499Y Thesis Proposal

1 Introduction

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Committee Chair: Dr Andreas Buttenschoen.
Thesis Subject: Mathematics.

Agent-based models (or cell-based models) of multicellular systems are used to simulate mechanical and physiological phenomena in cells and tissues. They are becoming indispensable in biomedical research. Many different agent-based model types exist, each having their advantages and disadvantages. Agent-based models can roughly be categorized into on-lattice and off-lattice models. Here we focus on off-lattice models, in which each cell is represented individually and can move continuously in space.

Off-lattice or lattice-free models are roughly categorized as center-based models, deformable models, or hybrid approaches. This model variety allows to simulate a broad scale of phenomena, ranging from monolayer growth, tumor growth, wound healing, to organ modeling. However, every approach brings its own difficulty and demands a particular care and expertise.

In this project, we study computational models of cellular mechanics from the single cell to the multicellular dynamics level. This includes a survey of theoretical mathematics and accompanying experimental biology literature, collation and comparison of various biophysical models and their first principle derivations from justified modeling assumptions, and the use, customization and development of computational tools for simulating experimental hypotheses. Preparatorily, a background in Dynamical Systems, Physical Modeling and Mechanics is essential. For computational experimentation, we will utilize existing tools such as PPlane, Morpheus, Scipy, and an in-house cellular simulator 'T-Sim'. Custom code will likely be written in Python or C++ using their numerical computing packages (Numpy, Eigen, boost, etc.).

This is in preparation of the thesis goal in which we study particular collective migration scenarios using these theoretical and computational methods.

2 Learning Goals

- To understand and apply the modeling life-cycle with application to cellular mechanics.
- To propose a novel physical model for a experimentally studied biological phenomenon, and validate the model on biological observations.
- To gain an understanding of biophysics, and the associated numerical and computational background.
- To be able to identify significance of research literature, to aggregate and compare existing resources and readings in the subject field, and to interpret student's results arising from the modeling life-cycle.

3 Key Readings

The following literature is expected to be useful for a background in the mathematical models of cell migration and accompanying biological background:

1. S. Lo Vecchio et al. "Spontaneous rotations in epithelia as an interplay between cell polarity and boundaries". en. In: *Nat. Phys.* (Jan. 2024). Publisher: Nature Publishing Group, pp. 1–10. ISSN: 1745-2481. DOI: 10.1038/s41567-023-02295-x. URL: https://www.nature.com/articles/s41567-023-02295-x (visited on 01/29/2024)
2. Arnold Hayer et al. "Engulfed cadherin fingers are polarized junctional structures between collectively migrating endothelial cells". en. In: *Nat Cell Biol* 18.12 (Dec. 2016). Number: 12 Publisher:

Nature Publishing Group, pp. 1311–1323. ISSN: 1476-4679. DOI: 10.1038/ncb3438. URL: https://www.nature.com/articles/ncb3438 (visited on 01/31/2024)
3. Shreyansh Jain et al. "The role of single-cell mechanical behaviour and polarity in driving collective cell migration". en. In: *Nat. Phys.* 16.7 (July 2020). Number: 7 Publisher: Nature Publishing Group, pp. 802–809. ISSN: 1745-2481. DOI: 10.1038/s41567-020-0875-z. URL: https://www.nature.com/articles/s41567-020-0875-z (visited on 01/31/2024)
4. P. Van Liedekerke, A. Buttenschön, and D. Drasdo. "Off-Lattice Agent-Based Models for Cell and Tumor Growth". en. In: *Numerical Methods and Advanced Simulation in Biomechanics and Biological Processes*. Elsevier, 2018, pp. 245–267. ISBN: 978-0-12-811718-7. DOI: 10.1016/B978-0-12-811718-7.00014-9. URL: https://linkinghub.elsevier.com/retrieve/pii/B9780128117187000149 (visited on 01/13/2024)
5. Andreas Buttenschön and Leah Edelstein-Keshet. "Bridging from single to collective cell migration: A review of models and links to experiments". en. In: *PLoS Comput Biol* 16.12 (Dec. 2020). Ed. by Alex Mogilner, e1008411. ISSN: 1553-7358. DOI: 10.1371/journal.pcbi.1008411. URL: https://dx.plos.org/10.1371/journal.pcbi.1008411 (visited on 01/21/2024)
6. A. Buttenschön et al. "Does single cell migration behaviour permit prediction of multi-cellular migration patterns: Lessons from a physics-based model". In: *Preparation* (2024)

4 Communication

The following communication expectations and platforms are established:

1. Weekly meetings – 60-90 minutes – in-person, or online, physical presence permitting.
2. Online Collaboration Platforms – Overleaf, GitHub Repository, E–Mail.

