Multiscale Modeling of Cancer

An Integrated Experimental and Mathematical Modeling Approach

Mathematical modeling, analysis, and simulation are set to play crucial roles in explaining tumor behavior and the uncontrolled growth of cancer cells over multiple time and spatial scales. This book, the first to integrate state-of-the-art numerical techniques with experimental data, provides an in-depth assessment of tumor cell modeling at multiple scales. The first part of the text presents a detailed biological background with an examination of single-phase and multi-phase continuum tumor modeling, discrete cell modeling, and hybrid continuum-discrete modeling. In the final two chapters, the authors guide the reader through problem-based illustrations and case studies of brain and breast cancer, to demonstrate the future potential of modeling in cancer research. This book has wide interdisciplinary appeal and is a valuable resource for mathematical biologists, biomedical engineers, and clinical cancer research communities wishing to understand this emerging field.

Vittorio Cristini is Professor of Health Information Sciences and Biomedical Engineering at the University of Texas, and of Systems Biology at the MD Anderson Cancer Center, Houston. He is also Honorary Professor of Mathematics at the University of Dundee, Scotland. Professor Cristini is a leading researcher in the fields of mathematical and computational biology, complex fluids, materials science, and mathematical oncology. He has published several chapters in books and over 60 journal articles. His research has been supported by various institutions, including the US National Science Foundation, the National Institutes of Health, the Cullen Trust for Health Care, and the US Department of Defense.

John Lowengrub is Chancellor's Professor of Mathematics, Materials Science, and Biomedical and Chemical Engineering at the University of California, Irvine. He has published over 80 journal articles along with several book chapters. Professor Lowengrub is a leading researcher in the fields of mathematical and computational biology, mathematical oncology, complex fluids, and materials science. His research has been supported by various institutions including the National Science Foundation, the National Institutes of Health, and the State of California.

This past decade in the field of cancer research can be described as a decade of data generation. The next step in the war on cancer is figuring out what to do with the data. Cristini and Lowengrub have put together a remarkable treatise on ways to interpret these data and start modeling cancer behavior. This book presents a multi-scale approach toward understanding the behavior of cancer – such an important beginning to a critical field.
Professor David B. Agus, M.D., *University of Southern California Keck School of Medicine*

Cristini and Lowengrub have leaped over an obstacle previously assumed to be insurmountable: how to model complex biological systems without precise measurements of every event. Biologists are struggling to produce such measurements, which could take centuries to accomplish. In an unprecedented tour-de-force through a number of peer-reviewed publications synthesized in this book, Cristini and Lowengrub found a way to reliably predict biological behavior, thereby circumventing the need for precise measurements to generate predictive modeling. Their method assumes that the physical laws of nature are obeyed by biology – what could be more simple? By making this assumption, they have generated useful and predictive models of cancer progression that apply to pathological diagnosis. Such predictive modeling will be a powerful tool for diagnosis, prognosis, and treatment in the next decade.
Professor Elaine L. Bearer, MD., *University of New Mexico Health Sciences Center.*

This is a comprehensive and authoritative account . . . by leading experts in the field. The work brings powerful new ideas and tools of mathematical and computational modeling to the field of cancer research.
Professor J. Tinsley Oden, *The University of Texas at Austin*

This is a wonderful book covering most of the literature that has appeared in the last ten years on cancer modeling. It covers both theoretical and experimental aspects, drawing a strong link between them, and describes all phases of tumor growth, from the avascular to the vascular phase through the angiogenic process. It presents both discrete and continuous models, with the aim of linking them in line with the current thought that important insights into the complexity of tumour growth can only be reached by closely relating the phenomena occurring at the sub-cellular, cellular and tissue scale. Though at present multiscale models can be considered still in their infancy, this book gives a lot of ideas on how such models could be developed. For this reason, the book is of great value for young researchers who want to devote their attention to this crucial aspect of mathematical modelling in medicine in general.
Professor Luigi Preziosi, *Politecnico di Torino, Italy*

If you've ever wondered what mathematical and computational modeling can do for the field of cancer research, this book is a key to finding compelling reasons to integrate theory and experiment to unlock the mysteries of tumor growth and invasion. *Multiscale Modeling of Cancer: An Integrated Experimental and Mathematical Modeling Approach* tells the complex and dynamic story of tumorigenesis, vascular tumor growth, and invasion from the latest mathematical perspective, in less than 300 pages. I'm recommending this book as a must-read for all of my graduate students and postdocs!
Professor Trachette Jackson, *University of Michigan*

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VC: This work is dedicated to my wife, Jennifer, and to my children Giovanni, Gabriella and Tizita, to my mother and father, and to the excellent scientists I have been fortunate to train, without whom this work would not have been possible.

