Mathematical modeling of tumorigenesis: mission possible

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Purpose of review
Mathematical modeling of tumorigenesis is a fast-growing area of research. This review describes recent (since July 2003) advances in this area and discusses possible implications for the field of cancer biology in general.
Recent findings
Broadly speaking, there are three major areas in which theory has contributed the most to cancer research: (1) modeling in the context of epidemiology and other statistical data, (2) mechanistic modeling of avascular and vascular tumor growth, and (3) modeling of cancer initiation and progression as somatic evolution. The first area uses models to fit the existing data, the second approach takes advantage of methods of physics and engineering to describe tumor growth, and the third method looks at cancer progression as a local, Darwinian evolution.
Summary
The article describes new, interesting ideas put forward in the last year, and suggests that to make the modeling effort more relevant, a better dialogue should be developed between theorists and experimental biologists. The author believes this is possible.

Keywords
multistage carcinogenesis, vascular and avascular tumor growth, mutations, genetic instability

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Introduction

People who are not mathematicians are strange. At least, they think differently. Things that mathematicians take for granted are exciting news for them. Problems that are most interesting for mathematicians do not even register with them. And, most annoyingly, they have a habit of asking really difficult questions. For instance, you are working on a model of colon cancer initiation. The biologist keeps asking, "Can you include this? Can you include that in your model?" You smile meekly ("It's hard!"), and then, just to finish you off, he adds, "By the way, things work differently whether it is in the front or on the back of the colon." You didn't tell him that you modeled the colon as a sphere . . .

Something has to change. This article reviews the current state of affairs of mathematical modeling of cancer, and discusses ways in which it could be made more useful. It begins by asserting that cross-pollination among fields is helpful and important. In principle, new methodologies may lead to breakthroughs and exciting discoveries in traditional fields. However, to be useful, the new methodologies should be integrated in the knowledge accumulated in the field. In the past year, several interesting and unexpected ideas came from people of different backgrounds, including statistics, material science, fluid mechanics, population dynamics, and evolutionary game theory. These ideas are reviewed in the following sections. The reasons that theory and experiment still have a long way to go before harmony is reached are discussed in the Conclusion section.

Statistics and modeling

One of the oldest and most successful methodologies in theoretical cancer research is using the available incident statistics and creating models to explain the observations. This field was originated by Suresh Moolgavkar and colleagues [1] almost 3 decades ago.

Age incidence curves and multistage carcinogenesis models

Several articles looked at age incidence curves [2,3,4•] and death statistics [5•]. In the last article, the statistics of fluctuations in cancer deaths per year led to an intriguing discovery: there is a big difference between cancers of young ages and cancers after 40. The authors suggest that cancers attacking older people behave like

critical systems in physics and can be considered as an avalanche of malfunctions in the entire organism.

A statistical analysis of somatic mutations in embryonic development leading to somatic mosaicism was performed by Frank [4•], which has relevance for cancers caused by two recessive mutations. Frank [6••] also used the classic Armitage and Doll model of multistage carcinogenesis to apply the concept of robust genetic control network. If a cancer requires a consecutive accumulation of many mutational events, this will statistically delay the onset of cancer but at the same time allow the accumulation of deleterious mutations in the population. Moolgavkar and Luebeck [7••] applied an extended Moolgavkar-Venzon-Knudson model of carcinogenesis to the incidence of cancer and found that if clonal expansion of partially altered cells is properly accounted for, then it is unnecessary to invoke genomic instability as an early event in malignant transformation. This is related to another topic, the role of genetic instability in cancer, which has attracted a lot of attention and is considered here.

Statistics and modeling in the study of chromosome aberrations

Combining data analysis and modeling led to interesting results when looking at distributions of chromosome aberrations [8••]. Statistical tools were used to analyze the patterns of chromosome aberrations in tumors. The observation was that the number of chromosomal imbalances per tumor follows a power law (with the exponent 1). The main idea of a model explaining this behavior is as follows. The karyotype in unstable cancers evolves gradually, in such a way that the variability is proportional to the number of changes that already exist. The authors propose two possible interpretations of the model. One is that the rate at which changes accumulate increases as cancer progresses (this is consistent with the notion of a mutator phenotype of Loeb). The other is the evolving and increasingly permissive tumor environment. Similar theoretical and computational tools were applied to testicular germ cell tumor karyotypes [9•]. It was shown that two distinct processes are operating in the karyotypic evolution of these tumors: whole-chromosome changes originate from a multipolar cell division of a tetraploid cell, whereas imbalances accumulate in a stepwise manner.

