag{3}$$

for

$$c_i = (il - T(G_1) - T(S)) \bmod \tau. \tag{4}$$

Now we can derive Agur's conclusion [1-3] that, for a given $\delta < \tau$, minimum damage is caused to the normal cells for

$$l = n\tau, \text{n integer.} \tag{5}$$

It is clear from (4) that in such a case all c_i's are equal, so that the cell x is killed by the drug iff

$$A_x \epsilon [c_0, c_0 + r]_o. \tag{6}$$

Thus for l satisfying (5) only the fraction of the population satisfying (6) is killed by the drug, whereas when l does not satisfy (5), the c_i's are not equal so that additional fractions of the population are killed as well.

To simplify (4) let us define B_x by a $T(G_1) + T(S)$ shift of A_x:

$$B_x = (A_x + T(G_1) + T(S)) \bmod \tau. \tag{7}$$

With this notation x is killed iff

$$B_x \epsilon [c_i', c_i' + r]_o \tag{8}$$

for i, $0 \leq i < n$ and

$$c_i' = (il) \bmod \tau. \tag{9}$$

Let us assume that l is a multiplication of τ_H as a constraint. Then for a given l one can compute n. the number of drug applications required for the eliminating all abnormal cells. We normalize the series c_i' to be a series $\{i\phi\}$, where $\phi = \frac{l}{\tau_A}$, by dividing (6) by τ_A, so that the interval $[0, \tau_A]$ becomes an interval $[0, 1]$. The sequence $\{i\phi\}$ divides the segment $[0, 1]$ into parts. When all parts are less than $\varepsilon = \frac{r}{\tau_A}$, all the abnormal cells are eliminated.

Now our problem can be restated as follows: for a given sequence $\{i\phi\}$, i integer, ϕ positive, and for a given ε, what is n such that the parts resulting from the division of the segment [0,1] by $\{i\phi\}$, $0 \leq i < n$, are all less than ε.

We do not have a solution to this problem, but we can derive a fast algorithm to compute such n. In order to do so let us first look at the "Steinhaus's conjecture", or "the three steps theorem".

Let $P_i = \{i\phi\}$, $0 \leq i \leq N - 1$, then $0 \leq P_i < 1$. We say that P_r i. p. P_s (P_r immediately proceeds P_s) if $P_r < P_s$ and there are no P_i in-between them. Let the interval [0,1] be cyclic (i.e. identify 0 with 1) and let P_b be the

closest point to 1 so that P_b i. p. P_0; let β be the length of the step between P_b and 1. Take a such that P_0 i. p. P_a and let α be the length of the step between P_0 and P_a. The following theorem with a proof appears in Slater [7]

theorem 1

$$\left.\begin{array}{llll} (i) & 0 \le s < N-a; & P_s \, i.\ p.\ P_{s+a}; & N-a \ steps, length\ \alpha, \\ (ii) & N-a \le t < b; & P_t \, i.\ p.\ P_{t+a-b}; & a+b-N \ steps\ \alpha+\beta, \\ (iii) & b \le u < N; & P_u \, i.\ p.\ P_{u-b}; & N-b \ steps\ \beta. \end{array}\right\} \quad (10)$$

This means that a step between two succeeding points can have one of three typical lengths, α, β and $\alpha+\beta$. If now we add one more point to the sequence, it will affect the step lengths α, β and $\alpha+\beta$ in one of the following ways:

1. $a+b-1 > N$ and $N \ge \max(a,b)$. From (7) we see that adding one point P_N does not change α or β and there still exists at least one step with the length $\alpha+\beta$.

2. $N = a+b-1$, adding one point P_N leaves at least one step of length α and a step of length β, but no step of length $\alpha+\beta$.

3. $N = a+b$ and $\alpha > \beta$. Adding one point P_N we will calculate the new step lengths by using the fact that the step length between P_b and P_0 must be the same as the step length between P_{a+b} and P_a. This is so because the difference between the indexes is also the same. Now, as $\alpha > \beta$, $P_{N=a+b}$ lies between P_0 and P_a, creating a new α, $new\alpha = old\alpha - old\beta$. Note that steps of length $old\alpha$ still exist so that the maximum length of α has not changed.

4. $N = a+b$, $\beta > \alpha$. This case is similar to the previous one: we create a new β, $new\beta = old\beta - old\alpha$. Here too, steps of length β still exist so that the maximum length of β has not changed.

5. $N = a+b$ and $\alpha = \beta$. Here $N\phi = 0$ and P_N falls on P_0. In such a case ϕ is rational and if $\alpha > \varepsilon$ our demand will never be satisfied. For the chemotherapy problem this means that the treatment will never eliminate the abnormal cells.

