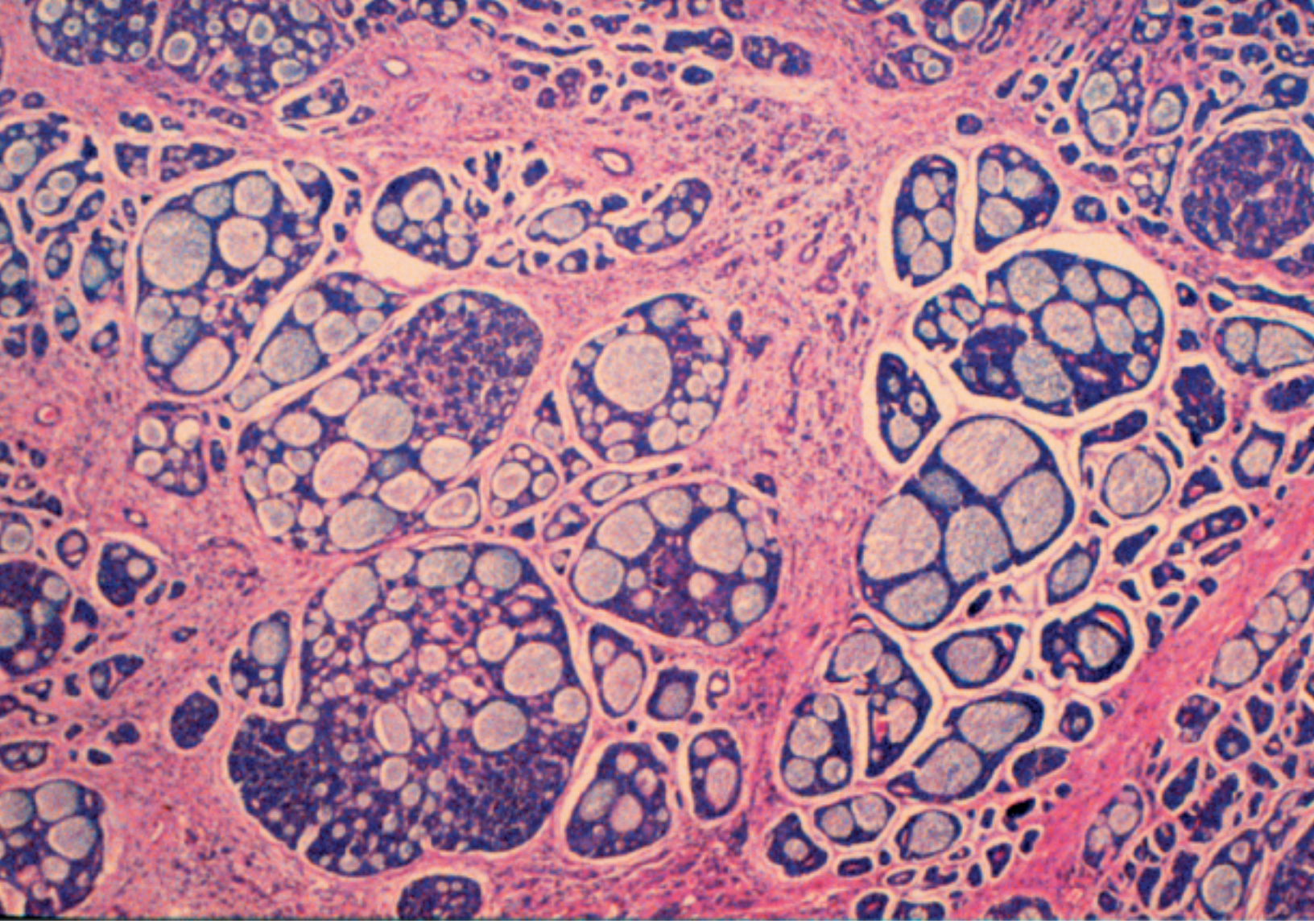
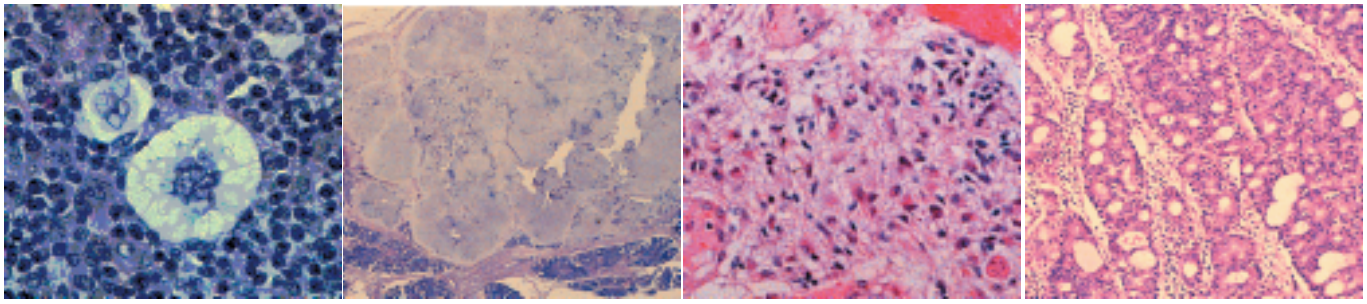


