COMPUTATIONAL MODELING OF POPULATIONS OF CELLS

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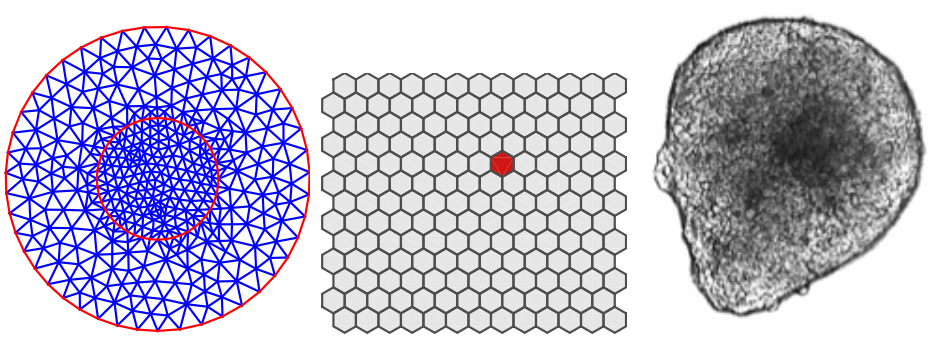

Effective summary

Correctly bridging single cell descriptions with models of a large interacting cell population is a challenge due to the vast scale separation in both time and space. Research in the biosciences has now advanced to the stage where sophisticated predictive models of single cell processes may be formed. However, a range of emerging Life science applications require models consisting on the order of millions of living cells. In this research we target this modeling gap in three complementary tracks of research:

A. Numerical analysis: for spatial stochastic models describing a single cell or a population of cells.
B. Computational modeling: focused around a simulation software www.urdme.org and a novel model formulation.
C. Bayesian inference: development of simulation-based posterior exploration algorithms, to support rigorous data-driven modeling within the context.

The main focus of this project lies in parts (B) and (C). For (B), the main goal is to seamlessly be able to merge detailed models of the inside of a tightly packed cell with models of the cell population, this is *the multiscale challenge*. For part (C), synthetic examples will initially serve as the targets for this study, but data from tumors grown *in vitro* is available via collaborators and make up an end-challenge. This is the *data-driven modeling challenge*.

Background

This project deals with computational modeling of processes taking place inside and among living cells. The concrete ***aim*** is to be able to accurately and consistently simulate

large multicellular systems. The multiscale challenge is that models of cells at the population level take place on a different temporal and spatial scale compared to the single cell dynamics. Another outstanding difficulty is the issue with model calibration in the presence of process noise, and, importantly, understanding the inherent limitations with such parametrization techniques. These challenges call for novel fast multiscale simulation algorithms equipped with a consistent analysis and supported by sound parametrization procedures.

To handle the complicated geometry of the single cell, unstructured meshes, e.g., triangularizations, stand out as a ubiquitous tool. Also, noisy cellular processes at the molecular level should rightly be described in a *stochastic* framework. Taken together, this leads to the *Reaction-Diffusion Master Equation* (RDME) framework as implemented in the openly available software URDME, www.urdme.org.

At the cell population level, computational modeling is a promising approach to generate, test and refine hypotheses as to the relative contributions of various mechanisms to tissue-level behaviors. For reasons of computational efficiency, the focus in this proposal lies at so-called *on-lattice* cell-based models, where cells are distributed over a discrete grid and where state update rules codify the dynamics of the population.

Given these brief considerations, within this project we will focus on coupling together single-cell models described within the RDME-framework with a novel on-lattice method, dubbed *Discrete Laplacian Cell Mechanics* (DLCM).

This project

Multiscale modeling of cells: The inside of a living cell is packed with geometrical specifics that are difficult to resolve in detail. Similarly, the cell environment is crowded with neighbor cells to which cell-to-cell communication takes place by different means. A new multiscale simulation framework will be developed, suitable to accurately describing such an interacting population of cells in a bottom-up fashion. An important outcome of the project will be openly available implementations.

Bayesian inference: A computational framework which aims to support data-driven discovery should be able to estimate parameter posterior distributions when confronted with data. For this purpose a methodology for posterior exploration within the modeling context will be developed. Concrete applications in the parametrization of tumor models will be considered.

Candidates with a background in one or more of Scientific Computing, Applied Mathematics, Computer Science, Computational Physics, or Molecular Biology are more than welcome to contact me for further information.

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