The Rise of Mathematical Oncology

Kiran George, R. Malathi, and J. Krishnan
Department of Electronics and Instrumentation Engineering, Bioengineering Group, Annamalai University, Annamalai nagar-608 002, Tamil Nadu, India.
Email: kirangeorge01@yahoo.com, {vsmalu, krishnanj70}@gmail.com

Nisha Susan Thomas
Department of Biochemistry and Biotechnology, Cancer Biology Group, Annamalai University, Annamalai nagar-608 002, Tamil Nadu, India.
Email: nishakiran31@gmail.com

***Abstract*—Cancer research has produced tremendous basic and clinic levels of information. So far, to validate this information has become a most challenging task for researcher and clinician. However the information validated by mathematical models provides an opportunity for the researcher and clinician. The field of mathematical oncology has received great attention and increased enormously in the ongoing battle against cancer. This short review comprises the complexity of mathematical oncology and the new strategy of hybrid mathematical model of tumor growth. In addition we suggest how these new directions could contribute to addressing the current challenges of understanding of tumor mechanisms.**

***Index Terms*—complexity of mathematical oncology, multiscale modeling, modeling techniques, drug modeling.**

I. Introduction

Mathematical modeling of cancer is still in its infancy but it's not new, it goes back over half a century, but experimental oncologists have largely ignored it. Today, the field of mathematical oncology has received great attention and increased enormously, but over-optimistic estimations about its ability have created unrealistic expectations. Mathematical models are too simplistic and cannot model realistically a disease as complex as cancer. However what we understand about cancer is extremely complex, thus difficult to model. Mathematical modeling provides a rigorous framework for understanding disease evolution and for testing biological hypotheses. By translating biological complexity and translating biological components of cancer development into mathematical terms, the modeling process describes cancer-related phenomena as a complex set of interactions with the emerging outcome predicted by mathematical analysis that defines the field of mathematical oncology. Computational oncology uses mathematical techniques to extract information from large datasets (such as transcriptome, proteome, or imaging data) where extensive computational resources are utilized either by means of statistical and [1] bioinformatics methodologies or for the study and quantitative prediction of tumor behavior by means of data-driven models. Physical oncology views tumors as complex systems that result from biophysical interactions and processes. This leads to mechanism-driven models that aim at the identification and analysis of biophysical laws to quantify and predict cancer progression.

In this contribution, we aim at equipping the reader with a perspective of mathematical modeling in cancer. We hope that the reader will obtain an insight that stretches far beyond actual examples. First, we discuss about complexity of mathematical biology. Then, we end this contribution by a discussion of mathematical modeling of cancer.

II. Is Mathematical Oncology So Complex?

Cancer mechanisms have been designed by evolution; they are often complicated, subtle, and very special or unusual. To understand them, one must immerse oneself in the messy, complex details of the biology; that is, you must work directly with biologists. To model cancer system, one should understand how the behavior of the system at one level arises from structures and mechanisms at lower levels. How does the biochemistry of a cell allow it to receive signals, process them, and send signals to other cells? How does the behavior of groups of cells in the immune system give rise to the overall immune response? In the case of tumor these questions are even more difficult, because the objects at the lower level have been designed by evolution to have just the right special properties to give rise to the behavior at the higher level. And it is usually not easy to decide what the important variables are at the lower level. If your model has considered only few parameters, then you will not be studying the real tumor mechanism. If your model has too many, it may be so complicated. You need to be able to deduce the consequences from the assumptions. That is what mathematicians are good at. Finally, it is characteristic of living systems that the parts themselves are not fixed but ever changing, sometimes even affected by the behavior of the whole system. A researcher who uses animal models in his research work gets very unusual results, and the results were not repeatable week to week. For all these reasons, biological data must be approached cautiously and critically [1].

Manuscript received June 28, 2014; revised September 4, 2014.

doi: 10.12720/jomb.4.4.293-296

Since tumor systems are so diverse and everything seems to interact with everything else, there are many possible measurements, and enormous amounts of data can be produced. Don't do mathematical oncology to satisfy a desire to find universal structural relationships; you'll be disappointed. Don't waste time developing methods of mathematical biology; the problems are too diverse for central methods. What's left is the biology. You should do mathematical oncology only if you are deeply interested in the science itself. In complex biological problems, you must have ideas about how the structure of the whole is related to the assumptions about the parts. Thinking through such ideas and proving the consequences of the assumptions are important ways to model the whole cancer systems.