Cancer's Complex Nature

by Daniel Rockmore

Much of what goes on at SFI, indeed even the very creation of SFI, is and was inspired by a desire to study and understand life, from its origins in some primordial molecular soup to the complicated web of interactions into which it has evolved. Nevertheless, many of the tools developed at SFI to plumb the mysteries of the growth and evolution of living systems can also be used to shed light on those darker processes that bring life to an end. These final phenomena range in scale from the grand to the minute: the catastrophic phase transition that could produce a "Day After Tomorrow"-like snowball earth; the cascade of extinctions modeled by the dynamics of a food-web network; the emergent behavior that signals a market crash; or the progress of disease, either across a society or within an individual or even a single cell. It is the last of these, and in particular, toward understanding the etiology of cancer, where SFI scientists are making some significant contributions.

Editor's Note: This is an expanded version of an article that ran in the previous Bulletin.



CELLULAR MANIFESTATIONS OF CANCERS

Cancer as a Complex Adaptive System

At some level of consideration, the healthy human body is a multi-dimensional mosaic of cells, differentiated by their various functions (e.g., skin cells or muscle cells). Cancer develops as an uncontrolled reproduction of abnormal cells, which can then embark on a deadly cycle of invasion and destruction of nearby tissues that spreads throughout the body. Organs become a competitive landscape where abnormal and normal cells are actors fighting it out for resources. Should the abnormal cells gain the upper hand, the function of the organ may be in jeopardy: a liver that suddenly does not have sufficient healthy tissue to maintain the body's chemical balance, or lungs lacking the healthy tissue to absorb the oxygen that sustains life or so heavy with tumor that they collapse under their own weight.

Within this competitive landscape, the etiology of cancer can take on an evolutionary interpretation. Cells reproduce, compete, and evolve with a clear advantage (toward an end goal of population dominance) conferred on that cell type that reproduces the quickest. Evolutionary pressures are also induced by therapies, pushing a "natural selection" of those cells resistant to treatment. The language of evolution, selection, and competition puts cancer research squarely into SFI's purview.

