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Actin filament branching and protrusion velocity in a simple 1D model of a motile cell

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Abstract

We formulate and analyse a 1D model for the spatial distribution of actin density at the leading edge of a motile cell. The model incorporates nucleation, capping, growth and decay of actin filaments, as well as retrograde flow of the actin meshwork and known parameter values based on the literature. Using a simplified geometry, and reasonable assumptions about the biochemical processes, we derive PDEs for the density of actin filaments and their tips. Analytic travelling wave solutions are used to predict how the speed of the cell depends on rates of nucleation, capping, polymerization and membrane resistance. Analysis and simulations agree with experimental profiles for measured actin distributions. Extended versions of the model are studied numerically. We find that our model produces stable travelling wave solutions with reasonable cell speeds. Increasing the rate of nucleation of filaments (by the actin related protein Arp2/3) or the rate of actin polymerization leads to faster cell speed, whereas increasing the rate of capping or the membrane resistance reduces cell speed. We consider several variants of nucleation (spontaneous, tip, and side branching) and find best agreement with experimentally measured spatial profiles of filament and tip density in the side branching case.

Keywords: Cell motility; Mathematical model; Actin dynamics; Lamellipod

1. Introduction

1.1. Cell motility

Animal cells move in response to an external signal by remodelling their cytoskeleton, composed of the abundant biopolymer, actin (Kurner et al., 2004). The motility of these cells is essential in embryogenesis, development, immune surveillance, wound healing, and many other cell functions (Tojima and Ito, 2004; Mandato and Bement, 2003). It is also implicated in disease processes such as rheumatoid arthritis and metastatic cancer (Lambrechts et al., 2004).

It is currently accepted that protrusion of the cell at its leading edge is mediated by actin filament tips pushing on the membrane. This results in extension of a long, flat, actin-rich protrusion called a lamellipod (Pollard and Borisy, 2003; Small et al., 2002). Actin filaments are polarized, and grow fastest by adding monomers at their plus (also called "barbed") ends, directed mainly toward the cell membrane. One mechanism that has been proposed to explain the force generated by polymerization of monomers at these ends is the thermal ratchet model (Mogilner and Oster, 1996, 2003). In order to limit potentially explosive elongation of filaments, capping proteins bind to barbed ends and prevent growth (Schafer et al., 1996; Pantaloni et al., 2000). Polymerization ceases when barbed ends are capped. Actin filaments are broken down by depolymerization and other recycling mechanisms, so that the monomers can be recharged, and reused in promoting new growth at the leading edge of the cell. As filaments age, they become more prone to degradation. Hence, depolymerization dominates in the rear parts of the lamellipod structure.

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A small but distinct rearward flow of the actin meshwork has recently been observed in the lamellipodia of moving fish epidermal cells called *keratocytes* (Ponti et al., 2004; Jurado et al., 2005; Vallotton et al., 2005). Previously this had only been observed in slower moving cells such as fibroblasts (Ponti et al., 2005; Henson et al., 1999). In keratocytes, the lamellipod is separated from the cell body by a band rich in myosin II, a motor protein that binds to actin filaments and moves towards the barbed end of a filament (Svitkina and Borisy, 1999). Since most actin filaments in the lamellipod are oriented with their barbed ends in the direction of motion (Svitkina and Borisy, 1999), the interaction of myosin II with the actin filaments in the lamellipod causes a bulk flow of the actin meshwork away from the leading edge. Retrograde flow in keratocytes is smallest in the middle of the lamellipod (approximately $0.01\,\mu m\,s^{-1}$) increasing to approximately $0.05\,\mu m\,s^{-1}$ at the edges, in cells moving $0.2–0.3\,\mu m\,s^{-1}$.

