# Modeling Cancer Dynamics and Tumor Heterogeneity

Cancer is the second leading cause of death in most countries, both advanced and developing. Worldwide, cancer accounts for roughly one out of every eight deaths, or about 7.6 million per year. The wide variety of cancer manifestations makes it one of the most challenging diseases for the medical community to treat. Recent advances in experimentation provide an opening for the mathematically minded to study several aspects of cancer, such as:

- Modeling the progression of cancer, specifically, explaining the observed pattern of progression whereby a tumor has a long quiescent period lasting many years, often followed by a period of very rapid growth.

- Capturing the response of tumors to therapy whereby they become both more homogeneous and more resistant to therapy.

- Predicting the response of tumors to a combination of two drugs on the basis of the response to each drug individually.

The first two of these challenges are discussed in more detail on the following page.
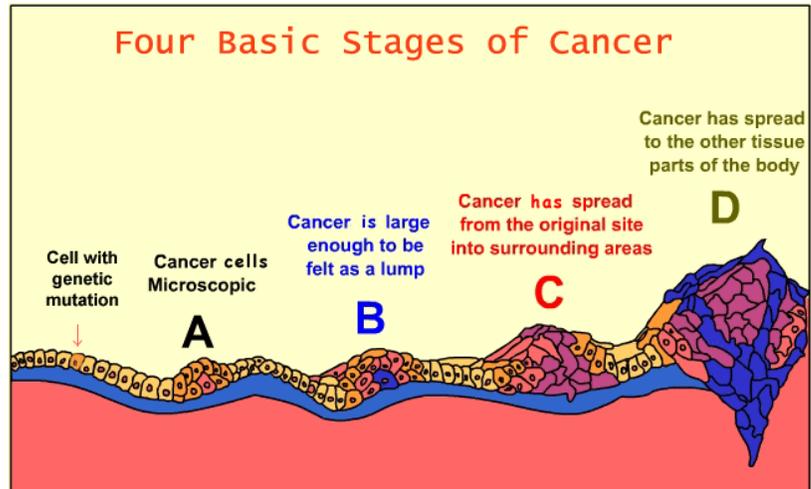
*Source: National Cancer Center of Singapore, http://www.ncs.com.sg*

A Brief Sketch of Cancer

The human body contains about 50 trillion cells, each of which contains (in principle) an identical copy of one's DNA. Human DNA consists of roughly 22,000 genes. Cells undergo division at a rate of roughly once a day; they also undergo programmed death, known as apoptosis. With so much division going on, occasionally errors in DNA replication can occur, leading to mutations. Also, exposure to external agents such as radiation or other carcinogenic substances can cause mutations. When a cell's DNA gets mutated, it might gain a "fitness advantage" over normal cells whereby it divides more quickly or dies at a slower rate, or both. Starting from a small benign population of cells with mutated DNA, the number of such cells usually exhibits a very slow and sustained growth pattern, often lasting many years, before (in many cases) suddenly bursting into a period of rapid growth.

Models of Tumor Growth: Today's State of the Art

Models for tumor progression are based on population genetics. One of the more biologically realistic models is the so-called Wright-Fisher model wherein a population of fixed size consists of two or more subtypes and individual cells make a transition from one subtype to another in a Markovian manner.

Simulation results with this approach are illustrated in the figure on the following page. Each gene is assumed to undergo mutation at a fixed rate, which is the same for all genes. Also, a mutation in any one gene confers a fitness advantage to the cell, and the overall fitness advantage is a simple sum of the advantages arising from individual gene mutations. Finally, the mutations in each gene are assumed to be independent of those in all other genes. With this model, and realistic parameters for various rates, the growth in the number of cells that contain a certain number of mutations can be simulated. The figure on the following page shows that as time passes, the average number of cells with mutations increases linearly; however, this linear progression is not supported by experimental evidence on the growth of actual tumors.

