Physica D 318–319 (2016) 34–49

Contents lists available at ScienceDirect

Physica D

journal homepage: www.elsevier.com/locate/physd

Approaches to myosin modelling in a two-phase flow model for cell motility

L.S. Kimpton [a], J.P. Whiteley [b], S.L. Waters [a], J.M. Oliver [a,*]

[a] Mathematical Institute, University of Oxford, Andrew Wiles Building, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG, UK
[b] Department of Computer Science, University of Oxford, Wolfson Building, Parks Road, Oxford, OX1 3QD, UK

HIGHLIGHTS

- We model myosin transport and kinetics in a two-phase flow model for cell motility.
- Myosin-driven contraction destabilizes a stationary steady state.
- Steady travelling-wave solutions for gliding cells are obtained numerically.
- A boundary layer problem is studied in the strong adhesion limit.

ARTICLE INFO

Article history:
Received 3 July 2015
Received in revised form
30 September 2015
Accepted 7 October 2015
Available online 21 October 2015

Keywords:
Two-phase flows
Cell motility
Myosin

ABSTRACT

A wide range of biological processes rely on the ability of cells to move through their environment. Mathematical models have been developed to improve our understanding of how cells achieve motion. Here we develop models that explicitly track the cell's distribution of myosin within a two-phase flow framework. Myosin is a small motor protein which is important for contracting the cell's actin cytoskeleton and enabling cell motion. The two phases represent the actin network and the cytosol in the cell. We start from a fairly general description of myosin kinetics, advection and diffusion in the two-phase flow framework, then identify a number of sub-limits of the model that may be relevant in practice, two of which we investigate further via linear stability analyses and numerical simulations. We demonstrate that myosin-driven contraction of the actin network destabilizes a stationary steady state leading to cell motion, but that rapid diffusion of myosin and rapid unbinding of myosin from the actin network are stabilizing. We use numerical simulation to investigate travelling-wave solutions relevant to a steadily gliding cell and we consider a reduction of the model in which the cell adheres strongly to the substrate on which it is crawling. This work demonstrates that a number of existing models for the effect of myosin on cell motility can be understood as different sub-limits of our two-phase flow model.

1. Introduction

1.1. Biological background

Cell crawling is characterized by the extension of a persistent, flat sheet of cytoplasm (termed lamellipodium) at the front of the cell and is typically seen in cells migrating over flat substrates [1]. Within a cell actin monomers polymerize to form filaments in the cell's cytoskeleton. There is significant actin polymerization towards the front of the lamellipodium [2], where high volume fractions of actin network are observed [3]. High densities of polymerized actin are also observed where the lamellipodium meets the cell body [4]. The control of the actin network depends on a huge number of auxiliary proteins that allow the cell to respond to its environment [5]. Depolymerization of the actin network in the lamellipodium occurs preferentially at the lamellipodium/cell body junction and releases actin monomers that are recirculated via the cytoplasm towards the front of the cell [2,6]. As the cell crawls forward, the network at the leading edge undergoes retrograde flow and is swept backwards in the stationary lab frame [2,7,6,8]. The actin network in the rear of the cell flows forwards in the stationary lab frame [6,8].

Myosins are small motor proteins that can bind to the actin network and move towards the barbed end of the actin filament. Their action causes neighbouring actin fibres to slide relative

* Corresponding author.
E-mail address: oliver@maths.ox.ac.uk (J.M. Oliver).

http://dx.doi.org/10.1016/j.physd.2015.10.003
0167-2789/

to each other, generating stress in the network [1]. Myosin is observed in high concentrations at the rear of migrating cell fragments [3] and where the lamellipodium meets the cell body in whole, migrating cells [4]. Myosins that are not currently bound to the actin network are termed free and can be transported through the cytoplasm. A much more comprehensive discussion of the dynamics of the actin network and how cells crawl can be found in [1]. One further experimental observation, particularly relevant to this paper, is that cells crawl more quickly on surfaces with moderate adhesion strengths and more slowly when they adhere very weakly or very strongly [9].

1.2. Previous modelling approaches

A wealth of mathematical models have been developed to aid the understanding of cell motility, ranging from discrete models of actin filaments (*e.g.* [10]), to reaction–diffusion models for a cell's biochemistry (*e.g.* [11]), to continuum models with a biomechanical focus (*e.g.* [12]). A discussion of the progress made by these different approaches can be found in the recent reviews [13–16]. We are primarily interested in continuum models, specifically two-phase flow models. This approach treats the actin network and the surrounding cytoplasm as two distinct fluid phases, termed 'network' and 'solution,' respectively. This framework was established by [17] and further developed in [12,18–30]. Variations of the framework in which the network phase is elastic are considered in [31] and [32]. The two-phase flow framework has proven to be a very flexible tool with which to model *inter alia* polymerization and depolymerization of the actin network; swelling and contraction of the actin network and the forces between the network and the cytoplasm.

