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# APPLICATION OF ECOLOGICAL AND MATHEMATICAL THEORY TO CANCER: NEW CHALLENGES

According to the World Health Organization, cancer is among the leading causes of morbidity and mortality worldwide. Despite enormous efforts of cancer researchers all around the world, the mechanisms underlying its origin, formation, progression, therapeutic cure or control are still not fully understood. Cancer is a complex, multi-scale process, in which genetic mutations occurring at a sub-cellular level manifest themselves as functional changes at the cellular and tissue scale.

In recent years, cancer research became an interdisciplinary field and mathematics started to play an important role in understanding and modeling complex biological processes of cancer initiation and progression and in development and analysis of anti-cancer therapies.

In May 2014, a group of applied mathematicians and biologists met in the National Institute for Mathematical Sciences in Daejeon, South Korea to discuss current state-of the-art and challenges in mathematical and computational modeling of cancer-related processes on cellular and tissue levels, and development and analysis of strategies for cancer treatment.

Among the goals of the workshop "Application of ecological and mathematical theory to cancer: new challenges" were:

- to analyze computational and analytic approaches to mathematical modeling of tumor growth;
- to discuss *in vitro* experiments required to confirm results of mathematical analysis of cancer models;
- to improve biochemical/biomechanical understanding of fundamental mechanism of tumor growth through the analysis of signaling pathways;
- to apply concepts from epidemiology and ecology to describe the processes responsible for formation of neoplasms;
- to present novel strategies for anti-cancer therapies based on rigorous mathematical approach and confirmed by the experimental data.

The Special Issue of the Mathematical Biosciences and Engineering presents selection of papers based on the topics discussed during the workshop. This volume is not intended as a comprehensive proceedings of the workshop. However, the papers selected for the Special Issue showcase the most important challenges in oncology, such as prognostic screening, monitoring of tumor cell response to various treatments, inter- and intra-cellular signaling pathways in cancer cells, evolutionary cancer cell biology, and interactions of tumors with their microenvironment. One of major topics of the workshop was modeling of cancer treatment. The number of papers discuss surgical-, chemo-, radio-, immuno-, and oncolytic virus treatments for various cancers and related issues. From mathematical point of view, the papers in this collection represent the most advanced modeling techniques based on ordinary and partial differential equations as well as individual-cell-based models and hybrid approach. All manuscripts underwent a rigorous review process. It was

a hard work, but also a rewarding process, as the joint efforts of the authors and the referees led to significant improvements and enrichment of the papers.

The papers included in the Special Issue can be divided into three groups: (i) cancer modeling; (ii) cancer treatment; and (iii) micro- and macro biological processes that play important role in tumorigenesis.

*The following papers discuss the various aspects of modeling cancer growth and progression:*

Hybrid discrete-continuous models of tumor growth, provide a flexible framework that enables to model alterations of cell-level properties and detailed descriptions of the interaction with the tumor environment, yet retain the computational advantages of continuum models where appropriate. *Kim and Othmer* review this approach and discuss its applications to modeling tumor growth and invasion in breast cancer and glioblastoma.

Glioblastoma multiforme is an aggressive fatal brain cancer. It is characterized by both rapid proliferation and large amounts of migration, which contributes to the difficulty of treatment. Previous models of this type of cancer growth often include two separate equations to model proliferation or migration. *Stepien* et al. propose a single equation model which uses density dependent diffusion to capture the behavior of both proliferation and migration. The authors analyze the model to determine the existence of traveling wave solutions. To prove the viability of the density-dependent diffusion function chosen, the model is validated using the *in vitro* experimental data.

*Lee* et al. reformulate the classical diffuse interface model of tumor growth based on the fourth-order Cahn-Hilliard equation via the second-order Allen-Cahn equation. With help of the specially designed computationally effective hybrid numerical method, the authors show that the new model properly represents the number of experimentally confirmed features such as distributing excess mass from inside of the tumor to its boundary.

Invasion and metastasis are the main cause of death in cancer patients. The initial step of invasion is the degradation of extracellular matrix (ECM) by primary cancer cells in a tissue. In his paper, *Ichikawa* investigates the role of enzymes, known as metalloproteinases, and their inhibitors in the degradation of ECM. The author compares the number of strategies aimed to avoid such degradation and eventually block cancer invasion and metastasis.

