

MINISYMPOSIUM

MULTI-SCALE MODELS OF CELL BEHAVIOUR

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Mathematical models are vital interpretive or predictive tools used to assist in the understanding of cell migration. There are typically two approaches to modelling cell motion, either micro-scale, discrete or macro-scale, continuum. The discrete approach, using agent-based models (ABMs), accounts for properties at the cell-scale, while the continuum approach, often presented as a system of partial differential equations (PDEs) or stochastic partial differential equations (SPDEs), provides a global description of the migration at the population level. Continuum models have the advantage that they are generally more amenable to mathematical analysis and can lead to significant insights for situations in which the system comprises a large number of agents, at which point simulating the ABMs becomes computationally expensive. Nevertheless, finding the appropriate continuum model to describe the collective behaviour of a system of moving agents can be a difficult task and continuum models are often specified on a phenomenological basis, which reduces their predictive power. It is essential, therefore, to establish direct connections between micro-scale properties, which can be inferred directly from experimental data, and macro-scale dynamics.

In this mini-symposium we will discuss the latest advances in connecting individual-level and population-level models of cell behaviour. We will bring together some of the leading experts in the field with the purpose of sharing knowledge, techniques and expertise. This exchange will help to seed ideas and generate new collaborations for the next generation of efficient multi-scale methodologies.

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MODELLING PERSISTENCE IN MOTION OF INTERACTING CELLS AT MULTIPLE SCALES

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Joint work with Christian A. Yates (University of Bath)

Keywords: Persistence, Velocity-jump process, Exclusion process, Cell aggregation.

Persistence of motion is the tendency of an individual to maintain motion in a direction for short time scales without necessarily being biased in any direction in the long term. One of the most appropriate mathematical tools to study this motility mechanism and its implications at multiple scales in a multiple-agent system is the *velocity-jump* process. In the absence of agent-agent interaction, the system can be described at the population level using the hyperbolic telegraph equation. In the long time limit the behaviour of this model is diffusive. However, when agents interact with each other directly, a diffusive limit has not previously been obtained. In this talk, I will present a generalisation of the velocity-jump process on a two-dimensional lattice with three forms of agent interaction. This generalisation allow us to take a diffusive limit and obtain a faithful macroscopic description. I will present the properties of the model and elucidate some of the key characteristic features of interacting persistent agents, present at both the micro- and macro-scales.

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BIOLOGICAL LATTICE-GAS CELLULAR AUTOMATON MODELS FOR THE ANALYSIS OF COLLECTIVE BEHAVIOUR IN INTERACTING CELL POPULATIONS

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Keywords: Lattice-gas cellular automata, Collective cell migration.

As a cellular automaton, a BIO-LGCA is defined on a regular lattice, where the nodes of the lattice take a certain number of discrete states. As a lattice-gas, the state space of a BIO-LGCA is related to the lattice geometry. Each node can be occupied by “biological agents”, e.g. biological cells, characterised by their velocities which are restricted to the unit vectors connecting a node to its nearest neighbors. Agents move along the links and interact on the nodes of the lattice. This interaction can change the number of agents at individual nodes (birth/death processes) and may depend on the states in neighbouring nodes which allows to model collective effects. Meanwhile, the BIO-LGCA has been established as discrete lattice- and agent-based model which permits multi-scale analysis and efficient large-simulations [2].

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SEMBLANCE OF HETEROGENEITY IN COLLECTIVE CELL MIGRATION

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Keywords: Neural crest migration, Leader, Motion.

Cell population heterogeneity is increasingly a focus of inquiry in biological research. For example, cell migration studies have investigated the heterogeneity of invasiveness and taxis in development, wound healing, and cancer. However, relatively little effort has been devoted to exploring when heterogeneity is mechanistically relevant and how to reliably measure it. Statistical methods from the animal movement literature offer the potential to analyze heterogeneity in collections of cell tracking data. A popular measure of heterogeneity, which we use here as an example, is the distribution of delays in directional cross-correlation. Employing a suitably generic, yet minimal, model of collective cell movement in three dimensions, we show how using such measures to quantify heterogeneity in tracking data can result in the inference of heterogeneity where there is none. Our study highlights a potential pitfall in the statistical analysis of cell population heterogeneity, and we argue that this can be mitigated by the appropriate choice of null models.

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INCORPORATING A MULTISTAGE REPRESENTATION OF THE CELL CYCLE INTO MODELS OF CELL MIGRATION

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Keywords: Fisher wave, Multi-stage cell cycle, Erlang distribution, Markov property, Multiscale.

The stochastic simulation algorithm commonly known as Gillespie's algorithm (originally derived for modelling well-mixed systems of chemical reactions) is now used ubiquitously in the modelling of biological processes in which stochastic effects play an important role. However, Gillespie's algorithm is routinely applied to model biological systems for which it was never intended. In particular, processes in which cell proliferation is important (e.g. embryonic development, cancer formation) should not be simulated naively using the Gillespie algorithm since the history-dependent nature of the cell cycle breaks the Markov process.

Here we suggest a method of modelling the cell cycle that restores the memoryless property to the system and is therefore consistent with simulation via the Gillespie algorithm. By breaking the cell cycle into a number of independent exponentially distributed stages we can restore the Markov property at the same time as more accurately approximating the appropriate cell cycle time distributions. We demonstrate the importance of employing the correct cell cycle time distribution by recapitulating the results from models incorporating cellular proliferation. In particular, we analyse the effect of incorporating the multi-stage cell cycle distribution on the wave-speed in a pulled-front Fisher wave from both individual-based and continuum perspectives

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