Special Session 31: Mathematical Models of Cancer and Cancer Therapy

Yangjin Kim, KonKuk University, Korea

Cancer is a complex, multiscale process, in which genetic mutations occurring at a sub-cellular level manifest themselves as functional changes at the cellular and tissue scale. The main aim of this session is to discuss current development and challenges in modeling tumor growth and cancer therapy. Specific goals of the session are to bring together (both computational and analytical) solutions to challenges in mathematical modeling, laboratory experimentation, and clinical diagnosis, and to improve our understanding of fundamental mechanism of tumor development leading to better clinical outcomes. Both the immediate microenvironment (cell-cell or cell-matrix interactions) and the extended microenvironment (e.g. vascular bed) are considered to play crucial roles in tumour progression as well as suppression. Stroma is known to control tumor growth and invasion to surrounding tissue. However, it also prohibits therapeutics from accessing the tumor cells, thus causing drug resistance. Therefore, a thorough understanding of the microenvironment would provide a foundation to generate new strategies in therapeutic drug development. At the cellular level, cell migration is a key step for metastasis and further development of cancer in a given microenvironment. Thus, understanding of cell motility under the control of signal transduction pathways would improve technical advances in cancer therapy by targeting the specific pathways that are associated with the diseases. Analysis of mathematical models would identify fundamental (abstract) structure of the model system and shed a light on our understanding of tumor growth in the specific host tissue environment and interactions between players in cancer progression. More comprehensive multi-scale (hybrid) models can be used to meet the needs of developing patient-specific drugs. The focus of this session is threefold: (a) to present mathematical models of tumor growth and analysis of the models, (b) to discuss many aspects of (patient specific) drug development, (c) to showcase mathematical models incorporating mechanical aspects of movement and growth of cancerous cells and tissues.

An agent based evolutionary model of prostate cancer

David Basanta
H. Lee Moffitt Cancer Center & Research Institute, USA
david@CancerEvo.org

Heterogeneity in prostate cancer is the driving force in somatic evolution which explains the emergence of resistance to therapies and relapse. We will show a computational agent based model of prostate cancer where tumour cells can adapt to the microenvironment and show how this evolutionary process is responsible and exploits the heterogeneity that makes prostate tumours so difficult to treat.

$$\longrightarrow \infty \diamond \infty \longleftarrow$$

Cell migration features in glioma growth and invasion: mathematical modeling and analysis

Arnaud Chauviere
University of New Mexico, USA
AChauviere@salud.unm.edu

Gliomas are very aggressive brain tumors, in which tumor cells gain the ability to penetrate the surrounding normal tissue. The invasion mechanisms of this type of tumors are not yet fully understood. In a first part, we will present mathematical approaches to model and investigate one particular mechanism, the migration/proliferation dichotomy, i.e. the antagonistic migratory and proliferating cellular behaviors in a glioma cell population, which has been hypothesized as playing a central role in the development of these tumors. By using a combination of numerical and analytical techniques, we will show how these models provide insights into the dynamics of avascular glioma growth and capture in vitro observations. In a second part, and based on recent in vivo data, we will present preliminary analysis of the effect of vascularization on glioma growth, which is known to be a major component of in vivo development.

$$\longrightarrow \infty \diamond \infty \longleftarrow$$

Hypoxia inducible factors mediate the inhibition of cancer by GM-CSF: a mathematical model

Duan Chen
Mathematical Biosciences Institute, USA
chen.906@mbi.osu.edu
Julie M. Roda, Clay B. Marsh, Timothy D. Eubank, Avner Friedman

Under hypoxia, tumor cells and tumor-associated macrophages produce VEGF (vascular endothelial growth factor), a signaling molecule that induces angiogenesis. The same macrophages, when treated with GM-CSF (granulocyte/macrophage colony-stimulating factor), produce sVEGFR-1 (soluble VEGF receptor-1), a soluble protein that binds with VEGF and inactivates it. The production of VEGF by macrophages is regulated by HIF-1 (hypoxia inducible factor-1), and the production of sVEGFR-1 is mediated by HIF-2. Recent experiments were conducted to measure the effect of inhibiting tumor growth by GM-CSF treatment in mice with HIF-1-deficient macrophages or HIF-2-deficient macrophages. In the present work we rep-

resent these experiments by a mathematical model based on a system of partial differential equations. We show that the model simulations agree with the above experiments. The model can then be used to suggest strategies for inhibiting tumor growth. For example, the model quantifies the extent to which GM-CSF treatment in combination with a small molecule inhibitor that stabilizes HIF-2 will reduce tumor volume and angiogenesis.

