Introduction
Multicellular systems biology is an emerging field aiming at a mechanistic understanding of developmental, physiological and pathological processes by studying the multiscale interactions at the subcellular, cellular and tissue levels. Increasingly, computational simulation is needed to explore and predict a system’s behavior and to integrate quantitative data.
Recently, a number of modeling and simulation platforms are have recently become available that facilitate the construction and simulation of multiscale models of multicellular systems. This mini-symposium provides a comprehensive overview of these new modeling platforms as well as a comparison of common approaches and future challenges for multicellular systems biology.
We are delighted to host this session with talks about seven different modeling platforms that together from the state-of-the-art in in computational methods for multicellular systems biology. The mini-symposium brings together developers and users to identify common approaches and future challenges concerning multiscale integration, model specification, model exchange, scalability, workflow management as well as compliance to standards and guidelines. In this way, we hope to stimulate the adoption of these platforms and contribute to innovation in the field.

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Date and Location
The minisymposium will be held on the June 19, 2014 as part of the European Conference on Mathematical and Theoretical Biology in Gothenburg, Sweden. Details on location will be announced later.
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Chaste: An open source C++ library for computational physiology and biology

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Chaste (Cancer, Heart And Soft Tissue Environment) is an open source C++ library for the simulation of mathematical models developed for physiology and biology. Code development has been driven by two initial applications: cardiac electrophysiology and cancer development. A large number of cardiac electrophysiology studies have been enabled and performed in Chaste, including high-performance computational investigations of defibrillation on realistic human cardiac geometries. New models for the initiation and growth of tumours have also been developed in Chaste. In particular, cell-based simulations have provided novel insight into the role of stem cells in the colorectal crypt. Chaste is constantly evolving and is being applied to a far wider range of problems. The code provides modules for handling common scientific computing components, such as meshes and solvers for ordinary and partial differential equations (ODEs/PDEs). Re-use of these components avoids the need for researchers to 're-invent the wheel' with each new project, accelerating the rate of progress in new applications. Chaste is developed using industrially-derived techniques, in particular test-driven development, to order to increase code quality, re-use and reliability. The Chaste source code, both for specific releases and the development version, is available to download under an open source Berkeley Software Distribution (BSD) licence at http://www.cs.ox.ac.uk/chaste, together with details of a mailing list and links to documentation and tutorials. In this talk I will provide examples that illustrate the types of problems that Chaste can be used to solve, highlight some scientific studies that are using Chaste and the insights they have provided, and discuss the Chaste team’s collective experience of the development of such software tools in an academic setting.
Modeling tissues using CompuCell3D

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Modeling tissues with cellular and subcellular resolution requires clever representations of single cell complexity. Too much detail can saturate even most powerful computers while too simplistic approaches have usually limited predictive power. As it is usual in sciences the demands and capabilities are orthogonal to each other.

To solve simple cell-sorting problem, in 1992 Graner and Glazier [1] introduced cellular Potts Model (CPM) which currently is one of the most popular ways to model tissues, organs or even organisms with single-cell resolution. CPM represents cells as spatially extended domains and allows relatively faithful model representation of basic cellular behaviors such as adhesion, growth, death, mitosis, chemical secretion, absorption etc. Over the years CPM evolved to become one of the most popular methods used in single-cell-based tissue simulation.

In this talk I will present CompuCell3D (CC3D) simulation environment [2] that allows building running and testing CPM-based models of tissues. CC3D is an open source project with fairly rich set of tools that facilitate model construction, visualization and post-processing. CC3D has Python interpreter that gives modelers great flexibility in customizing their models without requiring code recompilation. In fact bulk of the typical CC3D model is written in Python. I will present brief demo of the CC3D package and conclude the talk by addressing most pressing software-related issues facing multi-cell tissue modeling community.

EPISIM Platform: Graphical multi-scale modeling and simulation of multicellular systems

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Comprehensive multi-scale systems biological models are increasingly developed. The creation of such models is highly complex as they incorporate modeling formalisms originating from various disciplines. As multi-scale models continuously grow more complex, there will be a growing demand for a solid dedicated tool base. Such tools should enable building and sharing re-usable modular model entities that can be semantically linked to a multi-scale model. This requires a clear separation of model complexity and technical complexity. To this end, we developed the EPISIM platform\cite{1,2} for graphical multi-scale modeling and cell-based simulation of multicellular systems.

