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OPTIMAL CONTROL ANALYSIS IN THE CHEMOTHERAPY OF IgG MULTIPLE MYELOMA

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This paper uses the Gompertzian model for the growth of a cancer cell population subject to losses due to the action of cycle nonspecific therapy for the determination of a chemotherapy program obtained from optimal control theory. Application of the analysis to control of the bone cancer IgG multiple myeloma is presented. The program obtained from optimal control theory is compared with clinical results.

1. Introduction. From about 1950 there has been a dramatic upsurge in the contributions to the scientific literature dealing with all kinds of cancers. An important recent review article is presented by Aroesty *et al.* (1973). One of the highlights in this review is in the area of obtaining models which can allow one to predict tumor response to chemotherapy. Associated with the prediction problem is the approach to the optimal scheduling of the drug regimen and it is this feature with which the present paper is concerned. Since the review by Aroesty *et al.* is extremely thorough, no repetition is given here of previous work reviewed by them excepting as it directly pertains on the discussion of the present paper. Also, only those models concerned with cycle nonspecific therapy are presented, with the exception of Bahrami and Kim (1975).

Other background material relevent to the present paper is contained in the books by Busch and Lane (1967), and Pratt (1973). More intensive and detailed work on cancer problems is provided in the four-volume work edited by Becker (1975) which has recently appeared.

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Consider a population of living organisms which are taken to be cancer cells. Let $N(t)$ denote their total number at time t and assume that it is a solution of the equation

$$\dot{N} = g(N), \quad N = N(0) \text{ at } t = 0, \tag{1}$$

where $\cdot$ means differentiation with respect to time t, $g(N)$ is assumed to be a function only of N, i.e. the differential equation is autonomous, and the population size is $N(0)$ at some initial time. In a tumor growth situation $g(N)$ is, in general, a monotone function which approaches zero as N tends to a saturation value θ and $g(N)$ approaches a non-zero constant for small values of N where log-phase growth is expected.

A commonly used assumption is that at some initial time a dose of drug is given which instantaneously reduces the number of cells by a fraction. Assume that the tumor now grows according to (1) from this new initial condition. After a time interval T, a second dose of drug is administered and is the same magnitude as the first. The process is then repeated indefinitely. The application of this approach in a control and harvesting situation for logistic growth, modified logistic growth and Gompertz growth is given in detail by Swan (1975). Berenbaum (1969) presents a related discussion for exponential growth, Gompertzian growth and steady-state growth. One expects from these models that, for a given drug dose if the time interval T is small enough, so that tumor regrowth is small with the therapy cycle then cell killing always dominates tumor regrowth.

A commonly used representation to the function $g(N)$ in (1) is that of Gompertzian growth. (For example Simpson-Herren and Lloyd (1970) use the Gompertz equation to describe the growth of nine experimental tumors).

Gompertz introduced his equation in 1825 to help in his studies of rates of human mortality. Laird in the early 1960's, by introducing a sign change, converted it into a growth equation which was subsequently used by her on interpretation of data on carcinomas in rats. Since that time many people in cancer work have used this growth form of the Gompertz equation The Gompertz equation is used in this paper not because it is known to be the most appropriate, but rather because it is convenient and many clinical results are cast in terms of it. Under Gompertzian growth (1) becomes

$$\dot{N} = -\alpha N \ln (N/\theta), \tag{2}$$

where α is a constant and θ the equilibrium value of N previously mentioned. This equation may be integrated to yield

$$N(t) = N(0) \exp [(A_0/\alpha)(1 - \exp (-\alpha t))], \tag{3}$$

where

$$A_0 = \alpha \ln (\theta/N(0)). \tag{4}$$

The clinical application of the Gompertz model (3) is given by Sullivan and Salmon (1972) for both the kinetics of tumor growth and regression in IgG multiple myeloma in humans using the cycle nonspecific drugs melphalan and prednisone. A fixed dose and schedule of the drugs are assumed. When the drugs are administered, it is assumed that a fixed fraction of the cancer cells are destroyed. Under these assumptions, (3) is used to obtain a discrete relationship which predicts the number of cancer cells present at the time for next treatment. This relationship predicts the existence of a plateau in the tumor regression where the regrowth balances the cell killing. This plateau is shown to be in agreement with data.

The work by Sullivan and Salmon is of particular importance in demonstrating the usefulness of the Gompertzian model for prediction of cancer regression under a given drug dose schedule. The effectiveness of a given dose schedule compared to another is of obvious interest and is the major concern of this paper. We will employ the methods of modern optimal control theory in conjunction with a modification of the model (2) to seek a dose schedule which will minimize the cumulative dose of the drugs used.

The concept of using optimal control theory in a biomedical context appears in the work of Petrovskii *et al.* (1973), Zakharova *et al.* (1973) and Petrovskii (1974). These papers contain references (in Russian) to work in this general area. For cancer problems, the paper by Petrovskii (1974) is of interest here. In it, two broad problem areas are delineated: one deals with individual prophylaxis and the treatment of cardiovascular and oncological diseases; the second deals with the application of the dispensary system and the organization of the treatment of large groups of the population in normal and epidemic situations. They present a mathematical model for the analysis of tumor model first proposed by Skipper (1969). But they do not use Skipper's equations however, Skipper (1974).

