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Synergy of vacuolation and cell-cell repulsion in lumen formation

New blood vessels form during physiological and pathological conditions including wound healing and tumor growth. The new vessels subsequently hollow to allow blood perfusion, a process called lumen formation. The mechanisms of lumen formation are a topic of ongoing debate. We present a mechanistic, multi-scale, agent-based (Cellular Potts Model) model to address this debate.

The debate on lumen formation revolves around two alternative, proposed mechanisms: vacuolation and cell-cell repulsion. In the vacuolation mechanism, large intracellular vacuoles coalesce into an intracellular lumen. The alternative cell-cell repulsion mechanism suggests that no intracellular vacuoles form, but that lumens form extracellularly by electrostatic repulsion of adjacent cells. Our model can reproduce lumen formation for both mechanisms by dynamically representing the underlying molecular processes, such as cell surface polarization, pinocytosis, and vacuole formation, coalescence and secretion

We have validated the model by mimicking experimental perturbations in parameter studies that varied the effectivity of the molecular processes. The model produces lumens most effectively when both mechanisms are operational, suggesting that the underlying molecular mechanisms function synergistically. Interestingly, when both mechanisms are active in the model, the hollowing process visually resembles the vacuolation mechanism when simulated in thin vessels, as lumens form intracellulary. In thicker vessels the same mechanisms produces lumens between cells, visually resembling the cell-cell repulsion mechanism. The model thus provides a possible explanation for the contradictory experimental observations that sparked the scientific debate on lumen formation.

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Cellular Potts Models for Cell Migration

Multiscale problems are ubiquitous and fundamental in all biological phe- nomena that naturally emerge from the complex interaction of processes which occur at various levels. A number of both discrete and continuous mathematical models and methods have been developed to address such an intricate network of organization. One of the most suitable individual cell-based model for this purpose is the well-known cellular Potts model (CPM, [1]). The CPM is a dis- crete, lattice-based, flexible technique that is able to accurately identify and describe the phenomenological mechanisms which are responsible for innumer- able biological (and nonbiological) phenomena. In this presentation, we first give a brief overview of its biophysical basis and discuss its main limitations. We then propose some innovative extensions, focusing on ways of integrating the basic CPM, operating at the mesoscopic scale, with continuous approaches accurately modeling microscopic dynamics. The aim is to create a nested and hybrid environment, where the evolution of a biological system is realistically driven by the constant interplay and flux of information between the differ- ent levels of its organization [2, 3]. Our CPM extensions are then tested with sample applications that show a qualitative and quantitative agreement with experimental data [4, 5].In particular, we analyze cell migration within fibrous extracellular matrices and bio-engineered microchannels, showing the relevant role played by a compartmentalized represention of cells, i.e., differentiated in the nucleus and the cysolic region. Finally, we conclude by discussing further possible developments of the method.

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Multiscale techniques in cancer modelling and treatment prediction: A Compucell3D approach

Each individual cancer cell within a cancer cell mass is unique, with its own internal cellular pathways and biochemical interactions. These interactions contribute to the functional changes at the cellular and tissue scale, creating a heterogeneous cancer cell population. Multiscale mathematical models incorporating such complex interactions can help in studying cancer progression and serve as an *in silico* test base for comparing and optimising various multi-modality anticancer treatment protocols. In this presentation we discuss a multiscale modelling approach using the Compucell3D framework, incorporating single cell based intracellular dynamics, the cell microenvironment and cell-cell interactions to study the growth and progression of cancer cell mass. We will then use the model to study cell-cycle-based tumour heterogeneity and analyse how it contributes to the potential chemotherapeutic drug resistance within a heterogeneous tumour.

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Measuring and modeling dynamics of VEGF retention in vascular patterning

How blood vessel networks form is a key question in developmental biology as well as in tissue engineering. Although it is known that chemoattractants such as vascular endothelial growth factor (VEGF) are important in this process, their role in driving endothelial cells to assemble into network patterns remains under debate. The combination of the cellular Potts model (CPM) with reaction-diffusion systems forms an appropriate framework to represent the feedback between VEGF dynamics and endothelial cell motility. We have used this framework in previous work to theoretically demonstrate that cellular networks can arise as a result of chemotaxis towards paracrine VEGF bound to extracellular matrix components [Köhn-Luque et al., 2011]. Now, to test this hypothesis experimentally, we have quantitatively analysed the dynamics of VEGF in a controlled *in vitro* situation of human umbilical vascular endothelial cells (HUVECs) in Matrigel [Köhn-Luque et al., 2013].
Using a variety of techniques such as fluorescence recovery after photobleaching (FRAP), we demonstrate that VEGF accumulates in pericellular areas and decays in a cell-dependent manner and that binding/unbinding dominates diffusion near cells, providing experimental evidence for matrix-retention of VEGF around endothelial cells.
To investigate network formation under realistic biophysical conditions, we parameterized and calibrated the CPM/reaction-diffusion model using our measured kinetic rates for VEGF dynamics. Indeed, simulation of this quantitative multiscale model using the Morpheus modeling environment [Starruß et al., 2014] confirms the formation of cellular networks under these conditions on a realistic time scale.
Together, these theoretical and experimental results demonstrate that matrix binding of exogenous VEGF is a key regulator of vascular pattern formation. Additionally, the cycle of theoretical modeling, experimental validation and subsequent quantitative modeling demonstrates the role and value of multiscale cellular Potts models for the study of complex biological processes in multicellular systems biology.

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The Cellular Potts Model in the context of Cell Surface Mechanics

The biophysical characteristics of cells determine the shape of individual cells and their packing within tissues. Cells can form regular or irregular epithelial structures, round up and form clusters,or deform and attach to substrates. The acquired shape of cells and tissues is a consequence of internal cytoskeletal processes, such as actin polymerisation and cortical myosin contraction, of adhesion molecules within the cell membrane that interact with substrates and neighbouring cells, and of processes that regulate cell volume. Although these cellular processes seem relatively simple, when combined they unleash a rich variety of cellular behaviour that is not readily understandable outside a theoretical framework. We here present through mathematical and computational analysis how the Cellular Potts Model (CPM) can be considered to form an integral part of the larger set of Cell Surface Mechanics models that describe cell surface mechanics using energy-based approaches. We show how forces and tensions can be derived and cell behaviour and tissue packing predicted, allowing for an intuitive, biologically relevant mapping between the modelling parameters and experiments. The biological insights and qualitative cellular behaviours closely agree with the analytical study, not only for the CPM, but even across different model formalisms. This illustrates the generality of energy-based approaches for cell surface mechanics and highlights how meaningful and quantitative comparisons between models can be established. Moreover, the mathematical analysis yields direct links between known biophysical properties and specific parameter settings within the CPM.