Mathematical and Computational Modeling from Sub-Cellular to Collective Behaviour in Cells
Modélisation mathématique et computationnelle du comportement subcellulaire au comportement collectif dans les cellules

(Org: **Andreas Buttenschoen** and/et **Leah Keshet** (University of British Columbia))

ANDREAS BUTTENSCHOEN, University of British Columbia
Non-Local Cell Adhesion Models: Steady States and Bifurcations

In both normal tissue and disease states, cells interact with one another, and other tissue components using cellular adhesion proteins. These interactions are fundamental in determining tissue fates, and the outcomes of normal development, and cancer metastasis. Traditionally continuum models (PDEs) of tissues are based on purely local interactions. However, these models ignore important nonlocal effects in tissues, such as long-ranged adhesion forces between cells. For this reason, a mathematical description of cell adhesion had remained a challenge until 2006, when Armstrong et. al. proposed the use of an integro-partial differential equation (iPDE) model. Since then this approach has proven popular in applications to embryogenesis (Armstrong et. al. 2009), zebrafish development (Painter et. al. 2015), and cancer modelling (e.g. Painter et. al. 2010, Domschke et. al. 2014, Bitsouni et. al. 2018). While popular, the mathematical properties of this non-local term are not yet well understood.

In this talk, I will present our recent results of a study of the steady-states of a non-local adhesion model on an interval with periodic boundary conditions. The significance of the steady-states is that these are observed in experiments (e.g. cell-sorting). Combining global bifurcation results pioneered by Rabinowitz, equivariant bifurcation theory, and the mathematical properties of the non-local term, we obtain a global bifurcation result for the branches of non-trivial solutions. Using the equation's symmetries the solutions of a branch are classified by the derivative's number of zeros. We further show that the non-local operator's properties determine whether a sub or super-critical pitchfork bifurcation occurs.

DAN COOMBS, University of British Columbia
Multistate modelling and parameter inference for cell surface receptor tracking analysis

T and B cells of the immune system detect and respond to foreign invaders using surface receptor molecules. These molecules can be labelled and their motion tracked on an individual basis on live cells. I will present recent work on quantitative methods for studying single receptor motion using hidden Markov models, including constrained and infinite state models. This is joint work with Rebeca Cardim Falcao, Tommi Muller and Dr. Libin Abraham.

GERDA DE VRIES, University of Alberta
A Model of Microtubule Organization in the Presence of Motor Proteins

Microtubules and motor proteins interact in vivo and in vitro to form higher-order structures such as bundles, asters, and vortices. In vivo, the organization of microtubules is connected directly to cellular processes such as cell division, motility, and polarization. To address questions surrounding the mechanism underlying microtubule organization, we have developed a system of integro-partial differential equations that describes the interactions between microtubules and motor proteins. Our model takes into account motor protein speed, processivity, density, and directionality, as well as microtubule treadmilling and re-organization due to interactions with motors. Our model is able to provide a quantitative and qualitative description of microtubule patterning. Simulations results show that plus-end directed motor proteins form vortex patterns at low motor density, while minus-end directed motor proteins form aster patterns at similar densities. Also, a mixture of motor proteins with opposite directionality can organize microtubules into anti-parallel bundles such as are observed in spindle formation.

LAURENT MACKAY, McGill University
The dynamics of mechanosensitive nascent adhesion formation

Cellular motility involves the integration of extracellular cues into a cellular motility system that is competent at adhering to the external environment as well as producing directional force. This is acheived by eukarotic cells through tightly regulated spatiotemporal interactions between the actin cytoskeleton, adaptor proteins, and integrin receptors. Complexes of these molecules form what are known as integrin-based adhesions. We present a mathematical model of integrin-based adhesions as co-localized clusters of integrins and adaptor protein. It assumes that integrins and adaptor proteins mutually hinder one another's mobility through a diverse set of interactions. This model is analyzed near equilibrium and stability conditions for its equilibria are found. The model outcome's dependence on biophysical parameters is then characterized, demonstrating that changes in integrin diffusion or binding have similar effects on adhesion size and integrin content. Furthermore, the effects of mechanical force are incorporated as the force-induced activation and ligand binding of integrin, predicting that adhesions will disassemble beyond a critical value of stress. Finally, we use stochastic simulations to demonstrate that this model can produce nascent adhesion assembly when initiated far from equilibrium, allowing us to draw conclusions about the mechanical conditions that allow for this assembly.

BRIAN MERCHANT, University of British Columbia

A Rho-GTPase based model explains spontaneous collective migration of neural crest cell clusters

We propose a model to explain the spontaneous collective migration of neural crest cells in the absence of an external gradient of chemoattractants. The model is based on the dynamical interaction between Rac1 and RhoA that is known to regulate the polarization, contact inhibition and co-attraction of neural crest cells. Coupling the reaction-diffusion equations for active and inactive Rac1 and RhoA on the cell membrane with a mechanical model for the overdamped motion of membrane vertices, we show that co-attraction and contact inhibition cooperate to produce persistence of polarity in a cluster of neural crest cells by suppressing the random onset of Rac1 hotspots that may mature into new protrusion fronts. This produces persistent directional migration of cell clusters in corridors. Our model confirms a prior hypothesis that co-attraction and contact inhibition are key to spontaneous collective migration, and provides an explanation of their cooperative working mechanism in terms of Rho GTPase signaling. The model shows that the spontaneous migration is more robust for larger clusters, and is most efficient in a corridor of optimal confinement.