A recent paper by Bahrami and Kim (1975) deals with the application of the methods of optimal control theory to minimize the size of the tumor cell population at some terminal time as well as the excessive use of the drug. They construct a performance functional

$$J = \alpha^T(N)\mathbf{x}(N) + \sum_{k=0}^{N-1} \beta_k u(k), \tag{5}$$

where α is a weighting vector with constant positive entries, N is the final stage in the system and $\beta_k > 0$ for $k = 0, 1, \ldots N-1$ are weights which modify the control effort u to take the system from stage k to $k+1$. The vector $\mathbf{x}$ has components whose magnitudes are proportional to the occupancy numbers in each subdivision of the total population of cells. Their method of constructing $\mathbf{x}(k+1)$ from a knowledge of $\mathbf{x}(k)$ is basically due to Hahn (1966, 1970). An application of their approach is made with the phase-specific drug vincristine

to spontaneous AKR leukemia, which has a cell cycle consisting of four distinct phases G_1, S, G_2 and M and cells in the dormant phase G_0. Their theory indicates that the optimal strategy is one of bang-bang control.

In the next section of the present paper, we modify the Gompertzian model (2) by adding a control term to account for cell population losses due to the action of a cycle nonspecific drug. An appropriate scheme is introduced to reduce the basic equations to a non-dimensional form. The section following then deals with the problem of minimizing the total amount of cytotoxic drug in the body, subject to the system equations derived in the mathematical model. This gives a formulation in terms of optimal control theory and one of the main results deduced is that there is a closed loop control between the control variable and a certain function of the non-dimensional cancer population. Dr. S. Salmon of the University of Arizona Medical School kindly supplied the authors with a selection of data on humans with IgG multiple myeloma which enabled us to specialize the model for this situation and also compare the results of using various control programs.

2. A Mathematical Model. We make the following basic assumptions:

(a) The untreated tumor grows according to Gompertz equation (2).

(b) The size of the tumor at the time $t = 0$, denoted by $N(0)$ is known from clinical observations.

(c) The action of the control agent at time t is taken to be proportional to the population size at time t and is written in the form $f(v)N$. Here $f(v)$ is the rate of control per cell and is a function of the control variable v, which itself can be a function of the time t. The quantity v represents the actual magnitude of the cycle nonspecific drug level at the cancer site.

Under these assumptions the kinetics of the tumor are described by

$$dN/dt = -\alpha N \ln (N/\theta) - f(v)N, \tag{6}$$

where

$$N = N(0) \quad \text{at } t = 0.$$

The exact form for $f(v)$ is a field of investigation in itself (see for example Himmelstein and Bischoff 1973a) and in order to make headway with the problem at hand we will employ the often used Michaelis–Menten type of saturation term.

(d) The rate of control per cell, is given by

$$f(v) = k_1 v/(k_2 + v), \tag{7}$$

where k_1 and k_2 are constants.

For the optimal control analysis, it will be assumed that the drug level v can be maintained at any desired level as required by the theory. However since

clinical data will be used to evaluate the constants in (6) and (7) we must temporarily include the effect of administering drugs at specific time intervals in order to simulate the situation for which the data was taken. This requires a pharmacokinetic model for v. For purposes of this analysis, we use the simplest pharmacokinetic model which will still characterize the process. This leads us to our final assumption.

(e) After the administration of a given dose at a given time the anti-neoplastic drug is assumed to decay with a time constant γ. Hence if $v(t)$ is the concentration of the drug at time t, it is obtained from

$$dv/dt = -\gamma v. \tag{8}$$

Alternative mathematical models of cancer growth problems are presented by Jusko (1971), (1973). His models assume exponential growth and that there is no saturation type of behavior in the loss function. More recently Himmelstein and Bischoff (1973a, b) introduce a von Foerster equation adjusted to include the Rubinow maturity variable. From this equation an asymptotic solution for the number density function is obtained which exponentially increases with time and has a multiplicative factor arising from a saturation type cell-loss term.

3. Evaluation of Parameters. The books by Engle and Wallis (1969), Waldenstrom (1970) and Snapper and Kahn (1971) and the survey article by Alexanian (1972) provide important information on the bone cancer in humans known as multiple myeloma. Earlier in the present paper special attention is given to the work of Sullivan and Salmon (1972). In particular, with the constraints (i) average survival time from diagnosis in untreated or drug-resistant cases, (ii) a threshold tumor cell number at diagnosis of at least 2.5×10^{11} myeloma cells in the body and (iii) an average tumor doubling time of 4–6 months during the clinical phase of the disease, together with an estimate of the retardation constant, they are able to construct the growth portion of the tumor. From their published results it is possible to deduce that the equilibrium value θ is of the order of 4×10^{12} cells for each patient. For purposes of data reduction in the present paper it is assumed that each patient has an equilibrium number of cells with $\ln \theta = 29 (\theta = 3.9313 \times 10^{12})$ and that an average value of α is 0.015 $(\text{day})^{-1}$ (Sullivan and Salmon obtain values of α from 0.004 to 0.026 per day).