A Universal Law for Tumor Growth

When Distinguished Research Professor (and now Interim President) Geoffrey West came on board at SFI, he was interested in bringing to the investigation of living systems an outlook that was honed over years of study of theoretical physics. In that rarified intellectual world of invisible and indivisible particles, the hallmark of success is the principled derivation of universal laws—simple mathematical formulas like Newton's "F=MA" or Einstein's "$E=MC^2$"—that apply with near, if not exact, agreement across a range of real-world phenomena. West wanted no less from his new work in biology. It is in this spirit that he, SFI External Faculty member James Brown, and Brian Enquist, of the National Center for Ecological Analysis and Synthesis, made their first big hit in the study of allometry. They took the very physics-like approach that fundamental principles for growth in any living form, be it microbe, marmot, or man, can be deduced from considerations of energy and resource transport that are independent of the organism. The crowning achievement of this work has been their discovery of a "universal growth law" for organisms, one that displays a three-fourths power relation between the body mass of an organism and its metabolic rate as well as a principled derivation of the evolved intricate branched systems (for example, the circulatory or pulmonary systems) whose fractal-like structures can be shown to optimize energy delivery and resource access.

West and his group are now using these same tools to try to develop a physics-based model of tumor growth. Herein the idea is to relate tumor growth to the development of the branching system of capillaries, a process called "neovascularization" or "angiogenesis" that is responsible for the delivery of energy to the surface of the tumor. Generally, cell survival is linked to proximity to blood supply, so that a better understanding of the formation and development of these new resource supply chains for tumor growth is a crucial component in understanding cancer. West, former SFI Postdoctoral Fellow Van Savage (now in the Department of Systems Biology at Harvard University), and SFI Graduate Fellow Alex Herman continue to push this work forward and are, according to Herman, "potentially laying the groundwork for theory-based extrapolation of experimental results in animal models of cancer to humans."

This allometric framework is also guiding the work of other cancer research groups. Of particular note is the work of Thomas Deisboeck (Harvard/MIT) who is using these ideas as a foundation for investigating tumor development. The coarse-scale characterization of tumor growth as a rapid (exponential) increase in volume fueled by the concomitant explosion in the number of conduits to sustain efficient blood flow share much with the basic allometric assumptions. By adapting the analysis of West, et al., Diesboeck's group derives an analogous "universal law for tumor growth." It is a first step in a back-and-forth dance between theory and experiment that already seems applicable to the design of therapies. Drug designers can take advantage of the detailed knowledge of the stages of tumor development. For example, just knowing the rate at which tumor cells are both generated and lost at different stages in development will give the clinician a benchmark for the evaluation of therapeutic strategies. Diesboeck, et al., believe that the allometric outlook will have "far-reaching implications" for our understanding of tumor ontogeny.

Cancer Research In Silico

SFI Research Professor and University of New Mexico Professor of Computer Science Stephanie Forrest is involved in a variety of active collaborations in cancer research. Her work in this direction seems a natural outgrowth and synthesis of past and continuing achievements in computational biology, the study of computer viruses and their prevention, as well as computational modeling and simulation.

"We're investigating various simple hypotheses for the dynamics of resource competition among pre-cancerous cells," says Forrest. Initial work with Carlo Maley of the University of Washington's Fred Hutchinson Cancer Research Center uses some of the tools of evolutionary simulation—the same agent-based modeling that came of age in the SFI-led investigations of "artificial life."

Like any good computational simulation, their work creates an in-silico laboratory, not just reproducing known phenomena, but also suggesting and explaining new ideas for therapies. A recent paper with another Hutchinson researcher Brian Reid, investigates the possibility of a new therapy. "Rather than killing off the cancer cells," says Forrest, "it instead seeks to boost the reproductive fitness of relatively benign cells, thereby allowing them to out-compete the cancer cells in the race for dominance."

These in silico ideas are finding an in vitro test site in the investigation of a particular type of esophageal cancer and its precancerous state, "Barrett esophagus," that arises in a significant fraction of those who suffer from gastroesophageal reflux disease. Forrest and Maley have begun the difficult process of tuning their general model to the data of this particular disease. This has already resulted in general insights (in the form of predictions) regarding genetic factors in cancer development.

