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978-0-521-88442-6 - Multiscale Modeling of Cancer: An Integrated Experimental and Mathematical Modeling Approach

Vittorio Cristini and John Lowengrub

Frontmatter

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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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Modeling Approach

VITTORIO CRISTINI

University of Texas

JOHN LOWENGRUB

University of California, Irvine



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Frontmatter
[More information](#)

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.

Contents

<i>List of contributors</i>	<i>page</i> xii
<i>Preface</i>	xv
<i>Acknowledgements</i>	xvii
<i>Notation</i>	xviii
Part 1 Theory	1
1 Introduction	3
2 Biological background	8
2.1 Key molecular and cellular biology	8
2.1.1 Tissue microarchitecture and maintenance	8
2.1.2 Cellular adhesion and cell sorting	10
2.1.3 Subcellular structure	11
2.1.4 Cell cycle, proliferation, and apoptosis	11
2.1.5 Genetics, gene expression, and cell signaling	13
2.1.6 Cell motility	16
2.1.7 Hypoxia, necrosis, and calcification	17
2.2 The biology of cancer	17
2.2.1 Carcinogenesis	17
2.2.2 Avascular solid-tumor growth	18
2.2.3 Interaction with the microenvironment	19
2.2.4 Vascular growth and metastasis	20
2.3 Concluding remarks	23
3 Continuum tumor modeling: single phase	24
3.1 Introduction	24
3.1.1 Background	24
3.2 Avascular tumor growth	26
3.2.1 Model without necrosis	26
3.2.2 Growth in heterogeneous tissue	29
3.2.3 Effect of stress	31

viii	Contents	
	3.3 Vascularized tumor growth	33
	3.3.1 Background	33
	3.3.2 Modeling of angiogenesis	35
	3.3.3 Basic model	36
	3.3.4 Coupling of tumor growth with angiogenesis	38
	3.4 Conclusion	39
4	Analysis and calibration of single-phase continuum tumor models	41
	4.1 Regimes of growth	41
	4.2 Linear analysis	43
	4.3 Nonlinear results	49
	4.4 Model calibration from experimental data	53
	4.5 Tumor growth with chemotaxis	57
	4.6 Tumor growth with necrosis	59
	4.7 Tumor growth in heterogeneous microenvironments	62
	4.8 Vascular tumor growth	64
	4.9 Conclusion	65
5	Continuum tumor modeling: multiphase	67
	5.1 Background	67
	5.2 General conservation equations	69
	5.3 A solid–liquid biphasic model	70
	5.4 Liquid–liquid mixture model I	71
	5.5 Liquid–liquid mixture model II	73
	5.6 A special case of the generalized Darcy’s law liquid–liquid mixture model	74
	5.7 Fluxes and velocities	75
	5.8 Mass-exchange terms	76
	5.9 Diffusion of cell substrates	77
	5.10 Mutation of tumor cell species	77
	5.11 Nonlinear results: avascular growth	79
	5.11.1 Morphological instability as an invasive mechanism	79
	5.11.2 Chemotaxis as an invasive mechanism	80
	5.12 Modeling angiogenesis in three dimensions	82
	5.12.1 Background	82
	5.12.2 Biased circular random walk	84
	5.12.3 Branches and anastomoses	85
	5.13 Nonlinear results: vascularized tumor growth	85
6	Discrete cell modeling	88
	6.1 A brief review of discrete modeling in cancer biology	88
	6.1.1 Lattice-based models	89
	6.1.2 Lattice-free models	89

