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Special Article

A Mathematical Model of the Development of Drug Resistance to Cancer Chemotherapy

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Abstract—*A mathematical model incorporating descriptions of tumour growth kinetics and the effects of cytotoxic chemotherapy on established tumours, is presented. It is shown how models of this kind may be used to investigate the potential of hypothetical chemotherapy strategies, and to identify general principles for successful treatment. The model is intended to be an aid to clinicians designing new chemotherapy programmes for diseases in which progress has been disappointing.*

INTRODUCTION

THE emergence of drug resistance in a previously drug-sensitive tumour is thought to be one of the main reasons why cancer chemotherapy is rarely curative. Biochemical or phenotypic resistance may arise in cells spontaneously [1] or be acquired as a result of exposure to the drug [2]. In addition, some cells may not be susceptible to therapy for kinetic reasons, since those in resting phase escape the action of cycle-specific cytotoxic agents.

Although each factor is known to be individually important to the success of chemotherapy, little is known about the interrelationships between the choice of drug(s), dose, method of drug delivery, the interval between treatments and the development of resistance to the chosen drugs. Most drug protocols have been developed empirically. For some tumour types, teratoma and high-grade lymphoma for example, the maximally-tolerated dose is given as frequently as the rate of bone marow recovery permits. If complete remission or cure of these malignancies are not achieved however, the surviving tumour exhibits resistance to most other effective drugs and the patient dies of his disease.

In the absence of more effective new drugs there is an increasing need to define better treatment strategies with existing agents. The design of such strategies should take into account knowledge of tumour growth kinetics, the factors governing the development of drug resistance, and how these are affected by therapy. A mathematical model will be presented in this paper to provide a framework within which this might be achieved. The model idealises the growth kinetics of tumours and the effects of cytotoxic chemotherapy. It can be used to describe the development of an untreated tumour, and the changing size and composition of a tumour in response to hypothetical treatment programmes.

The concepts underlying the model can be described briefly as follows. It is assumed that at any time tumour cells can be found in 1 of 2 states—a proliferating (cycling) compartment, and a resting compartment (G_0). Cells in the cycling compartment are assumed to divide at a constant rate. It is also assumed that there is a constant proportional flow of cells from the proliferating to the resting compartment, and that resting cells retain the capacity to re-enter cycle and do so also at a constant proportional rate. Cells may be lost

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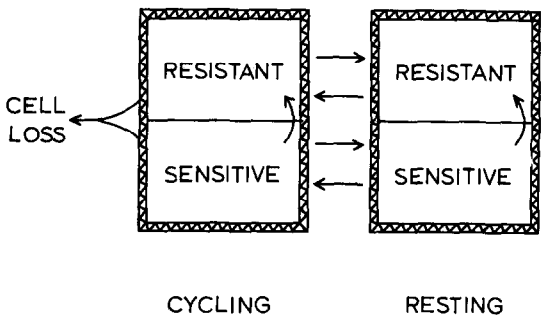


Fig. 1. Compartmental model of tumour development.

from the cycling compartment due to differentiation or death. It is assumed throughout that tumour size has no effect on the kinetic behaviour.

Fundamental to the model is that in each compartment there are 2 populations of cells, 1 of which is sensitive, the other resistant to the drug(s) used. Each identical course of chemotherapy is assumed to kill a constant proportion of the sensitive cycling cells, and to have no effect on all other populations.

In breast cancer—the disease for which the model was originally developed—there is a paucity of relevant data with which to estimate the model's parameters. Human cell lines do not accurately reflect behaviour *in vivo*, since cells with the highest growth fraction are selected and few kinetic parameters have been obtained directly from tumours *in situ*. Those parameters which have been determined directly or indirectly show a wide range [3–5]. There is heterogeneity in terms of both resistance and cell kinetics between tumours of the same histological type in different patients, between the primary and metastatic tumours in the same patient, and even within a single tumour site [5–7]. For all these reasons, the model has been developed to help identify principles of drug treatment and potentially effective novel strategies, rather than detailed protocols.

