Insights from modeling metabolism and amoeboid cell motility in the immune system

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Summary

The body is very active during an infection: it releases inflammatory compounds, raises the body temperature, and prompts immune cells to detect the infection. In this thesis, we study metabolism during infection, as well as the motion and navigation of immune cells. To this end, we develop mathematical and computational models.

In chapter 2, we study the metabolism of zebrafish larvae infected with *Mycobacterium marinum*, a relative of the bacterium that causes tuberculosis. We improve a published whole-genome metabolic network reconstruction of zebrafish metabolism, called ZebraGEM. Besides improvements on the network pathways, the major improvement in ZebraGEM 2.0 is the addition of Gene-Protein-Reaction associations (GPRs). These GPRs links the enzymatic reactions in the network to the genes coding for those enzymes. This makes it possible to predict changes in metabolic routes under gene knockouts. The model predicts reduced growth in 9% of the knockouts. From these knockouts, 15% also shows an aberrant phenotype in experimental studies. Morever, all growth reducing knockouts have a human homolog associated with metabolic diseases. The GPRs also facilitate integrating quantitative gene expression data into the model by limiting reactions with lowly expressed genes. We use this to predict zebrafish metabolism in control larvae and *Mycobacterium marinum*-infected larvae. The model predicts that infected larvae grow more slowly than uninfected larvae. Furthermore, four day old infected larvae have reduced histidine metabolism, in agreement with experimental observations.

Infections are cleared by immune cells. The next chapters study the motility and navigation of immune cells. In chapter 3, we study how the extracellular matrix, the protein network that surrounds most of our cells, influences the motility of immune cells. To this end, we extend a published model for persistent cell motility with the adhesion of cells to the matrix. The model can display multiple types of motility, which can be roughly divided into random walks with short or long persistence times (the time a cell will continue moving in the same direction), or a motility type where cells are stuck to matrix and pivot around their adhesive patch, and where the explored area remains small. On short time scales, we also observe accelerations when the cells have sufficient grip on the substrate alternated with the loss of grip and speed. Altogether, the model shows that the dynamics of adhesion between the cell and its surroundings regulate the speed and persistence of cell motility.

In chapter 4, we study a phenomenon called topotaxis: the shape of the environment guides the cells. One such environmental cue is the

density of obstacles such as other cells and extracellular matrix. As a model for obstacles within a tissue, we use a silicon pillar grid on which cells move in between the pillars. To study the effect of obstacle density, we change pillar density from left to right. As a model for motile immune cells, we study *Dictyostelium discoideum* cells, an amoeba that moves similar to immune cells, but can be cultured more easily. Previous studies on *D. discoideum* cells in such grids showed that cells drifted, on average, to the less dense area of the grid, i.e.: the cells perform topotaxis. A previous model of persistently moving particles showed that the loss of persistence upon collision can explain topotaxis in part. However, the particles drifted slower towards the less dense area than observed in cells. The Cellular Potts model (CPM) is a more realistic model for *D. discoideum* cells than the particle model, because it takes the malleability of cells into account. We model persistent cell motion in two ways: one is similar to the persistently moving particle model, the other is a variation of the CPM and closely resembles the amoeboid motion of immune cells and *D.discoideum*. Both persistence models perform topotaxis, the first model shows 1-2% of the cell speed. The second model shows more efficient topotaxis of 3-6% of cell speed and better resembles the experimental data of *D. discoideum* cells of 2.5-4% of cell speed. Further analysis shows that the more efficient topotaxis can be explained by the cells from the second model losing more of their persistence upon collision and sooner reorient themselves after that.

Upon infection or wounding, macrophages and neutrophils are recruited to the infected or wounded site by signalling molecules. In chapter 5, we study the trajectories of macrophages and neutrophils in zebrafish larvae upon a tailfin cut. We specifically study two mutants of the TLR2-signalling pathway which plays a role in recognizing microbial molecules: *tlr2* en *myd88*. Neutrophils of wild type larvae and mutant have similar speeds and displacements, but the mutant neutrophils show a less directed motion towards the wound. Mutant macrophages showed a lower speed beside a less directed motion towards the wound compared to wild type macrophages. We conclude that the TLR2 signalling pathway plays a role in the directed motion in wild type during the recruitment of immune cells upon wound healing.

The thesis ends with a summarizing discussion and suggestions for future work. We discuss how cells integrate multiple environmental cues, such as chemical and topographical signal, the interplay between cell motion and cell environment, the similarities and differences of motility parameters between cells of *in vitro* experiments and cells in live organisms, and combining metabolic models with the CPM.