	Contents	ix
	6.1.3 Comparison with continuum methods	90
	6.1.4 Some discrete modeling examples	91
6.2	An agent-based cell modeling framework	96
	6.2.1 A brief review of exponential random variables and Poisson processes	97
	6.2.2 A family of potential functions	99
	6.2.3 Cell states	99
	6.2.4 Forces acting on the cells	103
6.3	Subcellular modeling	109
6.4	Dynamic coupling with the microenvironment	110
6.5	A brief analysis of the volume-averaged model behavior	113
6.6	Numerical examples from breast cancer	114
	6.6.1 Baseline calibrated run	115
	6.6.2 Impact of hypoxic survival time	118
	6.6.3 Impact of the cell lysis time	119
	6.6.4 Impact of background oxygen decay rate	120
	6.6.5 Impact of cell motility	120
6.7	Conclusions	122
7	Hybrid continuum–discrete tumor models	123
	7.1 Background	123
	7.2 General concept and conservation laws	127
	7.2.1 Conservation laws in continuum models	127
	7.2.2 Conservation laws in discrete models	128
	7.2.3 “Inertialess” assumption	129
	7.2.4 Linking discrete and continuum variables	130
	7.3 Mass and momentum exchange	131
	7.3.1 The continuum-to-discrete (C2D) conversion	131
	7.3.2 The discrete-to-continuum (D2C) conversion	134
	7.3.3 Momentum exchange through continuum–discrete interactions	136
	7.3.4 Summary of the hybrid modeling framework	139
	7.4 A hybrid model of multicellular tumor spheroids (MCTSs)	139
	7.4.1 The continuum and the discrete components	140
	7.4.2 Continuum–discrete coupling mechanism	142
	7.4.3 Results	143
	7.4.4 Discussion	144
	7.5 A hybrid model of vascularized tumor growth	144
	7.5.1 The continuum and the discrete components	145
	7.5.2 The C2D conversion process	146
	7.5.3 The D2C conversion process	148
	7.5.4 Momentum exchange through continuum–discrete interactions	149
	7.5.5 Results	150
	7.5.6 Discussion	150

x	Contents	
8	Numerical schemes	153
8.1	Review of the multiphase mixture model	154
8.2	Uniform mesh discretization	156
8.2.1	The discrete gradient operator ∇_d	157
8.2.2	Treatment of the advection terms	158
8.2.3	Discretization of the boundary conditions	161
8.2.4	Mesh discretization across interfaces	162
8.2.5	Treatment of the source terms	162
8.3	Multigrid mesh hierarchy and block-structured adaptive mesh	164
8.3.1	Block-structured adaptive-mesh refinement	165
8.3.2	Initialization of the refined meshes	168
8.4	Multigrid method on adaptive meshes: the MLAT-FAS scheme	171
8.4.1	Operators and sources	171
8.4.2	The MLAT-FAS V-cycle method	173
8.4.3	Smoothing procedures	175
8.4.4	Restriction and interpolation	179
8.4.5	Criteria for mesh refinement	181
	Part II Applications	183
9	Continuum tumor modeling: a multidisciplinary approach	185
9.1	Introduction	185
9.1.1	Avascular growth	185
9.1.2	Vascularized tumors	187
9.1.3	Clinical observations	188
9.2	Application to brain cancer	188
9.2.1	Avascular growth	188
9.2.2	Vascularized tumors	192
9.2.3	Clinical observations	196
9.3	Modeling outlook	204
10	Agent-based cell modeling: application to breast cancer	206
10.1	Introduction	206
10.1.1	Biology of breast-duct epithelium	207
10.1.2	Biology of DCIS	209
10.2	Adaptation of the agent model	210
10.2.1	Oxygen and metabolism	210
10.2.2	Duct geometry	210
10.2.3	Intraductal oxygen diffusion	212
10.2.4	Numerical method	213
10.3	Patient-specific calibration with patient data	214
10.3.1	Estimating “universal” parameters	214

Cambridge University Press
978-0-521-88442-6 - Multiscale Modeling of Cancer: An Integrated Experimental and Mathematical Modeling Approach
Vittorio Cristini and John Lowengrub
Frontmatter
[More information](#)

	Contents	xi
10.3.2	Calibrating patient-specific parameters	215
10.3.3	Sample patient calibration and verification	218
10.4	Case studies	219
10.4.1	Estimating difficult physical parameters	220
10.4.2	Generating and testing hypotheses	222
10.4.3	Calibrating multiscale modeling frameworks: preliminary results	226
10.5	Concluding remarks	232
11	Conclusion	235
	<i>References</i>	238
	<i>Index</i>	275

List of contributors

Yao-Li Chuang, Ph.D.

