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# Mathematical Oncology 2013

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ISSN 2164-3679

ISBN 978-1-4939-0457-0

DOI 10.1007/978-1-4939-0458-7

Springer New York Heidelberg Dordrecht London

ISSN 2164-3725 (electronic)

ISBN 978-1-4939-0458-7 (eBook)

Library of Congress Control Number: 2014951354

Mathematics Subject Classification (2010): 92-XX, 92B05, 97M60, 37N25, 35Q92, 00A69, 92C37, 92B99

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Printed on acid-free paper

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# Preface

After a long incubation period in which only sporadic investigations were devoted to the applications of mathematics and physics to the study of tumors (see, e.g., the work of Doll and Armitage on tumorigenesis in the 1950s), in the early 1970s, the papers by Norton and Simon and by Greenspan were a turning point in the scientific interest on tumor modeling.

In this first phase, the majority of models were essentially population-based models. Although many important results were established—for example, the possible onset of a dynamic equilibrium between a tumor and the immune system, only recently experimentally confirmed—the majority of studies did not directly rouse the attention of the oncology world, with the remarkable exception of the papers by Goldie and Coldman on the Darwinian emergence of resistance to chemotherapy and of the above-mentioned works by Norton and Simon.

The pioneering work by Greenspan, where the modeling also involved physico-chemical aspects of tumor growth, remained almost isolated for two decades. Finally, in the 1990s, a large number of mathematical models were devoted to describing the spatial growth of tumors, with approaches ranging from simple diffusive models to complex multiphase mechanical models. Later, the interactions of the tumor with the immune system and with the angiogenesis process also became the object of extensive theoretical research.

The follow-up in the medical world, however, remained rather scarce. This is due mainly to the limited number of joint works between biomedical and biomathematical researchers, although there have been some isolated cases of theoretical scientists—for example, R. Jain—who have been so deeply involved in biological research as to become influential biomedical research leaders.

Things are, however, rapidly changing. In recent years, two major phenomena have given great momentum to research in mathematical oncology.

The first is of a technical nature—that is, the birth of multiscale modeling—where microstructures such as individual cells can be explicitly represented.

The second, and most important from a “sociological” point of view, is that a large number of biomedical scientists are becoming directly involved in quantitative research due to the need to decipher an ever larger mass of “omics” data (mainly from genomics and proteomics).

The increasing number of modeling papers published in journals devoted to oncology, and in particular the opening of the new section on mathematical oncology in *Cancer Research*, one of the most important basic research journals on cancer, is the most important evidence that tumor modeling is slowly but significantly impacting the oncology world.

Moreover, the fact that in these years a number of research groups—often led by biomedical scientists turned to computational sciences—are being “embedded” in research medical centers is further evidence of the scientific interest of the topic.

On the other hand, from the point of view of mathematicians, there is an increasing awareness that the applications of both classical mechanics and nonlinear analysis to the study of tumor growth translate into new challenging problems at the frontier of contemporary mathematics.

This is mirrored by the increasing number of papers on mathematical oncology that are published in mathematical journals.

This book is entirely composed of in-depth contributions reviewing personal research results of outstanding scientists in the field. It is aimed at providing both experienced researchers and the increasing number of newcomers with a careful selection of state-of-the-art results.

Many new researchers who are entering the field of mathematical oncology often experience significant difficulties. Starting work in mathematical cancer modeling, indeed, is a slow and difficult process that requires the acquisition of a special *forma mentis* that goes well beyond that of the usual applications of mathematics and physics, where the learning can be limited to the acquisition of basic concepts and methods of the domain of application. In tumors, on the contrary, many apparently different phenomena are interrelated, and all of them are strictly linked to clinical issues. We believe that in the chapters of this book the authors have successfully transferred not only their results but also, most importantly, their way of seeing and approaching problems.

In order to cope with the state of the art, the book covers different biological subjects and mathematical approaches.