JAY NEWBY, University of Alberta

Weaker is better: how weak transient molecular interactions give rise to robust, dynamic immune protection

The longstanding view in chemistry and biology is that high-affinity, tight-binding interactions are optimal for many essential functions, such as receptor-ligand interactions. Yet, an increasing number of biological systems are emerging that challenge this view, finding instead that low-affinity, rapidly unbinding dynamics can be essential for optimal function. These mechanisms have been poorly understood in the past due to the inability to directly observe such fleeting interactions and the lack of a theoretical framework to mechanistically understand how they work. In fact, it is only by tracking the motion of effector nanoprobes that afford detection of multiple such interactions simultaneously, coupled with inferences by stochastic modeling, Bayesian statistics, and bioimaging tools, that we recently begin to obtain definitive evidence substantiating the consequences of these interactions. A common theme has begun to emerge: rapidly diffusing third-party molecular anchors with weak, short-lived affinities play a major role for self organization of micron-scale living systems. My talk will demonstrate how these ideas can answer a longstanding question: how mucosal barriers selectively impede transport of pathogens and toxic particles, while allowing diffusion of nutrients.

ERIKUR PALSSON, Simon Fraser University

A 3-D Individual Cell Based Model (ICBM) for simulating cell mobility, cell-cell and cell-ECM interactions.

I present a 3-D Individual Cell Based Model (ICBM) for simulating and visualizing cell signaling, adhesion, motility, and stiffness and their affect on cell movements and growth in multicellular systems. The building blocks of the model are individual deformable ellipsoidal cells, with both mechanical and chemical response that depend on their internal parameter state (cell adhesion and stiffness) and on external cues from the neighboring cells, extracellular matrix, and chemical signals. Cell movement and deformation is calculated from the equations of motion using the total force acting on each cell. The

model uses experimentally measured cellular characteristics, can simulate over 100,000 cells, and is adaptable to many different systems. I highlight the many new unique features of this model such as non-uniform cell surface receptor density and secretion, as well as desmosome like lateral adhesion. Finally I show the ramifications of these interactions for a number of different biological systems (cervical tissue, mammary tumors, $zebrafish$ and $dictyostelium$ development) and demonstrate that the emerging cell patterns in these multicellular systems are distinctively different from that of an individual cell. The simulated cells are visualized using an openGL code. The visualization enables us to see how cells deform when moving past other cells inside mutlicellular tissues, and watch how chemical concentrations change over time at different locations. All this helps us compare the results to experimental findings and gain insight into what processes are important as we adjust the model to match the experimental results.

ZACHARY PELLEGRIN, University of British Columbia

A Model of Cell Signaling, Migration and Interaction through PDE Simulations in the Cellular Potts Model

In living organisms, various internal and external signals guide the behavior of cells. The internal chemical signals can be modeled by systems of partial differential equations called reaction diffusion equations. Solving these PDEs within a changing domain such as these cells is known to be a difficult computational problem. I explore computational numerical models that can represent these equations, and the cells they control. Specifically, I will show equations that represent signals influencing cell shape and movement by the proteins Rac and Rho. These equations can then be integrated into an energy-based model (the "Cellular Potts Model") commonly used to represent deformable cells. This allows the cells to move, reshape and interact with their environment. Results will then be presented for the behavior of these cells, as well as the interactions of the model cells with various external signals, such as the interaction of cells with barriers, other cells, or with chemical signals. These results allow us to gain a better understanding of the biology, and the behavior of living cells.

LISANNE RENS, UBC

Multiscale computational modeling of chemical and mechanical signaling in collective cell migration

Single and collective cell migration involves both chemical and mechanical signaling between cells and the extracellular matrix (ECM, a fibrous network surrounding cells). Regulatory proteins (Rho GTPases) coordinate cell shape changes and migration. Adhesive forces between cells and physical stresses from the ECM allow cells to coordinate their behavior with neighbouring cells. To study how force interactions between cells and the ECM may drive tissue organization, I previously developed a multiscale model. This model couples the Cellular Potts Model, an agent-based model that describes cell movement to a Finite Element Method that is used to calculate ECM stresses. In this model, 1) cells pull on the ECM, 2) strains are generated in the ECM, and 3) cells move along ECM strains. This model was used to study cell shape changes in response to matrix stiffness, vascular-like tissue patterns on compliant substrates and tissue orientation along ECM stresses. My next step is to study how feedback between Rho GTPases and physical forces drives cell migration. Rho GTPases are upregulated under force and in turn higher GTPase levels are associated with higher cell traction forces. I will discuss how such dynamics may be included in my modeling framework. I will model Rho GTPase dynamics by solving PDE descriptions of reaction-diffusion systems on a deforming domain (the cell). Finally, I will discuss next research directions with respect to single and collective cell migration.