From cell-cell interactions to embryo development:
Multiscale models and simulation in systems biology

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Computational systems biology. One important aim of systems biology is to understand the biological phenomena that we observe on a cellular, tissue and organism level, through the molecular interactions that occur inside individual cells. To that end, an interdisciplinary approach is necessary. Computational systems biology deals with computer assisted modeling in cell biology as well as the method development that enables such approaches. An important observation is that stochasticity can play fundamental roles for the dynamics of cellular control networks, and many methods have been developed to efficiently simulate reaction kinetics in a discrete stochastic setting [2].

Project goals. In this highly interdisciplinary project we will, assisted by data obtained from quantitative microscopy of stem cell patterning in fish and mouse embryos, develop multiscale models and algorithms with the fidelity to investigate how stochastic chemical interactions affect population level dynamics in groups of interacting, growing and dividing cells. Several modeling frameworks exists for simulations of groups of cells, but they rarely include interactions originating at the level of intracellular chemistry. The methods we will develop in this project will have the potential to greatly increase the level of realism of cell population models, and thus increase the range of biological processes that can be studied through computational analysis. Fig. 1 and its caption highlights some of the challenges involved.

Through image analysis and quantitative microscopy of cells in 3D images of developing embryos provided through our collaboration with the Adameyko group we will obtain the data needed to validate and calibrate the new computational methods, as well as to test novel hypotheses about patterns seen in the experimental data. The methods will also be used to address questions about the importance of cell-to-cell signalling in stochastic

models of gene regulatory networks with relevance to stem cell differentiation and cancer onset in collaboration with Mark Chaplain, Dundee, Scotland.