The model may be of help, for example, in the treatment of advanced breast cancer which is directed towards palliation of symptoms in the patient who will ultimately die of her disease. The relationship between drug dosage and the rate and duration of response in these patients is unclear. Higher doses generally mean greater subjective toxicity which many patients and clinicians find unacceptable. For the fortunate few patients who enter complete clinical remission with chemotherapy it is not known whether treatment should continue, whether the interval between treatments should be altered, or whether treatment should be stopped and recommenced with the same or different drugs when clinical relapse is detected. By using the model proposed here it will be possible to examine a variety of treatment strategies to shed light on these problems, and to suggest promising approaches for testing in future clinical trials.

The model has been designed for use by clinicians, and a simple interactive computer program has been written. By comparing the results of clinical experience with those obtained using the model, it will be possible to assess the aptness of our assumptions, and within the model's general framework, amended or additional assumptions could be accommodated if necessary.

THE MODEL

The model is shown diagrammatically in Fig. 1.

The tumour is idealised as a population of cells, each of which may be in 1 of 2 compartments: cycling and resting. With respect to a given drug or combination of drugs, cells may be classified within each compartment into resistant or sensitive subpopulations. Resistance has been taken to be absolute and irreversible.

In the absence of treatment, it is assumed that cells in the resting compartment are recruited into cycle in proportion to the size of the resting compartment.

Cells in cycle may divide, may be lost, or may transfer to the resting compartment. Each of these processes is assumed to occur in proportion to the size of the cycling compartment.

A process of spontaneous mutation towards drug resistance is assumed to operate at division [1], so that a sensitive cell may give rise to 2 sensitive cells, or to 1 sensitive plus 1 resistant cell, with specified probabilities. Back mutation (resistance to sensitivity) and double mutation (a sensitive cell giving rise to 2 mutants) are excluded from the present model, as is spontaneous mutation in the resting compartment.

At this stage all tumour cells have been assumed to have the same characteristics irrespective of their site.

A dose or course of chemotherapy has been modelled by assuming its effect on the tumour is in instantaneously reducing the size of the cycling sensitive cell population by a constant fraction [8]. It is assumed that all resting cells and resistant cells remain unaffected by the drug(s).

The model is formulated mathematically as a set of simultaneous linear differential equations which is presented in Appendix 1.

For a given set of parameter values, the solution allows one to predict tumour development over time in terms of the 4 cell sub-populations, and to model the effect of different theoretical treatment strategies, using drugs of differing effectiveness in the presence of different levels of phenotypic resistance. Computer programs, with associated graphical software, have been written (in BASIC and

FORTRAN) to allow such predictions and comparisons to be made interactively at a terminal.

ESTIMATING THE VALUES OF PARAMETERS IN THE MODEL

(i) *Tumour parameters*

To use the model to investigate potential treatment strategies, parameter values must be chosen which are consistent with experimentally observed tumour kinetic data. Breast cancer will be taken as an example.

As the model has been formulated, there are 4 unknown parameters relating to the tumour itself: the fractional rate at which cells are recruited from the resting to the cycling compartment (λ), and the fractional rates at which cycling cells divide (α), are lost (η) or transfer to the resting compartment (μ). Four items of physical information are required to estimate them.

To achieve this, values for the following quantities have been selected from ranges reported in the breast cancer literature: the cell-cycle time [9], the observed doubling time of established tumours [10], and the proportion of cells in cycle [11]. Although little is reported or known about the histories of cells in the resting compartment of tumours, an estimate of the average time spent in this phase by leukaemic cells has been made by Rubinow and Lebowitz [12]. As an order of magnitude estimate for illustrating the use of the model, a similar value of 20 days has been taken for breast cancer cells.

A summary of values used for the 4 quantities is given in Table 1(a). The values of the mathematical parameters corresponding to these data are shown in Table 1(b).

It must be emphasised that these values characterise only a single hypothetical tumour. The known heterogeneity of breast cancer will mean they are at best representative of only a few actual tumours.

(ii) *Treatment parameters*

For a given drug, or combination of drugs, there wil be a rate at which sensitive cells mutate to resistance. In accord with the recent literature (e.g. [1]) we have selected mutation rates in the range 10^{-5} to 10^{-7} for applications in the next section.

