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Mathematical Representations of Cancer Chemotherapy Effects

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Predictive models have been developed to simulate cancer cell populations under treatment with cytotoxic drugs, with both direct-acting and cell cycle specific drugs being considered. Models of cell growth kinetics have been combined with simple pharmacokinetic models to complete the cell-drug interaction system. The models depend on knowing the distribution of generation time in the cell population, the cell-drug interaction, and the local concentration of the drug at the effective site. All of the quantities can be obtained, in principle, from separate experiments and combined to form a model describing several aspects of the cell-drug response system.

KEY WORDS: pharmacokinetics; cancer chemotherapy; cell kinetics; mathematical model; cell cycle specific drugs.

INTRODUCTION

Models for drug distribution (pharmacokinetics) have been developed for several drugs employed in cancer chemotherapy. Their utility can be further improved by the development of models that describe the effect of the drug on the cancerous growth. In this paper, several models of overall cancer-drug relations are developed which include drug–host pharmacokinetics, cancer cell population kinetics, and drug–cell interactions. This work is a beginning attempt at synthesizing these various areas, and this paper provides mathematical results, subject to certain clearly stated assumptions, that can be tested against experimental data. A subsequent paper does this for the mouse L1210 ARA-C (cytosine arabinoside) system and serves to justify the models for at least this case. However, much more

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study will be required to really validate the possible models. (Also see the addendum to this paper.)

Several cell population kinetic models are available to describe cell kinetics—they are summarized by Fredrickson *et al.* (1) and by Weiss (2). For many of the drugs used in cancer chemotherapy, the drug effectiveness depends on the cell mitotic cycle. Thus a "structured" model described by Tsuchiya *et al.* (3) must be employed. This indicates that most simple gross descriptions, such as Michaelis–Menten–Monod models, are not sufficient. It is assumed here that some simple representation of the cell cycle, or maturity of the cell, is sufficient to describe the necessary cell cycle specification. A quantitative description of the detailed biochemical events would, of course, be more desirable but is not available at present; Werkheiser (4) has made a start in this direction.

Many investigators have studied von Foerster type models (5,6). These models belong to the group of models known as population balances, and Trucco (7,8) describes several mathematical solutions to these models. We will employ the model of Rubinow (9) for reasons discussed below.

Rubinow's model is based on time and a variable, here called the maturity, that describes the phase of the mitotic cell cycle. The maturity is defined such that all cells are born with a maturity of 0 and divide to form two cells at a maturity of 1. The maturity is assumed to be related to biological events and is operationally defined in terms of measured cell generation times. Rubinow assumes that the individual cells of any population inherit the cell characteristics such as the cell generation time from their parent cells. The observed variability in cell generation times in the cell population is included by assuming that there is a distribution of cell generation times among the cells in the population. That each cell's characteristics are determined by the parent cell allows the problem of randomness to be considered by adding the results of the model over all "groups" of cells found in the population. This approach leads to simpler mathematical description than is available with other approaches, such as that of Trucco (7,8).

Rubinow's population balance is, then,

$$\frac{\partial n}{\partial t} + \frac{\partial}{\partial \mu}\left(\frac{1}{\tau} n\right) = -\lambda n \tag{1}$$

where $n(\mu, t)$ is the cell density function, $\tau(\mu, t)$ is the population generation time, and $\lambda(\mu, t)$ is the death or loss rate of cells. The initial condition of the system is

$$n(\mu, 0) = N_0 g(\mu) \tag{2}$$

where $g(\mu)$ is the distribution of maturities among the N_0 cells present at

time zero. The boundary condition is given by binary mitosis:

$$\frac{1}{\tau(0, t)} n(0, t) = 2 \frac{1}{\tau(1, t)} n(1, t) \tag{3}$$

This boundary condition allows the separation of the effects of mitosis from other additions or losses such as migration or cell death which are included in the loss rate function. For cells with given generation times, the total number of cells in the population is given by

$$N_\tau(t) = \int_0^1 n_\tau(\mu, t)\, d\mu \tag{4}$$

and for a total population of cells containing a distribution of generation times, the total number of density and total number of cells are given by

$$\begin{aligned} n(\mu, t) &= \int_0^\infty W(\tau) n_\tau(\mu, t)\, d\tau \\ N(t) &= \int_0^\infty W(\tau) N_\tau(t)\, d\tau \end{aligned} \tag{5}$$

This model is used here to describe cancer cell kinetics, due to the simpler mathematical treatment possible and the separation of mitosis from other cell additions and losses.

