ECMTB-2014

Mini-Symposium: Spatial Models in Cancer Biology

Thursday, June 19: 9am-1.10pm

Organizers: J. Gevertz, J. Foo, K. Leder, M. Ryser

Session Abstract

Non-spatial cancer models are a useful tool in the study of blood-borne cancers and have been successfully applied to a wide range of problems in solid tumor growth. However, various aspects of carcinogenesis and tumor growth depend critically on spatial factors. For example, the geometry of organ-specific tissue architecture can impact the evolutionary process leading to cancer initiation. In addition, spatial heterogeneity of the tumor microenvironment and the tumor population itself can enable novel modes of adaptation. Clinically, intra-tumor heterogeneity has been associated with more aggressive phenotypes and worse patient outcome. It is therefore critical to develop mathematical modeling tools that capture the spatial aspects of carcinogenesis and enable the study of phenomena driven by the underlying tissue organization and nutrient transport.

Schedule

Time	Speaker	Title
9.00-9.30	Jana Gevertz	Exploring the emergence of anti-cancer drug resistance through a spatial model
9.30-10.00	Marnix Jansen	Clonal evolution of human intestinal stem cell niches
10.00-10.30	Coffee	Caffeine
10.30-11.00	Jasmine Foo	Dynamics of diversity in spatially evolving populations
11.00-11.30	Marc Ryser	Tracking the invisible: a probabilistic approach to field cancerization in head and neck carcinoma
11.30-11.40	Cigarette	Nicotine
11.40-12.10	Jill Gallaher	Understanding the relative roles of intrinsic and extrinsic heterogeneity in glioblastoma
12.10-12.40	Gibin Powathil	Radiation-induced bystander signals: Role of spatial effects in radiation response
12.40-13.10	Russel Rockne	Quantifying the effect of spatially varying factors of resistance to radiation therapy in primary brain tumors: predictions from a patient-specific model

Talk Abstracts

1. **Speaker**: Jana Gevertz
   Affiliation: Department of Mathematics & Statistics, The College of New Jersey
   Email: gevertz@tcnj.edu
   Co-Authors: Zahra Aminzare, Kerri-Ann Norton, Judith Perez-Velazquez, Alexandria Volkening, Kasia Rejniak
   Title: Exploring the emergence of anti-cancer drug resistance through a spatial model
   Abstract: Practically all chemotherapeutic agents, and many newer targeted cancer therapeutics, lead to drug resistance. Drug resistance can arise due to a number of different intracellular and microenvironmental causes. Further, drug resistance may be pre-existing, or can be acquired in response to treatment. With the goal of better understanding drug resistance and its implications for treatment, we have developed a hybrid discrete-continuous mathematical model of tumor response to a DNA damaging drug. In the hybrid model, drug and oxygen dynamics are described through partial differential equations, and a particle-spring approach is used to model individual cells which can grow, divide, and interact with other cells in their immediate neighborhood. We have thoroughly explored model behavior under the following common conditions: a fixed spatial configuration of cancer cells and vasculature, one mechanism of drug action, and one mode of drug resistance. We consider one set of simulations in which drug resistance existed prior to the start of treatment, and another set in which drug resistance is acquired in response to treatment. This allows us to compare how the timing of drug resistance influences both tumor heterogeneity and tumor expansion. The ways in which spatial features impact tumor response to anti-cancer drugs will also be explored. This research is in progress.

