

# LAMELLIPODIUM DYNAMICS AND REARWARD ACTIN FLOW DEPEND ON VINCULIN

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## Introduction

Cells migrate by cycles of edge protrusion, adhesion, and retraction [Giannone et al. 2007], which requires the coordination of two F-actin domains at the leading cell edge; the lamella, which consists of contractile actomyosin bundles that generate tension of focal adhesions, and the lamellipodium, composed of branched actin filaments associated with nascent adhesions [Burnette et al. 2011]. Periodic forward motions of the leading edge are driven by actin polymerization, which generates a pushing force against the cell membrane and a rearward actin flow that depends on matrix adhesion. We developed a 1D model to predict and understand how the focal adhesion protein vinculin modulates actin flow dynamics at the leading edge.

## Methods

Rearward actin flow in the lamellipodium is driven by the build-up of membrane tension  $f_{mem}$  due to actin polymerization, and modulated by myosin II motor forces  $f_m$  pulling periodically at the lamella border. Actin flow  $v_{ra}$  is slowed down by drag forces  $f_f$ , depending on the concentration of actin  $A_c$  and focal adhesions  $FA_c$ , and adhesion strength  $\kappa_{FA}$  (Fig. 1).

$$f_m + f_{mem} = f_f = \eta_f v_{ra}$$

where  $\eta_f = \eta_0 + \eta_{FA} = \eta_0 + \kappa_{FA} FA_c A_c$

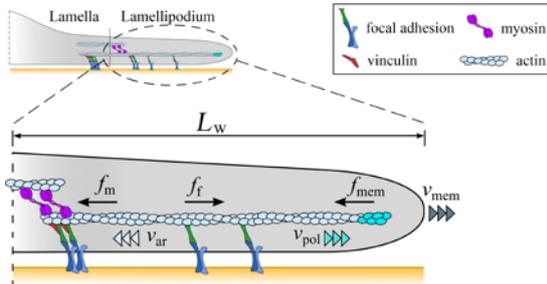


Figure 1: Leading edge movement and rearward actin flow depends on polymerization speed and a force balance between driving and opposing forces from membrane tension and friction due to focal adhesions.

## Results

The model correctly predicts the increase of period contractions and decrease of membrane speed after inhibition of actin polymerization

using Cytochalasin B [Giannone et al. 2007]. It also predicts a decrease in membrane protrusion and actin flow velocity, and an increase of contraction cycle length that is observed upon inhibition of myosin II using Blebbistatin [Burnette et al. 2011, Giannone et al. 2007]. Importantly, the model reproduces the increase in membrane speed and lamellipodium width observed experimentally when vinculin is knocked out (unpublished).

## Discussion

Our 1D model recapitulates the main experimental observations of lamellipodium dynamics with a minimum number of essential parameters: cell membrane protrusion depends on actin polymerization and retrograde actin flow. Periodically, myosin contractions in the lamella are triggered by a (currently unidentified) signal travelling across the lamellipodium with the actin, hence leading to cyclic retractions that are directly proportional to the lamellipodium width and inversely proportional to the actin speed. Rearward actin flow is opposed by frictional forces from focal adhesions that bind to the actin through vinculin and other focal adhesion proteins. The flow velocity is then governed by a force balance between friction, contractile forces and actin polymerization/membrane tension. New focal adhesions are formed during each contraction cycle, establishing the new lamella border and permitting a net advance of the whole cell edge. Following retraction, an actin-bound myosin-activating signalling protein is activated at the lamellipodium tip and starts in a new cycle its journey towards the lamella. Our model confirms the hypothesis that vinculin is an important mechano-coupling protein for transmitting frictional forces between the actin network in the lamellipodium and the extracellular matrix.

## References

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