We may now use these values to nondimensionalize (6). If we define a nondimensional cancer population by

$$y = \ln (N/\theta) \tag{9}$$

and a nondimensional time by

$$\tau = \alpha t, \tag{10}$$

then (6) becomes

$$dy/d\tau = -y - f(v)/\alpha. \tag{11}$$

If we now substitute (7) into (11) and define $p = k_1/\alpha$, $u = v/k_2$ we obtain the following equation for cancer growth

$$dy/d\tau = -y - pu/(1+u). \tag{12}$$

Finally by letting $\beta = \gamma/\alpha$, (8) becomes

$$du/d\tau = -\beta u. \tag{13}$$

Reduction of the equations to a non-dimensional system reveals the appearance of two basic parameters. The non-dimensional quantity p is the ratio of the interaction constant k_1 and the retardation factor α whereas β is the non-dimensional ratio of the time constant of the neoplastic drug γ and the retardation factor α. It is interesting to note that only one parameter appears in (12), a feature which will be exploited shortly.

Dr. Salmon provided the authors with raw data on ten patients who had undergone treatment with a melphalan, cyclophosphamide and prednisone program (MCP).

The actual data† used consists of the number of myeloma cells N present in the patient at the time of treatment. For brevity, four "typical" cases are presented and the data is listed in Table 1. Also listed are the dimensionless time τ, an estimate of the *drug interaction parameter* p and a quantity k, which is designated a *drug effectiveness parameter*. Although the therapy program is with three drugs it is assumed here that their cumulative contribution can be represented, albeit in a first approximation, by a single loss term and characterized by the single lumped parameter p in the right-hand side of (13).

For each patient the actual MCP program is described briefly as follows. On day *one* the patient is administered (i) orally, a certain dosage of melphalan (and this is repeated for the next three days), (iii) intravenously, a certain dosage of cyclophosphamide, and (iii) orally, a fixed dosage of prednisone (and this is repeated for the next three days). At a later point in time (usually about a month) these are repeated with generally, reduced amounts of each drug. In general the program continues until remission or replacement with an alternative program. The turnover time for each drug is quite fast. Pharmacokinetics studies are appropriate for the determination of the time course of each drug and its effects on the organs, tissue, etc. In the present paper the following approach is adopted: assume that the cumulative effect of the three drugs can be interpreted as being the same as if a single (fictitious) drug is administered at the end of each time interval. This means that (13) can be used and it remains to estimate the constant β.

†Data supplied by Dr. S. Salmon was obtained in the course of research supported by Grant CA14102 from the National Cancer Institute, Bethesda, Md.

TABLE I

Day	τ	$\Delta\tau$	Tumor cells ($\times 10^{12}$)	y	k
PATIENT B					
0	0	0	2.70	−0.375	
19	0.285	0.285	1.92	−0.717	0.578
29	0.435	0.150	1.77	−0.798	0.120
47	0.705	0.270	1.49	−0.970	0.473
68	1.02	0.315	1.68	−0.850	0.195
103	1.545	0.525	1.63	−0.880	0.638
138	2.07	0.525	1.58	−0.912	0.662
178	2.67	0.600	1.33	−1.08	1.06
$k_a = 0.545$, $p = 78.6$					
PATIENT D					
0	0	0	1.06	−1.311	
29	0.435	0.435	1.08	−1.292	0.685
61	0.915	0.480	0.955	−1.415	0.995
89	1.335	0.420	0.973	−1.396	0.710
110	1.65	0.315	1.01	−1.359	0.466
138	2.07	0.420	0.937	−1.434	0.823
$k_a = 0.736$, $p = 106$					
PATIENT C					
0	0	0	1.53	−0.944	
39	0.585	0.585	0.597	−1.885	2.44
66	0.990	0.405	0.556	−1.956	1.05
94	1.41	0.420	0.336	−2.460	1.79
122	1.83	0.420	0.355	−2.405	1.20
150	2.25	0.420	0.271	−2.675	1.67
$k_a = 1.63$, $p = 235$					
PATIENT A					
0	0	0	1.297	−1.109	
25	0.375	0.375	0.383	−2.329	2.28
dose given between day 25 and 71 but no cell count made					
71	1.065	0.690	0.108	−3.595	
155	2.325	1.26	0.0985	−3.687	9.40
159	2.385	0.06	0.0956	−3.717	0.260
182	2.73	0.345	0.0945	−3.728	1.55
189	2.835	0.105	0.0940	−3.733	0.418
$k_a = 2.78$, $p = 401$					

In the next few paragraphs is described the approach used in placing the mathematical models (12) and (13) in the context of an application to tumor regression in IgG multiple myeloma.