JL: This work is dedicated to my wife, Elizabeth, my children Catherine, David, Collette, Hillary and Mark, my parents Mort and Carol, to whom I am much indebted, and to my students and post-doctoral fellows, from whom I have learned more than I have taught.

Finally, we dedicate this work to the health care professionals and patients who bravely do battle every day on the front lines of the war against cancer.

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Paul Macklin, a lecturer at the University of Dundee, was formerly an assistant professor at the University of Texas Health Science Center in Houston. He completed his Ph.D. in applied and computational mathematics at the University of California, Irvine, and specializes in discrete and continuum biomathematics and computation with particular emphasis on cancer. He has recently focused on improving the state-of-the-art in patient-specific multiscale cancer modeling and enjoys the fusion of mathematics, computer science, biology, the physical sciences, and medicine that is necessary to describe and calibrate biophysical systems.

Steven M. Wise, Ph.D.

Steven Wise completed his Ph.D. in engineering physics at the University of Virginia and is now an assistant professor of mathematics at the University of Tennessee. He specializes in mathematical biology, computational and applied mathematics, and computational materials science and has helped to push forward the state-of-the-art in nonlinear multigrid solution techniques using adaptive meshes.

Preface

In the past several decades there has been significant progress in understanding and identifying the causes of cancer and in developing effective treatment strategies. Nevertheless, a cure remains frustratingly elusive. At its most essential level, cancer involves the abnormal growth and spread of tissues within a body. Yet each cancer is unique, based on the tissue in the body where it originates and the particular person who has it. While molecular mechanisms and cell-scale dynamics governing tumor cell migration and proliferation are well studied from a biological perspective, cancer progression actually involves events that occur at multiple time and spatial scales. What occurs at the nano-scale of molecules and micro-scale of cells affects the behavior of tissue at the centimeter-scale – and vice versa. In order to better understand these multiscale linkages, mathematical modeling, analysis, and simulation have been employed to study tumor behavior. The complex shapes and invasive behavior of tumors requires a nonlinear approach, meaning that effects at various physical scales within the tissue do not necessarily influence each other additively. Hence, the combination of events may yield a response greater or less than of each component, depending whether there is synchrony. The application of such computational models in the clinical setting, however, is still in its infancy.

In this book we outline recent advances in the field of mathematical modeling and the simulation of cancer, particularly with respect to multiscale, nonlinear, computational models that integrate theory and experiment. We present state-of-the-art numerical methods as tools for analyzing the nonlinear behavior predicted by the models. The book focuses on the challenging problem of developing models that connect intratumor molecular and cellular properties with critical tumor behaviors such as invasiveness and clinically observable properties such as morphology. In this context we discuss the incorporation of experimental and clinical data into predictive mathematical and computational models. The interactions between cellular proliferation and adhesion and other phenotypic properties are reflected in both the surface characteristics of the tumor–host interface and the invasive characteristics of the tumors. These cellular and molecular properties are influenced by the cellular genetics and by microenvironmental conditions such as oxygen deprivation (hypoxia). This close connection between tumor morphology and the underlying cellular and molecular dynamics is of fundamental importance, in that the cellular dynamics that give rise to various tumor morphologies also control its ability to invade. This allows the observable properties of a tumor, such as its morphology, to be used both to understand the underlying cellular physiology and to predict subsequent invasive behavior.

There are significant challenges in the multiscale and multidisciplinary modeling of cancer. These include the development of realistic models, the achievement of numerical solutions, and the incorporation of experimental and clinical data. This book offers three novel features to address these needs. First, we present and critically evaluate state-of-the-art mathematical models calibrated with experimental results. We demonstrate how experiments are used to determine functional relationships between the phenotypic variables and parameters of the models and the microenvironmental and molecular agents that affect tumor progression and invasion. Second, we evaluate patient-specific calibration protocols in a multiscale modeling framework spanning the cell-scale to the tissue-scale. Third, we present the state-of-the-art numerical algorithms that are indispensable tools for studying nonlinear predictions of the mathematical models. It is our sincere hope that the presentation of the material in this publication will further the goal of the eventual clinical application of multiscale modeling to cancer patients.

About the cover

Cover illustration: the computer simulation of a growing tumor and the corresponding host vascular response are shown in images representing predicted morphologies at 20, 40, 80, and 110 days since inception. The inner necrotic region is shown in dark red, surrounded by a layer of viable proliferating cells in blue. The blood-conducting vessels are indicated as thicker red lines, while sprouting (non-conducting) vessels are shown as thinner orange lines.

