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Application of quasi-steady state methods to molecular motor transport on microtubules in fungal hyphae

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HIGHLIGHTS

- We model transport of early endosomes by kinesin and dynein on microtubules (MT).
- Quasi-steady state reduction to a Fokker–Plank equation is solvable in closed form.
- We relate bulk diffusion-advection rates to motor speeds and state transition rates.
- MT polarity and motor competition bias cargo density (towards cell ends or centre).
- Motor mutations (kin-ts, dyn-ts) are linked to changes in motor/cargo distributions.

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ABSTRACT

We consider bidirectional transport of cargo by molecular motors dynein and kinesin that walk along microtubules, and/or diffuse in the cell. The motors compete to transport cargo in opposite directions with respect to microtubule polarity (towards the plus or minus end of the microtubule). In recent work, Gou et al. (2014) used a hierarchical set of models, each consisting of continuum transport equations to track the evolution of motors and their cargo (early endosomes) in the specific case of the fungus *Ustilago maydis*. We complement their work using a framework of quasi-steady state analysis developed by Newby and Bressloff (2010) and Bressloff and Newby (2013) to reduce the models to an approximating steady state Fokker–Plank equation. This analysis allows us to find analytic approximations to the steady state solutions in many cases where the full models are not easily solved. Consequently, we can make predictions about parameter dependence of the resulting spatial distributions. We also characterize the overall rates of bulk transport and diffusion, and how these are related to state transition parameters, motor speeds, microtubule polarity distribution, and specific assumptions made.

1. Introduction

Diffusion is a rapid and effective mechanism to disperse small molecules over distances of a few μm in living cells. It is quite ineffective at longer distances or for transporting large, bulky cargo such as vesicles or organelles. A typical neuron, for example, may be tens of centimeters long, requiring a specialized long-range transport mechanism for substances made in the cell body that are destined for use at the far end of the axon or dendrites. Many of these long-range transport processes are mediated by molecular motors walking along tracks composed of polar biopolymers called microtubules (MTs). We refer to the ends of microtubules as “plus” and “minus” in what follows.

Molecular motors of several classes participate in cargo transport. Kinesin family motors walk toward the plus ends, whereas dynein motors walk toward the minus ends of MTs. In some systems, motors compete for free cargo, or for dominance in shared cargo. Motors can also bind to and carry one another. Finally, motors and/or their cargo can fall off and rebind to a MT track, or skip from one track to another. Mathematical models can help to keep track of these transitions, and to make experimentally testable predictions based on hypotheses for the underlying mechanisms (Bressloff and Newby, 2013).

A convenient experimental system for studying long-range transport of cargo on MT tracks is the filamentous fungus *Ustilago maydis*, (see Steinberg, 2011). Insights obtained from such systems (and from

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mathematical models that represent them) would be transferable to an understanding of some neuronal transport processes. Neurons have similar motor systems (kinesin and dynein) with synergistic and competitive interactions that are not fully understood. MTs in axons (and distal dendrites) are unipolar, whereas MTs in proximal dendrites have mixed polarity. Some neuronal diseases are related to mutations in motors that are more easily studied in fungi. In general, we want to understand how defects in any one part of the transport system are related to overall defective function on the cellular level. Predictions of a model are more easily testable in the fungi, where genetic or chemical manipulation is straightforward.

In the long hyphae (filament-like cells, 80-100 μm long) of *U. maydis*, vesicles denoted "early endosomes" (EEs) are carried by two major types of motors walking along microtubules (2–4 MT, in bundles roughly 10 nm apart). See Fig. 1 for a simplified "cartoon" of this system showing the motors, the motor-endosome complexes, and MT arrays. Each endosome can simultaneously bind several kinesin-3 motors as well as a dynein motor. Early endosomes that bind (and adhere permanently to) kinesin-3 are transported towards a MT plus end. Occasionally, the complex is hijacked by a dynein motor that walks towards the MT minus end. The complex can also dissociate from and rebind to the MTs. Quantitative data and hypotheses for the molecular mechanisms governing transport of EEs in normal and mutant cells of *U. maydis* are becoming more available (Steinberg et al., 2001; Wedlich-Söldner et al., 2002; Lenz et al., 2006; Fink and Steinberg, 2006; Steinberg, 2011; Schuster et al. 2011a,b,c). Based on such data, mathematical modeling can help to select from among competing hypotheses about these molecular mechanisms.