It is possible that drugs affect growth rates, kill cells, or render them impotent. Depending on the exact biochemical mechanism involved, one could argue for several possibilities. As one possible general case, only drugs that kill or render impotent are considered; this is the most obvious basis to try and also leads to reasonably simple (mathematical) results, which seems to be appropriate at the present state of knowledge. It would be entirely possible that different classes of drugs would have different representations. This means, then, that the generation time of a cell is taken constant and all cell losses are described by means of the loss function. Thus equation 1 becomes

$$\frac{\partial n}{\partial t} + \frac{1}{\tau} \frac{\partial n}{\partial \mu} = -\lambda n \tag{6}$$

and equation 3 reduces to

$$n(0, t) = 2n(1, t) \tag{7}$$

In the sections below, equation 6 will be solved for several cases and the meaning of the loss function will be discussed.

DIRECT ACTION MODELS

If a cytotoxic drug kills a cell without respect to the cell cycle, then particularly simple representation of this phenomenon is possible as a solution of equation 6, $\lambda = \lambda(t)$ only. Such drugs are here termed direct action drugs. Small numbers of cells are probably not accurately described by equation 6, and a stochastic model would be required. Many large populations of cells are observed to be approximately in exponential growth:

$$N = N_0 2^{t/\tau} \tag{8}$$

It is assumed here that this is the way the cell growth would appear, except for the action of drugs. If some other representation were needed, then suitable solutions could be obtained in a manner similar to below.

The number density function yielding the proper exponential growth without drug and having the proper time-dependent loss function is found to be

$$n(\mu, t) = N_0(2 \ln 2) \exp[(t/\tau - \mu) \ln 2] \exp[-\Lambda(t)] \tag{9}$$

where the integrated fractional loss is

$$\exp[-\Lambda(t)] \equiv \exp\left[-\int_0^t \lambda(t')\, dt'\right] \tag{10}$$

and the total cell population is given by

$$N(t) = N_0 2^{t/\tau} \exp[-\Lambda(t)] \tag{11}$$

The details of this solution are given in the appendix to this paper. Thus, for a given loss function, the total number of cells in a population being treated by a direct action cytotoxic drug can be computed from expression 11.

CELL CYCLE SPECIFIC MODELS

The previous discussion of population drug effect models has been restricted to no dependence on the cell cycle. There are some drugs, however, that act during only portions of the cell cycle, and for this reason models including cell cycle specific characteristics will now be considered.

When the cell cycle specific problem is considered, it becomes immediately apparent that some model of the growth kinetics including an expression of the state of the maturity of the cells is needed. Rubinow's assumptions mentioned above concerning the inheritance properties of cell characteristics and the cyclical boundary conditions are again employed here. These assumptions provide a representation of the maturity level of the cells of the population. As an initial condition, synchronous birth is used. Any other suitable condition could also be assumed with a similar analysis. An expression similar to equation 6 was solved by Trucco (7)

for the case of time and maturity variable loss functions by integrating the characteristics of the equation in maturity. As it is intuitively less complex to trace the time loss function, equation 6 is solved here by integrating its characteristics in time.

Consider now the form that the loss function representing a cell cycle specific drug could take:

$$\begin{aligned} \lambda(\mu, t) &= 0 \qquad && \mu < a \\ &= \lambda(t) && a \leq \mu \leq b \\ &= 0 && \mu > b \end{aligned} \tag{12}$$

That is, it is assumed that the drug is effective only during the interval (a, b) representing some fraction of the cell mitotic cycle. If there is more than one such effective interval,

$$\lambda(\mu, t) = \sum_{i=1}^{m} \lambda_i(t)[U(\mu - a_i) - U(\mu - b_i)] \tag{13}$$

where a_i and b_i are the limits of the ith vulnerable phase of the cell cycle and $U(\ )$ is the unit step function. The limits of the vulnerable phases may be themselves functions of the generation times or other cell properties. While the case of only one vulnerable phase is treated here, the analysis could be expanded to include m vulnerable phases by the use of equation 13.

The initial condition is

$$n(\mu, 0) = N_0 g(\mu) = N_0 \delta(\mu) \tag{14}$$

where $\delta(\mu)$ is the unit impulse function. That is, at time zero N_0 cells are present, each with a maturity of $\mu = 0$.