Mechanistic models of tumor growth

An entirely different approach to cancer modeling is to look at the mechanistic aspects of tumor growth (see [10] for review).

Vascular and avascular tumor growth

Several articles described the growth of a tumor as a mechanistic system, concentrating on the avascular stage of growth [11,12•,13,14,15•,16•,17]. In some cases, tumor was described as a fluid (with a production term proportional to concentration of nutrients) [11,12•], or as a mixture of solid (tumor) and liquid (extracellular fluid with nutrients) phases [14]. Agent-based modeling was used to describe migration of tumor cells by means of a local search algorithm depending on nutrition and toxicity [18•]. Tumor growth was compared with ontogenic growth of organisms in search of a universal law [19•]. Other articles looked at the vascular stage and considered mechanisms responsible for angiogenesis [20••, 21•]. In these models, cells divide and migrate in response to stress and lack of nutrition. The process of angiogenesis was described by using the theory of reinforced random walks [22•]. Endothelial cells escape the parent vessel, invade the extracellular matrix, proliferate, and lead to capillary branching. This framework was used to examine the action of an inhibitor of angiogenesis, angiostatin. The effect of red blood cell heterogeneity was examined by means of a cellular automaton model superimposed on a mechanistic model of blood flow through a fixed network of vessels [23•]. Both vascular adaptation and cell cycle dynamics were taken into account in the model by Alarcon *et al.* [24••], which also investigated effects of p27 on the cell cycle.

Cancer research and cancer modeling: two different fields?

The work described here is a part of a large, long-term research effort to design mathematical methodology for studying tumor growth. It uses the tools of applied mathematics, such as nonlinear partial differential equations, on the one hand, and discrete, cellular automaton approaches on the other. It incorporates physical properties of soft biologic tissues and takes advantage of methods developed in material science and fluid mechanics. What is slightly disconcerting is that cancer modeling is often very detached from experimental and clinical cancer research. Because of the involved mathematical expositions, journals that publish theoretical work are mostly inaccessible to the wider, biologically oriented community. If fact, a separate mathematical cancer community has emerged that appears largely isolated from the rest of cancer research. This is very unfortunate, because experience of physical sciences can be very useful in studying many features of tumor growth, such as vascular collapse [25•]. In this article, the distribution of stress was calculated throughout the tumor as it changes in time as a result of cell division, and the vascular collapse was modeled by identifying the region where stresses exceed a critical value. Other examples of successful usage of mechanistic modeling come from the studies of drug therapy.

Probably the best results can be obtained if theory goes hand in hand with experimental studies. Unfortunately, there are only a few examples of that. Bru *et al.* [26••] observed a linear growth of the colony diameter in tumor

cell lines *in vitro*. The authors went on to develop a model that takes account of the fractal structure of a tumor. Most of the growth activity (*ie*, mitosis) was assumed to be concentrated on the boundary of the colony or tumor, which led to a linear growth law for the colony diameter.

Studying the effect of therapy: theory and experiment combined

Modeling was used to address practical questions of drug dosage and therapy timing. A model by Anderson and Chaplain [27] was adapted [28•] to incorporate endothelial cell proliferation because of tumor angiogenic factors, and also to include the action of endostatin. Numerical simulations showed vessel growth toward a tumor, where the mechanisms of haplotaxis, chemotaxis, proliferation, and degradation are taken into account. Different treatment regimes had different degrees of effectiveness in inhibiting tumor angiogenesis. Swanson *et al.* [29,30] studied cancerous growth for gliomas in the context of drug therapy. Their model included both cell proliferation and motility and took account of inhomogeneities of the brain tissue. The authors concluded that because of high diffusivity, any local treatment would fail. A mathematical model for the *in vitro* kinetics of the anticancer agent topotecan was developed [31•], with an emphasis on the structural identifiability analysis, which determined whether model outputs can uniquely determine all of the unknown parameters. A model for chronic myelogenous leukemia [32•] described the interaction of cancer cells with the immune system and used a thorough analysis of parameter dependence. The use of oncolytic viruses as therapeutic agents against cancer was discussed by Wodarz [33•].

Several collaborations between theorists and experimentalists were aimed at studying tumor drug responses [34•–36•]. Basse *et al.* [37•,38] used explicit modeling of a population of cells going through the cell cycle by including transition probabilities between different phases. The authors compared their results with DNA profiles from flow-cytometry experiments in which a melanoma cell line was exposed to the anticancer drug paclitaxel (mitotic inhibitor). Lupi *et al.* [39•] measured and predicted the outcome of various schedules of treatment of human ovarian cancer cell lines by topotecan. The authors used a previously developed model [40] and were able to predict results of complex treatment schedules.

