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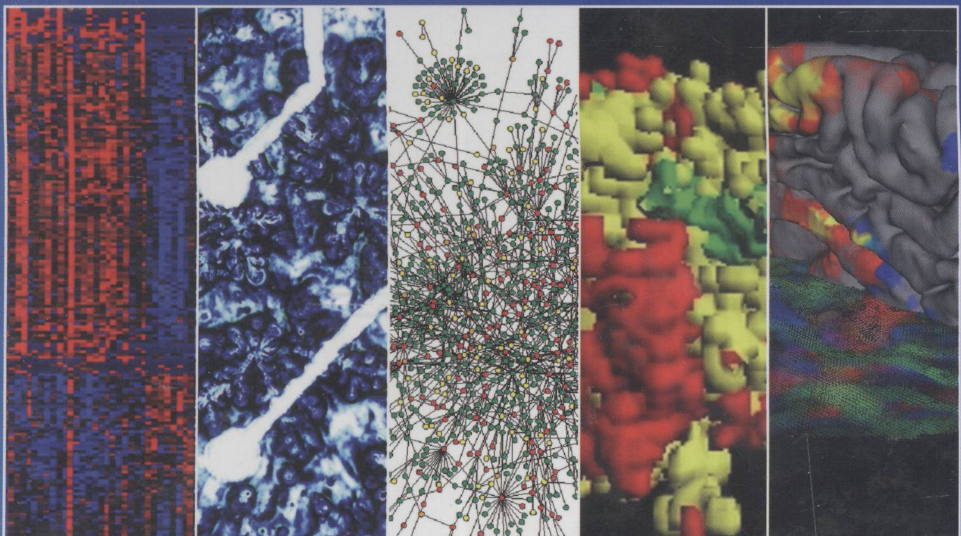
Complex Systems Science in Biomedicine



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Complex Systems Science in Biomedicine

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PREFACE

Work on Deisboeck and Kresh's *Complex Systems Science in BioMedicine* started years ago. In fact, thoughts and ideas leading up to this textbook date back to our first conversation, sometime in the fall of 1996. We quickly found common ground, and talked about emergence and self-organization and their relevance for medicine. We were both fascinated by the idea of complexity and marveled about its tremendous possibilities for cancer research, which was then and still is Tom's main scientific interest. Much has happened in science and technology since we first discussed our vision. For instance, in a remarkable international effort the human genome has been deciphered, nanotechnology has become a household name, and computing infrastructure, a critical enabler, is as powerful and affordable as ever before.

It is exactly *because* of this unprecedented progress that *Complex Systems Science in BioMedicine* is now making a case for a new approach in the life sciences. So let us start then with the obvious question first: why do we need a new fresh approach to ensure continued progress in the biomedical sciences? Did decades of methodically thorough research not yield great accomplishments and trigger an unparalleled productivity, with each year seeing thousands of scientific papers published in peer-reviewed journals? Certainly. *Reductionism* has led to ever-growing knowledge about isolated molecular pathways and selected portions of disease processes. We concede, dissecting biological mechanisms into bits and pieces has been utterly successful—if the number of fragmented discoveries is to be the decisive parameter. However, if we take understanding connectivity across scales, or better yet, *function* as the yardstick for measuring scientific achievements, much less progress can be claimed. Neither the vision nor the technical tools necessary to achieve these goals are "mainstream" yet. But there are signs in the biomedical sciences that things are changing—clear signs.

Indeed, most of the field involved in mapping the human genome in the 1990s is now engaged in *functional* genomics. Beginning to realize that the sum of its genes and proteins will not be able to explain a single cell's behavior, much less cell–cell interaction dynamics, let alone entire organ systems, we remember Aristotle, who had already argued that "*The whole is more than the sum of its parts.*" For biomedicine it means that, no matter how many more details we enthusiastically discover on ever smaller scales, we fail in deducing the complexity of a cell or multicellular tissue on the basis of this fragmented knowledge alone. In other words, piecing it together afterwards will not work. We need a new scientific approach, one that takes the nonlinearity of the majority of biological processes as much into account as their multi-scaled character. We believe that we are at a crucial bifurcation, where we need to integrate knowledge rather than dissect it, where we need to collaborate intensely across disciplines, theoretically and experimentally, in order to move forward. Complex systems science can match this challenge. Intrinsically multidisciplinary, it comprises concepts and quantitative tools that enable us to investigate how multiple biological elements interact and how molecular networks guide cell behavior and ultimately determine tissue function.

