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Multi-scale modeling of cells: concepts and open questions

The analysis of tissue organization and tumor growth is inherently of multi-scale nature. Extracellular signal molecules, metabolites, mutations may due to cascades of molecular intermediates modify the behavior and the physical properties of a cell resulting in re-organization processes on the tissue and organ level. Vice-versa, changes on the level of the tissue can feed back to the molecular regulation processes. Limits in computation time requirements and the great complexity of cells and tissues make it impossible to simulate the interplay of the different scales ranging from molecules to whole organs in great detail. On the other hand, many details on smaller scales have only small or no effects on processes on larger scales. In this talk we discuss different individual-based models to tissue organization including hybrid and multi-scale models.

(1) In the first part we introduce individual-based model concepts and demonstrate how they can be used to explain growth in biological models of tumor development, namely, monolayer, multi-cellular spheroids, and Xenografts (Drasdo et. al., J. Stat. Phys. 2007 and refs therein, Radszuweit et. al., Phys. Rev. E, 2009). We consider two model types: cellular automaton models and center-based models. The first model is parameterized by rules while the latter model is parameterized by measurable quantities, and directly represents physical forces between the cells, and between cells and extra-cellular structures. We will critically discuss advantages and pitfalls of the different model types and show how they can be linked to extracellular molecular concentrations to hybrid models.

(2) In a second step we show how intra-cellular, molecular core modules can be embedded into a single-cell-based model to a multi-scale model. We consider several examples: the integration of the beta-catenin core module to mimic the epithelial-mesenchymal transition during cancer invasion (Ramis-Conde et. al., Biophys. J. 2008), intravasation, the process by which a tumor cells enters a blood vessel (Ramis-Conde et. al., Phys. Biol. 2009), mesenchymal stem cell differentiation (Krinner et. al., Cell Prol. 2009; BMC Syst. Biol. 2010), and the change of cell metabolism during liver regeneration after drug-induced damage. (3) Finally

we show how individual-based models can be used to guide the development of continuum models considering growth of disperse and compact tumor phenotypes (Byrne and Drasdo, J. Math. Biol. 2009).