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IFAC-PapersOnLine 49-26 (2016) 103–108

# A curvilinear Model Approach: Actin Cortex Clustering Due to ATP-induced Myosin Pulls

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**Abstract:** The actomyosin cortex is involved in a range of many cellular processes like cell division, motility or shaping. To obtain this variety of functionalities the membrane-bound actin mesh has to be reconstituted by the motor protein myosin. But little is known about the underlying mechanism, which control the different tasks. An underlying in vitro study of a synthetic actomyosin cortex has shown that the cortex organizes into spatial clusters for certain ATP concentrations. Here we develop a curvilinear model that captures the viscoelastic material behavior and the kinetics of the myosin cross bridge. Further, we suggest a formulation for the active contractile stress produced by the motor protein myosin. We demonstrate that the spatial pattern generated by the curvilinear model is consistent with the experimental observations, including mesh clustering due to contractile forces and an absence of contraction for low and high ATP concentrations. Additionally we show that the cluster positioning can be tuned by the ATP-gradient.



*Keywords:* Actin-Myosin Cortex, Dynamic Modeling, Distributed Model, System Analysis, Synthetic Biology

## 1. INTRODUCTION

The cell cortex formed by actin filaments is an important functional unit of almost all eucaryotic cells. As one of the three cytoskeleton components actin is involved in a variety of basic cellular processes such as cell division, motility, formation and stabilization of cell shape, or exocytosis and endocytosis (Theriot et al., 2002). Therefore it is a very interesting system for the bottom-up synthetic biology, which pursues the goal of creating minimal cell-imitating entities from non-living biological components such as lipids, proteins and DNA (Schwille, 2011).

### *1.1 The Actomyosin Cortex*

The monomer globular G-actin polymerizes, both spontaneously and regulated by a variety of factors, to filamentous F-actin which forms a meshlike structure via crosslinker proteins like Arp 2/3 or Filamin (Stossel et al., 2001). Membrane anchors interlink the inner plasma membrane with the F-actin and create a region of high F-actin density close to the membrane in the so-called cell cortex. Due to the additionally occurring depolymerization of F-actin the whole network is a very dynamic structure, which is jointly responsible for some of the key functions of actin. The mesh-like structure causes the viscoelastic or gel-like material behavior of the F-actin, and thereby, combines the characteristics of a fluid and solid, which is closely connected to the generated forces by the network (Claessens et al., 2006). In addition to these internal forces, the motor protein myosin II contracts the meshwork through consumption of chemical energy provided by the cellular energy storage molecule ATP and converting it into mechanical energy. Myosin II is a complex filamentous protein (myofilament) with a variety of myosin heads, also known as motor domain, on both opposite sides of the protein, and a head-free neck domain in between. The underlying myosin cross bridge cycle for a myosin head (Rayment et al., 1993) is a well known and well described biochemical circuit (Fig. 1A). In a simplified consideration the circuit can be described by four main reaction steps. The first step ($r_1$) is a hydroxylation of ATP to ADP which is linked to an myosin head ($M$) . This hydroxylation step

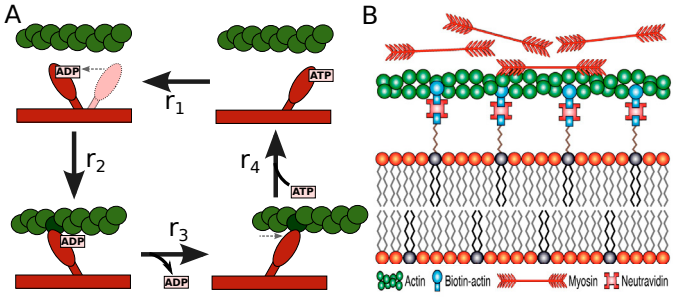


Fig. 1. (A)Biochemical myosin cross bridge cycle of a motor domain which is responsible for the conversion of chemical into mechanical energy. (B) Scheme of a minimal actin cortex MAC (Vogel et al., 2013)


10.1016/j.ifacol.2016.12.110

provides the energy for a conformational change of the myosin head into the active state ($M'$). In the active state the myosin head is able to interact with the F-actin ($r_2$) and to form an active actomyosin complex ($A$-$M'$).
The unstable active actomyosin complex is converted very fast into the inactive state ($A$-$M$) by releasing the bound ADP ($r_3$). In addition, the ADP dissociation causes a further spatial conformational change of the myosin head and, because of the mechanical coupling, an acceleration of the F-actin filament. Considering that motor domains on both sides of myosin can interact with F-actin, the acceleration or power stroke of myosin heads could result in a buckling, breakage and compaction of a F-actin filament and finally due to cross connections in a contraction of the meshwork.

