UBC Math 563: Mathematical models in cell biology

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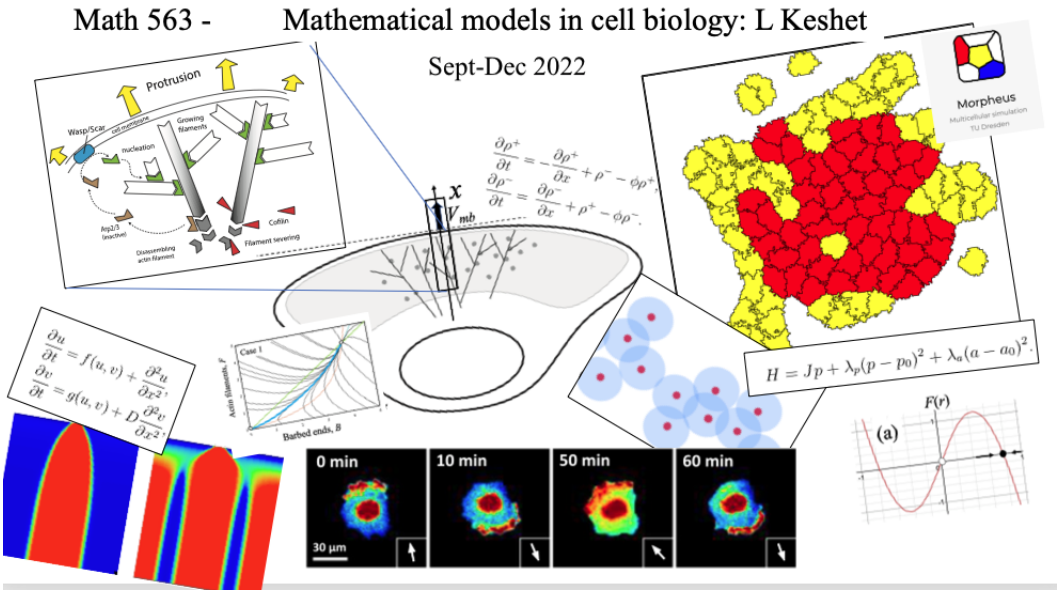
1 Abstract

Cell biology provides many interesting challenges across many spatial scales. Mathematical and computational modeling are tools that can help gain a better understanding of cellular phenomena. At the small scales, there are puzzling examples of patterns formed by proteins inside cells, and dynamic rearrangement of cellular components that enable cells to actively move. At higher scales, cells sense chemical gradients, exhibit active motility, and interact with other cells to form functioning tissues and organs. Mathematical and computational models allow us to explore many of the leading questions at each of these levels. How do patterns for spontaneously? What are the limits of cell sensing? How do cells polarize and migrate in a directed manner? How does a collection of cells self-organize into a structured tissue? In this graduate course, we will explore such questions in the context of deterministic models (ordinary and partial differential equations) as well as stochastic simulations that emphasize multiscale approaches.

The course is designed to be equally suitable for mathematics graduate students looking to learn advanced modeling methods, interesting applications, and topics for further analysis, and biologists who want to understand and critically assess models and carry out advanced multiscale simulations. All participants will learn multiscale simulations (using the open source software Morpheus) to visualize behaviour that emerges from intracellular signaling systems, cell migration, and cell-cell interactions. An emphasis will be on communication across disciplines, matching students from distinct disciplines for joint presentations and projects. Learning goals, expectations, assignments, and grading will take into account the student background.



2 Syllabus

In this course, we will explore both classic and current mathematical vignettes motivated by the biophysics of cell shape, cell motility, cell signaling, and pattern formation in mammalian cells. We will consider how cells interact with one another and how they coordinate into multicellular groups and tissues. From the mathematical perspective, we will showcase several important models (with applications beyond cell biology) where analysis provide insights and helps to understand underlying mechanisms. We also highlight several "classics of mathematical cell biology", papers of recent vintage that have become influential or paradigm-shifting in modern cell biology. While analysis will concentrate on deterministic models, the computational component will include stochastic simulations that incorporate noise and fluctuations. The course will include tutorials and hands-on exploration of the open source software, Morpheus, to simulate multiscale computational models of cells and tissue. The course will be based on a textbook, "Mathematical Models for Cell Biology" currently under development by the instructor, as well as papers from the literature.

A list of topics covered is given below, not necessarily in the order in which they are presented. We will "mix and match" to get students acquainted with simulations early in the course.

Part I: Subcellular dynamics

1. **Motion in the cellular world** A quick tour of "life at low Reynold's number" where cells have to keep pushing in order to move.

2. **Cell structure and models for actin assembly:** Actin is a biopolymer that provides the structural framework that gives shape to a (eukaryotic) cell. Actin is the main component of the "cytoskeleton", a dynamic, assembling and disassembling meshwork that also powers the migration of motile cells (e.g, white blood cells). We will explore models for biopolymer (dis)assembly, and length distributions, briefly highlighting how such polymerization can create the force that powers the motion of a cell.

