

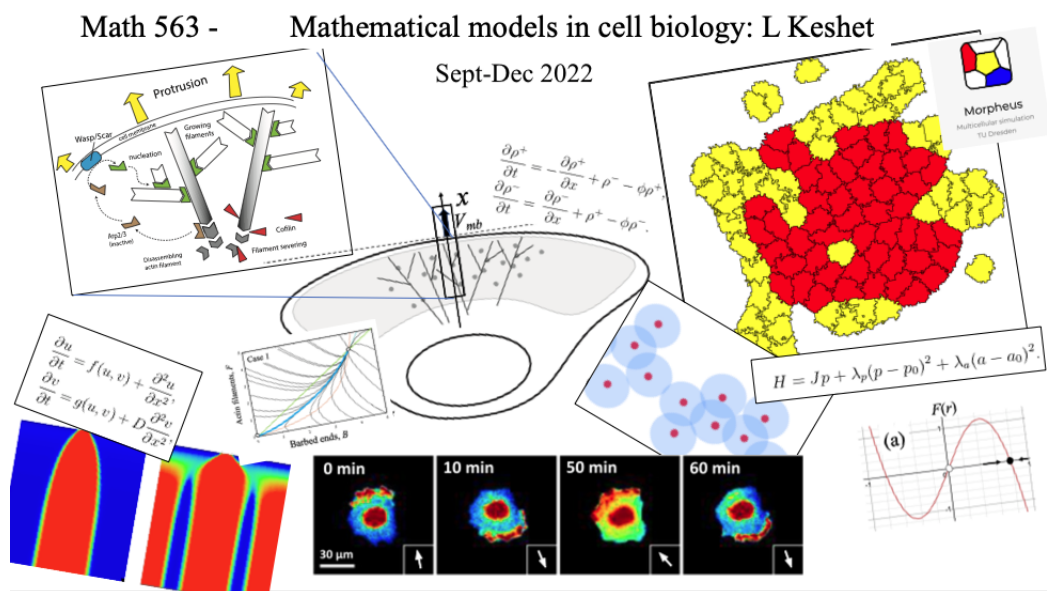
UBC Math 563: Mathematical models in cell biology

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1 Background

The course was successfully run in spring 2020 with graduate students from UBC Math, SFU Math, and several from UBC Biomedical Engineering and UBC Cell Biology. It 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 modeling and carry out advanced multiscale simulations. Graduate students from non-math disciplines will learn how to interpret and understand models in the cell-biology literature, and how to construct mathematical models of their favorite system(s). 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. Grades will be based on homework, class presentations, and interdisciplinary projects where math and bio students are paired, where possible.



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 concentrate on ordinary and partial differential equations, i.e. deterministic models in this course.) We will see that models that prove useful in many other areas of science (ecology, population biology, social aggregation), suitably reinterpreted, can provide a foundation of understanding in the micro-world of cells. (Hence this course will also serve as a survey of PDEs that are important in STEM.) We also highlight several “classics of mathematical cell biology”, papers of recent vintage that have become influential or paradigm-shifting in modern cell biology. 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.

Approximate order of topics covered is given below.

Part I: Subcellular dynamics

1. **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.
2. **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.
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.

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.
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. But what determines the types of patterns that can form? Here we will examine simple ideas (due to Stan Mareé) that help predict stripes, spots, and other pattern features. This material, while basic and informative, has never appeared in a readable form in any book!
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.
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.

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 4-5 homework sets (10% each), short presentation(s) of a paper from the literature and chapters of the textbook (20%), and a final term project (30-40%).

4 Acknowledgements:

I would like to thank the entire team of Morpheus developers (including Lutz Brusch and Joern Starruss) at the Technical University Dresden for help with the open-source software platform Morpheus.