The effectiveness of a given dose of drug is measured in the model by the proportion of cycling sensitive cells which it instantaneously kills. Values of 0.95, 0.60 and 0.30 have been chosen for this quantity, to represent high, moderate and low levels of effectiveness.

The schedule of administration of a particular treatment will be specified in terms of the intervals between successive doses.

Table 1(a) Observed data

Average cell-cycle time	2 days
Observed doubling time	150 days
Proportion of cells in cycle	20%
Average time in resting phase	20 days

Table 1(b) Model parameters (days^{-1})

λ	0.050
α	0.500
η	0.477
μ	0.218

APPLICATION OF THE MODEL

Using the parameters given in Table 1, and starting with a single sensitive cell, the model predicts the growth of the total tumour shown in Fig. 2(a). The predicted growth rapidly becomes exponential with the specified doubling time of 150 days, and the proportion of cells cycling at any time also quickly reaches an equilibrium value of 20%.

The development of the resistant sub-population within the tumour is shown alongside this curve, for the case in which the mutation rate towards resistance is set at a value of 10^{-7}. By the time the tumour has reached a size of 10^{11} cells, approx. 1 in 10,000 cells will be resistant. Of course, higher mutation rates will increase the level of resistance (e.g. 1 in 100 cells is predicted for a mutation rate of 10^{-5}).

The composition of the tumour can be traced over time and a profile after 9 years is shown in Fig. 2(b).

To illustrate how the model can be used to investigate chemotherapy strategies, 4 hypothetical treatments will be applied to the tumour of Fig. 2(a) when it contains 10^{11} cells:

Treatment 1

One hundred doses of drug A (for which the mutation rate is 10^{-7}) delivered at intervals of 21 days, where each dose is assumed to kill 95% of sensitive cycling cells.

Treatment 2

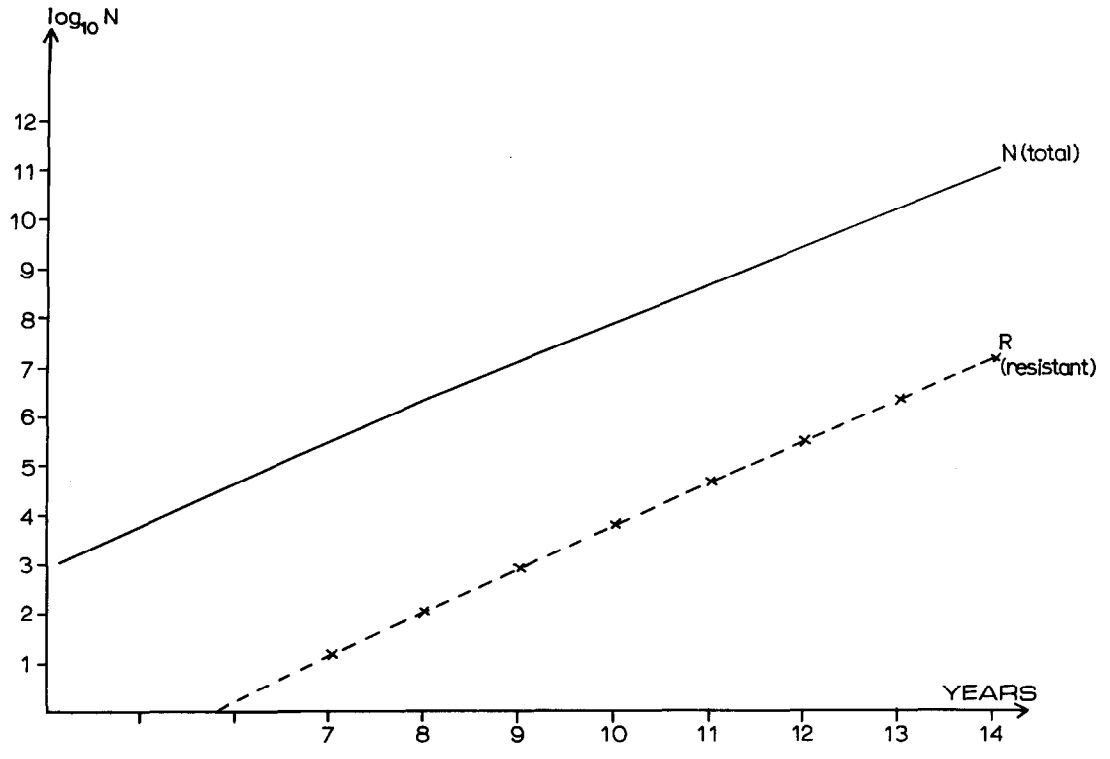
The same as Treatment 1 with a reduced dose achieving only 60% cell kill.

