Report on BIRS workshop 05w5004
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The BIRS conference "Mathematical Biology of the Cell: Cytoskeleton and Motility" (05w5004) took place on July 16 - 21, 2005. The motivation for this workshop was that cell biology and mathematics have traditionally been distinct areas of science, each with its own techniques, culture, and set of interests. Until recent times, the only points of contact were a few key biophysical concepts (with relevant mathematical formulation) that were applied in a cell biology context. However, this situation has changed within the last 5-6 years, as a result of explosive growth of computational biology that was accompanied by the use of mathematical, as well as of purely computational methods to gain a deeper understanding of the cell. Partly, this growth was stimulated by an outcome of a number of seminal publications that crossed a barrier between cell biologists and mathematicians. Some of these, notably [1-3], are now cited throughout the biological literature, because they helped to answer important questions of interest to biologists. At the same time, this theoretical work was based on sophisticated methods of applied mathematics (singular perturbation theory, dynamical systems, nonlinear partial differential equations) in the form of novel mathematical models. Much work is now carried out at the interface between the two sciences, in partnerships between experimentalists and theoreticians.

The revolutionary factor is this 'marriage' of mathematics and biology, i.e. an unprecedented level of communication and close collaboration between mathematical modelers and experimental biologists. In a way, cellular and molecular biology have matured into a science akin to classical physics, where theory and experiment go hand in hand, one informing the other. This situation, however, presents a set of formidable challenges. First, the quantitative biological data and mathematical models have to be converted into mutually compatible format. Second, a new generation of researchers must be educated in both disciplines, and trained to bridge the traditional gaps between the two cultures. A lively exchange between the open-minded leaders of quantitative biology and applied mathematics is essential to achieving these goals.

The meeting focused on one area of cell biology where this integration of applied mathematics into the process of biological discovery was especially rapid and successful: cell motility and cytoskeleton. This area is especially promising due to the recent and continuing appearance of highly quantitative experimental data. Further, the modular character of a motile cell permits relatively simple sub-models to be developed and tested, and then integrated into larger scale models. This sub area of cell biology has great significance for fundamental biology (20-25% of the American Society for Cell Biology members are involved in cell motility research). It also holds tremendous promise for biomedical applications to the immune system, cancer, and wound healing. Last, but not least, biologists in this area see the need for mathematical analysis of complex pathways and data sets that cannot be understood by traditional methods.

At the meeting, we wanted to highlight the juxtaposition of the biological experimental observations with the theory that aims to elucidate underlying mechanisms. By bringing

together the people who carry out experiments with those who work on the theoretical basis of the field, we tried to facilitate new scientific developments that intersect both. For this reason, we have selected a slate of speakers that included both internationally recognized leaders in cell biology (known to be open minded and interested in the exchange of theoretical ideas) and those known for their theoretical work.

Cell motility is based on a complex self-organized mechanochemical machine consisting of the cytoskeleton: actin polymers, microtubules, accessory proteins and molecular motors [9-12]. The polymer/motor network is heterogeneous and dynamic. It is characterized by large stochastic fluctuations, yet often exhibits remarkably precise and reliable spatial and temporal organization. The machine is regulated and self-organized by a complex and redundant network of biochemical reactions coupled to force and movement generating processes. Cells at rest on a surface have a characteristic "fried egg" shape, with a mound of cell body (nucleus and organelles) in the center, and flat margins. Locomoting cells, on the other hand, are polarized, with the cell body at the rear, and a pseudopod - a cytoskeletal protrusion largely devoid of organelles - at the front. The motile cytoskeleton mainly consists of actin - flexible rod-like filaments, with plus and minus ends having dissimilar polymerization kinetics. The actin network is regulated by a host of actin sequestering, capping, severing, nucleating, and depolymerizing proteins, and organized by crosslinking and force generating (myosin) molecules. The cell is steered by microtubules.

Some of the deepest questions being addressed in the area of cell motility and cytoskeleton include the following:

(1) How do the components of the cytoskeleton operate together, and how do they control the shape and the motion of a cell?

(2) What controls the dynamics of these components? How do they respond to signals that a cell receives?

(3) How can we understand the links between the biochemical and mechanical properties of various components (actin, microtubules, motors, binding proteins, and signalling proteins), and how do these relate to the properties of the next higher level - i.e. the emergent behavior of the cell?

The opening talk at the workshop was by Tom Pollard (the Higgins Professor of Molecular, Cellular & Developmental Biology at Yale, past president of the Salk Institute, and a member of the National Academy of Science). Pollard's lab uses a combination of biochemical, biophysical, cellular and genetic experiments to test hypotheses about molecular mechanisms of actin-based cellular movements and cytokinesis, still one of the most mysterious of cellular processes. Prof Pollard spoke about quantitative analysis of actin-based cellular motility and cytokinesis, giving an overview of the current open questions and relevant quantitative experimental data. Pollard discussed the dendritic-nucleation model for protrusion, the first step in cell

migration. The theory currently lacks quantitative backing, prompting Pollard to call for more active mathematical modeling.