To date there has been limited explicit modelling of the effects of myosin within the two-phase flow framework. In [18], the authors present a coupled advection–reaction–diffusion system for free and bound myosin. However, they consider only the limit in which the free myosin concentration is spatially uniform, there being no advection of myosin and the binding/unbinding being at equilibrium, so that the concentration of bound myosin is a prescribed function of the network volume fraction.

Single phase continuum models of cell motility have incorporated myosin modelling in a variety of ways. In [33–35] the distribution of free myosin is assumed to be spatially uniform, while the distribution of bound myosin varies with space and time, and the model accounts for binding and unbinding of myosin to the network. A similar reaction–advection model for myosin transport is used in [36] where free myosin is neglected, but the binding rate for bound myosin is a constant. This approach is taken one step further in [37], where the diffusion of free myosin and the binding/unbinding rates are assumed to be fast, so that the concentration of bound myosin is proportional to the local cytoskeletal density multiplied by the local myosin binding rate. A similar approach is adopted in [38], where the authors introduce a third myosin species and distinguish between bound, inactivated and bound, activated myosin. They model the concentration of free myosin as spatially uniform and have constant binding/unbinding rates. Their activation rate for the bound myosin molecules and the actin density are both prescribed functions of distance along the one-dimensional cell, thus, the concentration of bound, activated myosin is a prescribed, time independent function. Both [39] and [40] implement an advection–diffusion equation for bound myosin, which in [39] is justified by fast rates of unbinding and rebinding of myosin to the network. A single-phase viscoelastic model in [41] considers a model in which the concentration of bound myosin satisfies an advection–reaction equation and the free myosin satisfies a reaction–diffusion equation.

1.3. Paper outline

Treatment of myosin within the two-phase flow framework has been very limited to date. In this paper we formulate minimal two-phase flow models for a crawling cell that explicitly track the distribution of myosin. The first advantage of this approach is that we can formulate constitutive equations for the swelling and contraction of the actin network that depend both on the local volume fraction of the actin network and the local concentration of myosin bound to the network. These constitutive laws will be more biologically realistic than comparable constitutive assumptions that are unable to use myosin concentrations. The second advantage of modelling myosin explicitly is that it provides an extra piece of information to compare to biological observations.

We begin in Section 2 by outlining our one-dimensional poroviscous two-phase model for cell crawling and coupling it to a fairly general set of equations governing the kinetics and transport of myosin. In Section 3, we identify a number of biologically plausible sub-models and discuss how these sub-models allow us to understand existing models from the literature as different limits of our more general governing equations for myosin. In Section 4, we select two of the sub-limits that we name the 'kinetic' and 'diffusion' models and explore the stability of the stationary steady state in each of them. We proceed to present numerical solutions of these two models in Section 5. Numerical simulations indicate a boundary layer structure in the travelling-wave solution of the diffusion model in the strong cell–substrate adhesion limit. In Section 6 we analyse the boundary layer structure using matched asymptotic expansions and compare our asymptotic and numerical solutions. Finally the results of the paper are summarized in Section 7.

2. Model formulation

2.1. Mass and momentum conservation

We append equations governing myosin transport and kinetics to our simple two-phase flow model for a crawling cell presented in [27]. Here we therefore briefly outline the derivation of the one-dimensional model in which x is the distance along a strip of cytoplasm parallel to the crawling direction and the location of the strip $a(t) < x < b(t)$ must be determined as part of the solution. We do not impose a direction of motion. The volume fraction of the network phase at time t is $\theta(x, t)$ so, enforcing no voids, the solution phase has volume fraction $1 - \theta(x, t)$. Conservation of mass for the incompressible phases is stated as

$$\frac{\partial \theta}{\partial t} + \frac{\partial}{\partial x}\big(\theta u\big) = -J, \tag{2.1}$$

$$\frac{\partial}{\partial t}\big(1-\theta\big) + \frac{\partial}{\partial x}\big((1-\theta)v\big) = J, \tag{2.2}$$

where $u(x, t)$ and $v(x, t)$ are the network and solution velocities, respectively, and J represents polymerization ($J < 0$) and depolymerization ($J > 0$) of the actin network.

The force balances on the network and solution phases are given by

$$-\theta\frac{\partial p}{\partial x} - \frac{\partial \Psi}{\partial x} + \frac{\partial}{\partial x}\left(\mu\frac{\partial u}{\partial x}\right) = H(u-v) + \beta u, \tag{2.3}$$

$$-(1-\theta)\frac{\partial p}{\partial x} = H(v-u), \tag{2.4}$$

where $p(x, t)$ is the hydrodynamic pressure, Ψ is the swelling/contractile pressure in the network, μ is the (effective) network viscosity, H is the network-solution drag coefficient and β is the adhesion or network-substrate drag coefficient. For simplicity the