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## *Perspectives and Commentaries*

# Mathematical Models to Predict Behaviour of Tumours?

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(A COMMENT ON: Birkhead BG, Rankin EM, Gallivan S, Dones L, Rubens RD. A mathematical model of the development of drug resistance to cancer chemotherapy. *Eur J Cancer Clin Oncol* 1987, **23**, 1421–1427.)

**Abstract**—*Mathematical modeling is an important tool in science that allows the investigator to examine phenomena that are not easily studied by direct experiment. The growth of neoplasms and their response to treatment are processes that appear particularly well suited for study by this approach. The ready availability of inexpensive powerful microcomputers and sophisticated software makes this research avenue open to all experimental and clinical oncologists.*

UNLIKE disciplines such as physics, chemistry and engineering, clinical medicine has not tended to utilize the approach of mathematical modeling to solve difficult problems. Mathematics and statistics are used extensively in epidemiological studies and in clinical trials data analysis, but not generally to increase our understanding of specific disease processes. This may be partly because clinicians distrust a technique that they think utilizes abstruse mathematics to tell them something that is intuitively obvious. And it may also be because of the general reductionist approach that has traditionally been applied to clinical problems. Implicit in this reductionism is the belief that it is only as great detail is learned about a disease that it becomes feasible to apply rational solutions to its control.

This latter assumption need not be correct. Curative treatments for a number of types and stages of malignancy have been developed in this century and have preceded any real comprehensive understanding of the nature of malignancy at the molecular level. Curative forms of cancer therapy have generally stemmed from the identification of a stage in the disease process that is vulnerable to a particular type of intervention. Thus, it was appreciated that surgery can be curative if the tumour is widely excised before metastases have occurred. An extension of this approach is to utilize adjuvant chemotherapy in conjunction with the surgery at a time when the metastases are still undetectable, but are potentially curable by drugs.

The development of mathematical modeling is generally considered to have three principal components. The first is the construction of the model itself, a process which involves a mathematical formalism that is intended to represent key elements of the system that is being studied. The second part consists of fitting the model to real data and, finally, using the model to simulate the behaviour of real systems and to test the model's ability to predict the behaviour of the system when it is perturbed.

In the 1960s, Skipper and his colleagues developed what amounted to a simple mathematical model of tumour behaviour based on their studies of transplantable mouse leukaemia [1]. Their work indicated that the process of neoplastic growth and dissemination could be treated in quantitative terms and that chemotherapy was effective to the extent that it was capable of producing cytocidal effects on the neoplastic cell popu-

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lation. Their work indicated that to be curative, chemotherapy had to be successful in eradicating the last surviving viable leukaemic cell, and hence the necessity for multiple courses of therapy past the point of complete remission induction. This approach has been adopted so implicitly into the background thinking in present day clinical cancer chemotherapy that it is instructive to go back and read the literature from the late 1940s and 1950s. Clinical chemotherapy done during that time was very phenomenological in its approach and clinicians had great difficulty in comprehending why, for instance, leukaemia would so quickly relapse following the discontinuance of drug treatment. The quantitative approach adopted by Skipper and others shed great light on this phenomenon and made it possible to begin to plan chemotherapy strategies in a rational fashion.

The whole process of neoplastic growth and dissemination and response to treatment modalities such as chemotherapy and radiation lends itself very readily to mathematical modeling and computer simulation. A recent issue of the *Bulletin of Mathematical Biology* [2] was devoted entirely to the question of simulation in cancer research. Interested readers are encouraged to review this publication for a detailed introduction to the topic. In that issue Skipper [3] describes a simple computer model developed by Lloyd which is capable of simulating, to a first approximation, large numbers of experiments involving a variety of transplanted tumours and antineoplastic agents. Had the technology been available to do this easily a generation earlier then it seems likely that a lot of trial and error in experimental chemotherapy studies could have been eliminated.

In our own work we have used mathematical modeling techniques to study the process of drug resistance postulating that it is the appearance of such resistance that constitutes a major impediment to effective treatment [4, 5]. Using this approach one can derive a number of general rules about chemotherapeutic strategy that seem compatible with what has been learned through years of empiric clinical trials. These include such general inferences that small tumour burdens will more likely be curable than large, that combination chemotherapy will have a greater curative potential than a single agent, that there will be an inherent variability in response from individual to individual, and that certain sequences of administering antineoplastic agents will be more effective than others.

A logical next step in the modeling process is to see whether useful models of specific tumour types and particular treatment protocols can be constructed. This may then permit the development of more specific rules that would have applicability to a particular clinical malignancy and would make testable predictions about protocol structure. To do this with any measure of precision for actual clinical disorders is clearly going to be a complex task. That it may be possible to do this, however, is given credence by the degree to which it has been possible to simulate outcomes in experimental chemotherapy and that the general types of lessons that can be learned from such an exercise appear to be applicable to a broad range of clinical neoplasms.