III. An Exciting New Development

Cancer modeling comes in a wide variety of styles. Indeed, it can involve almost any type of applied mathematics. There is a long tradition of mathematical models of tumor growth, ranging from simple temporal population dynamic models to full three-dimensional spatiotemporal models [2]. Over the past 10 years or so there has been a rapid growth in deterministic reaction–diffusion models that explicitly consider the tumor as a single continuous density varying in both space and time. Generally these have been used to model the spatial spread of tumors in the form of one-dimensional invading waves or as two-dimensional patterns of cancer cells [3]-[5]. Other numerical approaches have been considered [6]-[8], but these still treat the tumor as a continuous mass. Although all these models are able to capture the tumor structure at the tissue scale, they fail to describe the tumor at the cellular level. The development of single-cell-based modeling techniques provides such a description and allows one to easily model cell–cell and cell–microenvironment interactions. Several different individual-based models of tumor growth have been developed recently, including cellular automata models [9]-[13], potts models [14]-[16], agent-based models [17] or lattice-free models [18], [19]. Ordinary differential equations can be used to study the growth of tumor cell populations, often leading to a conclusion of Gompertzian growth. Partial Differential Equation (PDE) model using cell densities and nutrient concentrations as state variables can be used to analyze various spatiotemporal phenomena. Individual and agent-based models that treat cells as discrete objects with predefined rules of interaction can offer an improvement over PDE methods in some situations. Agent-based systems are one of many computationally intensive methods and are often components of multiscale models. Many of these models are also hybrid by definition and couple the advantages of individual-based models, representing cells, with continuous reaction–diffusion models that better represent environmental variables such as nutrients or tissue. Such hybrid models also allow one to link multiple models across multiple spatial scales, from genes to organ. The ability to bridge scales makes them ideal for cancer modeling as they effectively compartmentalize each scale and allows processes to bridge these compartments [10], [11], [8], [12], [14], [15], [19]. Therefore, these so-called multiscale models are far more accessible to the biologist both in terms of understanding and in terms of experimental validation.

IV. Multiscale System Modelling

Tumor cells have heterogeneous nature whose growth fully relay on surrounding microenvironment and cell interactions. This interactive processes act together to control cell proliferation, apoptosis, and migration. These dynamical interactions cannot be investigated completely through biological experiments; rather they must be computed with mathematical models, which guides through new experimental design and interpretation. Mathematical modeling helps the understanding of cancer initiation and progression by investigating cancerous system as a whole by analyzing how individual components interact to give rise to the function and behavior. Decades of dedicated efforts of modelers developed multiple biological scales (different spatial scales and temporal scales), which play an important role in moving the field of cancer systems biology toward clinical implementation. Present *in silico* cancer models are having the capability to (a) simulate experimental procedures, to optimize and predict clinical therapies and outcome, and (b) test and refine medical hypotheses [20].

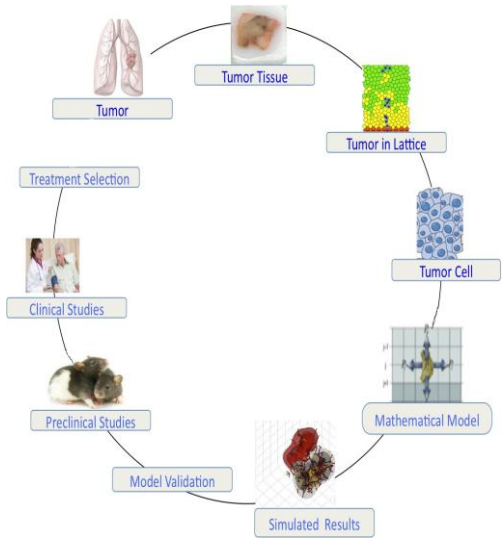

Figure. 1. Multi scale model of tumor mechanisms

Multiscale cancer modeling encompasses many different spatial and temporal scales, ranging from nanoseconds to years in time and nanometers to centimeters in scale. Developing more realistic and more accurate predictive model is a challenging task for the modelers. The main reason is that, in multiscale modeling more number of model parameters is to be considered as these parameters will have to be defined, quantified, and frequently adjusted according to data from the literature and from experiments. Besides, if the model links bi-directional, need to be higher- and lower-level variables, parameters, and functions characterizing