Yao-Li Chuang, who holds a Ph.D. in physics from Duke University, is a post-doctoral researcher at the University of Texas Health Science Center in Houston. He specializes in nonlinear dynamical systems, with an emphasis on the statistical and numerical analysis of discrete many-body problems and their continuum limit. His areas of interest include the formation and stability of patterns arising in ordinary and partial differential equation systems, with a recent focus on the high-performance scientific computing of Cahn–Hilliard equations applied to tumor growth modeling.

Mary E. Edgerton, M.D., Ph.D.

Mary Edgerton, who holds an M.D. from the Medical College of Pennsylvania and a Ph.D. in biophysics from the University of East Anglia (United Kingdom), is an Associate Professor at the M. D. Anderson Cancer Center. Dr Edgerton’s research focuses on the discovery of mechanisms in cancer genesis and progression. She has worked on the development of mathematical models for computer simulations of the spread of ductal carcinoma in situ and on the role of cell motility in extensive disease. She researches methods for the analysis of gene-expression array data for pathway discovery. She has published articles on the application of these methods to lung cancer and breast cancer profile data. Dr Edgerton has also worked on the development of integrated information platforms for tissue acquisition, clinical annotation, and molecular profiling.

Hermann B. Frieboes, Ph.D.

Hermann Frieboes, who completed a Ph.D. in biomedical engineering at the University of California, Irvine, is a postdoctoral researcher at the University of Texas Health Science Center in Houston and works in collaboration with the Department of Mathematics at the University of California, Irvine. He specializes in applying computational and experimental cancer modeling techniques to predictive oncology. His interests include the development of quantitative approaches to the study of tumor growth and treatment, furthering the interaction of basic research with clinical and translational programs and exploring the use of nanotechnology in disease diagnosis and treatment.

Fang Jin, Ph.D.

Fang Jin, who holds a Ph.D. in chemical engineering from Johns Hopkins University, is a postdoctoral researcher at the University of Texas Health Science Center in Houston

and works in collaboration with the Department of Mathematics at the University of California, Irvine. He specializes in scientific modeling and toolset design in the simulation and visualization of multiscale problems. His areas of interest include surface tension induced morphology changes in the micro-size environment, angiogenesis network topology modeling in the human body, and the modeling of tumor growth with discrete–continuum multiscale interchange.

Xiangrong Li, Ph.D.

Xiangrong Li completed his Ph.D. in mathematics in 2007 from the University of California, Irvine. He is now a postdoctoral researcher at the Center for Mathematical and Computational Biology at the University, Irvine. His research focuses on tumor modeling and moving-interface and free-boundary problems.

Paul Macklin, Ph.D.

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.

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[More information](#)

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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[More information](#)

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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 : $\{(a, b) \text{ such that } a \in A \text{ and } b \in B\}$
$\bigcup_{i=1}^N A_i$	Union of sets A_i for $i = 0$ to N

Number systems and operations

\mathbb{N}	Natural numbers (0, 1, 2, ...)
\mathbb{Z}	Integers (... - 2, -1, 0, 1, 2, ...)
\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}
$ \mathbf{v} $	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., $\{\mathbf{v} \text{ such that } \mathbf{v} - \mathbf{x} < r\}$
$\partial\Omega$	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 $f(x_1, x_2, \dots)$ with respect to (w.r.t.) x_i
Df/Dt $= \partial f / \partial t + \mathbf{u} \cdot \nabla f$	Advective derivative of $f(\mathbf{x}, t)$ in a velocity stream \mathbf{u}
$\frac{\delta f}{\delta \varphi}$	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
$\text{Ex}[X]$	Expected value of the random variable X
$\text{Var}[X]$	Variance (standard deviation squared) of the random variable X