Treatment 3

Three hundred (further reduced) doses of drug A given every 7 days, each dose killing only 30% of sensitive cycling cells.

Treatment 4

Forty doses of drug A at a level and frequency specified in Treatment 1, followed by 60 similarly-



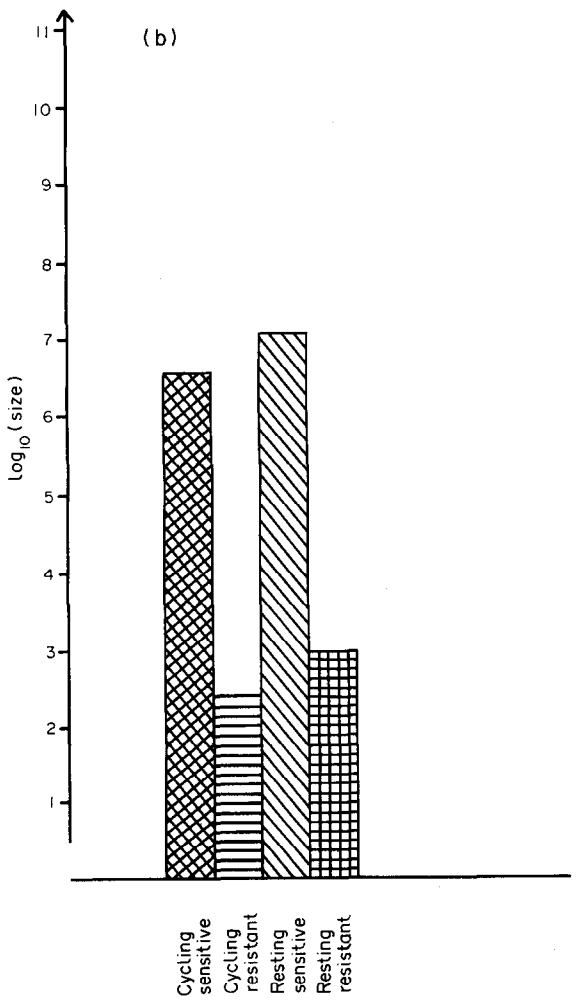


Fig. 2(a). Growth of tumour and resistant sub-population of cells. (Parameters as in Table 1).
Fig. 2(b). Composition of the tumour after 9 years.

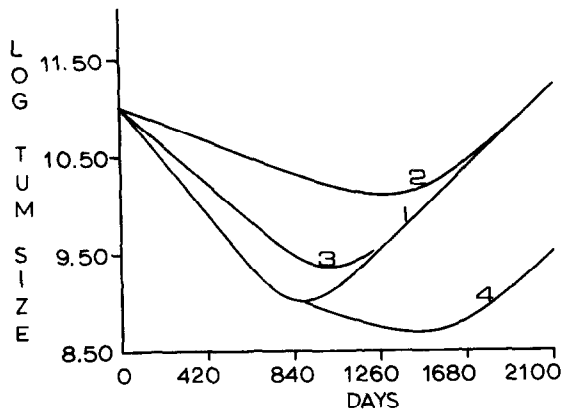


Fig. 3. Tumour response under Treatment 1–4.

