## FINDING GENERAL PRINCIPLES FOR MEDICINE

By David C. Krakauer

## What might it mean to have a unified theory of medicine? In

physics, the search for a unified theory suggests determining the nature of physical laws, and how these interact with fundamental building blocks to capture essential regularities in the behavior of matter, such as galaxy formation among selfgravitating masses. In the physical domain, the ultimate goal of theory is generality achieved through highly compressed mathematical descriptions, leading, in turn, to accurate predictions. There is little of a dichotomy between a theoretical and a practical science, as both are served by the reductionist program: experimental reductionism to sub-atomic particles, and mathematical reductionism, to, for example, symmetry principles. These have proven to be efficient paths to successful interventions into the physical world: the space program, transistor technology, and lasers attest to this.

In biology, theory and experiment have remained more divided. This is primarily a result of the huge, combinatoric space afforded by DNA and protein sequences, and the resulting multiplicity of cellular and multicelluar organization. The huge degeneracy of biological forms seems to require a detailed understanding of each system in terms of its own unique history. The experimental reduction to chemical constituents has not been paralleled by a complementary mathematical reduction. Might there be some general principles by which we could organize biological diversity? This is one of the aims of systems biology. We have one extremely successful example: Darwin's theory of evolution by means of natural selection. Although Darwin's theory helps us to understand the biological world, it does not really allow us to predict future events or to intervene into these events purposefully. In the biomedical sciences, which have no unifying theory, understanding biosystems has been far less important than remedying them. Voltaire wrote the following: "The art of medicine consists in amusing the patient while nature cures the disease." Before we establish the mathematical foundations of a theoretical medicine, it will be necessary to identify regularities in the system dynamics of the body. Such a program requires a quantitative approach that spans the existing specialties. This was the objective of a recent meeting at SFI on the Foundations of Theoretical Medicine, sponsored by the National

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Computer artwork shows a molecule of deoxyribonucleic acid (DNA) on a human hand. DNA is composed of two strands twisted into a double helix. Each strand consists of a sugar-phosphate backbone (orange) attached to nucleotide bases (blue). There are four different bases: guanine, cytosine, thymine, and adenine. DNA contains sections called genes, which encode the body's genetic information.

## Institutes of Health.

Practicing physicians have always been aware of important parallels among medical specialties. There has never been, however, a systematic way of identifying commonalities in the etiology of disease and their mechanisms of origin. With such an understanding there would be a prospect of improved health care through a selective targeting of overlapping causes. While it is clear that patients show significant variability in susceptibility to disease and in response to treatment, this variation need not be understood exclusively in terms of the







detailed differences in their physiological and cellular processes. Similarly, some diseases are clearly very complex, involving multiple organ systems and symptoms; without a consistent framework for understanding the meaning and mechanisms of such complexity, we tend to ascribe these patterns to the unique interactions in any given patient.

In order to establish a theoretical medicine, the consensus of the meeting was that we need to come to a better understanding of a number of core concepts, which include variability, complexity, modularity, adaptability, robustness, and scaling. These concepts have been at the forefront of research in complex adaptive systems at SFI, spanning genomics, immunology, evolution, statistical physics, and economics. At the meeting at SFI, we explored each of these themes and attempted to identify their relevance to a new theoretical medicine.

We concluded that an understanding of key concepts from the study of complex systems will pave the way to a more unified, predictive medicine by supplementing the current focus of research on properties unique to the organ system and the individual, with properties shared by multiple, hierarchical systems. On the one hand, this should give us greater insight into core inter-dependencies that need to be considered with targeted treatment regimes. Secondly, this would introduce a new form of treatment aimed at modifying coarsegrained, or multi-system properties neglected by the current preference for focal therapies. Some of the areas in which we made progress at the meeting were in reviewing relevant measures of complexity in physiological time series related to statistical correlates of health and recovery, the relationship between neural events and immune system dynamics, and the vital role played by sleep cycles in

disease susceptibility. What struck many of us as a surprise is that several of the concepts that we had assumed rarified and the subject of pure research, could come to provide a potential foundation for the study of truly complex systems—the human body and mind. For example, in the analysis of the electrocardiogram (ECG) trace, information theoretic measures of heart rate that show a self-similarity over multiple scales of time are diagnostic of good health. This combination of information theory and scaling theory is an active area of research at SFI under the robustness program.

The meeting comprised 15 faculty members and 20 graduate students, selected nationally from the biomedical sciences. The faculty represented immunology, neurology, cardiology, chronobiology, internal medicine, and mathematical biology. Both a medical doctor and a researcher in the field represented each discipline. The 7-day meeting was principally aimed at educating the next generation of medical students in mathematical techniques and integrative, cross-disciplinary styles of thinking. It encouraged a high frequency of discussion and a very iconoclastic attitude towards existing medical education and practice. At the end of the meeting, one of the more frequent remarks from the students was, "Now that we understand how bad the situation in medicine is, and how many new ideas and mathematical techniques are required, how can we return to our medical schools, where few will understand what we are talking about and where we will not learn what we need to know?" If there ever was a potential role for SFI-to provide the mathematical and conceptual foundations for a new approach to medicine in schools and research labs-this might be it.

David C. Krakauer is an SFI professor.