The EPISIM Platform consists of two ready-to-use software tools called EPISIM Modeller and EPISIM Simulator. These tools allow the creation and simulation of multi-scale cell-based tissue models based on the developed EPISIM model architecture. Within the frame of this architecture multi-scale models are composed of modular models entities that are semantically integrated to tissue models by automatically generated model connector components (MCCs). Each EPISIM tissue model comprises a cell behavioral and a biomechanical model (CBM and BM). The BM covers all spatial and biophysical cell properties. Different BMs (lattice and off-lattice) are offered. These models can be dynamically linked to a CBM which is graphically modeled with process diagrams in EPISIM Modeller. The graphical CBMs are automatically translated into executable code which is loaded by the EPISIM Simulator conducting an agent-based tissue simulation. Moreover, automatic semantic integration of quantitative subcellular SBML models is offered. This allows the combination of discrete (deterministic and/or stochastic) and continuous models on cellular on subcellular scale. Such a model is linked to the tissue scale by the used BM. Reaction-Diffusion models of e.g. chemokines can be integrated with extracellular diffusion fields.

We realized a multi-scaled simulation of human epidermal tissue homeostasis by integration Tyson's cell cycle model into a graphical cell behavioral model of keratinocyte proliferation and differentiation. With another keratinocyte model we were able to reproduce a novel wound repair mechanism \textit{in silico}. This mechanism was revealed by in vitro experiments with our standardized wound model based on full thickness tissue cultures. Finally, we were able to qualitatively reproduce the spatial T-cell arrangement around secretory cells with a chemotaxis model.


CellSys: Modular software for physics-based tissue modelling in 3D

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The task of testing biophysical hypotheses about tissue growth, degeneration, and regeneration generally involves the modelling of processes on many scales ranging from the molecule up to the whole organ level. Advanced imaging methods often reveal characteristic spatial patterns emerging from an interplay involving molecules, cells, functional tissue units, or even central control instances. As it is often not feasible to simultaneously access the different components, the processes underlying the patterns can often not be clarified.

CellSys is a software simulation tool to test hypotheses on monolayers, multi-cellular spheroids, and complex tissues at histological scales that involves the interplay of components on many scales. CellSys combines an image processing and analysis component with a modelling environment. A graphical user interface (GUI) makes setup and execution of model simulations more accessible for non-experts.

One feature of CellSys is that it permits passing statistical information acquired from imaging data directly to the modelling engine, thus models can directly be generated from images. The centre of the modelling engine is an agent-based simulation framework for off-lattice, physics-based tissue models.

Since the spatial and temporal scales involved may span many levels, the resulting simulation code can have an enormous complexity. The software toolkit of CellSys addresses the variety of models by facilitating the programming of new models with existing modules. The software focuses on extensibility of existing models by developers, as well as on reducing the effort to integrate user-interaction with models in a GUI by providing pre-defined tools and data structures. CellSys’ software modules are engineered for re-use with newly developed elements such as new cell types, so that models with new elements are quickly integrated.

While CellSys primarily has been developed to implement off-lattice physics- and centre-based models as those for liver regeneration [1] it is now being extended to feature a module for cells with more resolved surfaces, as well as flows in tissues.

Modeling animal tissues in VirtualLeaf: Towards an off-lattice Cellular `Potts’ model

