

Special Session 24: Mathematical Problems in Cancer Research

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Modelling hematopoiesis with applications to Chronic Myelogenous Leukemia

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Hematopoiesis is a complex biological process that leads to the production and regulation of blood cells. It is based upon differentiation of stem cells. This process sometimes exhibits abnormalities in blood cells production, causing the so-called dynamical hematological diseases. A severe hematological disease is Chronic Myelogenous Leukemia (CML), a cancer of white blood cells. In some cases, Chronic Myelogenous Leukemia exhibits periodic oscillations in all blood cell counts, with periods falling in the range of 30-110 days, but usually about 70-80 days. In this work, we present a model of hematopoiesis dynamics. We analyze the asymptotic stability of the steady states and we numerically illustrate our results and obtain very rich dynamics of our model that we relate to observations of periodic chronic myelogenous leukemia.

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A multiscale mathematical model of tumor-induced angiogenesis

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A solid tumor needs nutrients and oxygen supply to grow. Angiogenesis is the process by which malignant tumor cells can induce the formation of new blood vessels from a pre-existing vasculature.

Angiogenesis plays a crucial role in primary tumor growth and in metastatic dissemination of tumor cells. Many anti-angiogenic drugs have been studied in clinical trials in the past few years and some of them have been approved by the US Food and Drug Administration (FDA). However, angiogenesis com-

plexity makes empirical strategies to optimize anti-angiogenic treatments difficult and potentially dangerous for treated patients.

In order to better understand anti-angiogenic drugs effect on cancer growth, we develop a multiscale mathematical model of angiogenesis molecular and tissular regulation. This model is based on hyperbolic-parabolic systems of partial differential equations (PDE's) describing the behavior of endothelial cells (proliferation, migration toward the tumor, ...) and that of some pro- and anti-angiogenic substances. Moreover it takes into account modifications induced by oxygen supply on tumor growth.

This multiscale mathematical model describes the interplay between the complex process of angiogenesis and the dynamic of tumor growth. It allows simulation of anti-angiogenic drugs effect on tumor growth, and numerical results are in agreement with biological experiments.

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Modeling and Local Filtering of Noise Embedded in Genome-Scale Microarray Datasets

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The genomes of numerous organisms have been sequenced. This advancement creates new opportunities in biomedical research. Microarrays are experimental tools that assay the relative abundance of transcripts from tens of thousands of genes at a time. Unfortunately, microarray data are very noisy. This presentation details procedures to collect and model the noise embedded in microarray datasets, and methods to filter it. The results lead to an algorithm that yields highly accurate discovery of the relative abundance of genes between two biological samples. We define a function whose zero set collects a sample of the noise embedded in a dataset. The noise sample is modeled as a 3-manifold. Filters, based on the local geometry of the noise sample, are constructed to eliminate most of the noise remaining in the dataset. The model includes parameters that

are optimized in reference to experiments designed to yield expression ratios > 1 (true positives) or $= 1$ (true negatives). The algorithm offers significant improvements in both specificity and sensitivity; specificity is at least 1000-fold better and sensitivity is 2-fold higher than existing state-of-the-art methods. Highly specific discovery has numerous applications in biomedical research and medicine.

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Breast Cancer and Thermal Imaging

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At least 10% of the women in the western world face the prospect of developing breast cancer. Breast cancer is the fifth most common cause of cancer death. The number of cases has significantly increased since the 1970's.

Mammography is today the golden standard in early detection of breast cancer. According to the clinical guide lines of Linda L.Humphrey et Al on breast cancer screening, "Mammography reduced breast cancer mortality rates among woman 40 to 74 years of age" and "the number needed to screen cancer to prevent one death from breast cancer after 14 years of observation was 1224". The sensitivity of mammography is in the range 71% to 95% depending on the age of the woman. The most frequently discussed adverse effect of mammography are the anxiety, discomfort, and cost associated with positive test results, many of which are false positive.

Alternative and/or complementary screening methods that can fix some of these limitations are potentially interesting. We will discuss in our presentation a theoretical framework for thermal imaging applied to breast cancer detection and review the bibliography available on this technology. Recent progress in thermal sensors and image analysis motivate this studies.

