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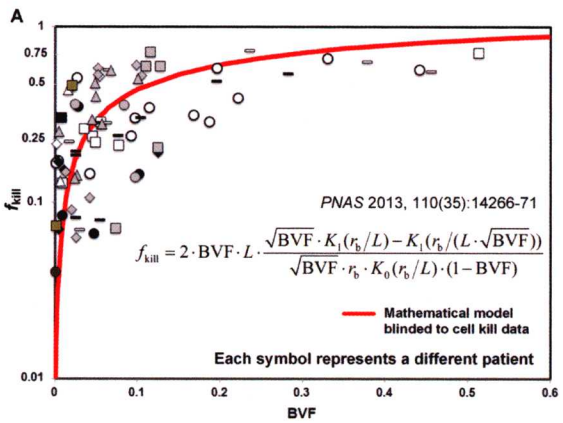
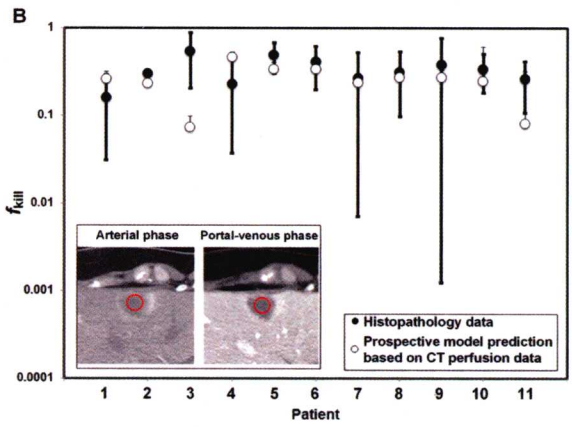
AN INTRODUCTION TO PHYSICAL ONCOLOGY

How Mechanistic Mathematical Modeling Can Improve Cancer Therapy Outcomes





Vittorio Cristini
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An Introduction to Physical Oncology

How Mechanistic Mathematical Modeling Can Improve Cancer Therapy Outcomes

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With contributions by
Jason Fleming, Sofia Merajver, John Lowengrub, and others

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"The application of concepts and tools from the physical sciences will fundamentally change our understanding of cancer. These novel insights will impact the way we diagnose malignant tumors and, ultimately, they should lead to new and patient-specific paths to treat the disease more successfully. The authors are at the forefront of this most promising endeavor and they have produced a book that, ranging from chemotherapy response to immunotherapy modeling, highlights both critical research accomplishments and early clinical applications. This up-to-date book should be required reading for everyone interested in applying cutting-edge data-driven modeling to the field of oncology."

Thomas S. Deisboeck, MD MBA
Harvard Medical School

"This book provides an important introduction to the emerging field of physical oncology. It examines cancer growth and treatment outcomes in the context of physical and biological processes across microscopic and macroscopic scales. The work is at the forefront of the convergence between physical science and cancer research. Seminal work by the authors and their collaborators from medicine, biology, engineering, mathematics, and physics discussed in this book includes the development of 'master equations' from first principles to quantify penetration of free drugs and nanoparticles across tumor tissue, and relating these ideas to their potential for impact on patients. This book is a 'must-read' for researchers interested in applying principles of physical sciences to cancer biology."

Anil K. Sood, MD
Department of Gynecologic Oncology and Reproductive Medicine
and Department of Cancer Biology, UT M. D. Anderson Cancer Center

"This timely book presents and discusses a range of highly promising, clinically relevant mathematical models of cancer progression and treatment. The authors use bio-physical laws informed by biological measurements to describe the processes of tumor growth and drug transport in tumor tissue to make predictions of outcomes for patients. Their work is informed by quantitative measurements from standard-of-care diagnostics, such as CT, histopathology, and MRI. In doing so, they seek to render individualized rubrics for each patient, based on his or her specific tumor characteristics. This provides a fresh take on the modern concept of 'Precision Medicine'. The pioneering models described here can pave the way for new, accurate clinical decision tools, which can be used by physicians to predict and thus optimally plan current and new individualized treatment strategies for patients."