2. **Speaker**: Marnix Jansen, MD MSc PhD
   Affiliation: Barts Cancer Institute
   Email: m.jansen@qmul.ac.uk
   Title: Clonal evolution of human intestinal stem cell niches
   Abstract: Cancer is a genetic disease that develops over many years, providing a 'window of opportunity' for early treatment. Tumor growth is initiated by mutations in tissue-specific stem cells, which initiate a process of Darwinian clonal competition, selection and expansion. The mouse intestinal crypt has become a favored model system for investigating patterns of stem cell competition and the effect of pathogenic (K-Ras, APC, p53, and so on) mutations. These techniques however depend on the transgenic introduction of lineage markers, something not feasible in cancer patients. Alternatively, non-pathogenic naturally-occurring mutations that occur due to background mutation can be used as neutral lineage markers in patient material. We have developed a novel system to trace the clonal output of a single stem cell lineage within stem cell niches in the human large bowel. We find that crypts in the large bowel contain multiple stem cells, which compete for space within the niche. Individual lineages undergo drift consistent with neutral competition. We have also applied this technique to crypts harvested from patients afflicted by Familial Adenomatous Polyposis (FAP). These patients are at increased risk of developing colorectal cancer due to a germline APC mutation, which leads to the development of numerous dysplastic colorectal cancer precursor stages. Some of these dysplastic precursor lesions inevitably progress to cancer. We have compared stem cell behavior in normal-appearing crypts and dysplastic crypts from these FAP patients and compared these patterns to normal controls. Chemopreventive drugs

may tip the balance to favor the clearance of mutated stem cells in intestinal stem cell niches

3. **Speaker**: Jasmine Foo
   Affiliation: School of Mathematics, University of Minnesota – Twin Cities
   Email: jyfoo@umn.edu
   Title: Dynamics of diversity in spatially evolving populations
   Abstract: Many cancers arise as a result of the accumulation of mutations and their subsequent clonal expansions through epithelial tissue. This process leads to a spatially heterogeneous, evolving premalignant tissue that forms fertile ground for the growth of neoplasms. In fact, several clinical studies have correlated genetic diversity within premalignant tissue with a higher chance of progression to cancer. Thus we aim to develop a quantitative understanding of the temporal dynamics of diversity in a spatially structured population. In this talk I will discuss a stochastic spatial model of the emergence and spread of new types in a population. I will discuss and characterize several measures of diversity (both spatial and non spatial) within a spatially evolving population. In particular, how do the temporal dynamics of diversity depend on the parameters of the tissue and selective advantage of mutants? If time permits, I will also discuss the application of this model to designing sampling procedures in suspected premalignant tissue.

4. **Speaker**: Marc Ryser
   Affiliation: Department of Mathematics, Duke University
   Email: ryser@math.duke.edu
   Title: Tracking the invisible: a probabilistic approach to field cancerization in head and neck carcinoma
   Abstract: Head and neck cancers often emerge within genetically altered fields of premalignant cells that appear histologically normal but have a high chance of progression to malignancy. Clinical consequences of this so-called field cancerization are multifocal lesions and high recurrence risks after excision of the primary tumor. We develop a spatiotemporal stochastic model of head and neck tumorigenesis, combining evolutionary dynamics at the phenotypic level with a general framework for multi-stage progression to cancer. Based on the model, we derive probabilistic distributions for clinically relevant quantities such as size of the invisible premalignant field at time of cancer diagnosis, and risk of local and distant recurrences. Finally, we discuss how our model can be combined with patient-specific measurements to optimize surgical excision margins and post-operative monitoring.

5. **Speaker**: Jill Gallaher
   Affiliation: Integrated Mathematical Oncology, Moffitt Cancer Center
   Email: jill.gallaher@moffitt.org
   Co-Authors: Peter Canoll, Kristin Swanson, and Alexander R. A. Anderson
   Title: Understanding the relative roles of intrinsic and extrinsic heterogeneity in glioblastoma
   Abstract: Glioblastoma is noted for its ability to aggressively invade the brain tissue beyond what may be visualized clinically. This is due in part to the unique architecture of the brain, and also to the aggressiveness of the invading glioma cells. To a good degree, the bulk growth and extent of invasion of each patient's tumor can be estimated from imaging, and the future growth dynamics can be predicted. But the response following treatment is less predictable, because the same growth parameters can be present with

different heterogeneous tumor compositions, which could lead to different post-treatment responses.