The details of the mathematics leading to the solution are again contained in the appendix. The final result for the total number of cells is

$$\begin{aligned} N(t) = N_0 \int_t^{\infty} W(\tau) \exp \Bigg[&- \left\{ U\left(\frac{t}{\tau} - a\right) - U\left(\frac{t}{\tau} - b\right) \right\} \int_{a\tau}^{t} \lambda(t')\, dt' \\ &- U\left(\frac{t}{\tau} - b\right) \int_{a\tau}^{b\tau} \lambda(t')\, dt' \Bigg] d\tau \\ + N_0 \sum_{j=2}^{\infty} 2^{j-1} \int_{t/j}^{t/(j-1)} W(\tau) \exp \Bigg[&- \left\{ U\left(\frac{t}{\tau} - j + 1 - a\right) \right. \\ &\left. - U\left(\frac{t}{\tau} - j + 1 - b\right) \right\} \int_{(j-1+a)\tau}^{t} \lambda(t')\, dt' \\ &- U\left(\frac{t}{\tau} - j + 1 - b\right) \int_{(j-1+a)\tau}^{(j-1+b)\tau} \lambda(t')\, dt' - \sum_{i=1}^{j-1} \int_{(i-1+a)\tau}^{(i-1+b)\tau} \lambda(t')\, dt' \Bigg] d\tau \end{aligned} \tag{15}$$

It can be noted that although both variation in generation times among the cells and the drug effectiveness depend on the cell mitotic cycle, the only independent variable in equation 15 is time. Thus, with suitable representations of the distribution function and the time-varying dependency of the loss function, the total population number can be calculated.

DRUG DEPENDENCY OF THE LOSS FUNCTIONS

In the above development, the loss functions were considered only generally. In this section, more complete descriptions of these functions are made so that the models presented above can be used to predict the kinetics of populations being treated by cytotoxic drugs. It is assumed here that a drug destroys cells by physically killing them or renders them nonproliferative and that this can be represented by the loss function included in the analyses above.

In the absence of a drug, a constant loss function would represent the normal death of cells due to natural causes. The integrated fractional loss becomes

$$\exp[-\Lambda(t)] = \exp\left[-\lambda \int_0^t dt\right] = e^{-\lambda t} \tag{16}$$

While the assumed form does not consider the possibilities of the susceptibility of cells to death as a function of maturity, as a function of the number of neighbors, or as a function of a changing environment, this loss function may adequately represent the observed decay of a population when combined with a suitable kinetic model of the population.

The overall effect of a drug on a cell population must include the various possible factors that may influence the action of the drug, such as drug concentration, drug uptake, exposure time, and the biochemical mechanism of action. Here the drug effects are considered to be a function of some nominal drug concentration such as the plasma (or other local) concentration in the host organism.

A simple model of the drug action can be developed by assuming a first-order relationship where the instantaneous loss function is directly proportional to some power of the drug concentration. Thus

$$\exp[-\Lambda] = \exp\left[-K \int_0^t \{C(t')\}^p \, dt'\right] \tag{17}$$

This model is the simplest possible to still contain the time variable effect of drugs. A model that may be more widely applicable is one that has the

form

$$\lambda = K_1 C(t)/[K_2 + C(t)] \tag{18}$$

At values of $C(t)$ much less than K_2, the relationship between the drug and loss function is approximately proportional. When $C(t)$ is much greater than K_2, the loss function is approximately constant. Thus this model accommodates saturable interaction behavior.

The loss function of a drug may, in fact, follow the form proposed by either of the drug-dependent functions hypothesized above except that below some threshold concentration the drug is ineffective. In this case, the integrated fractional loss function can be given by

$$\begin{aligned} \exp[-\Lambda] &= F(C(t)) \qquad C \geq C^* \\ &= 1 \qquad\qquad C < C^* \end{aligned} \tag{19}$$

where C^* is the threshold concentration.

Combinations of loss functions may be useful when, for instance, a population is growing in a rather hostile yet constant environment and is also subjected to some sort of drug. In this case, the loss function could then be given by

$$\lambda = \lambda_c + KG(C(t)) \tag{20}$$

and the integrated fractional loss is

$$\exp[-\Lambda] = \exp[-\lambda_c t] \exp\left[-K \int_0^t G(C(t'))\, dt'\right] \tag{21}$$

Extending this result, if the various loss functions of a population are additive, then the various loss functions can be superimposed to present a more comprehensive model of the total fractional loss of a population.

The effect of a drug may not be constant on a given population. It has been assumed to this point that the independent variables time and maturity are sufficient to describe the population. However, the population may well be nonhomogeneous with respect to drug action. In that case, it would be expected that the more susceptible cells would be killed more rapidly and the hardier ones at a slower rate, if at all. If some cells are inherently less susceptible than others, then one could hypothesize that there is a distribution of susceptibilities similar to the generation time distribution assumed in the development of two-population models above. One possible representation is by a distribution of interaction constants K such that

$$\exp[-\Lambda_K] = \omega(K) \exp\left[-K \int_0^t G(C(t'))\, dt'\right] \tag{22}$$

Then

$$\exp[-\Lambda] = \int_0^\infty \omega(K) \exp\left[-K \int_0^t G(C(t'))\, dt'\right] dK \tag{23}$$

Alternatively, if cells became less susceptible due to exposure to the drug, then it might be expected that the interaction constant itself is a function of time or drug contact. Some of these complications may be next to impossible to include, however, because of the difficulty of ever obtaining the requisite experimental data.

