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Reaction–diffusion–advection approach to spatially localized treadmilling aggregates of molecular motors

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HIGHLIGHTS

- Reaction–diffusion–advection model for the formation of spatially localized molecular-motor aggregates (pulses).
- Analytic trends of pulses properties via model parameters: shape and propagation velocity.

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ABSTRACT

Unconventional myosins belong to a class of molecular motors that walk processively inside cellular protrusions towards the tips, on top of actin filament. Surprisingly, in addition, they also form retrograde moving self-organized aggregates. The qualitative properties of these aggregates are recapitulated by a mass conserving reaction–diffusion–advection model and admit two distinct families of modes: *traveling waves* and *pulse trains*. Unlike the traveling waves that are generated by a linear instability, pulses are nonlinear structures that propagate on top of linearly stable uniform backgrounds. Asymptotic analysis of isolated pulses via a simplified reaction–diffusion–advection variant on large periodic domains, allows to draw qualitative trends for pulse properties, such as the amplitude, width, and propagation speed. The results agree well with numerical integrations and are related to available empirical observations.

1. Introduction

Molecular motors facilitate a mean of transport within cells, and are especially vital to chemical exchange in actin-based cellular protrusions [1], such as filopodia [2] and stereocilia [3]. Unconventional myosins (UM), constitute arguably the most important family of processive motors, moving and transporting chemical cargos to and from the plus-ends (growing tips) of actin-filaments; except for myosin-VI which is a minus-end directed motor. Thus, dynamical properties of UM are central to cell functionalities, example of which include migration, morphology, communication and morphogenesis [4,5].

Despite the tendency of UM to accumulate at the protrusion tips, where the plus ends of the actin filaments are located, there are many observations of retrograde motion of aggregates towards the protrusion base. These self-organized aggregates are common to both filopodia and stereocilia and are associated with myosin-X [6–9], myosin-XV [10], myosin-III [11] and myosin-Va [8]. The qualitative mechanisms of these motor aggregates can be captured through a continuum reaction–diffusion–advection model that constitutes three basic types of motors [12]: freely diffusing, actin-bound stalled motors advected by the retrograde flow of actin towards the protrusion base, and actin-bound processive motors that walk towards the tip. In particular, the model allows to distinguish between two transport modes: traveling waves and pulse trains.

Here we aim to develop a better understanding of *isolated* pulses, by further simplification of the original model through which only two motor types are considered: processive and stalled. Using asymptotic analysis in a co-moving coordinate frame, we derive trends for the amplitude, velocity and width of the pulses. We show that these analytically derived forms agree well with direct numerical integrations and also with pulses obtained in the original model, i.e., a model that includes also freely diffusing motors [12]. Finally, we confront the obtained results with experi-

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mentally observed features and make suggestions for future experiments.

2. Reaction–diffusion–advection framework for self-organization of molecular motors

Self-organization of molecular motors inside a cellular protrusion can be described by an effective one-dimensional projection of the emergent dynamics since the protrusions are usually thin compared to their length. The equations of motion then qualitatively incorporate continuum transport and interactions between three forms of the molecular motors [12]:

- m_f, motors which are not physically connected to actin filaments and thus freely diffuse with diffusion coefficient D. If the diffusion is very fast $D \gg \upsilon_b h$ (where υ_b is the retrograde speed of the actin and h is the length of the protrusion), or in an unbounded volume, it acts to diminish and eventually abolish the pulses [12].
- m_b, stalled motors that are physically anchored to the actin filaments and are transported towards the cell (protrusion base) with roughly the treadmilling velocity of the actin filaments υ_b. However even if stalled, these motors can still exhibit random forward and backward steps [8] which result in a small effective diffusion (D_b) along the actin filaments [13], i.e. $D_b/D \ll 1$. Such stalled movements of motors could arise when motors lose their cargo, or enter a self-inhibiting conformation [14,15].
- m_w, processive motors that are only walking against the actin polymerization towards the protrusion tip with velocity $\upsilon_w - \upsilon_b$ ($|\upsilon_b/\upsilon_w| \gg 1$).

The equations of motion read as [12]:

$$\frac{\partial m_f}{\partial t} = -\frac{\partial J_f}{\partial z} + \underbrace{\mathcal{L}_f\left(m_f, m_b, m_w\right)}_{\text{linear reaction}}, \tag{1a}$$

$$\frac{\partial m_b}{\partial t} = -\frac{\partial J_b}{\partial z} + \underbrace{\mathcal{L}_b\left(m_f, m_b, m_w\right)}_{\text{linear reaction}} + \underbrace{\mathcal{N}\left(m_b, m_w\right)}_{\text{nonlinear reaction}}, \tag{1b}$$

$$\frac{\partial m_w}{\partial t} = -\frac{\partial J_w}{\partial z} + \underbrace{\mathcal{L}_w\left(m_f, m_b, m_w\right)}_{\text{linear reaction}} - \underbrace{\mathcal{N}\left(m_b, m_w\right)}_{\text{nonlinear reaction}}, \tag{1c}$$

