Thursday, July 26th, 14:00 **Room: T.B.A.**

MINISYMPOSIUM

MIGRATION AND INVASION OF EUKARYOTIC CELLS: FROM EXPERIMENTS TO MODELS

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Minisymposium Keywords: Cell migration, cancer, angiogenesis, living tissues, collective motion

If most living cells have the ability to move, the motility of eukaryotic cells inside the tissue or the organism they live in displays specific aspects and specific challenges to the modelling effort. They deserve to be studied theoretically and numerically because eukaryotic cells move to achieve a variety of functions (e.g. development and growth from the beginning of the embryonic stage, wound healing and angiogenesis for the maintenance of the organisms), and because their motion is a key factor of progression of severe diseases (like in cancer cell invasion, metastatic progression and cancer neoangiogenesis).

Their specificity, as compared to e.g. bacteria, lies in the following empirical observations: they often have to move across an heterogeneous, complex medium, such as an extracellular matrix, their migration may show three-dimensional features that cannot be modelled in low dimensional spaces, and, in many situations, their migration involves collective effects, like indirect interaction through the remodelling of the environment (cells coming after may benefit from the modifications triggered by the first cell), cooperation of migrating cells, or "speciation" in terms of leaders and followers in a population of migrating cells. Therefore, a first challenge to the theoretician is to cope with the interactions between individual cells and to really deal with a population or a "crowd" of cells. The migration of a population of cells cannot be modelled as the mere superposition of individual motions, and studying the migration of a single cell may be a useful first step but is definitely not sufficient to address the full problem.

A second challenge is to take into account the environment where the migration takes place, which is often complex (made of different molecules, having a three-dimensional structures with a typical length scale of the order of a cell's size, which prevents to approximate it as a continuous medium,...), heterogeneous, and dynamically modified by cells (e.g. in angiogenesis or extracellular matrix remodelling).

The aim of this Minisymposium is to shed light on recent developments of modelling works of phenomena observed in experiments about migration or invasion of eukaryotic cells in different contexts, notably tumour progression. We will see examples involving a variety of tools, from discrete and stochastic simulations using cellular automata or cellular Potts models to PDE-based approaches.

The progress in this topic should have concrete impacts in biological and clinical research, allowing a better understanding of interactions between moving cells in the experiments, a reduction of the need of experiments thanks to more reliable semi-quantitative models, stimulation for new experiments, and, in the mid- to long term, advances in treatments of diseases.

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MODELING OF MECHANICAL AND CHEMICAL CELL-MATRIX INTERACTIONS DRIVING CELL MIGRATION AND INVASION

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Joint work with Lisanne (E.G.) Rens and Sonja Boas (CWI and U Leiden)

Keywords: Cell-extracellular matrix interaction, Mechanobiology, Cellular Potts model, Hybrid modeling, Angiogenesis.

During embryonic development, the behavior of individual cells must be coordinated to create the large scale patterns and tissue movements that shape the whole embryo. I will first discuss our recent multiscale model of angiogenesis in fibrin matrices; here the breakdown of fibrin and release of growth factors coordinates collective cell invasion. Apart from chemical signaling, it has recently become clear that mechanical cell-cell communication is equally important in the coordination of such collective cell behavior. To get a better understanding of mechanical cell-cell communication, we are developing computational models of cells and the extracellular matrix (ECM) - the hard or jelly materials (e.g. collagens, fibronectin) that form the micro-environment of many cells. The models are detailed enough for explaining the response of individual cells to the mechanical properties of the ECM, and sufficiently coarse-grained so as to allow for efficient computational upscaling to the tissue level and beyond. Recently, detailed measurements and new mathematical models of the kinetics of individual focal adhesions (the macromolecular assemblies responsible for mechanical cell-ECM interactions) have become available. In our ongoing work we have included kinetic descriptions of focal adhesions in our models. We will sketch how this approach will allow us to mechanistically predict changes in cell shape and in collective cell behavior from changes in focal adhesion kinetics. Altogether, our models suggest simple mechanisms by which local, chemical and mechanical cell-ECM interactions can assist in coordinating cell behaviour during collective migration.