Assume that at the times 0, τ_1, τ_2 . . . there is the single administration of the (fictitious) drug with dosage magnitude $u(0)$, the time interval $\Delta\tau$ between each administration being nonuniform, in general. Consider the regression and regrowth of the tumor in the non-dimensional time interval (τ_1, τ_2). Equation (13) integrates to give

$$u(\tau) = u(0) \exp [-\beta(\tau - \tau_1)]. \tag{14}$$

Substitution of this result into (12) gives, on integration,

$$y(\tau) = y(\tau_1) \exp [-(\tau - \tau_1)] - pu(0) \exp (\beta\tau_1 - \tau) \int_{\tau_1}^{\tau} \frac{\exp [(1-\beta)s] \, ds}{1 + u(0) \exp [-\beta(s - \tau_1)]}. \tag{15}$$

We will show later that $\beta \gg 1$, hence throughout (τ_1, τ_2) assume that $\exp (s - \beta s) \approx \exp (\tau_1 - \beta s)$ then (15) integrates to give

$$y(\tau) \approx [y(\tau_1) - k] \exp [-(\tau - \tau_1)] + \frac{p}{\beta} \exp [-(\tau - \tau_1)] \ln \{1 + u(0) \exp [-\beta(\tau - \tau_1)]\}, \tag{16}$$

where

$$k = (p/\beta) \ln (1 + u(0)). \tag{17}$$

Since $\beta \gg 1$ the effect of the drug is to reduce the number of myeloma cells over a very short time interval (τ_1, τ_i), where $\tau_1 < \tau_i \ll \tau_2$ and this is representative of the regression phase.

However, during the time interval (τ_i, τ_2) the effect of the drug on myeloma cells represented by the second term in (16) is negligible and there is a regrowth of the tumor. Accordingly, for $\tau > \tau_i$, we may approximate (16) by the first term only. Setting $\tau = \tau_2$ we use the first term to solve for k:

$$k = y(\tau_1) - y(\tau_2) \exp (\tau_2 - \tau_1). \tag{18}$$

The quantity k is referred to as a drug effectiveness parameter. The four quantities on the right of this equation are known from the raw data and this provides the values of k in Table 1.

It is apparent that the drug effectiveness parameter k not only varies from patient to patient, but may vary with time in an individual patient as well. Patient A has the largest variation in this parameter and patient C has the smallest, for the four cases shown. A value k_a to each patient is assigned by

averaging the computed k. Since k_a is known (17) is now used to define p,

$$p = \beta k_a / \ln (1 + u(0)) \tag{19}$$

in terms of k_a, β, and $u(0)$. So far only k_a is known. For the typical α value of 0.015 we have that $\beta = \gamma/(0.015)$. With the assumption that the turnover time for the (fictitious) drug is of the order of one day ($\gamma \approx 1$) then β is of the order of 100. We will assume $\beta = 100$ and it now remains to estimate $u(0)$. It would appear that the particular numerical value assigned to $u(0)$ is of no great matter as the value of p is correspondingly adjusted and then only slightly since the natural logarithm of $(1 + u(0))$ is taken. What does appear to be important is to what level of saturation an MCP program corresponds. (Saturation refers to the fact that as $u \to \infty$ the second term of (12) $\to p$.) Here, it is assumed that a standard MCP program is one that is administered every four weeks and with this time period the amount of drug given to the patient results in an initial saturation factor of 1/2. Thus $u(0) = 1$ for the "standard MCP program of the fictitious drug." Equation (19) simply becomes

$$p = (100/\ln 2) k_a. \tag{20}$$

and this equation was used to evaluate p in Table 1.

4. Evaluation of the Model. In Figures 1–4 the non-dimensional raw data is plotted as shown. Also plotted are the results for (i) a "standard" MCP program ($u(0) = 1$ every 4 weeks, the p value from Table 1, and $\beta = 100$) which is obtained by numerical integration of (12) and (13), and (ii) a modified MCP program ($u(0) = 1/2$ every 2 weeks, p value from Table 1 and $\beta = 100$). The initial value of y is the same for each case, but of course varies from patient to patient.

The results in Figures 1–4 are plotted only for the day of administration of the program, that is, each curve shown is the locus of the non-dimensional number of myeloma cells just prior to the administration of the drug. This method of presenting the data and our model results is consistent with the form of the raw data. Figures 1, 2 and 3 show good agreement between the data and program (i) and the model. Figure 4 is representative of a case with poor agreement. Of the ten patients, half of them showed good agreement as in Figures 1–3. Generally speaking good agreement is obtained when the drug effectiveness parameter k remains relatively constant with time for an individual patient. If it is assumed that this is a real effect, then, allowing for drug effectiveness variability from patient to patient, the mathematical model appear to be reasonable.

Although the MCP program used in the model treats the patient every four weeks, it is evident from the raw data that this schedule is not maintained with any degree of constancy, primarily to avoid excessive toxicity of the treatment

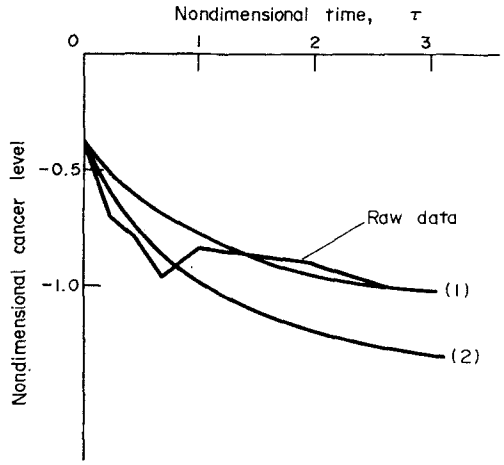

Figure 1.

