Mathematical modeling of collective cell migration

BSc Thesis with Lisanne Rens

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Biological background

During important biological processes in health and disease, cells migrate collectively. This can be beneficial, for instance during wound healing, but also harmful, for instance in cancer metastasis. Cell migration is regulated by the cytoskeleton, and the shape and flexibility of a cell play important roles. During collective migration, cells adhere to each other, pull on each other and squeeze themselves between others. Furthermore, the cells respond to chemical signals from their environment.

Project description

In this project we will focus on the collective behavior of fibroblasts, that are critical to wound healing and cancer metastasis. Fibroblast behavior is highly regulated by a protein called TGF-β. This protein is present in the extracellular matrix (ECM) that surrounds cells, where it diffuses and interacts with and signals to cells. It regulates proliferation and cell migration: cells move up the gradient of proteins, a process called chemotaxis. TGF-β is produced by macrophages that are clearing the wound, but it is also produced by fibroblasts themselves. TGF-β is produced in a latent (inactive) form bound to the ECM, and can be activated by various chemical and/or physical processes acting on them. For instance, if the latent form experiences a large force, it can get 'pulled out' the ECM and be activated and freely diffuse. Here, a positive feedback-loop exists: TGF-β drives the differentiation of fibroblasts into myofibroblasts, that are more contractile. Because of this higher contractility, myofibroblasts can activate more TGF-β, which again diffuses and triggers more cell differentiation.

Mathematical modeling

You will work with a open-source modeling platform called Morpheus (`https://morpheus.gitlab.io/` developed at TU Dresden, uses XML input files), that makes use of the cellular Potts model (CPM). The CPM is a type of agent-based / cellular automata technique where the tissue and cell shape is dicretized. The shape of a cell deforms as it experiences forces and migrates. The cell behavior can be linked to the level of TGF-β, which is described using partial differential equations. You will model the differentiation of fibroblasts into myofibroblasts, and TGF-β activation and signaling, with the aim of better understanding the role of cell shape and the positive TGF-β feedback during collective migration. As myofibroblasts have a distinct shape from fibroblasts (fibroblasts are generally elongated, whereas myofibroblasts have a more stellar/star-like shape), you will study the effect of cell shape on the system.

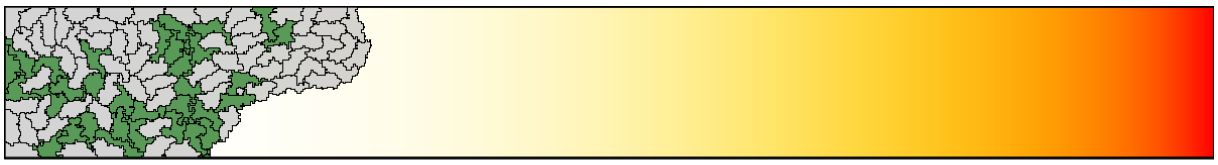

Figure 1: An example simulation of collective cell migration with two cell types (grey and green)