### *1.2 Experimental Motivation for this work*

To investigate the actin cortex in experiments in vitro under cell-free and thus noise-free conditions, 'minimal actin cortices' (MACs: Fig. 1B) were developed consisting of biotinylated F-actin filaments which are connected to a lipid bilayer via neutravidin linkers, myosin II motor proteins and enzymatically regenerated ATP (Vogel and Schwille, 2012). Experiments with MACs suggest that myosin contraction of the actin cortex causes initially some small F-actin clusters that merge to larger ones after a certain time (Fig. 2). In addition, the investigation of the ATP dependency of F-actin clustering revealed that no clustering occurs for a very low ATP level corresponding to a too low energy level (Vogel et al., 2013). Surprisingly, no contractions were observable either for higher ATP concentrations (Table 1). Thus pattern formations occur only for medium ATP concentrations, which could be a cellular control mechanism for actin cortex.
How the different functions and patterns of the actin cortex, like network reorganization while cell division, are cellularly regulated is poorly understood, despite a large number of in vivo and in vitro experiments. However it is very likely that the active contractions of the motor protein myosin under ATP consumptions play a key role in controlling pattern formations in the actin cortex.

### *1.3 Objective of this work*

Mathematical models support the experiments by providing insight into the system dynamics and unmeasurable states. Thus it is the aim of this work to develop a mathematical model, which reproduces the experimental observations and help to understand the pattern formation in the actin cortex. The model is based on previous work in literature (Lewis et al., 2014; George et al., 2013). As a new aspect of our model, compared to published work, the dependence of cluster formation on ATP is described by including the biochemical myosin bridge circuit in a spatially distributed model.

## 2. MODEL

In the following, a mathematical model is presented whose purpose is to explain the experiment findings in a qualitative manner. A two dimensional continuum model in polar coordinates has been developed as a cut through a spherical cell. For modeling the cortex it is assumed that the actomyosin species are located close to the inner site of the membrane in a very thin layer. Therefore it can be assumed that the actomyosin cortex does not change radially and has a fixed radius which is scaled to $R_0 = 1$. This results in a one dimensional ring geometry with periodic boundary conditions for the actomyosin species. In contrast, ATP diffuses through the whole two dimensional system and is only consumed by the membrane linked actomyosin cortex. For simplifying the model formulation, it is assumed that the forces generated by the surrounding medium (containing monomer G-actin) are negligible. Thus a one phase model is sufficient to describe the forces in the actin cortex. The balance of momentum density $J$ as a product of F-actin density $A$ scaled by a density parameter $\varrho_A$ and a velocity $V$ ($J = \varrho_A \cdot A \cdot V$) is expressed as

$$\frac{\partial J}{\partial t} + \frac{\partial J \cdot V}{\partial \varphi} = \frac{\partial}{\partial \varphi}(\sigma_V - \sigma_e + \sigma_m), \tag{1}$$

with the angular component $\varphi$ in a range of $[0, 2\pi]$. The left-hand side of the equation represents the material derivative of the momentum density which can be interpreted as the convective flux of momentum due to F-actin flow $V$. The terms on the right-hand side constitute the acting forces of the system. The first term models the viscous stress or shear stress

$$\sigma_V = \eta \frac{\partial V}{\partial \varphi}, \tag{2}$$

which is generated by F-actin filaments moving relative to each other . It is the one dimensional representation of the stress tensor $\tau_{\varphi\varphi}$ with viscosity parameter $\eta$ (Bird et al.,

Table 1. ATP dependency of myosin contraction (0,3 $\mu M$ myosin II) with enzymatically regenerated ATP. Contractions are meant as qualitatively visible rearrangement or clustering of MACs after myosin addition at a certain ATP level (Vogel et al., 2013).

| **Regenerated ATP concentration** [$\mu M$] | **Contraction** |
|---|---|
| 12.5 | No |
| 10 | No |
| 1 | Yes |
| 0.3 | Yes |
| 0.1 | Yes |
| 0 | No |

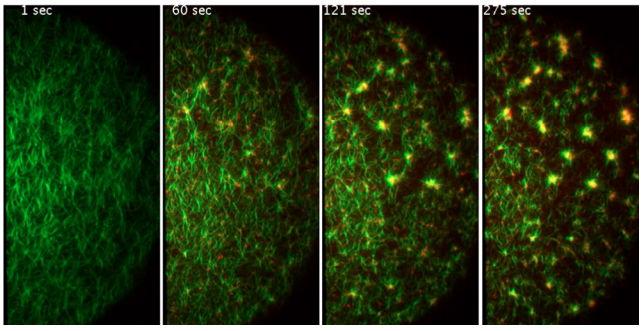


Fig. 2. Clustering of green labeled actin meshwork after addition of red labeled myosin II and ATP from Vogel et al. (2013).