$$\longrightarrow \infty \diamond \infty \longleftarrow$$

Stochastic differential models of tumor spheroid growth

Andrea De Gaetano
Cnr Iasi BioMatLab, Italy
andrea.degaetano@biomatematica.it
Simona Panunzi, Andrea De Gaetano

The mathematical modeling of tumor growth has become an important avenue for understanding cancer biology and eventually controlling neoplastic diseases. Tumor spheroids represent a simplified biological situation, in which a cluster of tumor cells is allowed to replicate and grow in vitro, subject to varying substrate and oxygen concentrations, allowing the experimenter to obtain serial measurements of the attained size. Models for these data have ranged from simple Gompertz growth to complex spatial PDE descriptions taking into account nutrient diffusion and local cell replication. The goal of the present work is to propose a simple Stochastic Differential model of tumor spheroid growth and to estimate its parameters from series of historical tumor spheroid growth data. The model is able to account for both the overall trend in tumor expansion (dependent on predictors such as oxygen and nutrient availability) and for its random fluctuations. Implications of the assessment of tumor growth volatility on the clinical management of cancer patients are discussed.

$$\longrightarrow \infty \diamond \infty \longleftarrow$$

Mechanistic modeling of myoferlin effects on cancer cell invasion

Marisa Eisenberg
Ohio State University, USA
meisenberg@mbi.osu.edu
Yangjin Kim, Ruth Li, William E. Ackerman, Douglas A. Kniss, Avner Friedman

Myoferlin is a member of the evolutionarily conserved ferlin family of proteins, noted for their roles in a variety of membrane processes, including membrane fusion and repair, vesicle transport, receptor recycling and stability, and cell motility. Thus, one might expect the ferlin family to be strong candidates for cancer proteins, although they have not previously been investigated in this capacity. In this talk, I will discuss our recent work showing that myoferlin plays a previously unrecognized role in cancer cell invasion, using a combination of mathematical modeling and in vitro experiments. Using a real-time impedance-based invasion assay, we have shown that lentiviral-based knockdown of myoferlin significantly reduced invasion of MDA-MB-231 breast cancer cells. Based on these experimental data, we developed a partial differential equation model of myoferlin effects on cancer cell invasion which we used to generate mechanistic hypotheses. Our model predictions revealed that matrix metalloproteinases (MMPs) may play a key role in modulating this invasive property, which was supported by experimental data using qRT-PCR screens. These results suggest that MYOF may be a promising new target for biomarkers or drug target for metastatic cancer diagnosis and therapy, perhaps mediated through MMPs.

$$\longrightarrow \infty \diamond \infty \longleftarrow$$

Non-stem cancer cell kinetics modulate solid tumor progression

Heiko Enderling
Tufts University School of Medicine, USA
heiko.enderling@tufts.edu
Charles I Morton, Lynn Hlatky, Philip Hahnfeldt

Solid tumors are heterogeneous in composition. Cancer stem cells (CSCs) are believed to drive tumor progression, but the relative frequencies of CSCs versus non- stem cancer cells span wide ranges even within tumors arising from the same tissue type. Tumor growth kinetics and composition can be studied through an agent-based cellular automaton model using minimal sets of biological assumptions and parameters. Herein we describe a pivotal role for the generational life span of non-stem cancer cells in modulating solid tumor progression in silico. We demonstrate that although CSCs are necessary for progression, their expansion and consequently tumor growth kinetics are surprisingly modulated by the dynamics of the non-stem cancer cells. Simulations reveal that slight variations in non- stem cancer cell proliferative capacity can result in tumors with distinctly different growth kinetics. Longer generational life spans yield self-inhibited tumors, as the emerging population of non-stem cancer cells spatially impedes expansion of the CSC compartment. Conversely, shorter generational life spans yield persistence-limited tumors, with symmetric division frequency of CSCs determining tumor growth rate. We show that the CSC fraction of a tumor population can vary by multiple orders of magnitude as a function of the generational life span of the non-stem cancer cells. Our study suggests that variability in the growth rate and CSC content of solid tumors may be, in part, attributable to the proliferative capacity of the non-stem cancer cell population that arises during asymmetric division of CSCs. In our model,