where the respective linear operators correspond to on/off transition rates between the free, stalled, processive motors and due to mass conservation of the motors $\mathcal{L}_f + \mathcal{L}_b + \mathcal{L}_w = 0$. The nonlinear reactions are related only to motors that propagate along the actin filaments since only these motors can create aggregates bearing a similarity to formation of traffic jams [15]. The local reaction terms in the three-state motor model and the fluxes in (1) are respectively, given by:

$$\mathcal{L}_f = -\left(k_1^n + k_2^n\right) m_f + k_1^f m_b + k_2^f m_w, \tag{2}$$

$$\mathcal{L}_b = k_1^n m_f - \left(k_1^f + k_3^n\right) m_b, \tag{3}$$

$$\mathcal{L}_w = k_2^n m_f - k_2^f m_w + k_3^n m_b, \tag{4}$$

$$\mathcal{N} = k_3^f \left(1 + k_{bw} m_b^2\right) m_w, \tag{5}$$

and

$$J_f = -D\frac{\partial m_f}{\partial z}, \tag{6a}$$

$$J_b = -D_b\frac{\partial m_b}{\partial z} - m_b \upsilon_b, \tag{6b}$$

$$J_w = m_w(\upsilon_w - \upsilon_b) \tag{6c}$$

where k_{bw} is a nonlinear transition rate and $k_1^{n,f}, k_2^{n,f}, k_3^{n,f}$ are first order on/off transition rates, respectively. Briefly, the model (1) describes an effective one-dimensional projection of the emergent dynamics along the actin bundle comprising the core of the cellular protrusion. Since the protrusions are usually thin compared to their length, we ignore variations within the cross-section of the protrusion. Furthermore, for simplicity we ignore dynamical variations in the length h of the protrusion. This is reasonable since many filopodia are observed to be stable on a time-scale that is long compared to the frequency of formation of retrograde motor aggregates [12], as filopodia are often stabilized by adhesion to the external substrate. In addition, we treat the retrograde flow of the actin filaments υ_b as constant. This flow is driven by the actin polymerization at the protrusion tip, and by the pull of myosin-II motors inside the cell cytoplasm. While the processive motors inside the protrusion could also contribute to this flow, these corrections are neglected in this model.

Eqs. (1) are supplemented with boundary conditions (BCs) that reflect realistic properties of motors [12]:

- At the protrusion base $z = 0$, $\left[m_f, J_b, J_w\right] = \left[m_f^0, -\upsilon_b m_b, (\upsilon_w - \upsilon_b)m_w\right]$, where the concentration of free (and actin-bound) motors is usually very low, i.e., $m_f^0 \to 0$;
- At the protrusion tip $z = h$, since the protrusion is closed there must be an overall zero flux condition which imposes a conversion rate according to $J_b = -\beta J_w, J_f = -(1-\beta)J_w$, where $0 \le \beta \le 1$. Here $\beta = 1$ corresponds to pure transition between the counter propagating subsets $m_w \to m_b$ (processive motors stall at the tip, Fig. 1(b)), while $\beta = 0$ denotes a pure transition to freely diffusing $m_w \to m_f$ (processive motors fall-off the actin bundle at the tip, Fig. 1(a)).

Unlike standard reaction–diffusion systems, mass conservation in the bulk introduces multiplicity of uniform states for which one of the fields, for example m_f can be considered as an additional control parameter. In a companion paper [12], we have demonstrated that pattern selection to traveling waves and pulse trains arise from BCs: for $\beta \to 0$ (Fig. 1(a)), and for small (realistic) values of m_f, the uniform states are linearly stable but the accumulation of motors at the tip arise in pulse trains, while the emergence of traveling waves ($\beta \to 1$) arise through a finite wavenumber instability (Fig. 1(b)), cf. [16]. The pulses are excitable pulses (dissipative solitons) which correspond to homoclinic orbits in the co-moving reference frame [17]. In this paper we focus on their qualitative core properties.

3. Isolated pulses

For isolated pulses, we require linear stability of uniform states by assuming $m_f \to 0$ and $m_f \ll m_b, m_w$, which also keeps fidelity to biology of motors inside the protrusion, i.e., UM usually have a high affinity to the actin filaments, so that the fraction of motors in the freely diffusing state is relatively small [8]. Since the equation of motion for m_f is linear, it is therefore enslaved to the nonlinear behavior of m_b and m_w. Moreover, the minimal requirement for homoclinic orbits in reaction–diffusion systems is a two variable system with differential advection and at least a single diffusing term [17,18], i.e., the role played by the third specie, the freely diffusing state, is negligible from the qualitative point of view. It is therefore, useful to study a simpler version of the model comprising only the processive and stalled species. In what follows, we demonstrate that the simplified model contains not only the ability to sustain propagating pulses, similar to the full