the model are influenced by one another. When developing multiscale modeling four main biological spatial scales are to be accounted: atomic, molecular, microscopic, and macroscopic. Each of these spatial scales have multiple temporal scales, normally atomic scale (intracellular) generally happen much faster than those at a macroscopic scale (organ); The time and space scales vary together, with nanoseconds to year at the time scale corresponding to nanometer to centimeter at the space scale [20].

V. Modeling Techniques

To design cancer system, discrete, continuum, or hybrid, modeling techniques are used in cancer system biology.

A. Continuum Model

Continuum technique is good for larger scale system often a lesser choice in the exploration of tumor cell. Continuum model takes into account variables like cell volume, fractions, density, and cell substrate concentrations, (e.g., nutrient, oxygen, and growth factors). This model is considered when studying the effects of genetic, cellular, and microenvironment characteristics on overall tumor behavior. But continuum models cannot be used to study an individual cell dynamics and discrete events. Discrete models are suitable for addressing these shortcomings because they function at the individual cells in space and time.

B. Discrete Model

Discrete models can easily incorporate on studying carcinogenesis, genetic instability, natural selection, cell-cell and cell-matrix interaction mechanisms. [21]. However, discrete techniques also have drawbacks, which limit the model to a relatively small number of cells. As a result, a typical discrete model is usually designed with a lower domain size [22]. For these reasons, cancer modelers are progressing to hybrid techniques that combine both continuum and discrete descriptions [22]-[24].

C. Hybrid Model

In hybrid models cells are taken into account as discrete in some parts of the domain and as a continuum in others [25]. Hybrid models have the potential to couple biological phenomena from the atomic scales to those at tumor scale. As in biological systems, the *in silico* cell in the hybrid model can perform fundamental intrinsic core processes, specifically ones known to drive cancer invasion. The hybrid model has great predictive power, even though these core processes are not specified in molecular detail [9]. Such molecular details could be incorporated at a later date to refine the effects of particular core processes (such as the cell cycle, or cell–matrix interactions), owing to the open multiscale architecture of hybrid model. In fact, current hybrid model predictions have indicated molecular processes that are in need of better specification and/or parameterization.

In the hybrid model, we further focus on the interface between cancer cell phenotype and microenvironment. Again, this captures a biological reality, because the interaction between the cell and its microenvironment is known to have a crucial role in cancer progression [26]. Therefore, in the model cells are represented as points on a lattice that represents the tissue microenvironment. Each *in silico* cell has a phenotype that comprises a set of traits that include, but are not limited to, proliferation, migration, adhesion and nutrient consumption. By representing the microenvironment as a lattice on which cells grow and interact, we can implement multiple environmental factors such as density of extracellular matrix (ECM) and the concentrations of nutrients and proteases. How these factors change over time on the lattice is then defined by a set of mathematical equations. Hybrid models are divided into two categories: composite hybrid modeling and adaptive hybrid modeling. In composite hybrid models, individual cells are treated discretely but interact with other chemical and mechanical continuum fields. In adaptive hybrid models, both discrete and continuum representations of cells are chosen dynamically and adaptively where appropriate [20]. Overall, the hybrid model provides a framework for quantitative analyses of cancer progression and is endowed with an intuitive link between in silico and real-life cancer biology.

