

# Preface

People who are not mathematicians are strange. At least, they think differently. Things that we take for granted are exciting news for them. Problems which are most interesting for us don't even get registered with them. And, most annoyingly, they have a habit of asking really difficult questions. For instance, you are working on a model of colon cancer initiation. The biologist keeps asking "Can you include this? Can you include that in your model?" You smile meekly ("It's *hard!*"), and then, just to finish you off, he adds: "By the way, things work differently whether it is in the front or on the back of the colon." You didn't tell him that you modeled the colon as a *sphere*...

Something has to change. Many mathematical papers have been written about cancer, many interesting models created, many challenging questions asked. However, theoretical work is only valuable to the field of cancer research if models are validated by experiment, predictions are tested, and models are revised in the light of empirical data. Such an integrated and multi-disciplinary approach is so far lacking in the context of carcinogenesis. Theorists sometimes do modeling for the sake of the mathematical analysis that they can successfully pursue, which is of zero relevance to the field of cancer research. This creates general skepticism among the experimentalists. On the other hand, experimental biologists are often unfairly dismissive of the role of theory. It is not uncommon to hear that all theory is naive and that theoretical biologists cannot possibly grasp the full complexity of the biological reality, leave alone modeling it accurately.

The broad aim of this book is to provide an introduction to mathematical modeling in cancer research, and we hope that this will contribute to bridging the gap between mathematical modelers and experimental oncologists. The book is written with this goal in mind. On the one hand we will

introduce the mathematical methodology which underlies the theoretical work. On the other hand, we discuss how the modeling results can help us generate new biologically relevant insights, interpret data, and design further experiments.

Which readership do we have in mind? On a sunny day we think that the book will be read with enthusiasm by both applied mathematicians who wish to learn about theoretical work in cancer, and by experimental oncologists who would like to bring new, interdisciplinary dimensions to their research. On a rainy day, however, we realize that this is easier said than done. The book is certainly suited very well for applied mathematicians, because they are already familiar with the backbone of theoretical biology: computation and mathematics. We hope that after reading this book, they will sense a longing to learn much more about cancer biology and to pursue modeling work which is closely linked to biological data. The book should also be relatively easy to digest by biologists who will understand all the concepts even if they might not be familiar with some of the math. It will motivate them to get more familiar with mathematical methods and to widen their horizons; or, in case of experimentalists, it will allow them to see that modeling can give rise to interesting concepts which could help them formulate new questions and experiments. *The biggest challenge*, of course, are biologists who close the book when they encounter an equation, or who have the preconception that all theoretical work is naive and useless. Having many more sunny than rainy days in California, however, we have an optimistic outlook. We think that if enough experimental oncologists become enthusiastic about collaborating with modelers, theoretical work will spread through the community and bring many interesting results.

Besides the weather, our optimism is also fueled by experiences from another biomedical discipline: the interaction between pathogens and the immune system. Before 1990, all of the research which was considered “biologically relevant” by immunologists and virologists was experimental, and theoretical work was met with great skepticism. Subsequently, a wave of interesting work emerged which involved collaborations between some experimental immunologists/virologists and mathematical modelers. In fact, one of the most influential and widely cited papers in AIDS research, which appeared in a couple of *Nature* papers in 1995, came about through collaborations between modelers and experimental labs. Today, theory plays a relatively large role in immunology, to the extent that experimental design and research directions can be influenced by results obtained from mathematical modeling.

Why has mathematical modeling become an integral part of immunological research? The interactions between pathogens and the immune system involves many different components which interact with each other. These interactions are highly complex, non-linear, and can result in counter-intuitive outcomes. People started to realize that simple verbal or graphical reasoning is not sufficient to obtain a complete understanding of these interactions. Instead, it became clear that mathematical models are essential. They provide a solid framework upon which to generate hypotheses, interpret data, and design new experiments.

Cancer research is similar in this respect. It involves multiple interactions between molecules, cells, and their environment. As in immunology, we expect that mathematical models are essential to complement experimental work in order to obtain a satisfactory understanding of this complex biological system. We hope that our book will help to push the field of cancer research a little bit in the direction in which immunology has developed over time.

This brings up an important question. Does this book cover all aspects of cancer research? Certainly not! In fact, this would be impossible, unless you write many many volumes. Cancer is a very complicated topic and can be studied on many different levels. We chose to focus on one particular aspect of cancer: the process of carcinogenesis as *somatic evolution* of cells. This is a suitable topic for the introduction of mathematical modeling. Besides being deeply rooted in cancer biology, it is also partly based on the principles of evolutionary theory (mutation and selection) - a field where mathematical modeling has played a significant role since the early 1930s.

We would like to thank a number of people who got us fascinated by cancer research and who ultimately enabled us to write this book. These are experimental oncologists who are already very open minded towards computational approaches, who are willing to discuss theoretical ideas, and who educate us about the field. Arnie Levine provided the initial stimulus which got us working on cancer. At the Institute for Advanced Study in Princeton, where this book was partly written, we enjoyed many interesting and important discussions. Rick Boland at Baylor University, Dan Gottschling, Lee Hartwell and Chris Kemp at the Hutch, Larry Loeb at the University of Washington, and Vladimir Mironov at Medical University of South Carolina have provided many useful discussions and insights which were essential for our modeling work.

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