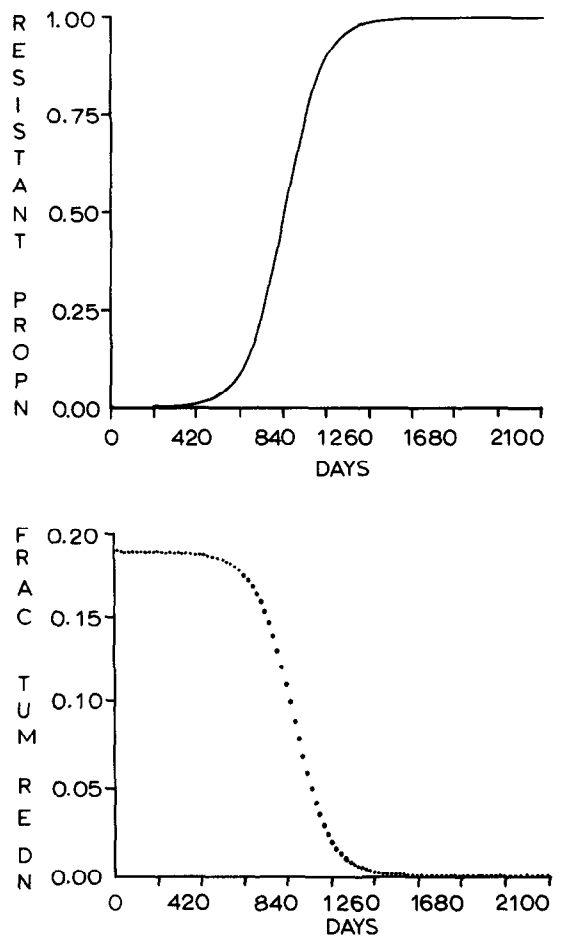


Fig. 4. Changing resistant proportion and fractional tumour reduction (Treatment 1).

spaced doses of a second non-cross-resistant drug, B, to which 1 in 100 of all cells surviving at the time of cross-over are assumed to be resistant (this corresponds to a mutation rate of approx. 10^{-5}). Each dose of drug B is assumed to kill 60% of cycling sensitive cells.

The predicted tumour response under each of these treatments is shown in Fig. 3.

The model simultaneously monitors changing sizes of all 4 sub-populations of cells throughout the treatment period. The computer programs also output predicted changes in the resistant proportion and the tumour reduction achieved by successive doses. These are plotted for Treatment 1 in Fig. 4.

The tumor nadir (of approx. 10^9 cells) corresponding to Treatment 1, is seen to occur at 840 days (40 doses) after the start of treatment, at a time when approx. 60% of the tumour is resistant to the drug. Almost total resistance (and therefore negligible tumour reduction) is reached after 60 doses. The last 40 doses administered are therefore superfluous, in that the tumour regrows (to clinical relapse) at its pretreatment rate during this period.

A comparison of the predicted patterns of tumour response to the 4 treatments (Fig. 3) shows that the effect of reduced cell kill from Treatment 1 to Treatment 2 is in a continued, but more gradual, tumour reduction for a longer period, at the expense of a reduced level of maximum regression. However, this can be offset if, with reduced doses, the frequency of administration can be increased, as can be seen from a comparison of Treatments 2 and 3.

Treatment 4 represents an improvement over the best (Treatment 1) of the 3 single drug regimens in this example, since, although there is a relatively high mutation rate to resistance to drug B, at the time when it is first employed almost 60% of the residual tumour is resistant to drug A (due to the selection effect of 40 doses of that drug). Thus, compared to continued treatment with the first drug, the (non-cross-resistant) drug B will be considerably more effective in achieving further tumour reduction.

DISCUSSION

The mathematical model that has been developed provides a means of evaluating different cancer treatment strategies and selecting the most appropriate for further investigation by clinical trial. Different scenarios can be examined by setting the parameters in the model appropriately.

The development of the model has relied heavily on close collaboration between clinicians and mathematicians in choosing those factors considered to be important to describe the growth of a tumour and its response to chemotherapy, and in establishing relationships between these factors. The model and its predictions rest on the simplifying assumptions which have been made. The aim has been to capture the clinicians's view of the process of tumour response and to use a mathematical formulation of it which allows different approaches to treatment to be investigated theoretically.