In a previous issue of this Journal Birkhead *et al.* [6] present a basic mathematical model for simulating the appearance of drug resistance in clinical breast cancer. The model incorporates the principle of mutations to drug resistance, exponential growth, cell loss, and a two compartment system in which cancer cells are either in a cycling or non-cycling state. Values for such key parameters as doubling time of tumour, cell loss factor, and log kill of each chemotherapy application are assigned. In some instances (i.e. clinical doubling time) accurate values can be given, but for many of the other parameters rough estimates or even guesses are the best that can be supplied.

It can be seen that the computer model in a relatively crude way does mimic the behaviour of the real system. That is, single agent therapy will produce a transient response followed by regrowth of the tumour after a period of time. If the treatment is made more effective by the inclusion of a second non-cross resistant drug then the results of treatment are greater though in this case it ultimately fails as well. Even at this level, the model can be useful as an educational tool both for instructing students in the dynamics of tumour growth and response to treatment and also in aiding clinicians to develop a better intuitive feel for what is going on during the course of clinical chemotherapy.

To be highly useful, however, a model needs to be capable of stimulating the behaviour of a real system with a degree of accuracy sufficient to permit one to make predictions about how the system will behave when treatment conditions are altered. To do this one needs to be able to estimate the 'internal parameters' of the neoplastic cell system with precision. This is where the difficulties arise and this in fact is where the technique of mathematical modeling allows one to attempt to develop useful estimates of phenomena that cannot be readily measured.

What for example is the mutation rate to resistance to methotrexate in the case of a typical patient with breast cancer or large cell lymphoma? There are no ready measurements that could be carried out on tumour material taken from the patient that will yield this kind of answer. One can attempt to

carry out a clonogenic cell assay in the presence of drug or one can establish *in vitro* tumour cell lines from the patient and then one can carry out some estimate of mutation rates. The value so obtained, however, is no longer derived directly from the initial *in vivo* tumour system. It, at best, is likely to be only a very crude approximation of what this true initial value really was. One can, however, begin to approach this problem by assigning a range of values of the mutation rate to resistance for the drug, combining it with a range in values for the log kill for each application of treatment and then test these values utilizing a simple kinetic model of tumour growth. Since there exists a body of clinical data documenting the response frequency and duration to single agents such as methotrexate, one can then quickly work through a vast range of permutations of log kill and mutation rates to see what range of values come closest to mimicking the behaviour of the real system.

Unrealistically high or low values for these parameters will quickly be discarded as yielding simulations that are not consistent with what is observed clinically. Once the best fit between simulated values and actual clinical behaviour is obtained the model can be further refined by making added assumptions (i.e. that there may not be a unique mutation rate to resistance to the drug in this class of tumours but the value may follow some type of distribution). This may well be true also for the log kill that can be obtained with each cycle of therapy. Different types of distribution functions can be employed and one can then see whether these assumptions improve the goodness of fit.

What type of answers can it be realistically expected that mathematical simulations of tumour behaviour will yield? It is certainly unrealistic to expect that out of these studies will fall magical formulae that will tell the clinician how to cure metastatic cancer. However, even at their present state of development it is reasonable to expect that such models will at least allow the researcher to gain some feeling for the types of processes that are occuring within the tumour and which may be contributing to treatment failure. If mutations resulting in drug resistance are the major barrier in a particular class of neoplasms then this will produce behaviour patterns different from a scenario in which the obstacle to cure is the persistance of non-cycling tumour stem cells which remain invulnerable to chemotherapy for protracted periods. Likewise, possibilities such as insufficient dose intensity of effective agents (whether given in an early or late time frame) or survival of cells in pharmacokinetic sanctuaries should produce simulations sufficiently different from one another that it may be possible to identify some of the dominant factors contributing toward treatment outcome. These may not be identical for every particular class of tumour.

Validation of such models will need to be carried out in the time honoured scientific way. Treatment failure attributable to subpopulations of non-cycling quiescent cells which only infrequently and randomly emerge into division would yield to a different chemotherapeutic strategy than failure attributable to heterogeneity and drug resistance. Clinical trials would need to be constructed in order to unambiguously distinguish between two such differing hypotheses. This, incidentally, would be another potential benefit from mathematical modeling. It should increase the necessity for developing clinical trials that will prospectively test important biological concepts.

Will this be labour intensive and time consuming? The answer is obviously yes, but certainly no more time consuming than the trial and error approaches that are still too frequently used in clinical oncology. The tremendous advances in computer technology over the past decade has made available powerful computing tools to virtually every clinical researcher. We have an obligation to ensure that this avenue of investigation, so rewarding in many other disciplines, is not neglected in cancer medicine as well.

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