PHARMACOKINETIC DRUG MODELS

To complete the modeling of cell population-drug interactions, the local drug concentration that is in contact with the cell population must be determined. This concentration is often a complex function of time, since the drug is dispersed in the host organism and may have complex binding and uptake properties. The book of Wagner (10) gives a summary of classical pharmacokinetic methods. Specific comprehensive models for cancer chemotherapeutic agents have been developed by Bischoff *et al.* (11). Several simple models will be used here, but more complex models may have to be used to completely describe some situations.

For a cell population exposed to a constant drug concentration, the pharmacokinetic model is simply

$$C(t) = C_0 \tag{24}$$

This expression is also useful in the case where constant perfusion of a host organism creates a constant concentration in the cell population.

If the disappearance of a drug from a system can be assumed to be first order after an initial injection, then the pharmacokinetics can be approximated by

$$C(t) = C_0 \exp\left[-\frac{(t - t_0)}{t_d}\right] U(t - t_0) \tag{25}$$

where C_0 is the concentration at the time of the injection (t_0). This type of approximation can be useful in the case of leukemia therapy where the plasma concentration is effectively the concentration that the cancer is exposed to.

For more complex systems, the drug concentration may not be easily expressed analytically. In such cases, numerically evaluated models or actual data may be required to allow the evaluation of the integrated loss function by a numerical method. Several simple models may be combined to predict the concentration-time relationship of multiple treatment dosage schedules. If the pharmacokinetics of a system can be approximated by the sum of the

concentrations due to the total number of doses, then a series of m doses of a drug produces a concentration given by

$$C(t) = \sum_{i=1}^{m} C_i(t) \tag{26}$$

For m equally sized and equally spaced (t_s) injections that can each be given by equation 25, equation 26 becomes

$$C(t) = \sum_{i=1}^{m} (C_0)_i \exp\left[- \left(\frac{t - (i-1)t_s - t_0}{t_d} \right) \right] U(t - (i-1)t_s - t_0) \tag{27}$$

where m is the most recent injection given.

TOTAL REPRESENTATIONS OF CANCER-DRUG SYSTEMS

In this paper, models to simulate the behavior of cell populations exposed to cytotoxic drugs have been developed. A comprehensive model for a given system is composed of suitable growth kinetic, drug-cell interaction, and pharmacokinetic models. The selection of each component part depends on the particular system under consideration. Methods of evaluation of the parameters in the component models must be available to apply the models to a given system; however, each of the component models can often be separately evaluated. The parameters in the kinetics and drug-cell interaction models might, for instance, be estimated with the use of *in vitro* cultures.

Several models can be combined to simulate a complex many-compartment system, each with its own growth kinetics and drug-cell interactions, using a pharmacokinetic model of the host organism to predict drug concentration in the various compartments. As a simplification, consider a two-compartment organism with different growth kinetics and drug-cell interactions. Such a system can represent a cancer cell population and normal but drug-sensitive tissue. The two populations can be modeled under given dosage regimens to develop useful dosage schedules that maximize cancer cell deaths and minimize toxicity effects in normal tissue.

EXAMPLES

Consider a hypothetical cytotoxic drug cell system with the cell growth characteristics of the *Tetrahymena geleii* HS cells studied by Prescott (12). This system is employed only to provide reasonable cell kinetics and cell maturity distribution kinetics. Rather than use the γ distribution employed by Rubinow to fit the generation time distribution, Rahn's (simpler) equation

can be used for the same purpose:

$$W(\tau) = \alpha\gamma \exp[-\gamma(\tau - \tau_0)]\{1 - \exp[-\gamma(\tau - \tau_0)]\}^{\alpha-1} \tag{28}$$

where $\alpha = 6.7$, $\gamma = 8.84$, $\gamma t_0 = 88.4$ min.

Here it is assumed that the cells are in exponential growth in a host organism when treated by a cytotoxic drug that may be either direct acting or cell cycle specific. That is, in the absence of drug effects, the cells are growing in a manner that is approximated by equation 8. In the computations when using the cell cycle specific model derived above, this is accomplished by allowing several generations of cells (more than ten) to "grow" before they are exposed to the drug. A single injection is given to the host-cell system; the drug concentration is given by equation 25 and the drug-cell interaction by equation 18. The constants chosen are $t_d = 0.25\tau_0$, $K_2 = 1.0$, $C_0 = 15K_2$, and $K_1 = 0.5$ to $2.0\ \text{hr}^{-1}$. These constants are of the order of magnitude found for several cytotoxic drugs being used presently. The generation time used for the direct action model is found by

$$\bar{\tau} = \int_0^\infty \tau W(\tau)\, d\tau \Big/ \int_0^\infty W(\tau)\, d\tau \tag{29}$$

or approximated by τ_0, the minimum generation time.