You might wonder how this is any different from, say physiology, a cornerstone of classic biomedical training. Indeed, physiology, the science of how living organisms function, may well be regarded as a predecessor of what many in the computational biology community now call "systems biology" and which clearly overlaps with complexity science in its goals. Where they differ, however, is in the *approach* to get there. Complex systems science applies a set of concepts and quantitative tools that are based on analogy and commonality, if not universality, between distinctively different systems, biologically or otherwise. Let us give you an example. The reason my, i.e., Tom's, laboratory developed an agent-based model to study cancer cell migration was an admittedly rather tired look out of a window while approaching London's Heathrow Airport by night several years back. What caught my attention was that, from above, the busy suburbs and streets resembled the cellular clusters and path patterns of a growing biosystem where single cells rather than people represent the system's individual "agents." Could one possibly investigate the metabolism-driven interaction of a rapidly evolving multicellular system, internally and with its microenvironment, in a way similar to how social scientists analyze the adaptive, economically driven behavior seen in expanding human societies? If so, then why not try an urban-planning approach for cancer research in an effort to better understand the dynamics of growth, migration and aggregation in tumor cell populations? Chapter 6.3 (Part III) summarizes some of the intriguing results arising from this line of work. This example illustrates how complex systems science approaches the problem at hand with tools adapted from nonlinear dynamics, applying sometimes rather abstract modeling and simulation techniques ranging from network theory to agent-based frameworks. It follows a "top–down" concept based on the claim that abstraction, not simplification, is the key to understanding the complexity of interaction between multiple parts on and across various scales of interest. That, however, is distinctively different from classic physiology, which uses biophysics and engineering concepts to describe the biological entity of interest in as much detail as available and, thus, "bottom–up." Let us emphasize that tackling the very same scientific problem from two seemingly opposing sides should not be seen as much as a case of competing approaches but as an exciting opportunity to exploit their mutual strengths in going forward.

Complex Systems Science in BioMedicine presents some of the fundamental theoretical basics of this rapidly emerging field and exemplifies the potential of the new approach by studying such diverse areas as molecular networks and developmental processes, the immune and nervous systems, the heart, cancer, and multi-organ failure. In this effort, the book itself follows a *multi-scaled* approach from molecular to macroscopic, thereby discussing both the normal and diseased states in selected topics. The invited contributions intentionally represent the dynamic state of the field in that biophysics, bioengineering, and computational biology modeling works are put side by side with complex systems-driven approaches. We believe that such juxtaposition not only anchors the new approach properly in established terrain but also helps showcase the differences.

A section on *emergent* technologies, no matter how long, can hardly ever be complete and, since the book was started years back, must run the risk of being outdated by the time of publication. By taking this risk we show by example that this novel approach has already led to and will continue to inspire design and development of cutting edge technology, ranging from micro-fluidics and innovative database management to multi-scale bioengineering, neuromorphic systems, functional MR imaging, and even operating room design. Undoubtedly, these and other techniques will feedback vital data and thus help complex systems science achieve its goals.

Finally, is there something like complex systems *science* at all or is it merely a powerful tool kit? As stated earlier and as reviewed in the book, there are certain techniques that are ubiquitous for the study of complex systems in economics, population dynamics, and biology. The title of the book reveals that we advocate the application of these techniques *also* to relevant areas in biomedicine where reductionism may have reached its limits. Nothing more, nothing less. As such, this book presents visionary ideas and their potential impact on future directions in biomedical research. It is not and cannot be definitive. Rather, we let the reader judge how far this, our field, has come, and if the presented work at this stage represents merely a promising, fresh approach or if it already signals the dawn of a new and yet to be fully defined science.

As described in detail in Yasha Kresh's introductory chapter, the origins of applying systems ideas in one form or another to the life sciences date back at least several decades. And while initial efforts to move complex systems further into the center of mainstream medicine were undertaken by a few pioneers, this has certainly changed. Over the last years, many colleagues have embraced the necessity of moving in this new direction, also documented by the enthusiastic feedback we received when we asked for participation in this multi-authored book. The newly established multidisciplinary graduate and postgraduate training curricula, sprouting complex systems-related academic centers as well as novel crosscutting grant funding programs, are testimony that these ideas are starting to catch on. What counts now are the steps we take in order to further foster this nascent development. As such, if *Complex Systems Science in BioMedicine* can help draw more attention to the application of complexity techniques to important questions in biomedicine and thus help support ongoing and upcoming scientific, teaching, and training efforts, we will consider it successful.

The quest for novel ways of thinking was what brought us together back in 1996, first as colleagues, now also as friends. It is the immense potential of complex systems science that provided a source of relentless energy for this textbook and that continues to fuel our scientific work.

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