A multi-scale model of cellular morphodynamics

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Because of its central importance in cell function, cellular morphodynamics has been a topic of extensive research during the past decades. Multiple efforts have been devoted to understanding the regulatory mechanisms of cell motility in different biological contexts, such as cancer cell invasion, wound healing, embryonic development, and phagocytosis. In order to understand the underlying principles governing cellular morphodynamics, we develop a multi-scale model of a motile cell of an arbitrarily complex shape. In this model, protrusive activity is bidirectionally coupled to the interplay between cell geometry, intracellular signaling events, and mechanical properties of the extracellular environment.

We describe cell as a discretized object on a square lattice, with a pixel size that matches the resolution of the live-cell imaging experimental that we use to verify model performance. The dynamics of cell edge is modeled as a stochastic process, where protrusion and retraction rates are defined by the local cell geometry and polymerization of actin at the cell edge. Under isotropic environmental conditions and in the absence of intracellular polarization cell maintains nearly round shape, exhibiting random fluctuations of the edge. Our algorithm ensures that the cell maintains continuity as it moves and interact with the microenvironment. Directional bias in cell migration is generated by intracellular signaling of small GTPases (RhoA, Rac, Cdc42) that regulate spatiotemporal dynamics of the actomyosin cytoskeleton. To model this GTPase regulation, we adapted the reaction-diffusion (RD) model of actin dynamics [1] for 2D simulations in a dynamically changing cell shape. This model reproduces a variety of patterns of actin organization inside the cell, including standing (cell polarization) and traveling waves. In the polarized state, the cell exhibits the characteristic random walk motion. The traveling wave regime very closely reproduces the actin dynamics in cortical layer of an oocyte [2].

The interaction with the extracellular environment in achieved through focal adhesion complexes that we model as discrete points regulating protrusion and retraction rates. On a mesh of intertwined extracellular fibers, our model shows that directional bias in migration is coupled to the structural organization of the fibers. This bias and the persistence of cell migration is also dependent on local regulation of actin dynamics by focal adhesions.

Finally, we applied this modeling approach to study the biomechanics of phagocytosis. It has been established that phagocytosis can occur in two different modes: FcγR- and CR3-mediated phagocytosis, in which pushing and pulling forces drive the engulfment of a particle, respectively [3]. We numerically simulated the engulfment of objects with different sizes and adhesiveness to investigate the distribution of forces generated by a phagocyte. Our results indicate that phagocyte can generate both pulling and pushing forces depending on the adhesive properties of the particle it engulfs.

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2. William M. Bement et al. (2015), Activator-inhibitor coupling between Rho signaling and actin assembly make the cell cortex an excitable medium, *Nat Cell Biol*. 17(11).

3. Tzircotis G et al. (2011), RhoG is required for both FcγR- and CR3-mediated phagocytosis, *J Cell Sci*. 24(Pt 17):2897-902.