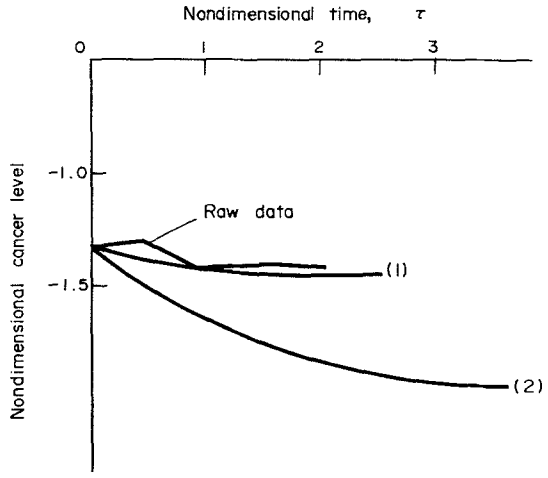

Figure 2.

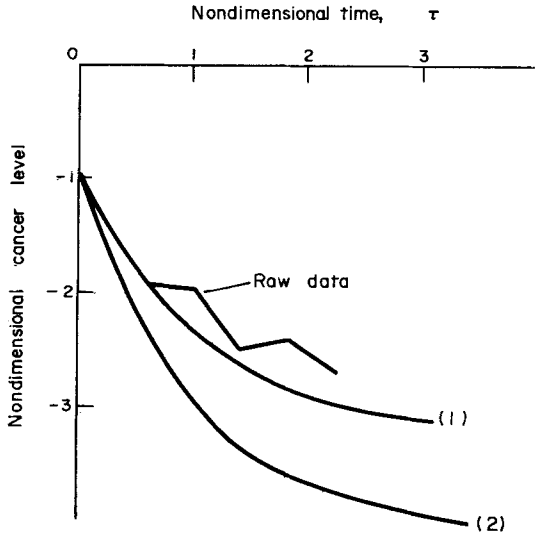

Figure 3.

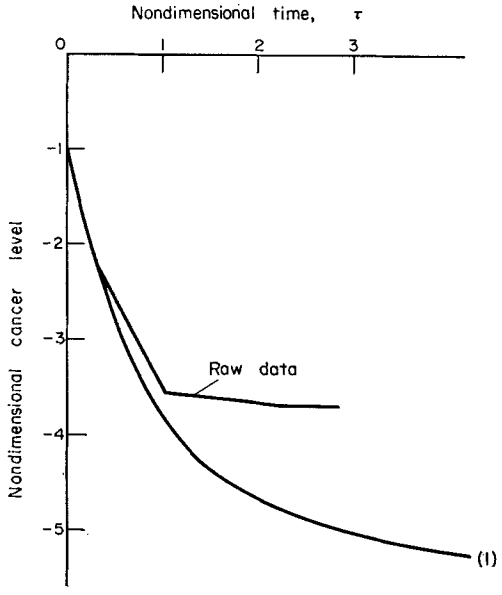

Figure 4.

to normal bone marrow cells. In view of this fact, it is encouraging that the model does give good agreement with the data for it indicates that the model is not overly sensitive with respect to the parameters and control program used.

Having gained some confidence in the model it is now possible to use it to predict the effect of alternate control programs. The modified MCP program (ii) is shown to predict better results in the sense of greater reduction of numbers of myeloma cells) in every case. To see why this is so it is instructive to examine in detail a particular case.

Consider now the detailed analysis of our standard MCP program (i) on patient B. Figure 5 illustrates the nondimensional myeloma level as a continuous function of time (contrast this with Figure 1), Figure 6 illustrates the

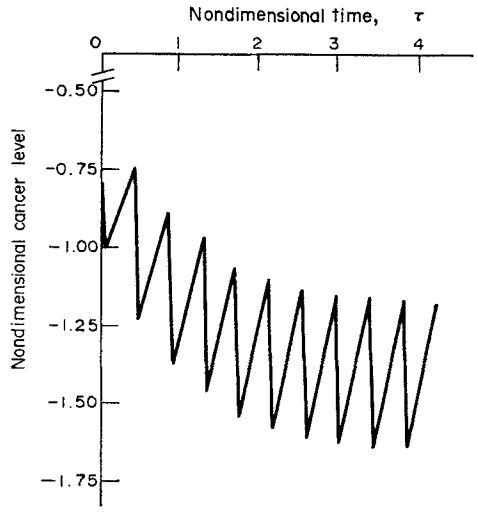

Figure 5.

level of drug as a function of time, τ, and Figure 7 shows the accumulative drug input to the patient as a function of τ (that is, the integral of the curve in Figure 6.). There is a significant decrease in y following the administration of drug subsequently followed by regrowth of the tumor. It is apparent that, if the time duration of the regrowth phase can be shortened, better use of the drug can be made. This is illustrated in Figures 8, 9 and 10 with the modified MCP program (ii). In this case the accumulated amount of drug is the same (compare Figure 10 with Figure 7). However by increasing the number of doses (Figure 9) a lower plateau is ultimately reached (Figure 1). Inspection of Figure 8 indicates that less time is spent on the regrowth phase.

