Periodic migration emerges from a physical model of cells on micropatterns

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***Short Abstract* — We extend a model for the morphology and dynamics of a crawling eukaryotic cell to describe cells confined on a micropatterned substrate. This model couples cell morphology, adhesion, and cytoskeletal flow in response to active stresses induced by the presence of actin and myosin. Simulated cells exhibit complex behaviors including steady motion, bipedal motion, stalling, and periodic migration, where the cell crawls persistently in one direction before reversing periodically. We show that periodic motion emerges naturally from coupling between cell polarization and cell shape by reducing the model to a simplified one-dimensional form whose behavior can be understood analytically.**

***Keywords* — cell crawling, adhesion, micropatterns, periodic migration**

Introduction

Cultured cells on two-dimensional substrates have traditionally been used as a convenient proxy for more biologically relevant situations, such as cells within a three-dimensional extracellular matrix (ECM). However, cells in three-dimensional ECM can exhibit qualitatively different modes of migration than cells on two-dimensional substrates, differing in speed, morphology, and dependence on myosin [1]. Even larger changes are possible; zyxin-depleted cells in a collagen matrix exhibit periodic migration, in which a cell crawls several cell lengths before reversing direction [2]. Interestingly, many of these features, including periodic migration, are recapitulated in studies of cells on effectively one-dimensional micropatterns [1-2]. In addition, more complex micropatterns have been used to set the direction of cell polarization and migration [3]. We study the dynamics of eukaryotic cells on micropatterns both for its inherent interest, and as a window into the more complex dynamics of cells in three-dimensional ECM.

Model

We generalize our earlier work [4] to describe the migration of cells on micropatterns. Our model, which is appropriate for the long (second-to-hour) time scale of cell migration, describes the cell's cytoskeleton as a highly viscous compressible fluid with surface tension and bending energy, driven by active stresses from actin polymerization and myosin contraction. We introduce the micropattern with the central hypothesis that protrusive stress is only generated where the cell contacts the micropattern [5]; using this hypothesis, our simulation shows that unpolarized cells contract to the shape of the micropattern, and polarized cells travel along it.

Complex migration behavior arises in simulation

By making this minimal extension to an established motility model [5], periodic migration, as well as many other behaviors, including turning and bipedal motion occur. Which morphology appears depends on the width of the micropattern and the strength of the protrusive and contractile stresses.

Periodic migration emerges from coupling between cell shape and polarization

We study the mechanism of periodic migration in detail. During periodic migration, polarized cells shrink; sufficiently small cells depolarize. These depolarized cells then grow, and once they reach a characteristic size, repolarize in the opposite direction to their initial travel, leading to periodic motion. We use sharp-interface theory to reduce our complex two-dimensional model to a significantly simpler one-dimensional model, which includes only a reaction-diffusion mechanism for cell polarization [6], protrusion and retraction of the cell edges, and myosin leading to cell contraction. This one-dimensional model captures the essential behavior of the full simulation, but can be understood analytically. We show that the amplitude of periodic motion is large compared to the cell's size only if either protrusive and contractile forces are carefully tuned so that the polarized cell contracts slowly, or the cell viscously resists changes in its size.

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