MODELLING THE MECHANICS OF THE PLASMA MEMBRANE AND NUCLEAR ENVELOPE: DYNAMICS AND DISEASE

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We study biomechanics of the cell plasma membrane and the nuclear envelope. Both of these are comprised of a biomembrane connected to a dynamic cytoskeletal layer on the inner side. In doing so, we develop mathematical models which are unlike well-established models in mathematical biology. For example, in reaction-diffusion or reaction-advection equations, the spatial coupling comes from transport and is therefore local. In contrast, in our equations the spatial coupling comes from the mechanics of a rigid, extended body that equilibrates rapidly on the timescale of the reactions, and therefore is not local. Here we describe three projects aimed at studying biomembranes, their associated cytoskeletal layers, and the resulting equations.

Project 1: Cellular Blebs.

Cellular bebs are pressure driven plasma membrane protrusions implicated in cellular functions such as cell division, apoptosis, and cell motility including motility of protease inhibited cancer cells. Because of their mechanical nature, blebs inform us about general cell surface mechanics including membrane dynamics, pressure propagation throughout the cytoplasm, and the architecture and dynamics of the actin cortex. Mathematical models including detailed fluid dynamics have previously been used to understand bleb expansion. Here we develop mathematical models on longer timescales that recapitulate the full bleb life cycle, including both expansion and healing by cortex reformation in 2D and 3D, in terms of experimentally accessible biophysical parameters such as myosin contractility, osmotic pressure, and turnover of actin and ezrin. The model provides conditions under which blebbing occurs, and naturally gives rise to traveling blebs. The model predicts conditions under which blebs travel or remain stationary, and predict the bleb traveling velocity, a quantity that has remained elusive in previous models. As previous studies have used blebs as reporters of membrane tension and pressure dynamics within the cell, we have used our system to investigate various pressure equilibration models and dynamic, non-uniform membrane tension to account for the shape of a traveling bleb. We also find that traveling blebs tend to expand in all directions unless otherwise constrained, suggesting the importance of cell surface heterogeneity. This work has been published in Biophysical Journal [Manakova et al. *Cell surface mechanochemistry and the determinants of bleb formation, healing, and travel velocity.* Biophys J, 110 (2016), pp. 1636-1647].

Project 2: Studying a class of integro-PDEs.

The types of equations which arise from this type of biomechanical modelling are often non-local and not well characterized. Here we seek to elucidate some features of one particular class of equations arising from ou cellular bleb model. An important element in our bleb model is the existence of travelling wave solutions. For some classical mathematical biology models, for example reaction-diffusion systems, the conditions allowing for travelling waves solutions are well established. This is not the case for our non-local system of equations, and therefore we are studying the existence of travelling wave solution for our non-local class of models. We derive a necessary condition for the existence of a travelling wave solution and demonstrate sufficiency numerically. As part of our future work, we plan to perform bifurcation analysis on our ODE system, obtained by removing spatial coupling, and characterize the transitions between the types of solutions. In particular, we believe that our fast-slow system exhibits a hopf bifurcation in conjunction with what is known as a canard explosion. Canard explosions are characterized by a sudden jump from a single steady state solution to large amplitude oscillations for very small changes in the bifurcation parameter, and are often observed in fast-slow systems.

Project 3: Nuclear Blebs.

An important application of these mechano-chemical models is to the identification of altered protein mechanics in disease states. Often diseases can be linked to a genetic mutation, but the specific effects that the mutation has on the gene product is much more difficult to resolve. We collaborate with the Grosberg and Zaragoza labs to study a mutation in LMNA gene which codes for the lamin A/C proteins. Lamin A/C proteins perform many functions in the nucleus, including localizing to the nuclear lamina, a network of proteins associated with the nuclear membrane which is thought to provide mechanical support to the nucleus. Patients with a mutated LMNA gene can suffer from a variety of disorders, collectively termed laminopathies. A common feature of all laminopathies is altered nuclear shape containing more bumps or "blebs." Nuclear blebs are also found in normal cells to some extent and a key step in learning about the mechanisms of the ensuing diseases is to understand how much nuclear defect is due to normal cell to cell variability and how much is due to the mutation. The underlying mechanism responsible for producing these nuclear defects is unknown. We developed a mathematical model of the nuclear lamina in 2D. We include mechanical properties such as surface tension, bending rigidity, and cytoskeletal forces. These laminar mechanical properties come from the mechanical properties of the lamin protein itself. Using this model we will explore various perturbations to the mechano-chemical properties of lamin to determine what is the specific defect in the lamin proteins of mutant LMNA patients.