Modeling and Computational Approaches to Individual and Collective Cell Movement in Complex Environments

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Overview of the Field

Locomotion of cells, both individually and collectively, plays an important role in development, the immune response, wound healing, and cancer metastasis. Movement requires force transmission to the environment, and motile cells are robustly-designed nanomachines that often can cope with a variety of environmental conditions by altering the mode of force transmission – which ranges from crawling to swimming. The shape and integrity of a cell is determined by its cytoskeleton, and thus the shape changes that may be required to move involve controlled remodeling of the cytoskeleton. Motion *in vivo* is often in response to extracellular signals, which requires the ability to detect such signals and transduce them into the shape changes and force generation needed for movement. Thus the nanomachine is complex, and while much is known about individual components involved in movement, an integrated understanding of single cell motility, even in simple cells such as bacteria, is not at hand. At the next level, collective movement requires coordination of these nanomachines, which introduces another level of complexity.

This complexity has stimulated mathematical modelling and computational simulations of cell and tissue movement at various levels, which has advanced our understanding of movement on multiple time and space scales. Existing mathematical models are based on high-level macroscopic models or detailed mechanical descriptions, leading to transport equations for density distributions in position, velocity and internal state, or to macroscopic continuum descriptions of spatio-temporal population densities. Computational models include continuum models, individual-based models, hybrid models, and stochastic models, and each type has led to new insights about movement and new mathematical and computational challenges.

This workshop brought together theoreticians and experimentalists to discuss the current state of knowledge about the various levels of experimental and theoretical problems of cell and tissue movement. In engaging talks we learned about the newest developments, engaged in lively discussions, and identified interesting open questions.

Recent Developments and Open Problems

Movement is a very complex process that involves the spatial and temporal control and integration of a number of subprocesses, including the transduction of chemical or mechanical signals from the environment, intracellular biochemical responses, and translation of the intra- and extracellular signals into a mechanical response. Recent experiments have shown that numerous cell types display enormous plasticity in locomotion in that they sense the mechanical properties of their environment and use the most efficient strategy for

moving in a given context. This adaptability has significant implications for developing new treatment protocols for cancer and other diseases, for it implies that it is essential to understand the processes by which cells detect extracellular chemical and mechanical signals and transduce them into intracellular signals that lead to force generation, morphological changes and directed movement.

In several talks the force generation mechanisms of cells in tissues were discussed. It became evident that many mechanical processes work in concert such as cell-cell adhesion, cell deformations, cell cytoskeleton dynamics, pressure differences, osmotic pressures, crawling, swimmig, and gliding. So far individual models have focussed on one of these mechanisms, but they have never been considered in combination. Modelling of the combination of different movement modalities is a big challenge for future research.

At the tissue level, collective cell movement requires cell-cell communication to maintain the integrity of the tissue and to control the mechanical forces needed to move. Cells are exposed to complex interactions with other cells, with chemical cues, and with mechanical constraints, all of which are used to determine how to move. Cells such as immune cells or fibroblasts move individually, while others in tissue development such as Drosophila border cells, move in tightly controlled cell collectives.

Mathematical modeling and computational analysis have played an important role in understanding how the numerous processes involved are integrated. The complexity of the underlying processes led to a broad spectrum of mathematical and computational models at different levels of description, ranging from the single-cell and sub-cellular levels to the population or tissue level. The topics of our workshop can be roughly classified according their biological scale as follows.

Meso scale: The mesoscale denotes a continuum description of individual cells either at the level of the biochemical and mechanical behavior of individual cells, or between the molecular and macroscopic levels. At one level detailed models are developed for individual cells to understand how they integrate signals to determine movement, which was a major topic of the workshop. At a higher level cells are characterized by their position, velocity, and internal variables, and population-level migration is then characterized using transport equations for the cell population density. This typically leads to integro-partial differential equations in which changes of the cell velocity are modeled using an integral operator of the type used in the Boltzmann equation from gas kinetics. This approach was introduced in [Othmer et al 1988] in order to describe the dispersal of living organisms by way of stochastic processes. This approach has been applied in a number of different contexts such as chemotaxis [Othmer, Stevens, Hillen, Chalub, Perthame et al.] cancer spread [Hillen, Painter, Swan] and generalised to a *kinetic theory of active particles* (KTAP) [Bellomo].

Macro scale: Macroscopic population-level descriptions are frequently based on laboratory experiments dealing with chemotaxis, hapotaxis, and tissue mechanics. Macroscopic models usually take the form of PDEs [Horstmann, Hillen, Painter, Marciniak-Czochra, Winkler, etc.], possibly derived from a kinetic description of the meso level [Othmer, Hillen, Perthame], or simply phenomenological models of various forms of taxis and cell-cell-adhesion [Armstrong, Painter, Sherratt].

Another direction of macro-scale modeling employs continuum mechanics. The mechanics of cell movement in various environments is based on mass, momentum and energy balances for a tissue or fluid with embedded cells [Tosin, Preziosi, Ambrosi, Byrne, Chaplain] . The rheology, stiffness, viscocity, of the underlying tissue is important, and these details can be used to describe the motion of single cells in a continuum in great detail. A full analysis of these complicated models, which employ high-level descriptions of cell and sub-cellular processes, is just beginning, and another focus of our workshop was to develop a better understanding of where such models are appropriate for describing cell movement. As this theory is rather new, it formed an stimulating point for discussions between theoreticians and experimentalists.

Multiscale approaches: A major question that arises naturally from the previous discussion is how cellular and sub-cellular level dynamics can be embedded in a continuum description without losing essential information of cell movement. Several experts on these scaling methods were present and details on hybrid models, scaling methods, mean-field methods, perturbation methods, and homogenizations were discussed during the meeting. Examples of *Dictyostelium discoideum* movement, cancer growth, and Drosophila development illustrate some of the issues concerning numerical and computational methods that arise in multiscale modeling. At present, efficient numerical algorithms are available to predict the shapes and evolution of cells described by minimal models, but new mathematical models that better describe the membrane and cytoskeleton require significant extensions of current computational and mathematical methods.

It is a very timely research problem to establish a relationship between individual cell behaviour, their function, movement and adhesion, and the macroscopic physical and mechanical properties of tissues.

Presentation Highlights

In addition to traditional contributed talks we started each day with a 2h pair-talk. Here we paired a theoretician and an experimentalist who have worked together on a common modelling problem. We encouraged the speakers to present the research as a dialogue between biology and mathematics, to see how ideas develop and how collaboration can work. The pair-teams were as follows.

- Paul Kulesa and Philip Maini, on modelling of embryonic development
- Luigi Preziosi and Nadia Loy, on modelling re-orientation under stretch
- Helen Byrne and Tomas Alarcon on angiogenesis
- Mark Chaplain and Alf Gerisch, on mechanical models for pattern formation in tissues

This combined format worked very well and led to lively discussions. Many remarked that they were a highlight of the conference.

In addition, the fact that we had twenty-five hours of talks over five days allowed us to invite a broad spectrum of speakers, including numerous junior mathematicians and biologists. These junior scientists were able to present unpublished work and gain important feedback on their work, as well as gaining exposure to the work of other young scientists. This led to numerous new contacts between researchers in the area cell motility.

The online format of the conference allowed us to extend participation beyond the group of speakers, and the total world-wide number of participants was close to 100.

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