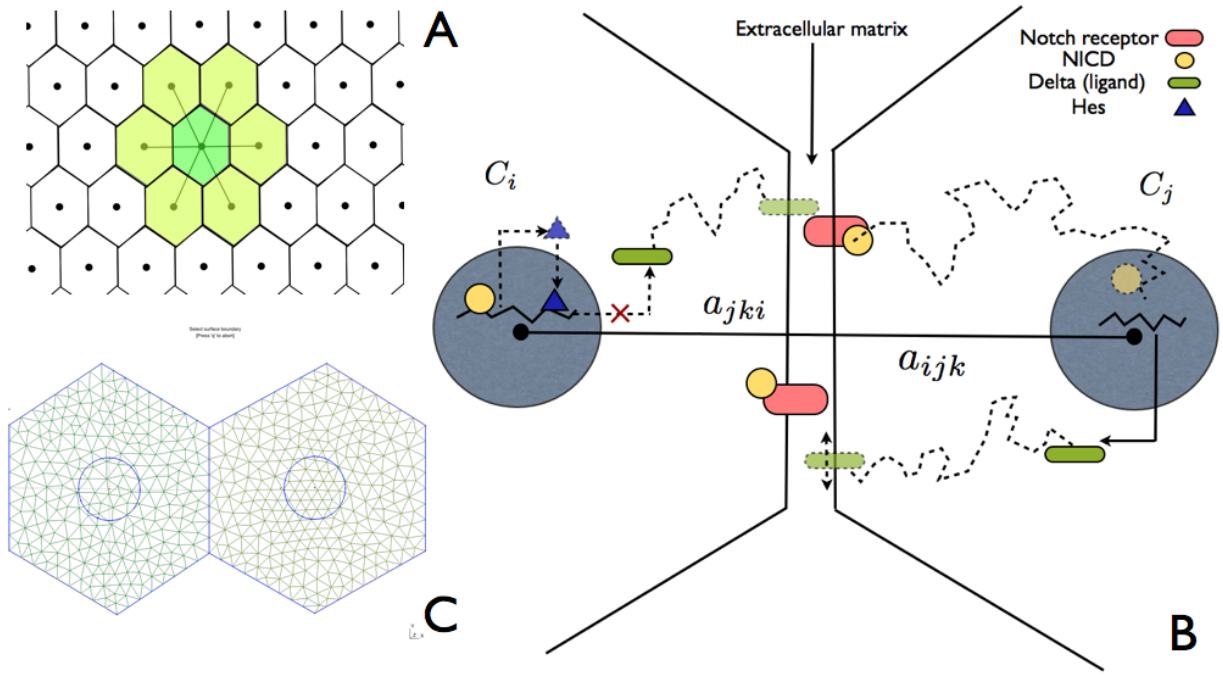

Fig 1. (A) Individual cells in a cell population can be modeled as Voronoi cells. The example here shows Voronoi cells in 2D, but the same principle holds true also for 3D. Cell-to-cell signaling can help to spread and maintain a collective differentiation decision to neighboring stem cells. (B) Close-up of an edge connecting two cells in (A) and a highly simplified schematic of Notch-Delta signaling, a crucial process in embryo development. The Notch receptor penetrates the cell membrane from the interior of the cell to the extracellular matrix. When a ligand in a neighboring cell binds to Notch, the Notch intracellular domain (NICD) is released, diffuses into the nucleus and affects the expression of the Hes and Hey family genes. This is one example of cell-to-cell signalling. (C) Inside individual cells a fine mesh can be used to simulate the stochastic reaction-diffusion processes with software such as URDME [1] (developed at TDB and UCSB) in order to determine the dynamics of the signaling network. One major aim of this project is to develop multiscale methods to bridge this detailed level of description of individual cells to the multi-cell case in (A).

Applications in biology. The methods development will be driven by biological applications in collaboration with national and international partners. Life forms develop from a single cell that divides. Every cell in our body is always produced from another cell. However, the process of coordinating division numbers with patterning and migration of

cells is still poorly understood. To address this question, model organisms where one can assign unique colors to stem cells, will let us produce experimental data showing how cells divide clonally and fill the space while making organs, tissue and defining shape. Through a combination of quantitative analysis of the microscopy images and simulations we will seek to better understand the roles of different types of cell-to-cell interactions, growth and migration in morphogenesis. This application will be studied in collaboration with Igor Adameyko.

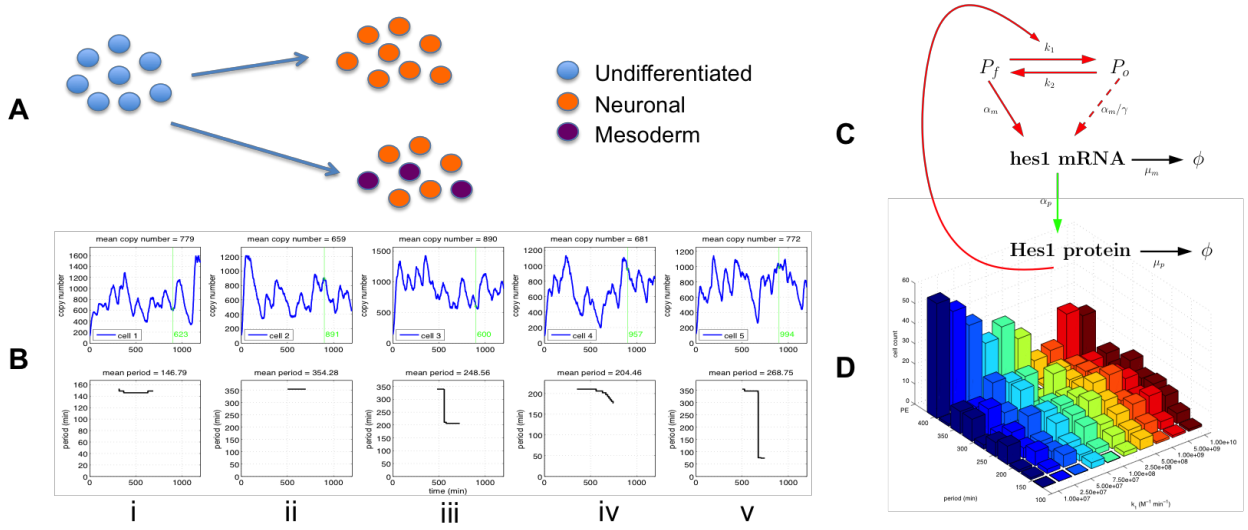

Fig 2. URDME [1] has been used to study oscillatory dynamics of Hes1 in embryonic stem cells (C,B). The noisy behavior of this cellular oscillator has been linked to the heterogeneity observed in stem cell differentiation in individual cells (A). In this project we will develop methods that can be used to extend this model to include stochastic cell-to-cell signalling.

