Modelling the Migration Phenomena of Cells

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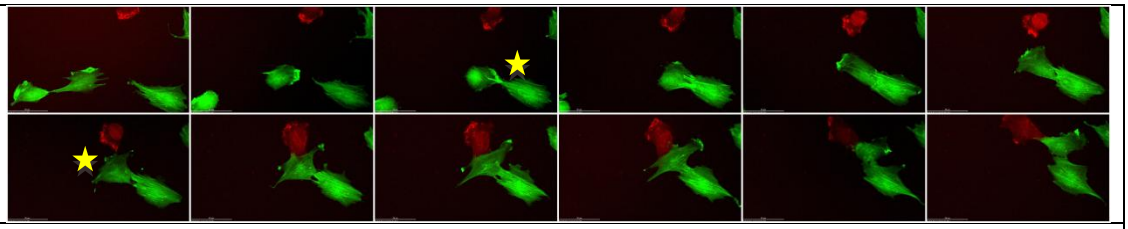
Directional cell migration is of crucial importance during embryonic development and wound healing, while deregulation of cell migration during metastasis is one of the most deadly features of cancer cells. Cell migration involves front protrusion powered by actin polymerisation, retraction of the cell rear by acto-myosin contraction, and traction mediated by integrin-containing adhesion sites that link the cytoskeleton to the extracellular matrix. In addition, it is thought that microtubules play an important role in maintaining cell polarity and steering migration direction.

For cells to reach their destination and desired distribution in the body, they need to communicate with each other and integrate signals from the extracellular space. In this project, we will use human pigment epithelial cells that form a single cell layer in the retina. In culture, these cells distribute evenly on 2D substrates while at the same time maintaining a minimal density. Thus at very low density these cells form colonies, this means that cells with a common ancestor stay together. At higher densities, cells freely explore the 2D space, but their behaviour appears to be guided by several principles rather than randomness. This is based on observations that cells can migrate in a straight line for several hours, thus internal feedback loops can robustly support cell polarity even in the absence of external gradients. However, we do observe that repolarisation and turns are almost always induced upon cell-cell contact or apparently spontaneously.



Consecutive frames of a time-lapse microscopy video depicting two consecutive contact-inhibition events (yellow star).

Aim of this project is to understand which guidance principles underlie these directional decisions in cell migration. You will simulate cell behaviour and generate synthetic data allowing for later comparison with ground truth experimental data collected by Straube in her lab using long-term imaging of cells at various densities. Guidance principles for which we want to generate simulations are focussing on contact-induced turns and spontaneous turns and take into consideration the distance to the nearest neighbour(s), traces left in the substrate from previous cells, time since last cell-cell contact, angle and position of cell-cell contacts. You will investigate finite-state machines [1] and petri nets [2] for modelling contact-induced and spontaneous turns in a non-deterministic fashion. The simulations will produce a graphical output to show how well these strategies allow distribution and colony formation.

In a related miniproject we will develop object-tracking algorithms, which will allow tracking cells and contact events in experimental data. A long-term goal of these studies and a possible **PhD project** derived from this miniproject is to develop a unified model of "random" cell migration that is based on statistical analysis of experimental data and in silico modelling of the major principles governing the migration of cells.

Bibliography:

[1] P. Boca *et al*. (2010) Formal Methods: State of the Art and New Directions, Springer.
[2] F. Bause and P. Kritzinger (2002) Stochastic Petri Nets – An Introduction to the Theory, Vieweg Verlag.