It is well accepted that brain tumors are heterogeneous genotypically, phenotypically, and spatially. Observations made from clinical imaging only gets to the level of bulk properties, so to get a better idea of the behavior of individual cells, we use an experimental rat model that simulates glioblastoma and allows for acquisition of single-cell, in situ, temporal migration and proliferation data. Tightly intertwined within these observed data is the net effect of both the possible phenotypic range that an individual cell may exhibit and the context-dependent manifestation of that phenotype due to a particular environment at a particular time. For tumor growth, this external and internal heterogeneity is present and impossible to separate. Many different solutions can be used to get similar bulk growth rates, but the individual cell heterogeneity becomes particularly significant when the environment changes through applied treatment.

In order to gain insight on the source of observed heterogeneity, we build an agent based model that examines each source separately, the autonomous individual and the external environment, while keeping the other constant. The distributions of proliferation and migration parameters from the experimental data are used to calibrate the cell based model. We simulate how these differences in phenotypes with variation in the environment (growth factor gradients and competition for space) affect the evolution of heterogeneity in a tumor both spatially and temporally and lead to both bulk tumor growth differences and variation in the distributions of individual cell observables.

6. **Speaker**: Gibin Powathil
Affiliation: Division of Mathematics, University of Dundee
Email: gibin@maths.dundee.ac.uk
Title: Radiation-induced bystander signals: Role of spatial effects in radiation response
Abstract: In addition to surgery, radiotherapy and chemotherapy are the two most common anticancer treatments used to treat cancer. The effectiveness of these anti-cancer treatment protocols is considerably affected by both intracellular and extracellular heterogeneities as well as by the dynamical changes within the tissue microenvironment. Hence, it is important to consider such spatio-temporal heterogeneities and changes when studying the effects of these treatments and their optimised scheduling, as this can help in improving the delivery of multimodality treatments.

The spatio-temporal changes in the intracellular cell-cycle dynamics and variations in microenvironment oxygen levels play a vital role in mediating a cell's sensitivity and response to the radiation therapy. Moreover, in addition to tumour control, the ionizing radiation indirectly induces other local and nonlocal bystander effects whose consequences are poorly characterised but which will certainly include secondary malignancies (metastases). Here, we consider a hybrid multiscale mathematical and computational model to study the direct effects of radiation as well as radiation-induced bystander effects on a tumour growing within host tissue. We use the model to study the role of radiation-induced bystander effects when tumour cells are treated with different therapeutic schedules and analyse their clinical and diagnostic implications.

7. **Speaker**: Russell C. Rockne, Ph.D.
Affiliation: Department of Neurological Surgery, Mathematical Neuro-Oncology Lab, Northwestern University
Email: russell.rockne@northwestern.edu

Title: Quantifying the effect of spatially varying factors of resistance to radiation therapy in primary brain tumors: predictions from a patient-specific model

Abstract: Radiation induces cell death primarily by damaging the cell's DNA. Cells undergoing mitosis are more susceptible to radiation-induced DNA damage and therefore have a higher probability of cell death, per area per unit dose. Due to the high proliferation rate of cancer cells relative to the normal surrounding tissue, radiation is often used as a treatment for cancer. Unfortunately, a byproduct of tumor growth is the production of factors which reduce the efficacy of radiation therapy (RT). The most widely characterized mechanism of resistance to RT is reduced oxygen in the tissue, known as hypoxia, which is created when the tumor outgrows the local blood supply. Hypoxia is known to vary within the tumor in space and in time, and may even be a byproduct of treatment. Tumor growth also produces local regions of necrosis and increased interstitial pressure which results in a spatially varying radiation effect, measured in part by the number of cells exposed per unit dose per cell cycle. Hypoxia, cell density, proliferation rate, and an intrinsic sensitivity to radiation are all independently recognized as factors which influence the impact of radiation as a cancer therapy. However, the spatial-temporal interplay of these factors vary within tumors and between patients, which creates a challenging clinical problem. I will present models of radiation-induced DNA damage and repair and tumor response to radiation therapy that are parameterized on a patient-specific basis that provide predictions of the spatial distribution of these resistance factors and their quantitative role in determining response to radiation therapy that can be tested with clinical data. I will focus on patient-specific understanding of the interplay of these factors for an aggressive and spatially heterogeneous form of a primary brain tumor known as glioblastoma.