The direct action model is found by substituting equations 21 and 18 into expression 11:

$$\frac{N(t)}{N_0} = 2^{t/\bar{\tau}}\left[\frac{K_2 + C_0U(t - t_0)}{K_2 + C_0U(t - t_0)\exp\left[-\left(\dfrac{t - t_0}{t_d}\right)\right]}\right]^{-K_1t_d} \tag{30}$$

The number function for a single-injection cell cycle specific system is found by substituting the loss function described above into the cell cycle specific number function (equation 15) and integrating the terms in the loss function:

$$\begin{aligned} N(t) = N_0 \int_t^\infty W(\tau) \exp\Bigg[& \left\{U\left(\frac{t}{\tau} - a\right) - U\left(\frac{t}{\tau} - b\right)\right\} K_1 t_d \\ & \cdot \ln\left\{\frac{K_2 + C_0U(t - t_0)\exp[-(t - t_0)/t_d]}{K_2 + C_0U(t - t_0)F_1}\right\} \\ & + U\left(\frac{t}{\tau} - b\right) K_1 t_d \ln\left\{\frac{K_2 + C_0U(b\tau - t_0)\exp[-(b\tau - t_0)/t_d]}{K_2 + C_0U(b\tau - t_0)F_1}\right\}\Bigg] d\tau \\ & + N_0 \sum_{j=2}^{\infty} 2^{j-1} \int_{t/j}^{t/(j-1)} W(\tau) \exp\left[\left\{U\left(\frac{t}{\tau} - (a + j - 1)\right)\right.\right. \end{aligned}$$

$$
\begin{aligned}
&- U\left(\frac{t}{\tau} - (b + j - 1)\right)\Bigg\}K_1 t_d \\
&\quad \ln\left\{\frac{K_2 + C_0 U(t - t_0)\exp\left[-(t - t_0)/t_d\right]}{K_2 + C_0 U(t - t_0)F_j}\right\} \\
&+ U\left(\frac{t}{\tau} - (b + j - 1)\right)K_1 t_d \\
&\quad \ln\left\{\frac{K_2 + C_0 U((b + j - 1)\tau - t_0)\exp\left[\dfrac{-((b + j - 1)\tau - t_0)}{t_d}\right]}{K_2 + C_0 U((b + j - 1)\tau - t_0)F_j}\right\} \\
&+ \sum_{i=1}^{j-1} K_1 t_d \\
&\quad \ln\left\{\frac{K_2 C_0 U((b + i - 1)\tau - t_0)\exp\left[\dfrac{-((b + i - 1)\tau - t_0)}{t_d}\right]}{K_2 + C_0 U((b + i - 1)\tau - t_0)F_i}\right\}\Bigg] d\tau
\end{aligned}
\tag{31}
$$

where

$$
\begin{aligned}
F_j \equiv\ & U((a + j - 1)\tau - t_0)\exp\left[\frac{-((a + j - 1)\tau - t_0)}{t_d}\right] \\
& + U(t_0 - (a + j - 1)\tau)
\end{aligned}
$$

Equation 31 looks rather complicated but can be easily evaluated (e.g., with a computer) taking due account of the meaning of the various step functions. For $(a, b) = (0, 1)$, the cell cycle specific model reduces to the direct action model, and equations 30 and 31 should give the same results for a desynchronized culture. Computations with equation 31 after several generation times, $t_0 > \sim 10\tau_0$, agree with the results of equation 30. The formal reduction of equation 31 to equation 30 could not be accomplished, however, nor was an asymptotic exponential solution for the cell cycle specific model found. The latter is not too surprising, since under some conditions a certain amount of resynchronizing could be expected to occur. For a double injection experiment, the result (equation 31) can be modified by assuming that the drug half-life is short compared to the time between injections so that there are comparatively small amounts of drug present at the time of the second injection. Thus the loss function $\exp[-\Lambda(\mu, t)]$ in equation 31 can be