There are three cases in which, by adding one point P_N, maximal step length changes: in case(2), in case(3) for b=1 and in case(4) for a=1. As these are the only cases in which the maximum step length changes, our interest is confined only to this case (for investigating this case see van Ravenstein at al.(1990)). Let N_i be a sequence of such N in upgrading order. Let e_i and f_i

be sequences such that $\{e_i, f_i\} = \{\alpha, \beta\}$, where α and β have been computed for $N = N_i$. Now, using cases 3,4 and 5 we can define:

$$e_{i+1} = \min(e_i, f_i) \tag{11}$$

$$f_{i+1} = |c_i - f_i|. \tag{12}$$

We continue until for some j, $e_j \leq \varepsilon$,$f_j \leq \varepsilon$.

There is a faster way one can derive e_j and f_j. Take $c_0 = 1$, $c_1 = \phi$ and while $c_k > \varepsilon$ then

$$c_{k+1} = c_{k-1} - m_k c_k, \tag{13}$$

where m_k is the largest integer such that $c_{k-1} \geq m_k c_k$. Stop calculations for $k = t$ such that $c_t \leq \varepsilon$. If $c_t = 0$ there is no solution. If $c_t \neq 0$ ($c_t \leq \epsilon$), then compute c_{t+1} with (13) and assign $\{e_j, f_j\} = \{c_t, c_{t+1}\}$.

From here we can go farther: (13) implies

$$\frac{c_k}{c_{k-1}} = \frac{1}{m_k + \frac{c_{k+1}}{c_k}}. \tag{14}$$

We can use this recursive equation to get

$$\phi = \cfrac{1}{m_1 + \cfrac{1}{m_2 + \cfrac{1}{\ddots + \cfrac{1}{m_{t-1} + \frac{c_{t+1}}{c_t}}}}}. \tag{15}$$

This form is called 'continued fraction' and it is extensively used in [6-9] to derive results about the series $\{i\phi\}$.

For some N, c_t and c_{t+1} are equal to α and to β, with no importance which is which. Our next purpose is to change ϕ to ϕ' such that $t' = t$ $m_i = m_i'$ and $c_t' = c_{t+1}'$. To make this change we take

$$\phi' = \phi + \frac{\beta - \alpha}{a + b}. \tag{16}$$

Note that the number of points is not altered by this change. Thus we can write:

$$\phi' = \cfrac{1}{m_1 + \cfrac{1}{m_2 + \cfrac{1}{\ddots + 1}}} \tag{17}$$

Now we can compute p, q, positive integers, such that $\phi' = \frac{p}{q}$. This can be computed by setting $p = q'$ and $q = m_1 q' + p'$ for

$$\frac{p'}{q'} = \frac{1}{m_2 + \ddots} \tag{18}$$

and so on. By induction one can see that p and q are relatively prime . $q\phi = p$. and the interval $[0, 1]$ is divided into q equal parts by $\{i\phi\}$. $n = q$ is the number of points such that α and β are less then ε and this n is what we actually are looking for.

The algorithm. Hereafter we present the algorithm for calculating the number of drug applications required for eliminating the abnormal cells. This algorithm summarizes the method described in this work.

(1) $i \leftarrow 1$
(2) $c_0 \leftarrow 1$
(3) $c_1 \leftarrow \{\frac{1}{\tau_A}\}$
(4) $\varepsilon = \frac{\delta + T(S)}{\tau_A}$
(5) if $c_i \leq \varepsilon$ go to 11
(6) $m_i \leftarrow \lfloor \frac{c_{i-1}}{c_i} \rfloor$[1]
(7) $c_{i+1} \leftarrow c_{i-1} - m_i c_i$
(8) if $c_{i+1} = 0$ then stop : no solution exists.
(9) $i \leftarrow i + 1$
(10) go to 5
(11) $m_i \leftarrow \lceil \frac{c_{i-1} - \varepsilon}{c_i} \rceil + 1$[2]
(12) $p \leftarrow 1$
(13) $q \leftarrow m_i$
(14) if $i = 1$ then stop. The answer is q.
(15) $i \leftarrow i + 1$
(16) $p' \leftarrow q$
(17) $q \leftarrow m_i q + p$
(18) $p \leftarrow p'$
(19) go to 14

[1]($\lfloor x \rfloor$ denotes the integer part of x)
[2]($\lceil x \rceil$ denotes the minimal integer larger than, or equal to, x).

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