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LEADING THE PACK: LEADER AND FOLLOWER IN COLLECTIVE CANCER INVASION

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Keywords: Cancer, Cell migration, Cellular heterogeneity, Collective motion.

A major reason for cancer treatment failure and disease progression is a heterogeneous composition of tumor cells at the genetic, epigenetic, and phenotypic levels. While tremendous efforts have been made to characterize the makeups of single cells, much less is known about interactions between heterogeneous cancer cells and between cancer cells and the microenvironment, especially in the context of cancer invasion. Indeed, clinical studies show that invasion predominantly occurs via collective invasion packs (heterogeneous populations of interacting cancer cells), which invade more aggressively and result in worse outcomes. Many fundamental questions remain: What is the division of labor within the heterogeneous invasion pack? How do the invasion packs remodel the extracellular space? How does the 3D ECM environment modify the social interaction network within the pack? Can this interaction network be exploited to devise novel treatment strategies? I will present recent experimental and modeling efforts that address these questions. Using non-small cell lung cancer spheroids in collagen, we show that the invasion packs consist of at least two distinct cell types: the leader and the follower. In vitro and in silico experiments show that leaders and followers engage in mutualistic social interactions during collective invasion. Analyzing this social interaction network can potentially reveal the 'weak-links', which when perturbed can disrupt collective invasion.

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IMPACT OF CELL MIGRATION PLASTICITY ON TUMOR GROWTH AND INVASION: A CELL-BASED APPROACH

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Keywords: Cancer, Cell migration, Cellular automata, Collective motion.

At any stage of tumor growth and invasion, cells are confronted with specific conditions of their microenvironment. Tumor cells possess the remarkable ability to adopt their migratory phenotype to the current specifics of the cellular and non-cellular microenvironment, a feature called phenotypic plasticity. A deeper understanding of how this plasticity affects tumor growth and dissemination can guide the identification of tumor-therapeutic targets. We model the cellular adaptation to the local cell density and the local density of the extracellular matrix in an suitably extended framework of cellular automata, and analyze the resulting models theoretically and numerically. Thereby we propose key model parameters for tumor growth and invasion that can be addressed potentially by future experiments. [1, 2, 3]

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FRONTS IN POPULATIONS OF SELF-REGULATING CELLS

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Keywords: Cell population, Homeostasis, Propagating waves.

To achieve homeostasis, i.e. maintain a uniform and constant density in a whole organ, living cells need to balance cell death with cell proliferation in an active and relatively controlled way. If they proliferate too much, they can leed to a tumour, then cancer. If they don't proliferate enough, at the right place and at the right time, the function of the tissue will be impaired and the organ will be defective. Therefore, cell proliferation must exactly compensate, in the long term, cell death or cell loss, while responding as quickly as possible to disturbances like (relatively small) injuries.

In the case of oligodendrocyte precursor cells (OPC), which build up the most abundant proliferating cell population in the adult brain and are believed to trigger some of the brain tumours, it has recently been shown experimentally that homeostasis is achieved through several phenomena including induction of cell death in regions where cells are too dense and induction of cell proliferation in the boundaries of regions where cells have been lost. In some circumstances, this can lead to detectable oscillations in the local density of cells.

We model quantitatively these phenomena in an ideal population of identical cells thanks to a cellular automaton, both in discrete and continuous space, in 2D and in 3D. In the case of almost uniform conditions, we observe oscillations of the cell number during relaxation to homeostasis. Using a simple mean field-like analytical approach, we are able to reproduce these collective oscillations and understand how their features (notably their period) are related to parameters of the cells' individual behaviour.

In the case of non-uniform conditions, we observe intriguing phenomena such as propagating waves, spiral waves, large transient oscillations, and even population extinction. They depend sometimes in counter-intuitive ways on parameters like the rate of proliferation and the rate of apoptosis.

We verify that they are robust against changes of dimensionality or even space structure (lattice or free space). Using extensive simulations in quasi-1D geometries, we study numerically the properties of the fronts and the influence of the (few) model parameters on their speed and shape. Alltogether, this shows that achieving homeostasis is not a straightforward task.

References

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