Anirban Maitra, MBBS
Sheikh Khalifa Bin Zayed Al Nahyan
Distinguished University Chair in Cancer Research
UT M. D. Anderson Cancer Center

"During the past decade, innovative researchers have applied principles of engineering and physics to cancer research, in an emerging field known as physical oncology. This multidisciplinary research effort has led to encouraging results towards a better understanding of different aspects of cancer biology and oncology, from quantitative understanding of tumor growth and progression to improved detection and the treatment of cancer. This book introduces and discusses the advances made at the interface of engineering/physical sciences and oncology and explores the new frontiers in this field. The chapters are well written and I am especially impressed by the approach to developing accurate mathematical predictions of tumor drug response in experiments and in patients. I think this book is a significant contribution towards the biomedical community's efforts to improve its quantitative understanding of the treatment of cancer. I hope the book will encourage more scientists to enter the field of physical oncology."

Sanjiv Sam Gambhir, MD, PhD
Stanford University School of Medicine

An Introduction to Physical Oncology

How Mechanistic Mathematical Modeling Can Improve Cancer Therapy Outcomes

CHAPMAN & HALL/CRC
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Preface

Of these sciences the gate and the key is mathematics.... He who is ignorant of [mathematics] cannot know the other sciences.... And what is worse, men ignorant of this do not perceive their own ignorance, and therefore do not seek a remedy.

ROGER BACON
Opus Majus, 1267

Cancer is a complex, heterogeneous, multifactorial, and multistage disease [1]. Its growth, invasion, metastasis, response to treatment, and therapeutic resistance all depend on multiple genetic and environmental cues [2]. It is currently the second most common cause of death in the United States after heart disease [3] and is on track to become the leading cause of death in the United States by 2030 [4]. Despite all efforts to fight the disease, including significant investments in basic and clinical research, it continues to impact every segment of society, leaving oncologists with the challenge of providing treatment for a diverse population across a vast area. At the same time, treatment costs continue to increase, treatment becomes more complex, and the ratio of patients to physicians increases as a result of population growth and aging, among other factors. The field of physical oncology involves novel approaches to battling the disease through the application of physical sciences, in most cases combined with mathematical modeling, to study various aspects of cancer, such as tumor growth and invasion dynamics, transport (and ultimately delivery) of drugs across tissue, cell death and genetic mutation, and even patient treatment outcome.

PHYSICAL ONCOLOGY

A significant problem in the treatment of cancer patients lies in the lack of widespread understanding and application of first principles of physical science, which function at multiple scales in time and space within tumors. From the atomic and molecular scales (e.g., the transport of pharmaceutical molecules across human cells) to the macroscale (e.g., tumor mass growth within organs and the human body), the dynamics of drug transport (perfusion, diffusion, and other means) and the dynamics of tumor growth can be described, explained, and modeled mathematically according to the universal conservation laws of physics. These mathematical models can be coupled to biological behavior and concepts that are derived from experiments, tissue specimens, and patient imaging, and are therefore specific to a particular cancer type, although they may vary across patients and within each patient's tumor.

While the focus on the development of new drug molecules has led to improvements in how specific cancers can be fought through multiple chemotherapy delivery systems, the fundamental problem of drug resistance within the human body (consisting of many interacting body systems) is still the main cause of poor patient prognosis; for example, only 26% of breast cancer patients survive five years beyond the beginning of their treatment [5,6]. Chemotherapy fails more often than it succeeds because the drugs, while effective in laboratory petri dishes and sometimes in animal models, often cannot kill the cancer in live patients as effectively. Drug delivery encounters resistance to its transport through blood vessels, extracellular diffusion in the tissue and cells surrounding cancer cells (stroma), and cell internalization because of the distance and associated "barriers" through which the drugs must pass in tissue. Delivering drugs into tumors (in therapeutically adequate amounts, for an adequate period of time, and with efficacy enough to kill tumor cells and prevent future proliferation) is driven by pressure and concentration gradients. Compounding this phenomenon is the presence of hostile microenvironments within tumors and treatment-resistant cancer cells that pass on their genetic data through natural selection. Oncologists commonly begin treatment of cancer based on measurements from initial tests, while further treatment decisions depend on empirical evidence gained through trial and error. This approach unsatisfactorily meets an individual patient's needs at the initiation of and throughout the course of treatment. We suggest that a comprehensive, inclusive, and theoretical approach to treating and understanding cancer based on the cooperation between physicists, chemists, engineers, pathologists, and oncologists can and should be adopted at the start of treatment if we are to hope for significant improvements in patient outcome.