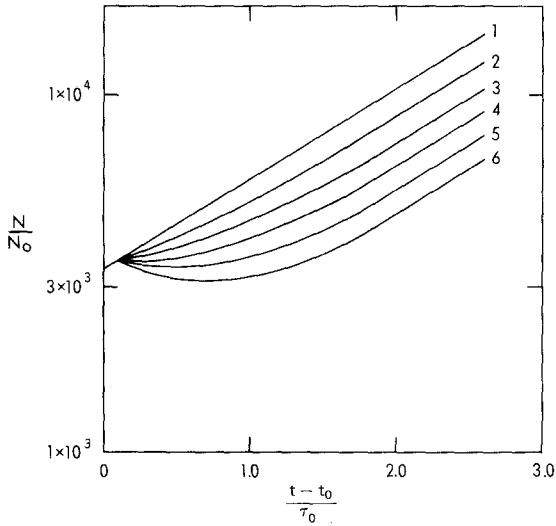

Fig. 1. Single injection with cell cycle specific drug model. Various active cell cycle limits (a, b): curve 1 (0.5, 0.5); curve 2 (0.4, 0.6); curve 3 (0.3, 0.7); curve 4 (0.2, 0.8); curve 5 (0.1, 0.9); curve 6 (0, 1). Other parameters: $K_1 = 1.0$, $K_2 = 1.0$, $t_d = 0.25\,\tau_0$, $t_0 \sim 10\,\tau_0$, $C_0 = 15K_2$.

replaced with

$$\exp\left[-\Lambda(\mu, t_{0_2})\right] \exp\left[-\Lambda(\mu, t - t_{0_2})\right] \tag{32}$$

where t_{0_2} is the time of the second injection.

The above expressions (equations 28, 30, 31, and 32) can now be used to demonstrate some of the characteristics of the models proposed. The expressions are evaluated numerically to demonstrate the effects of the magnitudes of cell cycle effectiveness limits (a, b), the interaction constant K_1, and the effect of the spacing of multiple injections.

Figure 1 shows the dependence of the number function on the active limits of the cell cycle for a single injection. With a drug active during the entire cell cycle, the result reduces to that predicted by the direct action model. When the cell cycle limits are set equal ($a = b$), the model naturally shows no drug effect. As the fraction of active portion of the cell cycle is increased, the fraction of cells killed varies directly. This result depends on the cells being in exponential growth during the treatment time, as the model depends on equal fractions of cells with any given maturity being available. If the cells were synchronized in any degree, then the above result could not be expected.

To further demonstrate the effect of the cell cycle specificity of a drug Fig. 2 shows the effect of a single injection with various values of K_1. As the

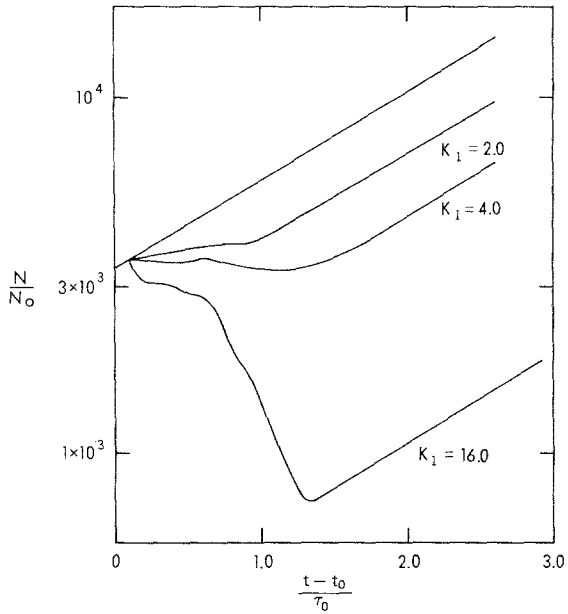

Fig. 2. Single injection with cell cycle specific drug model for various interaction constants (K_1). Other parameters are as in Fig. 1, and $(a, b) = (0.45, 0.55)$.

ability of the drug to kill cells increases, fewer cells are available with values of maturity in the susceptible range. The smooth curves found in Fig. 1 are replaced by curves that are much more irregular, indicating that many cells continue to grow despite the presence of a highly lethal but highly specific drug. This also indicates that the model can have some value in regions where the nominal cell growth kinetics are not exponential.

After an initial treatment of a population by a cell cycle specific drug, the number of vulnerable cells susceptible to a second treatment is dependent on the time of the second dose. This is demonstrated by Fig. 3. In this case, the drug time constant is set at $t_d = 0.025\tau_0$ so that the two injections are certainly far enough apart in time and equation 32 is valid. The second injection is given at various times after the initial injection. While the difference in population numbers is small, a definite dependence on the timing of the second injection is shown. The injection given $0.5\tau_0$ after the first injection is more effective than the one given at $1.0\tau_0$ since the void in the cells with susceptible maturities has not had time enough to be filled with cells from other generations, and the injection given at $0.5\tau_0$ is working on cells unaffected by the first injection.

