

MEDICINE

The Universal Darwinism of Disease

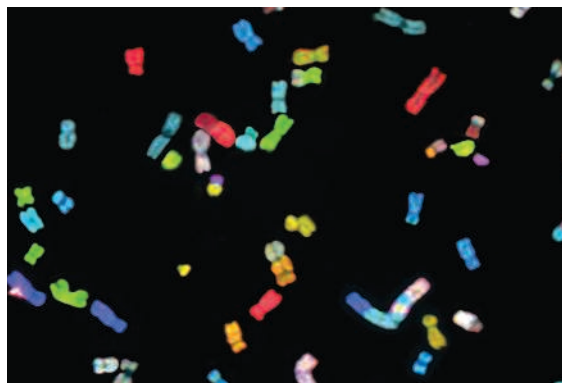
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Most remember the title of Darwin's revolutionary book, *On the Origin of Species by Means of Natural Selection*, but then forget the subtitle, *Or, the Preservation of Favoured Races in the Struggle for Life*. Whereas the former pertains to change and variation, the latter relates to stability and uniformity. The mathematical theory of evolution has sought to explore the consequences of mutation and variation on change and those constraints and evolved mechanisms that confer robustness on organisms. These robustness mechanisms are often dedicated to the prevention and elimination of disease.

Evolutionary theory is the right framework to adopt when we are seeking to account for the sources and constraints of variation in mutable lineages within large populations. This licenses, where appropriate, the application of Darwinism to a stunning range of phenomena, from the dynamics of genomes, the progression of disease, and the processes of speciation to the origin of language. In each case, we are dealing with random processes of variation, development, replication, drift, and selection. But the effectiveness of the theory, as for all powerful scientific theories, turns on the subtleties of quantitative rigor.

In *The Dynamics of Cancer*, evolutionary biologist Steven Frank (University of California, Irvine) explores a theoretical immunology perspective on cancer—seeking to connect abundant data on coarse-grained phenotypic patterns to detailed microscopic, mutation-selection dynamics. The core macroscopic focus of the book is the age incidence curve of cancer, and the microscopic explanation resides in multistage progression.

Age-specific incidence records the number of cancer cases per year for a particular age



Spectral karyotype. Multicolored painting probes reveal chromosomal rearrangements in an oral cancer cell.

Dynamics of Cancer Incidence, Inheritance, and Evolution

by Steven A. Frank

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group divided by the number of people in that age group. When representing age against incidence on a double logarithmic plot, one frequently observes a straight line that can be fit by a function of the form $I = ct^{(n-1)}$, where I is the incidence, t the age, and n the number of stages through which the cancer progresses. The constant c varies according to a number of different demographic and disease factors. Different cancers and different groups (males versus females, for example) tend to show very different patterns of incidence. Moreover, the slopes of these lines often depart from log-log linearity, and their age-specific gradients (acceleration) carry important information. It is these patterns—incidence and acceleration—that Frank seeks to explain, as he sees them as the primary, quantitative signatures of cancer.

The key to understanding incidence and acceleration is a multistage progression that describes a sequence of mutational events through which a tissue must transit on its path toward cancer. These mutations can be classified according to their impact on the balance of cell birth and cell death. Mutations in genes involved in programmed cell death abrogate the ability of cells to kill themselves when detecting damage. Mutations in tumor suppressors remove key constraints on cellular proliferation, and mutations in oncogenes typically stimulate cell division. Mutations in DNA repair pathways can lead to hypermutation and chromosomal instability, accelerating the rate

of mutation toward cancer. Lastly, mutations in certain genes cause tumors to promote the growth of blood vessels required for tumor survival. The mutational spectrum is vast, but the underlying logic is often fairly simple. Important contributions of the book are the two theory chapters in which Frank develops a series of simple mutation-selection models. Building on pioneering work of Knudson, Armitage, Doll, and others, he aims to capture how variation in the sequential accumulation of mutations can generate the panoply of age incidence curves.

Frank's forte in the book is his search for the simplicity that is often masked by the complexities of cancer. With his mathematical models in hand, he turns to the details of cancer genetics, carcinogens, and aging and provides novel integrative insights. For example, his models identify potential causes for the slow age acceleration of melanoma versus the rapid acceleration of pancreatic cancer. Frank's parsimony-based approach to theory leads him to stress comparative analysis rather than curve-fitting. The comparisons follow a hypothetico-deductive model, whereby differences in progression are used to hypothesize differences in the age incidence curves of different cancers, e.g., why males tend to have more cancers early in life than females. Fitting typically seeks to match a family of models to a single body of data in order to infer the underlying dynamics. With a comparative (bottom-up) approach, there are fewer parameters and very dramatic differences to explain; with fitting (top-down), there is a high likelihood that the fit reveals little beyond the flexibility of the model assumptions.

A pervasive theme in the book concerns the lamentable, growing distance between molecular genetics and the kind of macroscopic theory Frank favors. As our measurement technology has become more precise and efficient, microscopic data enumeration has been emphasized over synthesis. This tendency is driven partly by expediency in the laboratory and partly by the absence of theory in the training of many molecular biologists. One of systems biology's avowed objectives is to unite coarse-grained mathematical and computational theory with microscopic laboratory data. Cancer has had a long history as a test bed for this kind of interdisciplinary approach.

Dynamics of Cancer emphasizes both the multiscale dynamics of the disease and an approach that synthesizes empirical knowledge with parsimonious, mathematical theory. Frank moves the field forward, narrowing the gap between a tragic disease of everyday life and the Darwinian world of the genome.

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