RESISTANCE TO CHEMOTHERAPY

Current treatment strategies in oncology are limited by multiple factors, especially drug resistance, which is twofold mechanistically. First, tissue within the body at many scales resists the transport of drugs, just as a complex microstructured physical medium may resist molecular transport. Second, tumors become resistant to drugs when their microenvironments change and as the cancer cells proliferate according to natural selection. More specifically, chemotherapy drug molecules encounter resistance as they are transported through the blood, across organ tissue, and into the tumor. There, drugs must be absorbed across cell membranes and internalized into the cell to perform their function in killing cancerous cells. These initial elements of resistance—distance across which the drugs must transport and tissue barriers—constitute a tumor's first line of defense against prescribed drugs, which kill not only the cancerous cells but also healthy cells in the surrounding tissue. Once exposed to the drug, those cancerous cells that do not die (owing to physical [e.g., lack of drug access] or biological [e.g., efflux pumps and acquired mutations] drug resistance) can proliferate and pass their genetic material on to newly generated cells, which may inherit resistance to the drug. Cancers may develop rapidly after initial exposure to chemotherapy because of this natural selection, where drug-resistant cells survive chemotherapy and are selected to produce the next generation. Another factor limiting the efficacy of chemotherapy is the danger of creating

high toxicity levels within the patient. Since drug transport processes can be described by physical equations and associated parameters (of course under reasonable assumptions), predictive, mechanistic modeling can be instrumental in understanding how and why tumors offer resistance to chemotherapy. Mathematical models developed by the authors, applying essential parameters gained from histopathology and other imaging measurements in tumors, help explain and quantify the transport phenomena of chemotherapy drugs.

PATIENT-SPECIFIC STRATEGIES

Oncologists looking for the most successful patient outcome strive not to overprescribe chemotherapy to avoid creating overly toxic environments within the body. Prescribing the proper drug, delivery platform, dosage, duration, and frequency is usually performed according to established protocols derived from basic patient measurements, while ongoing treatment and strategy are primarily derived from empirical data and the physician's preexisting experiential knowledge. Physical oncology uses mathematical models to provide predictions of treatment outcome with acceptable accuracy based on biophysical equations where parameters are gained from individual tumors in specific patients. Being able to predict how a drug will physically interact with both normal and cancerous cells within the body, and taking into account the differences across patients (individualized treatment), can help alleviate the problem of toxicity. Measurements gathered from common imaging and diagnosis protocols, such as contrast-enhanced computed tomography scans, magnetic resonance imaging scans, and patient histopathology, can quantify those parameters necessary for understanding an individual patient's tumor [7–9]. For example, pathologists can measure (directly or indirectly) drug perfusion penetration distances across a tumor, the diameters of the blood vessels, and the blood volume fraction of the tumor to provide key parameters involved in the accurate predictive analysis of the amount of cancerous cells that will be killed in the tumor [7]. In fact, even the noninvasive process of performing contrast-enhanced computed tomography scans can provide patient-specific imaging "biomarkers" that are useful in designing patient-specific treatment strategies [8]. With this wealth of information, physicians may be better informed in decision making for the patient's health.

By collecting data from these common clinical tests (with the help of pathologists and radiologists), oncologists can develop patient-specific drug regimens per tumor, even when more than one tumor is present within the same organ. The authors' equations and mechanistic modeling approaches can provide predictions about many outcomes surrounding cancer treatment, including tumor growth, drug uptake, cell kill, and patient survival. Recently published results of studies on pancreatic cancer, colorectal cancer metastatic to liver, breast cancer, and glioblastoma provide evidence of the validity of the theories contained; this book summarizes the results of some of these studies and associated review and position papers recently published. Additionally, advances in *nanotechnology* [10,11] have been applied as a drug delivery method in these studies with encouraging results—in some cases with manyfold efficacy in killing cancer compared with conventional drug delivery.

PHYSICAL SCIENCES–ONCOLOGY CENTERS

In recent years, new research centers for the study of physical oncology have arisen all over the country with the mission of facilitating advances in the study of how first principles of physical science can be applied to the study of cancer. Physical Sciences–Oncology Centers (http://physics.cancer.gov/centers/), operated in part by research universities and the National Cancer Institute of the National Institutes of Health, engage in various aspects of this mission. Ongoing and recent work at Physical Sciences–Oncology Centers that pertains to the content of this book includes understanding the evolution of cancer resistance to chemotherapy (Princeton University), the study of physical mass transport processes in cancer (Methodist Hospital Research Institute, Houston), the modeling of cancer growth and response to chemotherapy (University of Southern California), and the study of cellular cancer genesis using mathematical modeling (H. Lee Moffitt Cancer Center).