*The number of cancer therapies have been modeled and analyzed using computational techniques in the papers below:*

The cancer-immune interaction is a fast growing field of research in mathematical biology, aimed at modeling and simulation of the activators of immune system pushing it to fight cancer more efficiently. *Friedman and Liao* discuss how the interaction between T cells and cancer cells may either slow or promote tumor growth. Their mathematical model consists of a system of PDEs and includes the tumor cells and T cells densities and immune regulators such as IL-27, IL-10, and IFN-$\gamma$. The model is validated experimentally on mice and the authors use it to suggest effective schedules for immunotherapy treatment.

Apoptosis resistance is a hallmark of human cancer, and tumor cells often become resistant due to defects in the programmed cell death machinery. Targeting key apoptosis regulators to overcome apoptotic resistance and promote rapid death of tumor cells is a new strategy for cancer treatment, either alone or in combination with traditionally used anti-cancer drugs that target cell division. *Cook*

et al. present a multiscale modeling framework involving an intracellular ODE-based model of cisplatin uptake coupled with another ODE model representing Bcl-xL-BM-1197 reactions. The authors investigate the synergism between traditional chemotherapy and BM-1197 targeted therapies aimed at critical regulators of apoptosis.

Oncolytic viruses (OVs) are used to treat cancer, as they selectively replicate inside tumor cells and destroy them. So far, the efficacy of this process is limited. However, new OVs are being designed to mediate tumor cell release of cytokines and co-stimulatory molecules, which attract cytotoxic T cells to target tumor cells, thus increasing the tumor-killing effects of OVs. To further promote treatment efficacy, OVs can be combined with other treatments. *Wares* et al. develop a mathematical model consisting of a system of ODEs and fit it to the experimental data. They use the model to determine the effect of varying doses of OV and test alternative treatment strategies.

Metronomic chemotherapy is the regular, almost continuous administration of chemotherapeutic agents at low dose, possibly with small interruptions to increase the efficacy of the drugs. There exists medical evidence that metronomic therapy has both anti-angiogenic and immune stimulatory effects. Using an optimal control theory, *Ledzewicz* et al. develop a 3-compartment model for metronomic chemotherapy involving cancerous cells, the tumor vasculature and tumor-immune system interactions. A mathematical model for angiogenic signaling is combined with the classical equations for tumor immune system interactions to capture major effects of low dose chemotherapy. This model exhibits bistable behavior with the existence of both benign and malignant locally asymptotically stable equilibrium points.

*The processes involved in tumorigenesis on both microscopic (inter- and extracellular) and macroscopic (tissue and living organisms) levels are modeled in the the following papers:*

*Aguda* et al. propose the hypothesis that for a particular type of cancer there exists a key pair of oncogene and tumor suppressor gene that is normally involved in strong stabilizing negative feedback loops of molecular interactions, and it is these interactions that are sufficiently perturbed during cancer development.

In recent years, protein-protein interaction (PPI) networks associated with various diseases have gained prominence as an actively developing area of research. *Hinow* et al. investigate algebraic and topological properties for PPI networks of 11 human cancers derived from the Kyoto Encyclopedia of Genes and Genomes database. The authors have found a strong correlation between relative automorphism group sizes and topological network complexities on the one hand and five year cancer patient survival probabilities on the other hand. Moreover, they identify several protein families that are repeated motifs in many of the cancer pathways.

Single-cell organisms use a variety of strategies for translocation, including crawling, swimming, drifting with the surrounding flow, and others. Some, such as bacteria, use agella, and others, such as paramecia, use cilia to swim, and both types use only one mode. *Wang and Othmer* study the spatio-temporal motion of small organisms in viscous fluids and show how the efficiency of movement depends on the geometric pattern of shape changes. The authors compare the efficiency of three models of shape changes that comprise a series of linked spheres, which can change their separation and/or their size, and show how these modes are used in different ways.

The vast majority of solid tumors arise in epithelia. Hence much research has been dedicated to investigation of the the growth, renewal and regulation of these tissues. In their paper, *Maclaren* et al. review a number of mathematical and computational approaches used to model epithelium. They compare ODE-based compartment models, individual-based models, and continuum models. The authors discuss a number of challenges one needs to overcome to fully exploit recently obtained experimental data, which might be used to validate the theoretical models.

*In conclusion, we hope the the present volume will demonstrate to the reader the broad range of research currently undergoing in mathematical modeling of cancer and the challenges ahead.*

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