Integrative and multi-level modeling of tissue organization: lessons from liver regeneration
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In this talk we will demonstrate, how the iterative application of a pipeline consisting of confocal scanning microscopy, image analysis and modeling can be used to set up a quantitative spatial-temporal agent-based model of liver regeneration (Drasdo et. al., J. Hepat. 2014), that by simulated predictions successfully guided experiments on spatial tissue organization processes (Hoehme et. al, PNAS, 2010), liver metabolism (Schliess et. al., Hepatology, 2014), and the molecular control of cell proliferation towards new biological insight. We use our image modeling software TiQuant, integrated in an analysis pipeline of standardized imaging protocols for confocal laser scanning microcopy and image processing to infer 3D volume data sets (Hammad et. al., Arch. Toxicol., 2014), to quantify and thereby objectify image information (Friebel, Bioinformatics, in rev.). Spatial temporal simulations are either performed directly in the reconstructed 3D images, or in representative tissue samples obtained by sampling from statistical distributions over the parameters chosen to quantify the image information. Hypotheses on the mechanisms underlying the observed tissue regeneration processes are generated and implemented in our simulation software TiSim (Tissue Simulator). A simulated sensitivity analysis is performed varying each parameter in its physiological range to identify the best agreement between model simulation and observed data. If no sufficient agreement is obtained, the model is modified and the same cycle is repeated. If more than one model mechanism permits to explain the data quantitatively, the model is used to search for an experimental situation where those mechanisms would yield a different result. For liver regeneration, in this way an order mechanism during regeneration of liver after toxic damage, the lack of a ammonia-detoxifying reaction and the timing and spacing of HGF-sources have been predicted.