Of great interest in the last decade is the complex Arp2/3, essential for cell motility and now known to nucleate new filaments. Arp2/3 undergoes activation at the leading edge, and then gives rise to new barbed ends that can grow into filaments. In previous years, there had been some debate whether Arp2/3 attaches to actin filament sides or to their barbed ends in order to nucleate new branches (Falet et al., 2002; Pantaloni et al., 2000). Some groups (Amann and Pollard, 2001; Fujiwara et al., 2002) favored Arp2/3 binding to sides, close to the tips of existing filaments. Existing technology does not allow direct imaging of Arp2/3 nucleation as it occurs in a motile cell, but a variety of other experimental observations and theoretical analyses (Carlsson et al., 2004) currently lead to strong support for side branching off pre-existing filaments.

Estimates for biochemical parameters such as capping and nucleation rates have been based on results of in vitro experiments using cell extracts (at protein concentrations similar to those found in cytoplasm), but not intact cells (Pollard et al., 2000). Thus, estimated biochemical rates and parameter values are still subject to experimental refinement. At the same time, visualization of the actin network (Bailly et al., 1999; Svitkina and Borisy, 1999) has allowed measurement of densities of polymerized actin, of filaments, and even of their barbed ends as a function of distance away from the leading edge. As yet, no theoretical treatment of these measured densities and the filament dynamics that account for these densities has been completed. This forms the subject of our paper.

In this paper, our aim is to derive and investigate a simple description of actin filament nucleation, capping, growth and depolymerization in a 1D model of the lamellipod. We ask whether the known events described above can account for (a) membrane speed, (b) the density profiles of filaments and ends, and (c) dependence of speed on biochemical parameters. We base the model on known biochemical parameters and use it to infer those that are not easy to measure.

1.2. Previous modelling efforts

A number of models have been proposed to investigate actin dynamics in motile cells. Some models focus primarily on the actin monomer cycle and actin polymerization at the leading edge (Mogilner and Edelstein-Keshet, 2002; Grimm et al., 2003). Using a 1D model, Mogilner and Edelstein-Keshet (2002) show how membrane speed depends on barbed ends and ATP-actin monomer concentration at the leading edge of a cell. Grimm et al. (2003) make predictions regarding the shape of the leading edge. Both papers employ a force–velocity relationship as the basis for membrane protrusion, but neither is concerned with the profiles of actin density or the biochemistry of branching mediated by Arp2/3. Carlsson (2001) uses a stochastic 3D model to simulate the growth of an actin network against an obstacle. Other models have been proposed for actin length distribution in a 1D strip of the lamellipod. Edelstein-Keshet and Ermentrout (2000) focus on cutting and severing of filaments rather than branching. In a more recent paper Carlsson et al. (2004) combine in vitro experimental work with modelling of actin dynamics in a well-mixed, spatially homogeneous setting and find that side branching provides the best fit to experimental data.

Our model complements previous approaches in several respects. First, (like Edelstein-Keshet and Ermentrout, 2000 but unlike Mogilner and Edelstein-Keshet, 2002) we are concerned with spatial distribution of actin filaments and their barbed ends; our model can then be used to compare against actin density distributions observed in experiments. We explore actin density evolution in a simplified 1D geometry (see Fig. 1) to investigate the interplay between filament branching, growth, and decay in proximity to the leading edge. Second, as in many previous models, we use both analytic and simulation techniques. However, since we study a minimal model, it is possible to find (in the simplest case) explicit forms of travelling waves that represent the steady state motion of a motile cell. This leads to analytic expressions for experimentally measurable quantities such as protrusion velocity and spatial density profiles in terms of kinetic parameters such as rates of capping, nucleation, polymerization and disassembly of actin. A primary focus is on the role of Arp2/3 in initiating branches on filaments. By explicitly incorporating Arp2/3 activation at the leading edge, its diffusion, and its role as a nucleator of new actin filament tips that push the membrane, we can investigate consequences of distinct types of branching on the resultant actin dynamics, distribution and cell speed.

2. Biological background

Actin polymerizes from its monomeric form (G-actin) to a filamentous form (F-actin). Filamentous actin is polar, with faster growth due to monomer addition at the barbed end than the pointed end. Polymerization of ATP-actin