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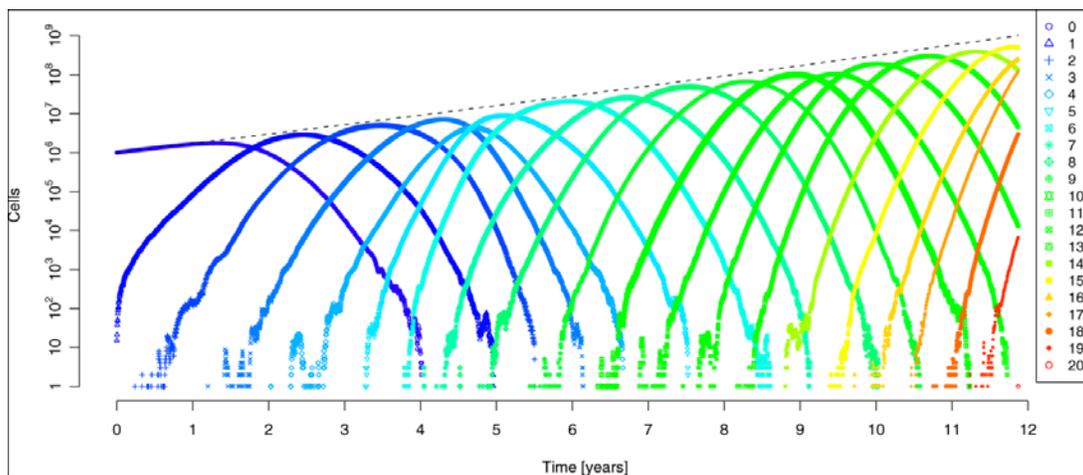
Growth in the populations of cells with increasingly many mutations based on the Wright-Fisher model. It takes approximately 12 years for cells with 20 mutations to begin to appear and roughly 20 years to reach a critical size of one billion (not shown in figure). (Source: N. Beerenwinkel et al., Genetic progression and the waiting time to cancer, PloS Computational Biology, vol. 3, no. 1, e225, 2007)

Challenge: Nonlinear and Probabilistic Models for Tumor Growth

One challenge is to replace the linear growth of the Wright-Fisher model. In reality, the number of cancerous cells does *not* grow linearly; rather, it initially increases at a linear, or a slow exponential, rate, followed by a period of rapid growth. Thus, the challenge is to construct a probabilistic model that shows this behavior *without* assuming that the physiological parameters change over time, as that would be unrealistic.

One suggested approach is to divide genes into two categories: "passengers" whose mutations are by themselves only marginally harmful and "drivers" that trigger rapid tumor growth when coupled with a sufficiently large number of passenger mutations. Biological studies strongly support the notion that mutations can indeed be divided into drivers and passengers. Thus, it may be possible to postulate a branching process model whereby the mutation rate for drivers is far less than for passengers; the passenger mutations accumulate at a rate similar to that in the figure above, but when a driver mutation takes place, tumor growth is accelerated. Although this sounds like a plausible model, the challenge is to turn this hand-waving argument into something more rigorous *and* to validate the postulated model through biological experiments.

Challenge: Modeling the Heterogeneity and Therapy Response of Tumors

Until recently, the dominant view was that a tumor consists of a mixture of one's normal DNA and one dominant mutant DNA. By determining the dominant mutation, the physician can then choose an appropriate therapy, which usually consists of killing off all mutant cells. The usual picture is that practically all patients "respond" initially in that the tumor shrinks or even "disappears" (meaning that it is too small to be detected); however, in many cases, the tumor recurs. The challenge therefore is to develop dynamical models for tumor growth before and after therapy whereby tumor heterogeneity and recurrence are built into the model.

When experimental techniques only permitted measurements of tens of thousands of cells at a time, it was reasonable to assume that tumors were quite homogeneous in having just one dominant mutation. But experimental techniques have now improved to a point where it is possible to study hundreds of cells and occasionally even a single cell. These studies suggest that a tumor can contain many different mutant forms of DNA. If therapy targets the most dominant mutation, the second most dominant mutation could take over; and so on. Thus, a working paradigm for therapy, which is yet to be validated, is as follows: When a tumor first grows, it consists of a mixture of several mutant DNAs, each of them having a fitness advantage over cells with normal DNA. When some therapy is applied, the tumor initially shrinks because the dominant mutation(s) are killed off, but the tumor eventually recurs due to other mutants. Moreover, the recurring tumor is often resistant to the original therapy.

Therefore, if it is possible to construct a mathematical model of such behavior and then to "identify the parameters" in the model based on molecular analysis of the tumors, the physician could be ready with a Plan B and a Plan C, etc., right from the outset. These mathematical models would have to be validated through experiments, but any progress in this direction would result in a fundamental paradigm shift in cancer therapy.