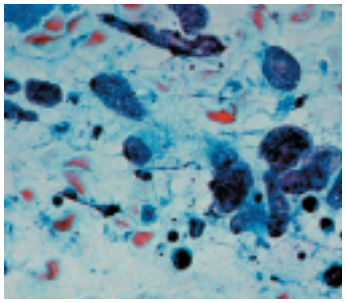
Lately, Forrest's computational approach to the study of cancer has acquired two new collaborators, Robert Abbott of Sandia National Labs and Kenneth Pienta of the Comprehensive Cancer Center of the University of Michigan. Together they have developed CancerSim, a new and improved artificial life-inspired computer simulation package for investigating tumor growth. CancerSim aims to "characterize the processes of cellular alteration that underlie tumorigenesis." This three-dimensional cellular automata evolves according to a set of rules born of "The Hallmarks of Cancer," a well-known paper written by Douglas Hanahan (UCSF) and Robert Weinberg (MIT) in which they identify six phenotypic cellular characteristics that appear to bear strongly on malignant tissue formation. Forrest and her collaborators translate these hallmarks into parameters for the simulation. Exploration of parameter space in the subsequent simulations allows the scientists to chart the many possible paths in the development of tissue as it grows from single cell to multicelluar entity, cancerous or otherwise. This work has already begun to yield interesting insights into how the hallmarks interact. Among these is a new point of view on the role of angiogenesis, which is the formation and differentiation of blood vessels.

This first version of CancerSim is necessarily a simplified, highly abstracted model of tumor growth. In an effort to make it more realistic, Forrest has begun working with Geoffrey West and Alex Herman, hoping to incorporate aspects of their allometric analysis into a next generation of the computational model.

In order to beat 'em, you've got to change 'em, and keep changing 'em…

Cancer is life run amok—causing the breakdown of a living system via the hatching of a cell that mutates to display a pattern of uncontrolled growth. The population of mutated cancer cells undergoes a "microevolution" in the organ. Therein selection pressure favors those cells that can overcome the "barriers" imposed by immune systems or resource competition. The behavior of the population of cancer cells, in essence, breaks the implicit social (and biological) contract binding together the cellular populations within the multicellular society that is a tissue.

One way in which cancer cells seem to win this microcompetition is through an ability to mutate at a tremendous rate. The sheer numbers of subtle variations achieved through this "genetic instability" effect a shotgun approach to finding routes through and over the life-preserving barriers. The minor genetic variations that occur across the range of cancer cells defines them as a "quasi-species," a notion first developed by SFI Science Board member Manfred Eigen and SFI External Faculty member Peter Schuster.



Genetic instability is on the one hand an advantage in the battle to overcome the natural barriers, but can also work against the survival of the "winning" strain which may simply mutate itself out of existence. External Faculty member Ricard Solé has looked into the effects of exploiting the long-term disadvantage of instability. In particular, one

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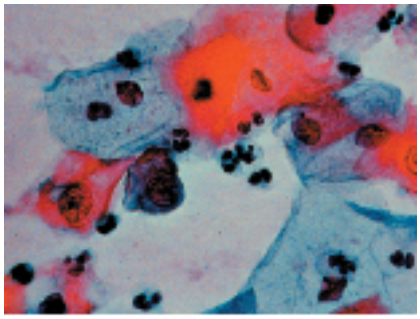
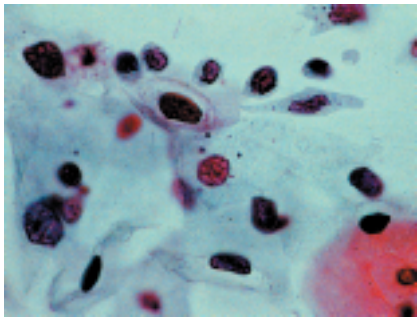
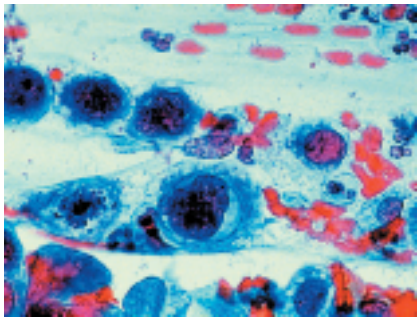
idea is to induce increased instability into the tumor cell population. This seems to be an especially promising avenue of therapeutic research for cancers that operate near an "instability threshold," defined as a level of instability close to one in which the tumor cells would begin to fall apart.