intermediate proliferative capacities give rise to the fastest-growing tumors, resulting in self-metastatic expansion driven by a balance between symmetric CSC division and expansion of the non-stem cancer population. Our results highlight the importance of non-stem cancer cell dynamics in the CSC hypothesis, and may offer a novel explanation for the large variations in CSC fractions reported in vivo.

$$\longrightarrow \infty \diamond \infty \longleftarrow$$

Are more Ccmplicated tumor control probability models better?

Thomas Hillen
University of Alberta, Canada
thillen@ualberta.ca
J. Gong, M.M. dos Santos, C. Finlay

Mathematical models for the tumor control probability (TCP) are used to estimate the expected success of radiation treatment protocols of cancer. There are several mathematical models in the literature and we made the experience that simple and complex models often make the same predictions. Here we compare six of these TCP models: the Poisson TCP, the Zaider-Minerbo TCP, a Monte Carlo TCP, and their corresponding cell cycle (two-compartment) models. Several clinical non-uniform treatment protocols for prostate cancer are employed to evaluate these models. These include fractionated external beam radiotherapies, and high and low dose rate brachytherapies. We find that in realistic treatment scenarios, all one-compartment models and all two-compartment models give basically the same results. A difference occurs between one compartment and two compartment models due to reduced radiosensitivity of quiescent cells. Based on our results, we can recommend the use of the Poissonian TCP for every day treatment planning. More complicated models should only be used when absolutely necessary.

$$\longrightarrow \infty \diamond \infty \longleftarrow$$

Modeling the effects of drug binding on the dynamic instability of microtubules

Peter Hinow
University of Wisconsin - Milwaukee, USA
hinow@uwm.edu
Vahid Rezania , Jack Tuszynski, Manu Lopus, Mary Ann Jordan)

We propose a stochastic model that accounts for the growth, catastrophe and rescue processes of steady state microtubules assembled from MAP-free tubulin in the possible presence of a microtubule associated drug. As an example for the latter, we both experimentally and theoretically study the perturbation of microtubule dynamic instability by S-methyl-D-DM1, a synthetic derivative of the microtubule-targeted agent maytansine and a potential anticancer agent. We find that among drugs that act locally at the microtubule tip, primary inhibition of the loss of GDP tubulin results in stronger damping of microtubule dynamics than inhibition of GTP tubulin addition. On the other hand, drugs whose action occurs in the interior of the microtubule need to be present in much higher concentrations to have visible effects.

$$\longrightarrow \infty \diamond \infty \longleftarrow$$

PDE tumor models - mathematical analysis and numerical method

Bei Hu
University of Notre Dame, USA
b1hu@nd.edu
Avner Friedman, Andrew Sommese, Wenrui Hao, Jon Hauenstein

We shall discuss the recent progress (joint work with many others) on the PDE tumor models, the stability of the tumor, the bifurcation diagram near the bifurcation point, the numerical methods and simulations, the bifurcation diam extensions, and the method for finding other possible stationary solutions.

$$\longrightarrow \infty \diamond \infty \longleftarrow$$

A model of prostate cancer progression under androgen ablation therapy

Harsh Jain
Mathematical Biosciences Institute, USA
harshvj@gmail.com
Arvinder Bhinder, Steven Clinton, Avner Friedman