As far as the tumor onset and early phases of tumor growth are concerned, Bortolusso and Kimmel investigate the interplay of spatiality and stochasticity in the process of tumorigenesis by stressing some exquisitely stochastic spatiotemporal phenomena without deterministic counterpart and the role of cellular cooperation. Fasano, Bertuzzi, and Sinisgalli focus on the role of the conservation laws of mathematical physics to decipher the dynamics of the early phases of neoplasias by means of the analysis of some free-boundary problems for partial differential equations. Techniques of nonlinear mathematical physics and statistical mechanics, as well as WKB approximations, are used by Ben Amar to treat two typical features of melanomas: morphological instabilities and phase

segregation. In her contribution, Ben Amar also provides an overview of the historical development of “mathematical biophysics” of tumors.

With regard to the intercellular interplay between tumor cells and other cells in the environment, Dyson and Webb extend their models that include the “cell cycle age” of tumor cells by also including the cell-to-cell adhesion theory by Painter and Sherratt and provide a complete mathematical analysis of the resulting model by using the theory of semigroups. Lachowitz, Dolfin, and Szymanska, in the framework of the kinetic theories of tumor-immune system interplay, provide a theoretical framework for the construction of micro- and meso-models that may be related to macroscopic models and that are able to take into account various additional aspects of the microscopic scale. Kareva, Wilkie, and Hahnfeldt review the role of the interplay of tumors with their microenvironment: This includes interplay with endothelial cells in the process of angiogenesis and with the immune system, as well as the role of recycling of nutrients.

Finally, as far as the modeling of antitumor therapies is concerned, de Pillis and Radunskaya review their models of tumor-immune systems and immunotherapies, as well as the effect of chemotherapies on normal, tumor, and immune cells. A variety of approaches are used by de Pillis and Radunskaya, ranging from ordinary differential equations to cellular automata. A hybrid multiscale framework—also including cell cycle dynamics of individual cells—is adopted by Powathil and Chaplain to model the spatiotemporal response of tumors to chemotherapy alone or in combination with radiotherapy. Clairambault reviews the chronobiology of tumor growth and antitumor therapies, i.e., he focuses on how to “exploit” the influence of circadian rhythms on the proliferation of tumors in order to maximize the effects of chemotherapies. Methods and tools of optimal control theories are introduced by Ledzewicz and Schaettler in the final chapter, which reviews the application of these theories to optimize antitumor treatments under various biologically meaningful conditions.

We end the preface with a brief consideration. The field of mathematical modeling of tumor growth and of related therapies has in recent years been named “mathematical oncology.” From the point of view of both a layman and of a pure mathematician, this could seem bizarre or as an overstatement. However, as we hope this book will demonstrate, this term is not an exaggeration as all major mathematical tools of analytical and computational mathematics can be fruitfully “exploited” in order to investigate the many problems of oncological interest—methods ranging from ordinary differentialequations to the statistical mechanics of phase transitions, from the theory of semigroups to Gillespie’s algorithm, from cellular automata to the geometric theory of optimal control, etc.

However, it is not only a question of adopting analytical theories or computational tools to tackle biological problems from a physical-mathematical point of view. No! The first challenge in mathematical oncology is for biological problems to provide an impetus to develop or substantially improve new mathematical theories and computational algorithms. This is exactly what happened to other related or unrelated branches of mathematical biology, as may be seen by taking a historical perspective of the developments of dynamical systems theory and computational

sciences, as well as classical and computational statistics. The second challenge is, of course, to develop and increment the collaboration with biomedical scientists. This point has been considered several times in the past but here we want to also stress that a major effort is needed from the didactic point of view. Indeed, a different and more integrated approach to mathematical oncology might lead to a new generation of theoretical biologists with backgrounds equally divided between quantitative sciences and biomedicine.

Lyon, France  
Rome, Italy  
Jan 15, 2014

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