In work with Dominik Wodarz, of UC Irvine, SFI Research Professor David Krakauer has studied the implications of genetic instability in the context of cellular evolution, which selects for the ability to promote angiogenesis. Their models suggest that while genetic instability is necessary initially, it becomes a disadvantage in the long run.







From Populations to Particulars

The competitive framework in which cellular phenotypes fight each other for dominance in the tissue casts the cancer problem squarely within the realm of population dynamics. It is an analysis that assumes that the battle within the body has already begun. As such, it begs the question of where and how did the fight begin? What is the set of subcellular conditions that gave rise to that first colony of rogue cancer cells? Our genes contain the basic data that provide each cell with instructions for growth, and Krakauer, as well as many other scientists, have begun to study and model the manner in which various genes work together (or against one another) in order to gain new insights to the origins of cancer.

Almost surely, cancer is a multigenic disorder whose understanding will require the unraveling of a complex tangle of genetic influences. Many scientists now see cancer as explained, in part, as a problem of aberrant gene regulation, an instance of confused information flow both into and within the cell. Krakauer is quick to point out that many of the mutations known to occur in cancer development are found in genes involved in signal transduction—meaning those genes that mediate the information flow among genes within the cell, thereby influencing the ways in which proteins are produced. Krakauer and SFI Steinmetz Fellow Sabrina Spencer have begun to study a highly simplified model of the cell, an abstraction that seems to focus on the guts of the problem. In their simplified model, the cell is pictured as housing the interactions of three genes: a proto-oncogene (cancer carrier), a tumor suppressor, and a "housekeeping gene." As Krakauer describes it, the proto-oncogene is the "foot on the gas pedal," and the tumor suppressor is the "brake." Ordinarily, keeping "the pedal to the metal" should put the cell on a road to ruin, signaling the beginning of "programmed cell death" or apoptosis, but what seems to happen in cancer is that the cell acquires the ability to ignore such signals and thereby take a joy ride of never-ending reproduction, whose numbers soon dwarf the population of healthy cells.

Separately, the tools of populations dynamics and genetic networks have each begun to shed light on the complex system that is cancer, but as Krakauer points out, "No one has yet done a great job of integrating the two." In particular, he believes that one huge open question is, "What is the right formalism for studying the logic of the relevant genetic interactions?" In this regard we have begun to see a resurgence of interest in Boolean networks, the forerunner of the modern study of genetic networks. These were first proposed almost 30 years ago by SFI pioneer Stuart Kauffman (who has just been asked to head a new Institute for Biocomplexity and Informatics at the University of Calgary). Krakauer's recent work with former SFI Postdoctoral Fellow Nihat Ay, has begun to develop a formal framework for quantifying the notion of system robustness in order to enable a rigorous analysis of the performance of genetic networks.

"RATHER THAN KILLING OFF THE CANCER CELLS," SAYS FORREST, "IT INSTEAD SEEKS TO BOOST THE REPRODUCTIVE FITNESS OF RELATIVELY BENIGN CELLS, THEREBY ALLOWING THEM TO OUT-COMPETE THE CANCER CELLS IN THE RACE FOR DOMINANCE."

With a little luck and much perseverance, perhaps these research collaborations at SFI and elsewhere will in time evolve toward a better understanding of cancer, generating new ideas that will speed us toward a cure, fueling a progress of development at an exponential rate, an ironic intellectual twin of the cancerous phenomena that this research seeks to erase.

Dan Rockmore is professor of mathematics and computer science at Dartmouth College and a member of the SFI External Faculty