Our goal is to use in clinical condition a model with the following characteristics:

- The model is image base and patient specific: the geometry and tissue properties are derived from other image modalities than thermal imaging.
- The model takes into account the biologic properties of a tumor at its early stage, by distin-

guishing metabolic heat source from vascularization heat source.

- We assume a priori spherical tumor nodules which is realistic for the early stage of the disease: this make the localization problem easier to solve.
- The model is time dependent, and allows the use of dynamic information provided by thermal imaging.

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Models for Cell Movement in Tissues: Some New Results

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Some metastatic cancer cells show an interesting form of movement through fibrous tissue, which is termed "mesenchymal motion"[3]?. Recently, I developed a mathematical model for mesenchymal motion, which is based on a kinetic equation for the moving cells and an ODE for the tissue fibers. In this talk, I will introduce this model and present some new mathematical results on existence, pattern formation and traveling waves. (Joint work with Z. Wang, P. Hinow, and M. Li).

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Multi-Control Problems Arising in Cancer Treatments Combining Angiogenic Inhibitors with Chemotherapy

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Heinz Schaettler and Alberto d'Onofrio

We investigate models for tumor anti-angiogenesis, a novel medical approach to cancer treatment that aims at preventing the development of the blood vessel network a tumor needs for growth. The basis is a mathematical model for anti-angiogenesis introduced by Hahnfeldt et al. from Harvard School of Medicine (Cancer Research 1999). In this model the dynamics of the system describes the growth of the tumor volume and its vascularization under the effects of control functions representing the dosage of angiogenic inhibitors with the total amount of inhibitors

to be administered imposed as a constraint. In previous research we analyzed this model as an optimal control problem with the objective of minimizing the size of the tumor at the end of therapy and obtained a complete solution in the form of a full synthesis of optimal protocols.

Synergies between chemotherapeutic and anti-angiogenic effects are the aim of medical research on combination therapies involving both agents. In this talk we will revisit the model by Hahnfeldt as an optimal control problem, but now with the action of a chemotherapeutic agent added in the dynamics which introduces a second control into the system. Due to the multi-control aspect, even with simplified dynamical equations, this becomes a challenging problem mathematically. We will analyze various biological scenarios including the simpler, but biologically intriguing problem of chemotherapeutic agents that also have anti-angiogenic effects. Results about dynamical properties of the system and the structure of optimal protocols will be presented and some open problems will be formulated. The talk is based on results for joint work with Heinz Schaettler (Washington University, USA) and Alberto d’Onofrio (European Institute of Oncology, Italy).

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multiscale models of solid tumor growth and angiogenesis

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We present and investigate models for solid tumor growth that incorporate features of the tumor microenvironment including tumor-induced angiogenesis. Using analysis and nonlinear numerical simulations, we explore the effects of the interaction between the genetic characteristics of the tumor and the tumor microenvironment on the resulting tumor progression and morphology. We find that the range of morphological responses can be placed in three categories that depend primarily upon the tumor microenvironment. In nutrient-poor microenvironments, tumors tend to break into small fragments and invade the surrounding tissue, regardless of the mechanical properties of the surrounding tissue. When placed in a nutrient-rich tissue, the tumor morphology depends upon the biomechanical characteristics of the tissue. Tumors growing into mechanically unresponsive tissue develop buds that grow into long, invasive fingers. Tumors growing into softer, mechanically responsive tissue develop buds that do not

grow, but rather connect with neighboring buds to capture external extracellular matrix (ECM). The overall morphology remains compact, with a large central abscess containing encapsulated ECM, fluid, and cellular debris similar to a necrotic core. We found that the qualitative behavior of the tumor morphologies was similar across a broad range of parameters that govern the tumor genetic characteristics. Our findings demonstrate the importance of the impact of microenvironment on tumor growth and morphology, and we discuss the implications for cancer therapy protocols.