Paul Janmey (Institute for Medicine and Engineering, U. Penn), a world-renowned scholar working at the interface of physics, biology, materials engineering, and basic biomedical research, gave the second major talk. It was on the rheology of actin gels. Much experimental data has been gathered recently on the peculiar visco-elastic properties of the cytoskeleton. These properties can be easily regulated by the cell biochemically by changing the average length and orientation of the cytoskeletal polymers and density and character of the crosslinking molecules. Peculiar nonlinearities and non-local character of mechanical moduli of the cytoskeleton are measured but poorly understood. Mathematical modeling of actin network architecture [7] is of great use for experimental studies of the rheology of the cytoskeleton [8], but too little is done so far.

Joseph Käs continued the theme started by Janmey, speaking about how to 'feel and influence' active intracellular polymer networks using forces created by laser beams in the so-called optical traps. While Janmey talked about in vitro experiments, Käs discussed the medical applications of cell mechanics, for example for diagnostics of cancer.

The biological complexity did not stop there: Dennis Discher and Boris Hinz reported crucial role of dynamic adhesions between the cells and surfaces on which the cells move. Alexander Verkhovsky showed maps of motion and assembly of actin and myosin II in living migrating cells, notably fish keratocytes. This system has been particularly attractive to modelers and experimental results interface closely with an emerging theoretical understanding. Adhesion molecules signal to the cytoskeleton making the latter change its mechanical properties. A theoretical talk was given on the subject by Fred MacKintosh who showed how sophisticated scaling arguments can give biophysical estimates of the deformation, shear response, and force transmission in cytoskeletal networks.

One of the most interesting and promising modeling approaches in modern cell biology is the so-called *in silico* reconstitution of biological system, which refers to computationally simulating the individual behaviour of every one of thousands of proteins constituting the cell. A lecture by Cécile Sykes, on “Squeezing, sucking and cracking in the actin propulsion system” explored this topic in detail. On the same topic, Jonathan Alberts presented his model of Listeria's propulsion. Listeria is a pathogen that hijacks the cytoskeleton of the host cell and assembles a comet-like actin tail that grows and generates the force of propulsion. In Alberts' model, each of the hundreds of individual actin filaments is modeled on the computer, all microscopic forces are calculated and balanced, and as a result a vivid and life-like trajectory of bacterium's movement is computed. Most importantly, Alberts discovered that the pathogen moves in nano-steps that stem from cooperative breaking of transient molecular links between the filaments and the bacterium's surface.

A combination of analytic methods of applied mathematics and numerical analysis of PDEs has been used to model the process of cell division being studied experimentally at the same lab [5]. Two researchers from this lab presented their work. Eric Cytrynbaum spoke about this topic. Then Jon Scholey described the model explaining mitotic spindle dynamics. These talks interfaced well with the lecture by David Odde, on " Modeling Kinetochore Microtubule Dynamics in Budding Yeast", which also explore microtubule dynamics in living cells, and the in vitro work by Marlieen Dogterom's talk on "Growth dynamics of force generating microtubule bundles".

Numerous researchers at Washington University (St Louis) apply a wide range of applied mathematics tools to study actin dynamics, with significant impact on interpretation of experiments [6]. Anders Carlsson from Washington University spoke about the regulation of actin polymerization by branching, capping, severing, and mechanical force. David Sept then discussed the molecular aspects of actin dynamics.

Several talks were directed at understanding the polarization of eukaryotic cells, in response to chemotactic signals. These included the talk by Pablo Iglesias on "Regulating actin dynamics during cell motility and cytokinesis" and Alexander Van Oudenaarden lecture on " Noisy cellular polarization". Ed Munro, spoke about the cytoskeletal dynamics and cortical mechanics underlying the establishment and maintenance of cell polarity in the early C. elegans embryo, showing computationally generated movies that were almost dizzying in their life-like quality.

In addition to the full-length talks, we had a number of short (15 min) talks, to give an opportunity to young participants and others to present their work. We also ran a poster session. There were many lively and productive discussions throughout the week, both in the lecture hall as well as the dining room, the lounge, and on many informal outings. The high profile participants particularly enjoyed the combination of great atmosphere, wonderful care and hospitality at BIRS, as well as the outdoor activities. One of our goals was to increase the entry of young talent into this field, so we selected participants with this in mind. One of our co-organizers (Eric Cytrynbaum) is a young scientist, who is a new faculty member at UBC. We included a significant proportion (~50%) of young scientists, students, and postdoctoral researchers.

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