The principal authors of this book, based at the University of Texas Health Science Center at Houston McGovern Medical School and the Brown Foundation Institute for Molecular Medicine, and at the MD Anderson Cancer Center—all within the Texas Medical Center in Houston—are contributing to physical oncology through novel approaches in mathematical modeling of tumor growth, drug uptake, and cellular death rates. These are paired with the use of common clinical tests such as contrast-enhanced computed tomography scans, magnetic resonance images, and histopathology, where new imaging-based biomarkers are discovered, which then effectively become input parameters needed to inform patient-specific mathematical models for predicting chemotherapy and other treatments' efficacy—even predictions of survival. Prediction accuracy has already been tested and confirmed in both "retrospective" and "prospective" patient studies in the form of significant correlations between model results and measures of patient outcomes. Such breakthroughs offer genuine hope for significant improvements in strategies for fighting cancer once the mathematical models have been refined to achieve satisfactory individual patient fidelity. Findings made in current research and reported in peer-reviewed publications suggest that clinical requirements for successfully implementing the science are already housed in most cancer treatment facilities; additionally, it is possible that the science can be applied to a wide variety of cancer types. In a brief summary, theoretical work is currently being applied to the study of colorectal cancer metastatic to the liver, breast cancer, pancreatic cancer, brain cancer, and lymphoma, with future "moon shot" studies underway designed to develop mechanistic strategies for modeling and treating these and other forms of cancer according to first principles of physical science.

TIMELINESS

Why are these advances timely? While both cancer incidence rates and investments in research and development are increasing, so is the cost of treatment; *inversely*, access to health providers decreases as the aging population and the number of cases increases. Our system demands greater efficiency, better patient outcome, and a clearer or transformed path for physicians in treating patients. Oncologists working together with pathologists, physicists, mathematicians, and engineers can develop a system for precise diagnosis

and patient-specific drug therapy that can effectively treat cancer and cure patients while increasing efficiency. The hope is that this book will create more awareness of these advances, demonstrate how this "physics and cancer" approach can address some of the major questions and barriers in cancer research and treatment through related modeling work, and finally, provide enough evidence for the public to better understand this approach, so that in the years to come, we may start implementing systems that lead to better quality of life overall.

Hopefully, this book provides the reader inspiration for further inquiry into the application of physical science to oncology. Our primary goal is to shed light on the evidence supporting physical theories of cancer growth, metastasis, and treatment, so progress may be made in increasing interdisciplinary collaboration that aims to eradicate cancer. With enough cooperation in the areas of cancer diagnosis, treatment design, and drug delivery, we can work together to improve the lives of millions of people who face one of life's greatest challenges.

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Contributors

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Jason Fleming, MD, attended Vanderbilt University as an undergraduate and received his MD from the University of Tennessee Center for Health Sciences School of Medicine in 1990. In 1999, Dr. Fleming completed a surgical oncology fellowship at MD Anderson Cancer Center and joined the faculty of the University of Texas Southwestern, where he became associate professor with tenure in 2005. Dr. Fleming returned to MD Anderson Cancer Center in 2006 to join the Pancreas Cancer Program. His clinical and research interests are solely focused on pancreatic cancer. These include the molecular genetics of pancreatic cancer metastasis, the development of early detection methods, and the preclinical and clinical testing of novel treatments for this disease.

John Lowengrub, PhD, who holds a PhD in mathematics from New York University, is a Chancellor's Professor of Mathematics, Biomedical Engineering, and Chemical Engineering and Materials Science at the University of California, Irvine. Dr. Lowengrub is also a coleader of the Systems, Pathways and Targets Program at the Chao Family Comprehensive Cancer Center at the University of California, Irvine. His research focuses on the use of mathematical modeling to understand how misrelated feedback signaling, metabolic reprogramming, and interactions between a vascularized tumor and its microenvironment can drive tumor progression and morphology and dictate the optimal course of treatment.

Geoffrey V. Martin, MD, who completed bachelor's degrees in chemistry, math, and physics from Ohio State University and holds an MD from the University of Cincinnati, is a radiation oncology resident at the University of Texas MD Anderson Cancer Center. His research has focused on the development of mathematical models to describe oncologic