Due to its dependence on androgens, metastatic prostate cancer is treated with the elimination of testosterone. However, such interventions are not curative because cancer cells evolve via multiple mechanisms to a castrate-resistant state, allowing progression to a lethal outcome. It is hypothesized that administration of anti-androgen therapy in an intermittent, as opposed to continuous, manner may bestow improved disease control. In this talk, I will present a biochemically motivated mathematical model of anti-androgen therapy that can be tested prospectively as a predictive tool. The model includes 'personalized' parameters, which address the heterogeneity in the predicted course of the disease under various androgen-deprivation schedules. Model simulations are able to capture a variety of clinically observed outcomes for 'average' patient data under different intermittent schedules. The model predicts that in the absence of a competitive advantage of androgen-dependent cancer cells over castration-resistant cancer cells, intermittent scheduling can lead to more rapid treatment failure as compared to continuous treatment. However, increasing a competitive advantage for hormone-

sensitive cells swings the balance in favor of intermittent scheduling. Given the near universal prevalence of anti-androgen treatment failure in the absence of competing mortality, such modeling has the potential of developing into a useful tool for incorporation into clinical research trials and ultimately as a prognostic tool for individual patients.

—→ ∞ ⬦ ∞ ←—

Multiscale study of angiogenesis from molecule to tissue

Yi Jiang
Georgia State University, USA
yijianglanl@gmail.com

Angiogenesis, growth of new blood vessels from existing ones, is an important process in cancer development. Anti-angiogenesis approach is still being intensively studied as a potential cancer therapy. To understand angiogenesis in cancer, we need to first understand normal angiogenesis, e.g. in development. In close connection with experiments, we have developed two cell-based multiscale models of angiogenesis, in retina and tumor, respectively. Our models consider intracellular signaling pathways (VEGF and Notch/Delta), cell dynamics, cell-cell and cell-environment interactions. The models reproduced sprouting morphology and dynamics. The simulations showed that 1) diffusible and matrix-bound VEGF isoforms result in distinctively different morphology, 2) VEGF and Notch/Delta pathways determine the vascular network patterns through dynamic regulation of endothelial phenotypes, and 3) extracellular matrix not only guides the collective migration of endothelial cells, but also participates in cell phenotype regulation. These results highlight the important role of extracellular environment, both biochemical and biomechanical, in sprouting morphogenesis, and suggest new hypotheses to be tested in experiments.

—→ ∞ ⬦ ∞ ←—

Signal transduction pathways in the growth and invasion of glioblastoma: a mathematical model

Yangjin Kim
KonKuk University, Korea
ahyouhappy@gmail.com
Soyeon Roh, Avner Friedman, Sean Lawler

Glioblastoma is a highly invasive brain tumor. This invasive behavior of tumor cells is responsible for low survival rates. Microenvironment plays an important role in the active migration and steady growth of glioma cells. A thorough understanding of the microenvironment would provide a foundation to generate new strategies in therapeutic drug development.

Recently, miR451 and its counterpart AMPK complex were recognized as key regulators of a balance between the migratory phase and proliferation mode. We developed a mathematical model of this signaling pathway to investigate the role of changing environmental factors such as fluctuating glucose levels in creating different invasion and growth patterns. We then analyze the growth behaviors of glioma cells in response to various challenges in the media and show that the various patterns observed in experiments can be obtained by simulating the model with tight regulation of this miR451-AMPK pathway. Using a hybrid model, we also develop several strategies to kill cancerous cells hidden in the microenvironment in addition to surgical resection of the main tumor core, leading to better clinical outcomes.

—→ ∞ ⬦ ∞ ←—

A clinical data validated mathematical model of prostate cancer growth with hormone therapy

Yang Kuang
Arizona State University, USA
kuang@asu.edu
Travis Portz, John D. Nagy

Prostate cancer is commonly treated by a form of hormone therapy called androgen suppression. This form of treatment, while successful at reducing the cancer cell population, affects quality of life and accelerates a recurrence of the cancer in an androgen-independent form. Intermittent androgen suppression (IAS) aims to alleviate some of these problems by cycling the patient on and off-treatment. Clinical studies have suggested that intermittent therapy is capable of maintaining androgen dependence over more treatment cycles while increasing quality of life during off-treatment periods. We presents a mathematical model of prostate cancer to study the dynamics of androgen suppression therapy and the production of prostate specific antigen (PSA), a clinical marker for prostate cancer. Preliminary models were based on the assumption of an androgen-independent (AI) cell population with constant net growth rate. These models gave poor accuracy when fitting clinical data during simulation. The final model presented hypothesizes an AI population with increased sensitivity to low levels of androgen. It also hypothesizes that PSA production is heavily dependent on androgen. The high level of accuracy in fitting clinical data with this final model strongly support these hypotheses, which are also consistent with biological evidences.