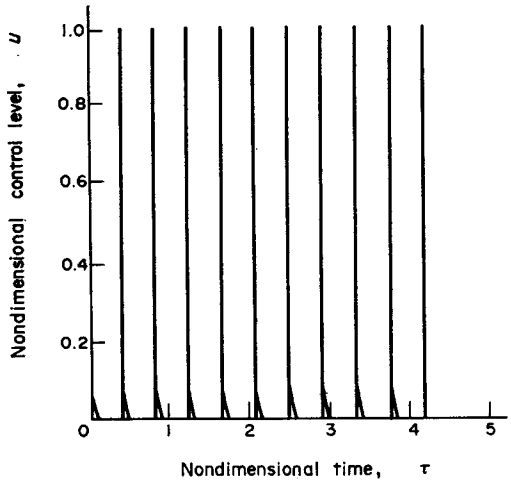

Figure 6.

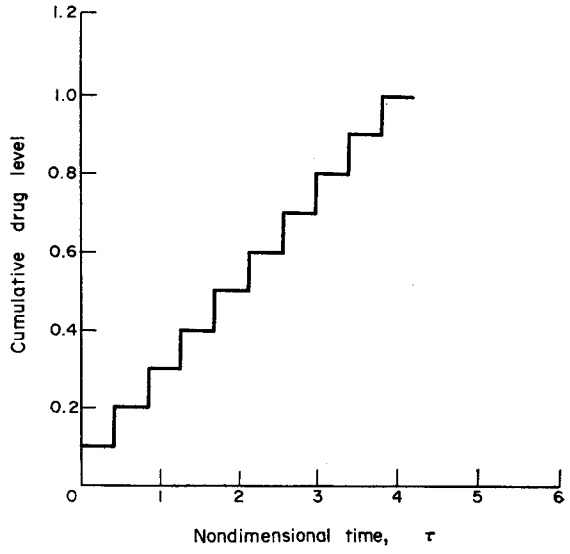

Figure 7.

C

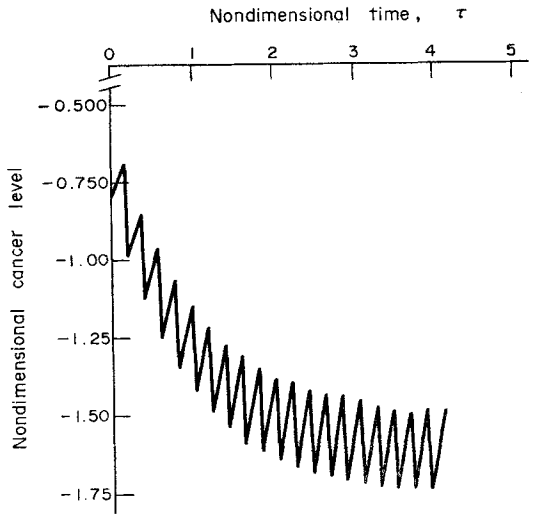

Figure 8.

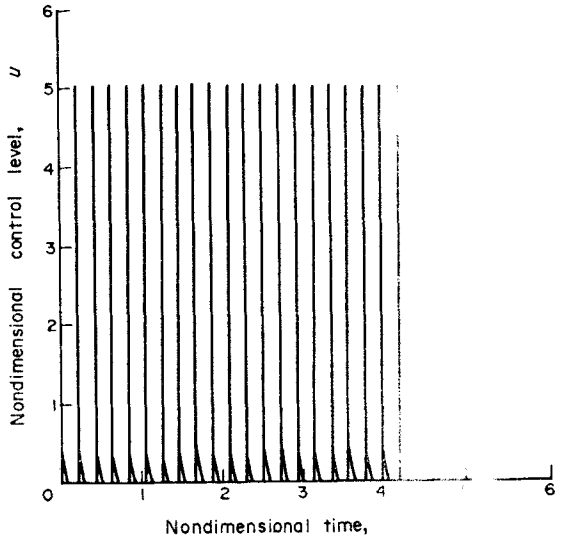

Figure 9.

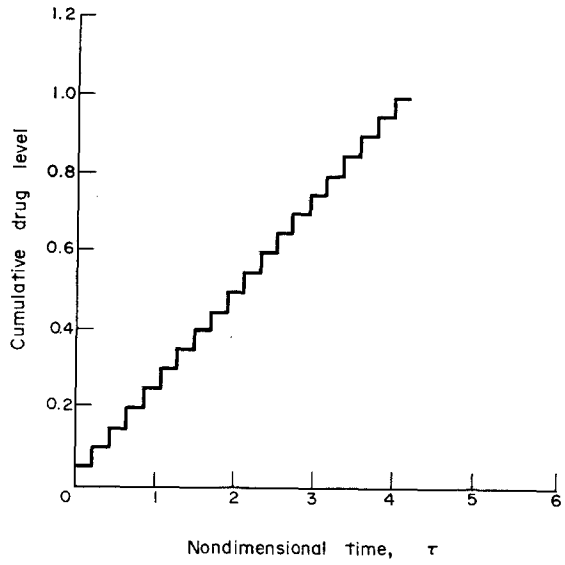

Figure 10.