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A Hybrid Model for Tumor Growth

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Yangjin Kim and Hans Othmer

Existing mathematical models of tumor development are either discrete (cell-based) models or continuum models. Both have advantages and disadvantages; the former allows for incorporation of significant cell-level information but is computationally expensive when growth and mechanics are incorporated, whereas the latter is easy to formulate and computationally straightforward, but to date it has been difficult to accurately translate cell-level information into the continuum description. In this talk we introduce a hybrid model that retains the advantages of both the discrete and the continuum models. In this model the surface layers of a growing multicellular spheroid are described by a cell-based model, whereas the interior quiescent and necrotic zones (when present) are described by a continuum model, as is the extracellular matrix. We will discuss the theoretical foundation of the model and the computational algorithms developed to analyze it, and present numerical results for a model of breast duct carcinoma.

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HIF1-Targeted Engineering of Tumor Hypoxic Response and Angiogenesis

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Metastases, insensitivity to radio- and chemotherapy, and inflammation are processes in cancer strongly correlated with the expression of a powerful transcription factor, hypoxia-inducible factor 1 (HIF1). In response to hypoxia, HIF1 activates hundreds of genes governing cellular homeostasis. Targeting HIF1 and modulating mechanisms of the HIF1 pathway are attractive therapeutic strategies in cancer and angiogenesis. Systematic regulation of the HIF1 system requires detailed temporal and quantitative understanding. To test hypotheses relating to HIF1 regulation and cellular hypoxic response, we developed computational models representing the HIF1 system. The models include molecular level models, a network signaling representation, and a cellular level model of angiogenic sprouting. The molecular model consists of kinetic equations predicting HIF1 protein degradation in normoxia, HIF1 synthesis in chronic hypoxia, and effects of the cofactors involved in HIF1 hydroxylation. The network model, a boolean analysis, includes interactions of HIF1 with reactive oxygen species. Finally, a cellular rule-based model, relates hypoxia to blood vessel sprouting, through the HIF1-dependent expression of the growth factor VEGF, and hypoxia-dependent cell proliferation. Combined, these models were used to address hypotheses as to what are the major determinants of HIF1 regulation at the transcriptional and molecular level, and how this regulation may affect phenotypic and metabolic response at the cell and vessel level. Results predict the temporal expression of HIF1 with and without succinate product inhibition, demonstrate how reactive oxygen species both up and down-regulate HIF1 expression and show vessel formation as a result of variable hypoxic stimuli. This multiscale computational modeling of the HIF1 system offers detailed, quantitative insight into the complex mechanisms underlying hypoxic response in cancer.

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Towards a mathematical theory of cytotoxic drugs delivery

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Modeling tumor growth using a multfluid approach

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Thierry Colin

In this talk, we present a mathematical model for tumor growth using a multfluid approach. This model accounts for many biological phenomena influencing this growth such as the cell-cycle or the effect of toxicity. This model computes the evolution of the cell densities in each phase of the cell cycle using advection equations. The movement is due to the change of volume occurring when cells divide or die. To compute the corresponding velocity, we use a viscoelastic formulation to account for cellular adhesion. Normal cells are considered moving elastically, and the interstitial medium as a liquid phase. The cancer cells are considered as viscoelastic as their cell-cell adhesion is weaker than for normal cells. Finally, we present several numerical experiments in 2 and 3 dimensions.

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A Compartment Model of VEGF Distribution in Blood, Healthy and Diseased Tissues

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Angiogenesis is the process of forming new capillaries from pre-existing blood vessels. Vascular endothelial growth factor (VEGF) is one of the most important angiogenic stimulators, involved in most types of cancer. VEGF and its receptors are therefore promising targets in anti-angiogenic therapies. We investigated the VEGF distribution in healthy and disease conditions in the whole human body. The computational model is composed of three main compartments (the healthy tissue, blood and tumor) in which concentrations of VEGF and its receptors are described in terms of ordinary differential equations with respect to time. We looked at how the distribution of VEGF within and between these compartments varies in response to changes in the VEGF secretion rate, the permeability between the compartments, and the clearance. This study aims at providing new insights in optimizing anti-angiogenic therapies targeting VEGF.

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