—→ ∞ ⬦ ∞ ←—

Robustness and sensitivity of optimal protocols for mathematical models for multi-drug cancer treatments

Urszula Ledzewicz
Southern Illinois University, USA
uledzew@siue.edu
Heinz Schüttler

In this talk we review some results and outline challenges one encounters in analyzing various models for cancer treatments as optimal control problems. The resulting optimal controlled trajectories, representing cancer treatments along with the corresponding response of the system, exhibit various levels of robustness and sensitivity. These are not only related to what is commonly understood and routinely tested when constructing the models which is the sensitivity to the values of the parameters. We also want to discuss how variations in the model assumptions, like the choice of the growth function for the cells, or moving from simpler to more complicated models, like adding more precise aspects such as pharmacokinetics of the drugs, drug resistance or cell cycle specificity, effect the solutions to the problem. We will illustrate it on various models for cancer treatment including models for cell cycle specific chemotherapy, antiangiogenic treatments alone and in combination with chemotherapy and radiotherapy as well as combinations of chemo- and immunotherapy. Examples of both very robust and very sensitive behaviors will be given and the effect of it on the qualitative and quantitative structures of solutions will be discussed.

$$\longrightarrow \infty \diamond \infty \longleftarrow$$

A mathematical model of lung cancer progression

Seongwon Lee
Pohang University of Science and Technology, Korea
dlimpid@gmail.com
Yangjin Kim, Hyung Ju Hwang, Yoon-Keun Kim

Lung cancer originates in the epithelial lining of the airway, but it can evolve into invasive carcinoma. Understanding the progression and how to effectively intervene in it presents a major scientific challenge. The extracellular matrix (ECM) in stroma contains several types of cells and several types of growth factors that are known to individually affect tumor growth, but at present the complex biochemical and mechanical interactions of these stromal cells with tumor cells is poorly understood. Here we develop a mathematical model that incorporates the cross-talk between stromal and tumor cells, and which can predict how perturbations of the local biochemical and mechanical state influence tumor evolution. We study a hybrid model for the interaction of cells with the tumor microenvironment (TME), in which epithelial cells (ECs) and other immune cells are modeled individually while the ECM is treated as a continuum, and show how these interactions affect the early development of tumors. Finally, we incorporate breakdown of the epithelium into the model and predict the early stages of tumor invasion into the stroma. Our results shed light on the interactions between growth factors, mechanical properties of the ECM, and feedback signaling loops between stromal and tumor cells. We suggest how immune response changes in lung tissue affect tumor progression.

$$\longrightarrow \infty \diamond \infty \longleftarrow$$

The interplay between microenvironmental heterogeneity and anticancer drug dynamics: a computational study

Katarzyna Rejniak
Moffitt Cancer Research Insitute, USA
Kasia.Rejniak@moffitt.org

Poor penetration of tumor tissue by drug particles contributes to low efficacy of therapeutic compounds, and, may result in the failure of the Phase II clinical trials. This may be attributed, at least partially, to the fact that experimental models do not recreate the process of drug penetration into the tumor tissue in a way it takes place in the patient body. We developed a computational model of drug penetration that operates on the microscopic tissue scale and recreates various physico-chemical conditions of the tumors. This model includes explicitly defined tissue morphology that is comprised of individual cells surrounded by the interstitial space filled with the fluid that impacts drug transport. We investigated the dynamics of a class of drugs activated in regions of low oxygen, and showed that they may lead to shifting of the tissue metabolic profile. Our computational results showed a non-linear relation between tissue permeability, its cellular density and penetration of drug molecules due to the convective interstitial transport. Moreover, we demonstrated that heterogeneity in tissue composition, such as irregular cell configurations, might solely be responsible for the emergence of tissue zones that are not exposed to drugs in concentrations sufficient to provide therapeutic action.

$$\longrightarrow \infty \diamond \infty \longleftarrow$$