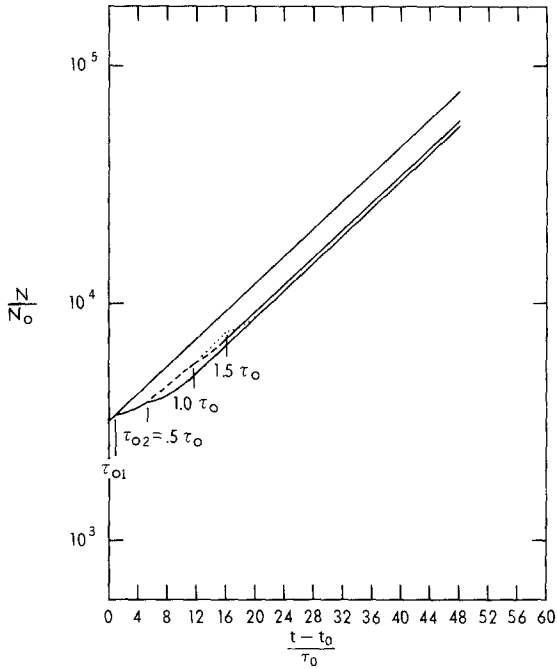

Fig. 3. Double injection with cell cycle specific drug model and various second injection times. Other parameters are as in Fig. 2, and $K_1 = 0.5$.

SUMMARY

The purpose of this study has been to develop predictive models to simulate cancer cell populations under treatment with cytotoxic drugs. The utility of such models is to aid the clinician in the screening and optimization of drug dosage schedules for the treatment of cancers in *in vivo* systems. Models have been developed that consider both direct-acting and cell cycle specific drugs. Several models of cell growth kinetics have been included and have been combined with simple pharmacokinetic models to complete the cell-drug interaction system. The models depend on knowing the distribution of generation times found in a cell population, the cell-drug interaction, and the local concentration of the drug at the effective site. All of the quantities can be obtained, in principle, from separate experiments and combined to form a model describing several aspects of the cell-drug response system. In a succeeding paper, some of these models will be applied to a real drug-cancer system to investigate their utility.

ADDENDUM

After this work was completed, Jusko (14) published models for pharmacokinetic-cancer chemotherapeutic drug effect interrelationships. The model utilizes classical compartmental analysis techniques wherein the peripheral drug concentrations from a two-compartment analysis directly act on the cells, which are assumed to have first-order growth and death kinetics. Good agreement for survival curves with osteosarcoma cells and non cell cycle specific drugs was obtained. Extensions to the cell cycle specific case utilizing the same compartmental techniques have also been done (15). Finally, Shackney (16) has utilized a very involved numerical stochastic model to study cancer cell kinetics and some chemotherapeutic drug effects.

APPENDIX: DETAILED SOLUTION OF CELL-DRUG MODELS

Direct Action Model

An asymptotic solution can be found of the following form (3):

$$n = N_0 \exp[-\Lambda(t)] h(\mu)\, e^{\beta t} \tag{33}$$

Substituting this assumed form into equation 6 and taking the derivatives,

$$\beta h(\mu) + \frac{1}{\tau}\frac{dh}{d\mu} = 0 \tag{34}$$

The solution of equation 34 is

$$h(\mu) = h(0)\, e^{-\beta\tau\mu} \tag{35}$$

Expression 35 must hold over all times, so that at time zero it must satisfy equation 4 and thus

$$\int_0^1 h(\mu)\, d\mu = 1 \tag{36}$$

Substituting equation 35 into equation 36 and integrating, the value of $h(0)$ is found, and

$$h(\mu) = \frac{\beta\tau\, e^{-\beta\tau\mu}}{1 - e^{-\beta\tau}} \tag{37}$$

Finally, the boundary condition (equation 7) applies, so that β can be found, and

$$n(\mu, t) = N_0(2 \ln 2) \exp\left[\left(\frac{t}{\tau} - \mu\right) \ln 2\right] \exp[-\Lambda(t)] \tag{38}$$

The total cell number is found by substituting equation 38 into equation 4:

$$N(t) = N_0 \exp[-\Lambda(t)] 2^{t/\tau} \tag{39}$$

Solution of Cell Cycle Specific Model

The solution of equation 6 is found by LaGrange's method (13) to be

$$n(\mu, t) = \Psi\left(\mu - \frac{t}{\tau}\right) \exp\left[- \int_0^t \lambda(\mu, t') \Big|_{c_1} dt' \right] \tag{40}$$

where Ψ is any arbitrary function and

$$\mu - t/\tau = C_1 = \text{a constant} \tag{41}$$

Combining equation 13 with $m = 1$ (equation 40) and the initial condition for synchronous birth (equation 14), the number density for the first generation is

$$n_1(\mu, t) = N_0 \delta\left(\mu - \frac{t}{\tau}\right) \exp\left[- \int_0^t \lambda(t')[U(\mu - a) - U(\mu - b)] \Big|_{c_1} dt' \right] \tag{42}$$