The question of the precise origin of neovascularization was addressed. The traditional view of angiogenesis emphasizes proliferation and migration of local endothelial cells. However, circulating endothelial progenitor cells have recently been shown to contribute to tumor angiogenesis. The article by Stoll *et al.* [41••] quantified the relative contributions of endothelial and endothelial progenitor cells to angiogenesis using a mathematical model, with implications for the rational design of anti-angiogenic therapy.

Cancer as somatic evolution

Several articles applied methods of population dynamics and evolutionary game theory to study cancer. First developed by ecologists and evolutionary biologists, these methods have been used to understand the collective behavior of a population of cancer cells. Gatenby and Gawlinski [42•] and Gatenby and Vincent [43••,44] used this methodology to study cancer growth [42•] and evolution [43••], with applications to therapy [44]. To study the evolvability of the population, the authors used an elegant approach of fitness generating function [43••]. This gives rise to an optimization problem on fitness landscapes. A quasispecies-type approach is also discussed [45•]. Combined with stochastic analysis of the Moolgavkar-Venzon-Knudson model, this method can lead to interesting biologic insights.

Role of genetic instability in cancer

Many cancers are characterized by a high degree of aneuploidy, which is believed to be a result of chromosomal instability. The precise role of chromosomal instability in cancer is still a matter of heated debate. A mathematical model was developed [46•] in which the role of chromosomal instability in inactivation of a tumor suppressor gene was considered. Both copies of a tumor suppressor gene need to be inactivated for a cell to acquire a malignant phenotype. Chromosomal instability results in an increased rate of loss of heterozygosity and can thus lead to the accelerated unmasking of an inactivating mutation in a tumor suppressor gene. At the same time, it can be costly for cells because of the increased number of deleterious mutations. It was found that the fitness of cancer cells is optimized if the rate of chromosome loss is of the order of 10^{-3} to 10^{-2} [47••,48••], which coincides with experimental measurements. It was further shown that chromosomal instability cannot arise simply because it allows a faster accumulation of carcinogenic mutations, but must be a consequence of alternative reasons such as environmental factors, oxidative stress, or carcinogens. An increase in DNA damage experienced by tissue favors instability, thus making chromosomal instability a driving force for cancer progression [49••].

Tissue architecture and accumulation of mutations

Frank and Nowak [50••] model cancer as an accumulation of somatic mutations. In a series of articles, they study how the architecture of renewing epithelial tissues could affect the accumulation of mutations. A possible mechanism of protection against cancer is stochastic elimination of cancer cells [51•]. It is shown that tissue design in which a hierarchy of stem cells replenishes the transient population of differentiated cells could reduce the accumulation of mutations. The effect of tissue com-

partment is also studied [52•]. Large stem pools will lead to cancer progression via initial tumor suppressor and oncogene mutations and rapid cellular proliferation. Small stem compartments may begin cancer progression with genetic instability. An elegant linear process of somatic evolution was introduced [53,54•] that in some sense mimics the dynamics of a stem cell renewing the tissue of a compartment. This process has the property of canceling out selective differences among cells, yet retaining the protective function of apoptosis. This design can slow down the rate of somatic evolution and therefore delay the onset of cancer. A more detailed stem cell model was proposed by Calabrese *et al.* [55••] in which clonal evolution in stem cell niches was considered. The specific selection pressures acting among stem cells with an a germ-line inactivated copy of the APC gene helped explain the experimentally observed methylation patterns in colon crypts characteristic of patients with familial adenomatous polyposis [56•]. It was argued that germline APC mutations might potentially alter niche stem cell survival through dominant-negative interactions or haploinsufficiency.

Conclusion

Many papers have been written, many interesting models created, many challenging questions asked. However, everyone knows that most of the models will never be checked, and most questions remain unnoticed by the wider community. What is lacking is mutual understanding and appreciation on the part of experimental and theoretical scientists. There are many reasons for this. Theorists sometimes do modeling for the sake of the mathematical analysis that they can successfully pursue, which is of zero relevance to the field of cancer research. This creates general skepticism among the experimentalists. On the other hand, biologists are often unfairly dismissive of the role of theory. It is not uncommon to hear that all theory is naive and the mathematicians cannot possibly grasp the full complexity of biologic reality, leave alone modeling it accurately. This may be true, but the author believes that the door should remain open for alternative views and refreshing ideas. Mathematicians think differently, but this may not necessarily be a bad thing.

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