Tuesday contributed talks 1

Leonie van Steijn

Leiden University

"Regulation of persistent cell migration by the extracellular matrix"

Amoeboid cell motility is an important process in many eukaryotic cell types such as immune cells. Adequate immune cell motility is necessary to clear infections. The motility of cells is affected by interaction with the extracellular matrix (ECM) as well as by chemoattractants and other molecular signals. To study cell-ECM interactions, we consider two situations that we study using a combination of experiments and mathematical modeling. These two environmental cues are also present for in vivo immune cells as they move through tissue filled with other cells and ECM. First is topotaxis where cell motion is guided by the topography of the environment. As a model of amoeboid cell motility through pores in the ECM, we study the motility of Dictyostelium discoideum cells on a substrate covered with microscopic pillars. The pillars are spaced widely enough to let the cells through and there is a gradient from densely packed pillars to more widely spaced pillars. Here the cells perform a random walk with a slight drift to the more widely spaced area. Using a Cellular Potts model, we study how cell persistence mode affect topotaxis using the actin-derived persistence of the Act-model and an active Brownian particle-based persistence. We find that both modes result in topotactic drift comparable to the experimentally found drift, but the actin-based persistent cells show a more efficient drift. Next we study how ECMs of more dense structure affect the motility of B-lymphocytes. B-lymphocytes show different motitility modes on different matrices: a slow but persistent random walk on collagen IV with low cell-ECM contact area and a faster Brownian walk on fibronectin with high cell-ECM contact area. Expanding the Act-model with cell-ECM bonds that can form, grow and shrink, and rupture, we can obtain different cell motion with by using different rupture energies and new bond formation. Simulated cells mostly show a persistent random walk, with low persistence and low diffusivity for poorly attached cells, and high persistence and high diffusivity for dynamically attached cells. Cells with sustained attachement show pivoting behaviour which was persistent in short time-scales, but subdiffusive on long time scales. We conclude that cell-ECM interactions can affect cell motility in multiple ways. ECM pores can steer cells from denser to looser ECM areas through topotaxis, whereas attachment to the ECM can alter the motility type of cells. Combined, these cues could lead to a range of different possible motility types. How in vivo cells integrate these cues together with other cues such as chemokine signalling is subject for further studies.

Emine Atici Endes

Heriot-Watt University

"Modelling Scratch Wound Healing Assay using an Improved Non-local Equation"

Wound healing assays, in the other words scratch assays, are based on observing cells migrate into a wound or open space created an artificial scratch on a monolayer of cells. The assays are commonly used to quantify the rate of gap closure, which is a measure of the speed of the collective motion of cells and they are able to evaluate cell migration usefully in vitro wound healing. Obviously, the actual wound is more complex than the wound is done by making a scratch on a cell monolayer, however; the scratch wound assay is a technically simple, inexpensive, and fast method for analysis of cell migration and does allow modeling and testing of cell migration under well-defined conditions. We introduce a novel continuum model that extended the derived continuous model of a single population of cells. To derive our continuum model, we consider an integro-advection-diffusion-reaction equation for the adhesion of the single-cell motility in one dimension. And in this specific study, we analyse the applicability of our model to scratch-wound healing assay based on some experimented cases.

Bradford Peercy

University of Maryland, Baltimore County

"A Minimal Model for STAT regulation in Initiation of Clustered Border Cell Migration"

Cell migration is pivotal in development as well as homeostasis, immune function, and pathology. It is important to understand the molecular activity that allows some cells to assume the migratory cell fate. The critical interaction we consider, in Drosophila melanogaster, is between the well-conserved Signal Transducer and Activator of Transcription (STAT) and downstream transcription factors Apontic (APT) and Slow Border Cells (SLBO). We derive a detailed mechanistic mathematical model and then reduce it to the three main transcription factors. The reduction maintains the steady state behavior including a bistable switch between stationary and migratory states. However, the basins of attraction vary, and the manifolds separating the basins can be associated with delays in cell fate decisions. Experiments with miRNA disruption of cell migration compare well with the equivalent model manipulation.

Ulrich Dobramysl

University of Cambridge

"Sensing and triangulation of chemical gradients"

In many biological processes, in particular embryonic and brain development, cells need to follow chemical gradients to arrive at a precise location. They need to determine the direction and position of sources releasing diffusing molecular guidance cues from information gathered by receptors located on the cell membrane. Using matched asymptotics, we developed a model that relates the chemical fluxes to receptors to the gradient source position. We learned that simple direction sensing using comparison of fluxes is strongly limited. In contrast, full recovery of the gradient source position from receptor fluxes is possible even over relatively large distances. We quantify the uncertainty associated with location triangulation and show how the accuracy depends on the number and distribution of receptors.

Dimitris Goussis

Khalifa University, UAE

"Endogenous and exogenous IgG competing for FcRn receptors: multi-scale analysis"

In many cases of IgG subclass deficiencies or FcRn malfunction, it is desired to elevate the levels of IgG, in order to strengthen the immune system. Conversely, in cases in which pathogenic or excess IgG antibodies are the aetiological agents, it is desirable to lower the IgG levels, in order to alleviate the symptoms; as in autoimmune diseases. One of the most efficient approaches to decrease the pathogenic IgG levels is to enhance its catabolism by administering recombinant IgG, which competes with the endogenous for the binding to the FcRn receptor. It was shown experimentally that the administration of exogenous IgG with high affinity, delivers better results in enhancing the degradation of the endogenous pathogenic IgG, than the classical intravenous immunoglobulin (IVIG) treatment, which is only effective in high doses. In this study, the competing interactions of the exogenous IgG and endogenous (pathogenic) IgG, when binding with the FcRn receptor are analyzed, on the basis of the model proposed in. A multi- scale analysis is carried out by employing the Computational Singular Perturbation (CSP) algorithmic methodology. With this algorithm, the constraints that develop progressively, form the start of the process to the fixed point, are identified, along with the reduced model that governs the evolution of the system within these constraints. CSP provides the tools for system-level understanding, by identifying the physical processes that (i) contribute to the emergence of the constraints (equilibria), (ii) drive the slow evolution of the system within these constraints and (iii) are responsible for the development of the fast and slow timescales in the dynamics of the model. The objective of this manuscript is to provide meaningful insights regarding the dynamical properties of the competitive binding of the endogenous and exogenous IgG with the FcRn receptor. Given that the modulation of the IgG-FcRn interaction allows for the control of the IgG half- life, the analysis provides a guideline to engineer effective recombinant IgG antibodies, in order to reduce the endogenous IgG levels.