3. **From actin distribution to cell shape and motion:** At the edge of a motile cell, actin filaments grow and push outwards. How does this lead to overall cell shape? We will examine a classic model (related to the famous correlated random walk) that provides insight into the emergence of the cell's shape. This module also serves as an introduction to the an important class of PDEs in STEM, leading to the so-called Telegrapher's equation and its solution.

4. **Dimensional analysis as a tool for biochemical discovery:** How can macroscopic data for biopolymer assembly help us to elucidate detailed steps in the mechanism of assembly? Here we will show that scaling arguments, together with appropriate data for polymerization kinetics can be used to decipher how a macromolecule assembles from its monomer components. The analysis is a marvel of applied mathematics as a tool in biochemical discovery.

Part II: Cell polarity and directed motion

1. **Direction sensing:** Cells have to interpret their surroundings. Directed cell motility requires that cells sense shallow gradients (as little as 2% across their diameter). We will explore limits to this sensing ability imposed by the "sensors" (cell surface receptors).

2. **Cell polarity and signaling:** Cells react to chemical, mechanical, and/or topographic stimuli to select a direction (to polarize). We explore the class of proteins that regulate cell polarity (and hence the direction of cell motion). This module will include a brief introduction to biochemical kinetics and derivation of models for intracellular signaling.

3. **Chemotaxis and cell migration:** The directed motion of cells up a chemical gradient can account for aggregation to form multicellular collectives. Classic and recent models for population chemotaxis will be discussed and simulated.

4. **Introduction to a multiscale model:** We will show how ideas about regulatory proteins can be implemented in models that span molecular to cellular behaviour. Illustrations will include cell division dynamics and cell polarity and motility.

Part III: Patterns and waves in and between cells

1. **Morphogens, chemical signaling, and intracellular gradients:** We will briefly survey the historical development of theories for morphogenesis, and the role of spontaneous formation of chemical gradients in shaping a tissue. We then delve into related ideas in the context of intracellular patterns.

2. Reaction-diffusion equations: Since the seminal work of Turing in 1952, we have known that chemicals that react and diffuse can form patterns spontaneously under specific conditions. We explain this theory both intuitively and using linear stability analysis. Then we simulate a host of patterns in various geometries: along a line (1D), in a rectangle (2D) and in other domain shapes. We show how domain geometry can influence the type of pattern that eventually forms.

3. Traveling waves and wave-pinning: Waves are ubiquitous in nature, and play an important role in cells and cellular interactions. We will first recap famous models that generate traveling waves (Fisher's equation and others), and then study a simple system (the "wave-pinning" model) where waves of activity stall. We explore striking examples of spiral waves and similar exotic cases.

4. Analysis shortcuts: Traditional methods of analyzing for reaction dynamics, and reaction-diffusion equations include linear stability and bifurcations, both reviewed in this course. We will also introduce a number of recent "shortcuts", including local perturbation analysis, tools that help to parameterize models and determine the number of distinct regimes of behaviour. If time permits, we use such methods to get an approximate view of the pattern forming regimes.

Part IV: Cell-cell interactions and collective behaviour:

While this topic is largely computational, some analytical and mathematical methods can be called upon to help with overall understanding of how behaviour of the group depends on features of the individual. We consider two related but distinct approaches.

1. Agent-based models for small groups of cells: Here we consider cells as individuals, whose position, velocity, etc. are observed. We consider models for cell interactions with both local and more long-ranged effect and show how predictions can be made in specific cases. We observe cases where cells form tight clusters, versus those in which they are well-spaced.

2. Continuum cell models and nonlocal interactions: We take a second approach for the case of large or dense cell populations, where individual cells are less prominent than their density or mean behavior. We use a hybrid integro-PDE system, show how it derives from chemical signaling between cells, and then analyze its behaviour. This topic links to "nonlocal" models for a swarm, and has many macroscopic analogues.

The above unit would be rounded out with numerical computations to explore multi-cell models in greater detail.

Part V: Multiscale models for cells and tissues

1. A computational platform for cell shape and cell-cell interactions: We introduce a common platform, the Cellular Potts Model, for describing the dynamics of cell shape changes, cell-cell adhesion, and cells reacting to chemotactic gradients. As a first step, we derive analytic conditions on the stability of cell size, and show how the parameters of the CPM relate to biologically relevant forces.

2. Computing a tissue: Using the open source software, Morpheus, we will study several examples of multiscale models, whereby the intracellular biochemistry affects cell behaviour (e.g. cell division) which then affects the growth and dynamics of a tissue as a whole.

3 Grading

The grading will be based on several homework sets (approx 10% each), several short presentations of papers from the literature and/or material from the textbook (approx 10% each), and a final term project ($\approx 30\%$).

4 Acknowledgements:

I would like to thank the Morpheus developers, Lutz Brusch and Joern Starruss at the Technical University Dresden for help with the open-source software platform Morpheus.

5 Contact

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