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Possible cell behavior strategies to escape biomechanical constraints in liver regeneration and tumor growth

In this talk we will show how cells can escape possible biomechanical constraints. We consider the examples of the growing monolayers and multi-cellular spheroids, as well as the proliferation and regeneration pattern in liver after drug-induced damage and after hepatectomy. For each example we compare experimental results with the simulation results of single-cell-based models. Our model of the center-based type considers each cell as an individual unit parameterized by cell- biophysical and cell-biological quantities. Cell migration is mimicked by an equation of motion for each cell, representing all forces on that cell and including the cells micro-motility. Part of the models is parameterized from image analysis of either bright field or laser scanning micrographs for quantitative comparison with data. We demonstrate that the growth kinetics of monolayers and multi-cellular spheroids can be consistently explained if proliferation is controlled not only by molecular factors but also by a biomechanical proliferation control. The same type of proliferation control is able to ensure that unrealistically compressed cell volumes during regeneration after partial hepatectomy in liver does not occur, and that during tumor growth in liver vessels are not pushed out of the tumor cell mass. After drug induced liver damage cells around the so called central veins show massive necrosis. The central vein forms the center of a liver lobule, the repetitive functional unit of liver. Healthy cells must move actively to escape unrealistic compressions. In the absence of such a mechanism, the experimentally observed regeneration and proliferation pattern cannot be reproduced. The models of regeneration of liver after drug induced damage and after partial hepatectomy made predictions that could subsequently be validated.

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