5. Optimal Control Analysis. If the drug is introduced into the body at $\tau = 0$ then the total amount of drug in the body up to the (nondimensional) time T is given by

$$J = \int_0^T u \mathrm{d}\tau, \; 0 < u \leqslant u_{\max} \tag{21}$$

We take as our objective the reduction of the number of tumor cells to a pre-assigned level and at the same time the minimization of the cumulative toxicity effect of the anti-cancer drug. Mathematically this problem can be cast into the format of modern optimal control theory: minimize J subject to the state equation (12) and such that at time $\tau = T$, $y = y(T)$. It is apparent that this selection for J is not unique. Other criteria are possible and remain for further investigation.

Equation (13) is not included in the optimal control analysis as we will not assume a priori that the drug is given in discrete doses at fixed time intervals.

Using standard techniques, e.g. Leitmann (1966), the analysis proceeds by first forming the Hamiltonian function

$$H = -u - \lambda[y + pu(1+u)^{-1}], \tag{22}$$

where λ may be thought of as a Lagrange multiplier. The H function contains the elements of the optimal control problem, the cost function and the system dynamics. As with familiar static optimization theory, a necessary condition

is obtained by setting the first partial derivative of H with respect to u equal to zero. Since the problem is one-dimensional, we are able to solve for λ from the auxiliary condition that at its minimum value $H = 0$. From the necessary conditions $H = 0$, $\partial H/\partial u = 0$, we obtain, using the fact that $u > 0$, and letting $x = -y/p$,

$$u(\tau) = (x(\tau) + \sqrt{x(\tau)})/(1 - x(\tau)). \tag{23}$$

This control program is in a most useful closed loop form, that is, the level of drug dose is given as a function of the nondimensional number of cancer cells present.

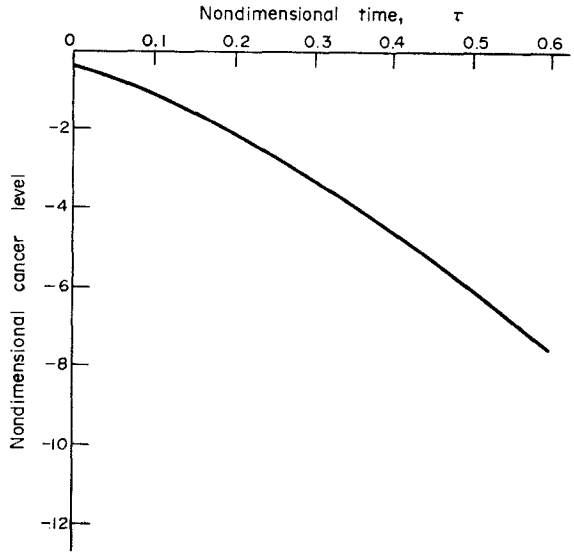

Figure 11.

Figures 11, 12 and 13 are obtained by integrating (12) with the control program (23) using patient B's data. In this situation the tumor is reduced in a continuous fashion (Figure 11) since the control program is administered continuously (Figure 12), that is, a level of the drug is continuously maintained in the patient. Note that the dose starts out relatively small (less than 1/10 of our standard MCP dose) and then *gradually increases* as the cancer cells decrease in number. Note that the number of cancer cells are at the plateau level for patient B (Figure 1) at about 0.15 units of time. Thus attainment of this level is much swifter than with the standard program. Also, from Figure 13, the accumulated amount of drug at this point is about 1/40 of the accumulated amount with the standard MCP program.

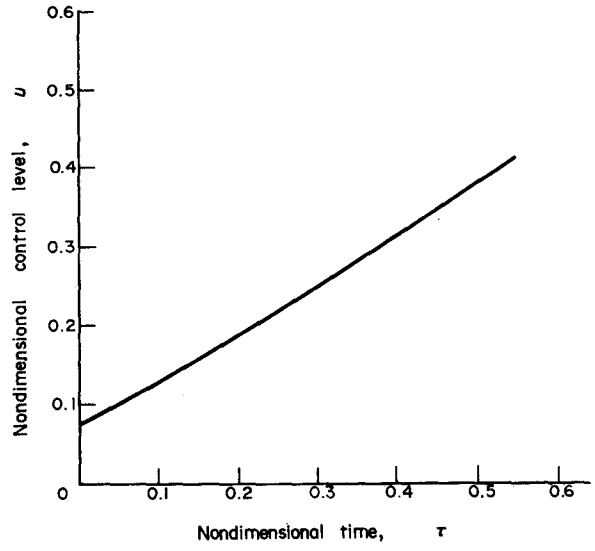

Figure 12.

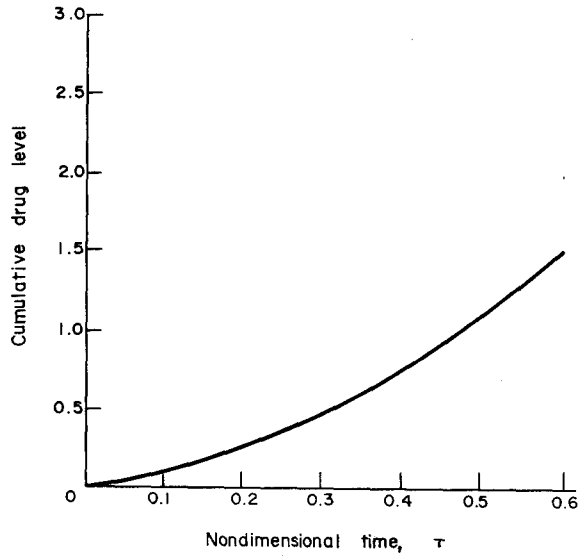

Figure 13.