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Notation

Sets and set operations

$\emptyset$	Empty set
$x \in A$	x is contained in the set A
$x \notin A$	x is not contained in the set A
$A \cap B$	The intersection of sets A and B
$A \cup B$	The union of sets A and B
$A \subset B$	Set A is a subset of set B
$A \subseteq B$	Set A is a subset of set B or identical to B
$A \setminus B$	Set A after subtraction of subset B, i.e., $x \in A$ such that $x \notin B$
$A \times B$	Cartesian product of sets A and B: $\{(a, b)$ such that $a \in A$ and $b \in B\}$
$\bigcup_{i=1}^{N} A_i$	Union of sets A_i for $i = 0$ to N

Number systems and operations

$\mathbb{N}$	Natural numbers $(0, 1, 2, \ldots)$
$\mathbb{Z}$	Integers $(\ldots - 2, -1, 0, 1, 2, \ldots)$
$\mathbb{Q}$	Rational numbers
$\mathbb{R}$	Real numbers
$\sum_{i=0}^{N} a_i$	Summation of a_i for $i = 0$ to N
$\forall$	"for all"

Vectors, matrices, and tensors

$\mathbf{v}$	Vector $\mathbf{v}$
$\mathbf{v} \parallel \mathbf{w}$	$\mathbf{v}$ is parallel to $\mathbf{w}$
$\mathbf{v} \perp \mathbf{w}$	$\mathbf{v}$ is perpendicular to $\mathbf{w}$
$\lvert\mathbf{v}\rvert$	Length of $\mathbf{v}$
$\mathbf{I}$	Identity matrix
$\mathbf{A}^T$	Transpose of a matrix (tensor) $\mathbf{A}$
$\mathbf{A}^{-1}$	Inverse of a matrix (tensor) $\mathbf{A}$

Topology

$[a, b]$	Closed interval of real numbers x satisfying $a \leq x \leq b$
(a, b)	Open interval of real numbers x satisfying $a < x < b$
$B_r(\mathbf{x})$	Open ball of radius r centered at $\mathbf{x}$, i.e., $\{\mathbf{v}$ such that $\lvert\mathbf{v} - \mathbf{x}\rvert < r\}$
$\partial\Omega$	Boundary of a domain Ω

Differentiation and integration

∇f	Gradient of f
$\nabla \cdot \mathbf{v}$	Divergence of $\mathbf{v}$
$\nabla^2 f$	Laplacian $(\nabla \cdot \nabla)$ of f
$\partial f/\partial x_i$	Partial derivative of $f(x_1, x_2, \cdots)$ with respect to (w.r.t.) x_i
$\mathrm{D}f/\mathrm{D}t = \partial f/\partial t + \mathbf{u} \cdot \nabla f$	Advective derivative of $f(\mathbf{x}, t)$ in a velocity stream $\mathbf{u}$
$\dfrac{\delta f}{\delta \varphi}$	Variational derivative of a functional f w.r.t. a variable φ
$\int_a^b f(x)dx$	Integral of f on $a \leq x \leq b$
$\oint_\gamma f(x)dx$	Line integral of f over the curve γ

Special functions

$\mathbf{1}_A(\mathbf{x})$	Characteristic function satisfying $\mathbf{1}_A(\mathbf{x}) = \begin{cases} 1 & \text{if } \mathbf{x} \in A, \\ 0 & \text{if } \mathbf{x} \notin A \end{cases}$
$(x)_+$	Positive part of x satisfying $(x)_+ = \max(x, 0)$
$\mathcal{H}(x)$	Heaviside step function satisfying $\mathcal{H}(x) = \begin{cases} 0 & \text{if } x < 0, \\ 1 & \text{if } x \geq 0 \end{cases}$
$\delta(x)$	Dirac delta function
δ_{ij}	Kronecker delta function satisfying $\delta_{ij} = \begin{cases} 1 & \text{if } i = j, \\ 0 & \text{if } i \neq j \end{cases}$
$[x]$	Nearest integer to a real number x

Probability and statistics

$\Pr(X)$	Probability of the event X
$\Pr(X\|Y)$	Conditional probability of the event X given the event Y
$\langle x \rangle$	Mean of the measurable quantity x
$\mathrm{Ex}[X]$	Expected value of the random variable X
$\mathrm{Var}[X]$	Variance (standard deviation squared) of the random variable X