VI. Modeling of Drug Delivery and Impact on Tumor Growth

Vast amounts of research directed towards the complexity of the disease and the understanding of the pathophysiology of cancer, its progression, mechanisms of drug resistance at various scales, as well as the optimization of drug dosage for effective treatment and prevention strategies. Due to the nature of experimental investigations it is difficult to assign quantitative weights to diffusion gradients of both drug and micro environmental substrates that induce physiologic resistance and decrease the efficacy of drug therapy, which can result in a poor response to chemotherapy from a combination of diminished drug delivery and lack of drug activity [27]. To understand the data produced in quantity by researchers and clinicians the conceptual framework is necessary. The overall tumor mechanisms and its treatment might benefit from an evaluation of mathematical modeling. This model can be coupled with biological experiments and clinical trials. Mathematical modeling can provide valuable information to plan effective biological experiments for testing theoretical hypotheses. Data from biological experiments provide necessary constraints for choosing appropriate model parameters. Therefore, pure theoretical or experimental investigations alone have inherent flaws and limitations. However a critical drawback of theoretical models is their plasticity in uncritically recapitulating training data, without regard to the model's actual validity and predictive capability [28].

VII. Conclusion

Mathematicians are not going to find a cure for cancer. However, they are needed in cancer research to help for analyzing the enormous amount of data generated by the various experiments and clinical trials being conducted around the world. They are also needed to develop and validate new mathematical models. These models can in turn be used to run simulations, test theories, and to determine the optimum dosage of new medicines being developed. Today, there does not exist any good mathematical description of biological properties. In fact, it seems like the available mathematical tools are not appropriate for the task. Through the search for a good mathematical model of cancer, it is actually predicted that fundamentally new mathematics will be developed.

ACKNOWLEDGMENT

We would like to thank UGC- BSR for supporting this research.