Accordingly one can conclude that the program (23) can result in significant improvements in recovery time with far less usage of drug. However this conclusion is made with the most guarded optimism. This is true only if the drug can be successfully administered in a continuous fashion, and hopefully toxicity effects are held to a minimum. Also, it is assumed, during the implementation of the optimal control program, that the drug effectiveness parameter does not change significantly due to a change in drug programs. This assumption is one which can only be proven or disproven by clinical trials.

Because of the importance of this last observation on the significance of the results it is (tentatively) suggested that some clinical experiments be performed to determine the nature and extent of variation of the drug effectiveness parameter.

It should be emphasized, even if the drug effectiveness parameter does vary considerably with an individual patient, that knowing the value of the parameter at the time of treatment still allows for use of the program (23) since it is a direct function of this parameter.

In view of these comments it is interesting to note that Waldenström (1970), p. 164, has discovered for melphalan that the ratio of total dosage to number of months that treatment lasted is sensibly constant at 30–40 mg per month. From this he implies that 0.8 to 1.2 mg a day might be ideal and suggests that one can give 1-mg tablet every day.

Conclusions and Discussion. Administration of a cycle-nonspecific drug at the end of equal fixed time intervals can reduce the number of cancer cells. Sullivan and Salmon (1972) show that the locus of the number of viable tumor cells just prior to the next dosage is a decaying Gompertz curve, the retardation constant of which is precisely the same as that of their original growth curve. Their analysis allows for a determination of the plateau when tumor growth exactly balances cell killing. The present paper extends the Sullivan and Salmon mathematical model by directly incorporating a cell loss term in the growth equation. This is a necessary feature in order to proceed with the optimal control analysis of the growth equation when cycle nonspecific therapy is used. Although present clinical treatments involve a combination of drugs the present paper gives an interpretation of the effect of lumping them together into a "single drug." Based on this premise the results from the mathematical model do compare favorably with actual data.

It should be noted that the modification of the Sullivan and Salmon model is twofold, involving continuity of the drug effect and saturation of the drug dose. They use a discrete analysis in which it is assumed that an instantaneous percentage kill is obtained which is directly proportional to dose. The model used here assumes a continuous kill rate proportional to dose subject to a saturation effect and a pharmocokinetic loss of the drugs with time. It may be

easily shown that for large values of the parameter β, both a discrete analysis and a continuous analysis will yield similar results.

The application of the Gompertz equation subject to MCP control, to Multiple Myeloma involves three drugs. Consequently the pharmocokinetics of the drug combination in the tissues would suggest the use of three compartments. In this paper such complexity is avoided by assuming three or more compartments to be equivalent to a hypothetical one. This assumption along with the simple decay equation (13) may account for the large variations in the drug interaction parameter p. Nevertheless, the lumped one-compartment model as used in this paper does appear to offer a reasonable first approximation. Note that (13) is not needed for the optimal control analysis and if p could be obtained by some independent means, the results are independent of specific pharmacokinetics.

It is clear from the results presented that the mathematical model given by (12) and (13) does a fair job of predicting behavior of some clinical data through adjustment of the single parameter p in (12). A real test of any model is to examine its predictive capability under a control program different from that in which the coefficients are estimated. Suppose the coefficients in the model are obtained, as was done here, by having a patient undergo treatment using a standard MCP program starting with an initial tumor size $N(0)$. Suppose then treatment was stopped and the tumor allowed to return to the level $N(0)$. At this time treatment was again initiated, but this time by means of a program based on the optimal control approach. If the basic mathematical model is sound then the theoretical predictions of the optimal approach will predict cell regression data in line with those obtained clinically. Clearly this experiment would be difficult to perform with patients, but it could be a possible basis for evaluating mathematical models used in this study of tumors in small mammals.

It should be noted that the control program (23) obtained here satisfies necessary conditions for the minimization of the total drug accumulation. Alternative criteria will in general result in different programs. Our motivation for minimizing total drug accumulation was based on a desire to minimize the toxicity and immunity effects of the drugs and still obtain significant cell reduction. Clearly one need not follow from the other and more work needs to be done in order to define precisely the cost function of interest.

As previously noted the model gave fair prediction of clinical data for about half the cases examined (as in Figures 1–3, patients BCD and poor agreement in the other half (as in Figure 4, patient A). Data on patients with poor agreement indicated that two had a high fever shortly after starting on the clinical MCP program and one showed no change in the level of myeloma cells at all. Another patient went 59 days between the first two treatments, and was somewhat irregular in following treatment schedules. This led to a rather large value of k_a. For the remaining two patients at certain times when they obtained

treatments there is no data record on number of myeloma cells, etc. Again the k_a values computed were much too large. Patient A (Table 1, part 1) and Figure 4 is an example. The best modeling results were obtained when a patient came for therapy at regular intervals of between 19 to 25 days and experienced no other apparent problems (such as a fever). In these cases the computed values of k did not differ much from the average value k_a.

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