It has been shown how the model may be used to predict the effects of administering a single drug at different intensities and frequencies, and the effects

of changing treatment from one drug to another. In the example discussed, although treatment programmes involving up to 100 courses have been used, by appropriate choice of treatment parameters those clinical situations in which much fewer courses result in observed tumour regression can also be investigated using the model. Particular parameter values have been chosen from the literature, and the results may be sensitive to such choices. A change in the mean time spent by cells in the resting phase, for example, will affect specific predictions about the rate and extent of tumour response to particular treatments. On the other hand, some inferences may be robust in that they do not depend on specific sets of parameter values. Some of these have already been established for the model as formulated. For example, with succeeding doses of a given drug, the fractional tumour reduction has been found generally to decrease until the point when further treatment becomes ineffective. A programme of research to investigate systematically other general treatment principles and to determine the sensitivity of the model's predictions to changes in parameter values is currently under way.

The model, as it stands, may be developed in many ways to take account of additional factors which may be suggested as being important. Possible enhancements which are currently being investigated include: allowing treatment to affect the rates of transition of cells between the resting and cycling compartments, and to induce resistance in some surviving sensitive cells; including a control mechanism to limit the rate of growth with increasing tumour size; and allowing cell-death (either natural or due to therapy) to occur from the resting compartment. The present formulation is also deterministic, and although this is probably a reasonable approximation for large tumours (such as those at diagosis), the randomness of cell-division and cell-death will influence the behaviour of small tumours, in particular it is likely to affect the chances of cure (i.e. the extinction of the tumour cell population).

As a means of evaluating treatment strategies this model concentrates solely on the response of the tumour to chemotherapy. A more complete evaluation would include an assessment of the toxic effects of the drugs used. Whether this can be incorporated in a more general model is a subject for future research.

The model is still at an early stage of development but represents a broad structure within which the evaluation of strategies for cancer therapy can take place. The process of validating the model against empirical findings, and an investigation of possible developments, is under way, and will be reported. It is hoped that this approach will eventually help clinicians in developing more effective treatments.

APPENDIX 1

The following notation will be adopted:

$x_1(t)$: The size of the sub-population of cells that are cycling and drug sensitive at time t.

$x_2(t)$: The size of the sub-population of cells that are resting and drug sensitive at time t.

$x_3(t)$: The size of the sub-population of cells that are cycling and drug resistant at time t.

$x_4(t)$: The size of the sub-population of cells that are resting and drug resistant at time t.

λ : The fractional rate at which cells are recruited from the resting to the cycling compartment.

μ : The fractional rate at which cells are recruited from the cycling to the resting compartment.

α : The fractional rate at which cells divide.

η : The fractional rate at which cell death occurs within the cycling compartment.

ϵ : The fractional rate at which cells in the cycling compartment acquire drug resistance.

The following set of differential equations derived from the assumptions presented in the main text, describe the time-dependent behaviour of the sub-populations of tumour cells in the absence of drug therapy:

$$\dot{x}_1 = (\alpha-\mu-\eta-\epsilon)x_1 + \lambda x_2 \quad (1)$$

$$\dot{x}_2 = \mu x_1 - \lambda x_2 \quad (2)$$

$$\dot{x}_3 = \epsilon x_1 + (\alpha-\mu-\eta)x_3 + \lambda x_4 \quad (3)$$

$$\dot{x}_4 = \mu x_3 - \lambda x_4 \quad (4)$$

where $x_i \equiv \dfrac{dx_i}{dt}$.

Differentiating these equations with respect to time and cross-substituting between them, yields an equivalent set of equations which is easier to deal with:

$$\ddot{x}_1 - (\alpha-\lambda-\mu-\eta-\epsilon)\dot{x}_1 - \lambda(\alpha-\eta-\epsilon)x_1 = 0 \quad (5)$$

$$\ddot{x}_2 - (\alpha-\lambda-\mu-\eta-\epsilon)\dot{x}_2 - \lambda(\alpha-\eta-\epsilon)x_2 = 0 \quad (6)$$

$$\ddot{x}_3 - (\alpha-\lambda-\mu-\eta)\dot{x}_3 - \lambda(\alpha-\eta)x_3 = \epsilon(\dot{x}_1+\lambda x_1) \quad (7)$$

$$\ddot{x}_4 - (\alpha-\lambda-\mu-\eta)\dot{x}_4 - \lambda(\alpha-\eta)x_4 = \mu\epsilon x_1 \quad (8)$$

This system of equations has a standard unique solution in terms of initial population sizes.

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