Together with Mark Chaplain (Dundee) and Mark Sturrock (MBI, Ohio) we are investigating spatial stochastic effects in the Hes1 gene regulatory network (Fig 2). Individual mouse embryonic stem cells have been found to exhibit highly variable differentiation responses under the same environmental conditions and experimental evidence suggests that the noisy cyclic expression of Hes1 is responsible for this [9]. Using URDME [2] we have developed a spatial stochastic model of the Hes1 network, and in contrast to previous simulations with well mixed stochastic or partial differential equation models, our model captures both the qualitative and quantitative behavior observed in experiments. Interestingly, the model suggests that intrinsic noise can explain population level heterogeneity in the differentiation response. In addition, the model reproduces the response to two known cancer drugs [3].
Our simulations show that the onset of oscillatory dynamics in individual cells is very robust to parameter variations, but that the oscillations are always highly stochastic. Cell-to-cell

communication via the Notch-Delta pathway in Fig. 1B can reduce this variability in cells during the process of somitogenesis [4], but the mechanism is not well understood. The methodology developed in this project can be used to address this issue.

Image Analysis. The analysis of the experimental data will require 3D segmentation of cells. This can be done using a region-based segmentation method in which seeds representing both object and background pixels are created by combining morphological filtering of both the original image and the gradient magnitude of the image. The seeds are then used as starting points for watershed segmentation of the gradient magnitude image [5]. This can be done in a fully automatic fashion, and in addition to the data used in [5], we will here also take advantage of the color information from the labeled stem cells.

Multiscale modeling and simulation. Biochemical processes inside a living cell occurs on a multitude of time and length scales. The number of molecules of different species (proteins, second messengers etc.) involved in the networks ranges from single molecules to thousands of molecules. For some processes, a microscopic resolution such as attained by Brownian dynamics is needed and for others macroscopic models such as partial differential equations is sufficient. Interaction between individual cells in colonies and tissue introduces additional scales, from cell-to-cell signaling over adjacent cell membranes to long range interactions due to molecules diffusing in the extracellular matrix.

Career outcomes. Systems biology is a rapidly growing interdisciplinary field that has embraced mathematical and computational modeling as part of the toolbox to advance our understanding of cell biology. The impact of modeling and simulations in molecular biology will grow rapidly, and there is a need for computational experts trained in an interdisciplinary fashion. The core programme in Scientific Computing and Image Analysis will provide a broad knowledge of state of the art techniques, and the specialization in Systems Biology and multiscale modeling will make the successful candidate uniquely positioned to take on advanced computational biology careers in both academia and industry.

Research environment. The prospective student will be affiliated with the Hellander (advisor) and Wählby groups (co-advisor). The student will work closely with the Adameyko group in interpreting results and addressing questions in embryonic development. The student will take part in the computational systems biology group at the Division of Scientific Computing. The group has three senior members: professor Per Lötstedt and senior lecturers Andreas Hellander and Stefan Engblom. Three PhD students Pavol Bauer, Jan Klosa, and Lina Meinecke work on different aspects of stochastic simulations in systems biology.

Candidate. The successful candidate will have a strong background in applied mathematics including scientific computing and computer programming. Basic knowledge of quantitative microscopy, cell biology and/or biophysical chemistry is considered a merit.

Collaborations. We are collaborating with Prof. Linda Petzold at the university of California, Santa Barbara (UCSB) and with Prof. Per Lötstedt (UU) on development of multiscale methods and software for stochastic reaction-diffusion simulations (www.stochss.org).

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Relevant web pages:
www.urdme.org
www.github.com/URDME/urdme
www.github.com/ahellander/pyurdme

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