Due to the initial condition, equation 41 becomes

$$C_1 = 0 - 0/\tau = 0 \tag{43}$$

and the maturity and time are directly related:

$$\mu = t/\tau \tag{44}$$

Substituting equation 44 into the integral term of equation 42,

$$\exp[-\Lambda(\mu, t)] = \exp\left[- \int_0^t \lambda(t') \left[U\left(\frac{t'}{\tau} - a\right) - U\left(\frac{t'}{\tau} - b\right) \right] dt' \right] \tag{45}$$

The integral in equation 45 can be evaluated:

$$\begin{aligned}
\exp[-\Lambda(\mu, t)] &= 1 && a\tau > t \\
&= \exp\left[- \int_{a\tau}^{t} \lambda(t')\, dt' \right] && a\tau \leq t \leq b\tau \\
&= \exp\left[- \int_{a\tau}^{b\tau} \lambda(t')\, dt' \right] && t \geq b\tau \qquad (46) \\
&= \exp\left[- \left\{ \left[U\left(\frac{t}{\tau} - a\right) - U\left(\frac{t}{\tau} - b\right) \right] \int_{a\tau}^{t} \lambda(t')\, dt' \right.\right. \\
&\qquad \left.\left. + U\left(\frac{t}{\tau} - b\right) \int_{a\tau}^{b\tau} \lambda(t')\, dt' \right\} \right] && \qquad (47)
\end{aligned}$$

where the last expression, and many succeeding ones, are found by careful use of unit step functions.

Applying the boundary condition between the first and second generations,

$$n_2(0,t) = 2N_0\delta\left(1 - \frac{t}{\tau}\right)\exp\left[-\int_{a\tau}^{b\tau}\lambda(t')\,dt'\right]$$

$$= \Psi\left(0 - \frac{t}{\tau}\right)\exp\left[-\int_0^t \lambda(t')[U(-a) - U(-b)]\,dt'\right] \tag{48}$$

Therefore, the second generation is given by

$$n_2(\mu,t) = 2N_0\delta\left(1 + \mu - \frac{t}{\tau}\right)\exp\left[-\int_0^t \lambda(t')[U(\mu - a) - U(\mu - b)]\Big|_{C_2} dt'\right]\exp\left[-\int_{a\tau}^{b\tau}\lambda(t')\,dt'\right] \tag{49}$$

In a similar fashion as equation 46 was evaluated, the integral term in equation 49 can be simplified by noting that

$$C_2 : \mu = t/\tau - 1 \tag{50}$$

for the second generation. The number density function for the second generation is

$$n_2(\mu,t) = 2N_0\delta\left(1 + \mu - \frac{t}{\tau}\right)\exp\left[-\left\{U\left(\frac{t}{\tau} - a - 1\right) - U\left(\frac{t}{\tau} - b - 1\right)\right\}\int_{(a+1)\tau}^{t}\lambda(t')\,dt' - U\left(\frac{t}{\tau} - b - 1\right)\int_{(a+1)\tau}^{(b+1)\tau}\lambda(t')\,dt' - \int_{a\tau}^{b\tau}\lambda(t')\,dt'\right] \tag{51}$$

The result can be extended to the jth generation by noting that during the jth generation the maturity and time are related by

$$\mu = t/\tau - (j-1) \tag{52}$$

The number density function for the jth generation is

$$n_j(\mu,t) = N_0 2^{j-1}\delta\left(j - 1 + \mu - \frac{t}{\tau}\right)\exp\left[-\left\{U\left(\frac{t}{\tau} - j + 1 - a\right) - U\left(\frac{t}{\tau} - j + 1 - b\right)\right\}\int_{(j-1+a)\tau}^{t}\lambda(t')\,dt' - U\left(\frac{t}{\tau} - j + 1 - b\right)\int_{(j-1+a)\tau}^{(j-1+b)\tau}\lambda(t')\,dt' - \sum_{i=1}^{j-1}\int_{(i-1+a)\tau}^{(i-1+b)\tau}\lambda(t')\,dt'\right] \qquad j \geq 2 \tag{53}$$

The total number density function for all generations is found from

$$n(\mu, t) = \sum_{j=1}^{\infty} n_j(\mu, t) \tag{54}$$

The total number of cells is found by substituting equations 47 and 53 into equation 54, using this in equation 4, and finally substituting the result into equation 5; this results in equation 15.

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