REFERENCES

[1] C. M. Reed, "Why is mathematical biology so hard?" *Notices of the AMS*, vol. 51, pp. 338-342, 2004.
[2] R. P. Araujo and D. L. McElwain, "A history of the study of solid tumor growth: The contribution of mathematical modeling," *Bull. Math. Biol*., vol. 66, pp. 1039–1091, 2004.
[3] R. A. Gatenby, *et al*., "Cellular adaptations to hypoxia and acidosis during somatic evolution of breast cancer," *Br. J. Cancer*, vol. 97, pp. 646–653, 2007.
[4] A. R. Anderson, M. A. J. Chaplain, E. L. Newman, R. J. Steele, and A. M. Thompson, "Mathematical modeling of tumor invasion and metastasis," *J. Theor. Biol*., vol. 2, pp. 129–154, 2000.
[5] R. K. Sachs, M. Chan, L. Hlatky, and P. Hahnfeldt, "Modeling intercellular interactions during carcinogenesis," *Radiat. Res*, vol. 164, pp. 324–331, 2005.
[6] P. Macklin and J. Lowengrub, "Evolving interfaces via gradients of geometry-dependent interior Poisson problems: Application to tumor growth," *J. Comp. Phys*, vol. 203, pp. 191, 2005.
[7] X. Zheng, S. M. Wise and V. Cristini, "Nonlinear simulation of tumor necrosis, neo-vascularization and tissue invasion via an adaptive finite-element/level-set method," *Bull. Math. Biol*, vol. 67, pp. 211–259, 2005.
[8] H. B. Frieboes, *et al*., "Computer simulation of glioma growth and morphology," Neuroimage, vol. 37, pp. S59–S70, 2007.
[9] A. R. Anderson, A. M. Weaver, P. T. Cummings, and V. Quaranta, "Tumor morphology and phenotypic evolution driven by selective pressure from the microenvironment," *Cell*, vol. 127 pp. 905–915, 2006.
[10] A. R. Anderson, "A hybrid mathematical model of solid tumor invasion: The importance of cell adhesion," *Math. Med. Biol*, vol. 22, pp. 163–186, 2005.
[11] P. Gerlee and A. R. Anderson, "An evolutionary hybrid cellular automaton model of solid tumor growth," *J. Theor. Biol*, vol. 246, pp. 583–603, 2007.
[12] T. Alarcon, H. M. Byrne, and P. K. Maini, "A multiple scale model for tumor growth," *Multiscale Modeling Simulation*, vol. 3, pp. 440–475, 2005.
[13] J. Smolle and H. Stettner, "Computer simulation of tumor cell invasion by a stochastic growth model," *J. Theor. Biol*, vol. 160, pp. 63–72, 1993.
[14] Y. Jiang, J. Pjesivac-Grbovic, C. Cantrell, and J. P. Freyer, "A multiscale model for avascular tumor growth," *Biophys. J*., vol. 89, pp. 3884–3894, 2005.
[15] E. L. Stott, N. F. Britton, J. A. Glazier, and M. Zajac, "Stochastic simulation of benign avascular tumor growth using the Potts model," *Math. Comput. Modeling*, vol. 30, pp. 183, 1999.
[16] S. Turner and J. A. Sherratt, "Intercellular adhesion and cancer invasion: A discrete simulation using the extended Potts model," *J. Theor. Biol*, vol. 216, pp. 85–100, 2002.
[17] L. Zhang, C. A. Athale, and T. S. Deisboeck, "Development of a three-dimensional multiscale agent-based tumor model: Simulating gene–protein interaction profiles, cell phenotypes and multicellular patterns in brain cancer," *J. Theor. Biol*, vol. 244, pp. 96–107, 2007.
[18] D. Drasdo and S. Hohme, "Individual-based approaches to birth and death in avascular tumors," *Math. Comput. Modeling*, vol. 37, pp. 1163, 2003.
[19] K. A. Rejniak, "An immersed boundary framework for modeling the growth of individual cells: An application to the early tumor development," *J. Theor. Biol*, vol. 247, pp. 186–204, 2007.
[20] T. S. Deisboeck, Z. Wang, P. Macklin, and V. Cristini, "Multiscale cancer modeling," vol. 13, pp. 127-55, 2011.
[21] G Schaller, Meyer, and M. Hermann, "Continuum versus discrete model: A comparison for multicellular tumour spheroids," vol. 364, pp. 1443-64, 2006.
[22] A. R. Anderson and V. Quaranta, "Integrative mathematical oncology," *Nat Rev Cancer*, vol. 8, pp. 227-34, 2008.
[23] J. S. Lowengrub, H. B. Frieboes, F. Jin, Y. L. Chuang, *et al.*, "Nonlinear modeling of cancer: bridging the gap between cells and tumors," *Nonlinearity*, vol. 23, pp. R1-R9, 2010.
[24] Z. Wang and T. S. Deisboeck, "Computational modeling of brain tumors: Discrete, continuum or hybrid?" *Sci. Model. Simul*, vol. 15, pp. 381-393, 2008.
[25] J. M. Osborne, A. Walter, S. K. Kershaw, G. R. Mirams, A. G. Fletcher, *et al*., "A hybrid approach to multi-scale modelling of cancer," *Philos Trans A Math Phys Eng Sci.*, vol. 368, no. 1930, pp. 5013-5028, 2010.
[26] M. M. Mueller and N. E. Fusenig, "Friends or foes - bipolar effects of the tumor stroma in cancer," *Nature Rev. Cancer*, vol. 4, pp. 839–849, 2004.
[27] V. Quaranta, A. M. Weaver, P. T. Cummings, and A. R. A. Anderson, "Mathematical modeling of cancer: The future of prognosis and treatment," *Clinica Chimica Acta*, vol. 357, pp. 173–179, 2005.
[28] S. Sanga, J. P. Sinek, H. B Frieboes, M. Ferrari, J. P. Fruehauf, and V. Cristini, "Mathematical modeling of cancer progression and response to chemotherapy," *Expert Rev. Anticancer Ther*, vol. 6, pp. 1361-1367, 2006.

Kiran George is a Ph.D. student at Annamalai University- India. His Research focuses on integration of Mathematical modeling and in vitro approaches of tumor mechanisms.

Dr. R. Malathi is a Professor of Instrumentation Engineering at Annamalai University- India. She received her Ph.D. from IIT Madras. Her Research focuses on the modeling of Cardiac diseases, Eye cell modeling and Cancer cell modeling

Dr. J. Krishnan is a Professor of Instrumentation Engineering at Annamalai University-India. He received his Ph.D. from IIT Karagpur. His Research focuses on the modeling of Cardiac Memory and Cardiac Arrhythmias and Eye cell modeling

Nisha Susan Thomas is a Ph.D. student at Annamalai University, India. Her Research focuses on Cancer biology and designing targeted cancer drug therapy.

