Cancer summed up

Robert A. Gatenby and Philip K. Maini

Experimental oncology is awash with data. In 2001 alone, over 21,000 articles on characterizing, diagnosing and treating malignancies were published. The powerful techniques of molecular biology have demonstrated innumerable cancer-related alterations in the structure and function of macromolecules that control life and death in mammalian cells. At least 200 genes that may promote or prevent cancer have been identified in the human genome. Remarkably, despite this wealth of information, clinical oncologists and tumour biologists possess virtually no comprehensive theoretical model to serve as a framework for understanding, organizing and applying these data.

Heeding lessons from the physical sciences, one might expect to find oncology aggressively, almost desperately, pursuing quantitative methods to consolidate its vast body of data and integrate the rapidly accumulating new information. In fact, quite the contrary situation exists. Mathematical models are typically denounced as "too simplistic" for complex tumour-related phenomena (ignoring, of course, the fact that similar simplifying assumptions are required in most experimental designs). Articles in cancer journals rarely feature equations. Clinical oncologists and those who are interested in the mathematical modelling of cancer seldom share the same conference platforms.

This attitude begins in medical and graduate schools, where curricula often fail to include theoretical analysis or the application of quantitative methods other than statistics. In fact, medical schools have generally eliminated mathematics from admission prerequisites, resulting in a generation of clinical and research physicians who lack expertise in or regard for biological mathematics.

Those of us who apply quantitative methods to cancer also bear responsibility. Too often we are content with work that is entirely phenomenological — 'curve-fitting' data — without developing mechanistic models that provide real insights into critical parameters that control system dynamics. We also tend to focus on narrow mathematical issues, such as existence and uniqueness theorems, that have no discernible medical application. Most importantly, we have not clearly demonstrated to our biologist colleagues a dominant theme of modern applied mathematics: that simple underlying mechanisms may yield highly complex observable behaviours.

So how might mathematical methods help oncology? Consider the well-known model of colorectal carcinogenesis that was developed by Eric Fearon and Bert Vogelstein. This theory correlates a sequence of genetic and epigenetic events with corresponding changes in tissue morphology as it proceeds serially from normal mucosa, to a small polyp, to a large polyp, and eventually to invasive cancer.

The 'Vogelgram' represents a word model, grounded in the linear logic that is typical of this approach. It can, however, form the schematic framework for mechanistic, quantitative models that incorporate more realistic properties of biological systems such as stochasticity and nonlinearity. As the outcomes of such interactions cannot be determined by verbal reasoning alone, they must be computed from general integrative models of carcinogenesis.

These models might, for example, adapt methods from game theory and population biology to frame the 'Vogelgram' mathematically as a sequence of competing populations that are subject to random mutations while seeking optimal proliferative strategies in a changing adaptive landscape. The phenotypic expression of each mutation interacts with specified environmental selection factors that confer a proliferative advantage or disadvantage. Such models will generate far less predictable (and more biologically realistic) system behaviour, including multiple possible genetic pathways and timelines in the somatic evolution of invasive cancer.

Critical parameters that emerge from mathematical modelling focus attention on issues that require further theoretical and experimental work. These include explicit identification of environmental factors that control clonal expansion and select the malignant phenotype, as well as how these microenvironmental selection parameters are perturbed by successive waves of increasingly transformed cellular populations.

Our own work addresses some of these questions by showing that system dynamics in early carcinogenesis are dominated by normal tissue-growth promoters and inhibitors. Mutations that alter cellular reception, production or processing of these signals will confer a growth advantage, providing a selection mechanism for the early gene mutations depicted in the Vogelgram. As the transformed populations expand, substrate limitations due to diminished blood flow and cellular crowding generate new selection parameters that favour cellular populations that are angiogenic and use rapid but inefficient glycolytic metabolism. Thus, properties that are typical of invasive cancers but are not included in the original model flow readily from quantitative methods. This can be further extended through models of tumour–host interactions showing that environmental perturbations induced by acid excretion from glycolytic metabolism can produce the invasive phenotype.

Existing mathematical models may not be entirely correct. But they do represent the necessary next step beyond simple verbal reasoning and linear intuition. As in physics, understanding the complex, non-linear systems in cancer biology will require ongoing interdisciplinary, interactive research in which mathematical models, informed by extant data and continuously revised by new information, guide experimental design and interpretation.

Fortunately, there are some signs of increasing acceptance of mathematical methods in experimental oncology. Analysis of complex genomic and proteomic data has placed bioinformatics in the biological mainstream. 'Systems biology' is applying interesting quantitative methods to the web of transcriptional and protein–protein interaction that follow perturbations in biological systems. Perhaps this presages a time in which mathematical oncology will become integral to the study of cancer. ■

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Mathematical oncology

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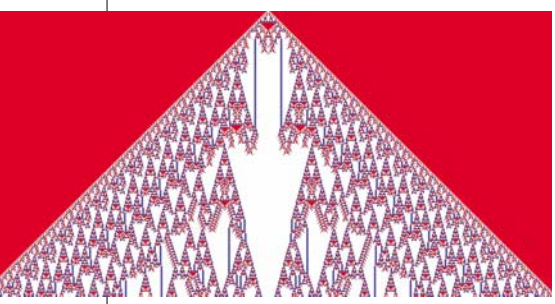

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FURTHER READING

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