COMPUTATIONAL CELL POPULATION MODELS: MULTISCALE AND MULTIPHYSICS MODELING

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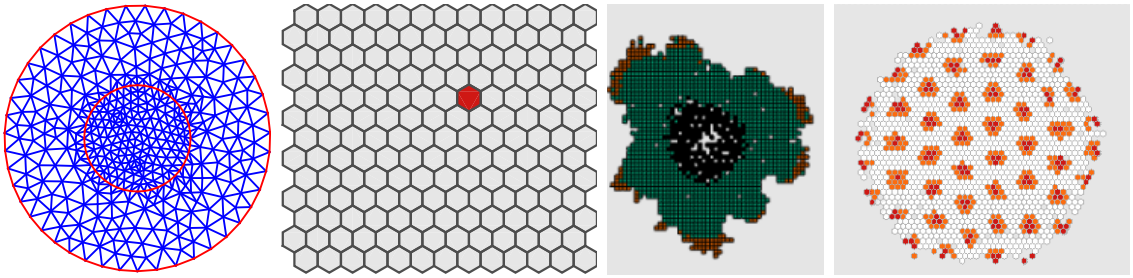

Fig. 1. *Left:* a numerical discretization of a single cell consisting of nucleus, vacuole, and membrane. *Middle-left:* a single cell positioned in a hex-mesh for a cell population. *Middle-right:* avascular tumor model, *right:* patterning process in a cell population.

Summary

This research is concerned with a novel modeling approach for processes taking place inside living cells and all the way up to a large population of interacting cells. In short, inspired by how Partial Differential Equations (PDEs) emerge in the continuum limit as a result of a multitude of processes and interactions taking place at a small/fast scale in space/time, one can derive stochastic evolution equations for how cells interact to form patterns, organoids, and how they induce tissue growth. This ansatz results in a computational modeling framework which has some desirable features, including interpretability and which is amenable to mathematical analysis. The work is centered around the numerical software "URDME"[1], a simulator for cell reaction kinetics and -population dynamics.

Currently, there are three open directions for projects:

A. Novel models for cell populations. We are particularly interested in *emerging properties*, or behaviors not explicitly encoded but which emerge when many cells cooperate. Examples are found in wound-healing processes and under *homeostatic*, or normal conditions, but also during embryogenesis and in pathological conditions like tumor growth. Relevant background for a candidate include computational science, cell-biology, or computational physics.

[1] http://www.urdme.org

B. Simulation efficiency. The evolution equations are relatively fast to simulate for small cell populations but become computationally intensive for populations of cells larger than about 10^4 or so. There are many numerical techniques available to help improve on the efficiency, including multigrid techniques or more specialized multiscale algorithms and it would be interesting to develop a faster simulation engine. A background in computational science or software engineering would be beneficial to this project.

C. Mathematical analysis. As mentioned, a strength with the framework is the connection with PDEs which means that mathematical analysis can be developed to further our understanding of a proposed model. This often involves stability- and bifurcation analysis and to some extent computational analysis of the findings. A background in applied mathematics or numerical analysis would be a good fit for this project direction.

Background

It is often of interest to understand the *emergent behavior* of cells: if a certain rule is followed by a single cell, what is the observed collective behavior at the population level? Across millions of cells? This is a true *multiscale challenge* and to solve it models at the single cell need to be consistently coupled with a model of the cell population which takes care of the mechanics of the whole population. Progress in bridging the gap between single cell models and cell population models could help in the study of a range of important processes, under healthy as well as under pathological conditions.

Specifics of these projects

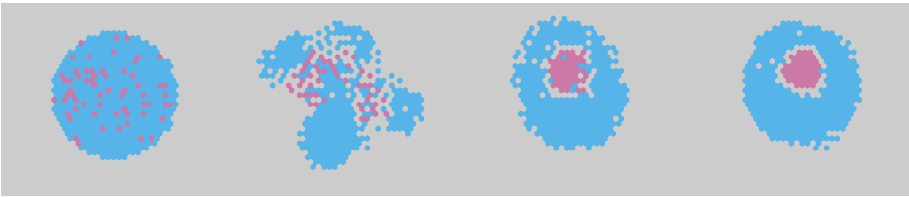

Fig. 2. Emergent *cell sorting* via surface tension. From an initial random configuration *(left)*, the two cell types sort themselves whenever they are able to express a sufficiently strong surface tension against each other.

A. Novel models for cell populations. Modeling cases of particular interest to develop include situations where there is a presence of signaling between cells: directly via cell-cell junctional contacts, or via cellular protrusions, and/or via chemical substances. Typical applications include tumor growth models, angiogenesis, morphogenesis, wound healing, and embryo development processes. The work will involve formulating the mathematical model, implementing it, and performing numerical experiments which ideally can be compared to observations from living cell populations.

B. Simulation efficiency. The most expensive part of the simulations lies in inverting matrices associated with the Laplacian operator over the cell population. This is also an operation for which *multigrid* is extremely efficient, for example there are algebraic multigrid packages that can be tried out and which will most likely speed simulations up by orders of magnitude. A distinct approach is to try to combine a macroscopic continuum model together with a more detailed model, and produce an approximate *hybrid* model which works well in the limit of sufficiently large cell populations. This project consists of implementing and testing out the software on a selected and pre-existing class of models.

C. Mathematical analysis. Thanks to the PDE interpretation, the models can often be meaningfully analyzed mathematically, ideally resulting in relations between the parameters for which different outcomes can be expected to be observed. A concrete example is for tumor models where a PDE-analysis shines light on conditions for which metastasis can be expected. This project is of more mathematical character and will evolve around one or a few selected models and an analysis of the expected behavior in a suitable region of parameter space.

Interested candidates with a background in one or more of computer science, software engineering, computational physics, scientific computing, molecular systems biology, or applied mathematics are more than welcome to contact me for a further discussion.

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