Multi-scale modeling platforms in multicellular systems biology
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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[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 Tysons 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 *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.

[1] T. Sütterlin, S. Huber, H. Dickhaus, und N. Grabe, „Modeling multi-cellular behavior in epidermal tissue homeostasis via finite state machines in multi-agent systems.“, Bioinformatics, Bd. 25, Nr. 16, S. 2057–63, Aug. 2009.

[2] T. Sütterlin, C. Kolb, H. Dickhaus, D. Jäger, und N. Grabe, „Bridging the scales: semantic integration of quantitative SBML in graphical multi-cellular models and simulations with EPISIM and COPASI.“, Bioinformatics, Bd. 29, Nr. 2, S. 223–9, Jan. 2013.