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Feedback Interactions of Polymerized Actin with the Cell Membrane: Waves, Pulses, and Oscillations[1]

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Polymerized filaments of the protein actin have crucial functions in cell migration, and in bending the cell membrane to drive endocytosis or the formation of protrusions. The nucleation and polymerization of actin filaments are controlled by upstream agents in the cell membrane, including nucleation-promoting factors (NPFs) that activate the Arp2/3 complex to form new branches on pre-existing filaments. But polymerized actin (F-actin) also feeds back on the assembly of NPFs. We explore the effects of the resulting feedback loop of F-actin and NPFs on two phenomena: actin pulses that drive endocytosis in yeast, and actin waves traveling along the membrane of several cell types. In our model of endocytosis in yeast, the actin network is grown explicitly in three dimensions, exerts a negative feedback interaction on localized patch of NPFs in the membrane, and bends the membrane by exerting a distribution of forces. This model explains observed actin and NPF pulse dynamics, and the effects of several interventions including i) NPF mutations, ii) inhibition of actin polymerization, and iii) deletion of a protein that allows F-actin to bend the cell membrane. The model predicts that mutation of the active region of an NPF will enhance the accumulation of that NPF, and we confirm this prediction by quantitative fluorescence microscopy. For actin waves, we treat a similar model, with NPFs distributed over a larger region of the cell membrane. This model naturally generates actin waves, and predicts a transition from wave behavior to spatially localized oscillations when NPFs are confined to a small region. We also predict a transition from waves to static polarization as the negative-feedback coupling between F-actin and the NPFs is reduced.

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