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Cell-based modeling is a computational modeling paradigm used for problems of biological development. It predicts collective cell behavior and morphogenesis from the underlying behavior of single cells. A widely used cell-based method is the cellular Potts model that represents cells as patches on a regular lattice and represents intercellular forces using a Hamiltonian description. A Metropolis algorithm mimics displacements of the cell-cell interfaces as a function of the Hamiltonian and a random cell motility term. As a disadvantage of the cellular Potts model, lattice artifacts may appear for some parameter choices. Off-lattice methods of course do not suffice from lattice artifacts, and include vertex-based approaches that describe cells as irregular polygons or as the faces in an irregular tessellation Many vertex-based approaches are limited in how well they represent membrane fluctuations: the cell-cell interfaces are straight by definition and deterministic solutions are used, precluding the modeling of phenomena driven by such fluctuations, e.g., differential-adhesion driven cell sorting. Here we introduce a recent extension of our vertex-based cell-based modeling framework for plant development, VirtualLeaf, for modeling cell motility in confluent tissues. VirtualLeaf represents membrane fluctuations by randomly moving the vertices at the cell-cell interfaces depending on a Hamiltonian. To represent relative cell movement, we introduce a new topological rearrangement operator, elementary to T1 and T2 transitions, that we named “slide”. The new model reproduces typical results of cellular Potts simulations, including differential-adhesion cell sorting, and gives new insight into published simulations of topological ordering in epithelial tissues. Although the new method is currently limited to the simulation of confluent tissues, it provides a first step towards an off-lattice solver of the Cellular Potts model.
Biocellion: Accelerating multicellular biological simulation

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Biological phenotypes of interest commonly result from complex, multicellular systems. From hundreds of cells that determine micro-environments to the billions of cells that make up complex organs. At the same time cellular and molecular biologists have unveiled intricate details on the intracellular processes that drive cell behavior and decision-making. Bridging this gap, between microscopic and macroscopic scales, is a critical challenge in systems biology. One potentially powerful tool is multiscale agent based modeling. With this strategy, discrete agents, such as cells, are computationally modeled on a high-resolution grid, which represents the extracellular space. However, the computational complexity can often force modelers to use low-resolution approximations of the biological system. To this end, we have developed Biocellion, a multicellular modeling framework that takes advantage of high-performance parallel computing. Biocellion relieves the modeler of common, yet complex computational problems allowing for computational efficiency and scaleability over multiple cores and machines. In this presentation, we will present the details of this new modeling platform in the context of two examples that demonstrate the computational power and flexibility of Biocellion. First, we will describe the implementation of an epidermal skin model described in the literature. We will demonstrate how Biocellion can be used to produce significant speed up of the simulation. This improved performance gives us the ability to increase the size and complexity of the model, which is important in simulating clinically relevant systems. Secondly, we will describe the use of Biocellion in modeling and design of microfluidic chips for the study of budding yeast. This study demonstrates the ability for Biocellion to quantitatively describe systems with complex geometries at the micrometer length scale. Finally, we will discuss future plans for Biocellion to help foster adoption in the community and provide high performance computing solutions to new, multicellular modeling challenges.
Morpheus: User-friendly modeling of multicellular systems

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Understanding how cells form tissues is not only central to developmental biology, but is also crucial to elucidate tissue and organ function and their dysfunction in disease. Increasing appreciation of this is causing a shift in systems biology to scale up to higher levels of biological organization and, in particular, to integrate molecular with cellular and multicellular systems. This requires novel computational tools that facilitate the construction, simulation and integration of multiscale multicellular models in reproducible and reusable ways. A major challenge in this field is to provide flexibility while maintaining usability and support an effective workflow in the collaboration and model sharing between modelers and biologists.

Morpheus is a user-friendly application for the modeling, simulation and integration of cell-based models, ordinary differential equations and reaction-diffusion systems that allows rapid and flexible development of complex multiscale models without programming [1]. It separates modeling from implementation by using a declarative domain-specific markup language for multicellular modeling. This language allows users to describe their complex models in familiar biological terms and mathematical expression using common infix notation and symbolic identifiers, similar to SBML. Morpheus automates multiscale model integration by appropriately mapping data between spatial models as well as scheduling numerical updates according to the dependencies between symbolic identifiers. The graphical user interface streamlines the modeling workflow by providing tools for model construction, simulation and model exploration as well as archiving and batch processing.

Due to its modular design, Morpheus facilitates the simulation of a range of disparate modeling formalisms, combining algebraic or differential equations, cell-based models and reaction-diffusion systems. To date, it has been applied to the study of collective motion in bacteria, cell fate decisions and pattern formation in the pancreas as well as vascular morphogenesis. The ease of use of this modeling and simulation environment has also proven to be useful in education, for mathematicians and physicists as well as biologists.