5 Evaluation

The following evaluation items are established:

1. Weekly meetings, progress catch-up with Committee Chair.
2. Summary of literature readings, and accompanying discussions.
3. Mid-semester manuscript identifying a research question along with associated steps and context.
4. Custom code for simple simulations.
5. Open source code extending existing in-development computational tools, if necessary.

6 Timeline

For the 499Y Honors Research Semester, the following plan shall be followed:

02/09/2024 Short summary of key readings 1 ([3–5]) to be submitted for review and discussion.

02/16/2024 Short summary of key readings 2 ([1, 6]) to be submitted for review and discussion.

02/23/2024 Short summary of key reading 3 – literature review ([2]) – to be submitted for review and discussion.

03/01/2024 Short summary of key readings identified from literature review ([2]) to be submitted for review and discussion.

03/08/2024 Short summary of key readings identified from literature review ([2]) to be submitted for review and discussion.

03/22/2024 Preliminary computational experiments using simulation tools such as Morpheus or T-Sim to be presented to the Committee Chair.

03/29/2024 Further computational experiments using simulation tools such as Morpheus or T-Sim to be presented to the Committee Chair incorporating feedback from the previous week.

04/05/2024 A 3-4 page document including a collated summary of key readings and background, identification of a research question, and highlighting the important experiments, computational tools, model types, and learning or reading references to be used for bridging the gap between coursework and the research project.

04/12/2024 Early discussions with faculty on selecting a second committee member.

04/19/2024 First Draft of 499T proposal to be submitted to the Committee chair for review, discussion and feedback.

05/10/2024 Last day to identify the second committee member in discussion with the Committee Chair, submission of the 499T proposal to CHC PATHS.

References

[1] A. Buttenschön et al. "Does single cell migration behaviour permit prediction of multi-cellular migration patterns: Lessons from a physics-based model". In: *Preparation* (2024).

[2] Andreas Buttenschön and Leah Edelstein-Keshet. "Bridging from single to collective cell migration: A review of models and links to experiments". en. In: *PLoS Comput Biol* 16.12 (Dec. 2020). Ed. by Alex Mogilner, e1008411. ISSN: 1553-7358. DOI: 10.1371/journal.pcbi.1008411. URL: https://dx.plos.org/10.1371/journal.pcbi.1008411 (visited on 01/21/2024).

[3] Arnold Hayer et al. "Engulfed cadherin fingers are polarized junctional structures between collectively migrating endothelial cells". en. In: *Nat Cell Biol* 18.12 (Dec. 2016). Number: 12 Publisher: Nature Publishing Group, pp. 1311–1323. ISSN: 1476-4679. DOI: 10.1038/ncb3438. URL: https://www.nature.com/articles/ncb3438 (visited on 01/31/2024).

[4] Shreyansh Jain et al. "The role of single-cell mechanical behaviour and polarity in driving collective cell migration". en. In: *Nat. Phys.* 16.7 (July 2020). Number: 7 Publisher: Nature Publishing Group, pp. 802–809. ISSN: 1745-2481. DOI: 10.1038/s41567-020-0875-z. URL: https://www.nature.com/articles/s41567-020-0875-z (visited on 01/31/2024).

[5] S. Lo Vecchio et al. "Spontaneous rotations in epithelia as an interplay between cell polarity and boundaries". en. In: *Nat. Phys.* (Jan. 2024). Publisher: Nature Publishing Group, pp. 1–10. ISSN: 1745-2481. DOI: 10.1038/s41567-023-02295-x. URL: https://www.nature.com/articles/s41567-023-02295-x (visited on 01/29/2024).

[6] P. Van Liedekerke, A. Buttenschön, and D. Drasdo. "Off-Lattice Agent-Based Models for Cell and Tumor Growth". en. In: *Numerical Methods and Advanced Simulation in Biomechanics and Biological Processes*. Elsevier, 2018, pp. 245–267. ISBN: 978-0-12-811718-7. DOI: 10.1016/B978-0-12-811718-7.00014-9. URL: https://linkinghub.elsevier.com/retrieve/pii/B9780128117187000149 (visited on 01/13/2024).