Mathematical models have been developed to describe molecular motor competition, tug of war, and transport processes. Examples include Klumpp and Lipowsky (2005), Chowdhury et al. (2005), Müller and Klumpp (2008), Müller et al. (2008), Vogel et al. (2009), Ashwin et al. (2010), Hendricks et al. (2010), Lin et al. (2011), Seamster et al. (2012), Frerking (2012) and Reis et al. (2012). In a preceding paper, Gou et al. (2014) developed a hierarchy of partial differential equation PDE) models for transport in *U. maydis*. They modelled the MT assembly into parallel polar arrays, the motion of kinesin-1 and dynein on those MT arrays, and the transport of the early endosome cargo by kinesin-3 and dynein. Despite the relative simplicity of their assumptions (including constant and spatially uniform parameters), the authors were able to account for several features of experimental data (Schuster et al., 2011a), including the spatial distribution of endosome density, the endosome run-length distribution, and behavior of mutants (kin-ts, dyn-ts) that lack one or the other motor function. The models also predicted fine structure (such as local minima/maxima in motor distributions) that are experimentally testable.

As in Gou et al. (2014), we use the framework of partial differential equations (PDE) and continuum transport equations for our models. These models do not follow the trajectories or states of individual components. Rather, they represent the time evolution of densities of motors and cargo in various states in the mean field limit. In the stochastic, small copy-number realm, the same models remain valid when reinterpreted as master equations governing the probability of finding motors or cargo in a given state at some time and position in the cell (Newby and Bressloff, 2010; Bressloff and Newby, 2013). PDEs have an advantage of classical and well-developed mathematical tools available for analysis. In some cases, full analytic solutions are available. As model complexity grows, analysis becomes progressively harder and less convenient, leading to a generally greater reliance on numerical computations.

This is where our current paper makes a contribution. We adopt some of the models of Gou et al. (2014), and revise others, but we supplement their simulations with new analytical results based on the rigorous quasi-steady-state (QSS) methods of Bressloff and Newby (2013) and Newby and Bressloff (2010). We first review an elementary model for kinesin moving along and switching between MTs via a freely diffusing state (Fig. 2a and b). In that case, we can fully solve for the steady-state kinesin distribution given the assumption that microtubule distribution is symmetric. We compare with a QSS approximation for the non-symmetric case. We then describe and analyze a model for dynein walking freely or being carried by kinesin-1, first with all transitions via a freely diffusing state (Fig. 2d), and then including transitions on individual microtubules (Fig. 2e). Finally, we model the transport of early endosomes by kinesin-3 and dynein (Fig. 2f). In all but the simplest case (which is solved directly), a QSS approximation leads to an advection-diffusion PDE, equivalent to a Fokker–Plank equation (in the low copy number regime), for total density of motors or cargo. The steady state can be found in closed form. This allows us to directly link the parameters in the problem to "effective diffusion" and "effective transport velocity" of the system as a whole. It also allows a deeper understanding of the roles of molecular-level transition rates in producing the overall steady state distribution.

2. Formulating the models

We consider a linear cell of length L, with x the distance from the left end of the cell ($0 \le x \le L$) and microtubules (MTs) distributed across this length. Let $0 \le P(x) \le 1$ be the fraction of MTs with plus ends pointing to the right at a point x. We refer to $P(x)$ as the MT polarity distribution. At first, we assume that $P(x) \equiv P$ is constant. Later, we relax this assumption and consider the specific MT polarity distribution found in *U. maydis*, as detailed in Gou et al.

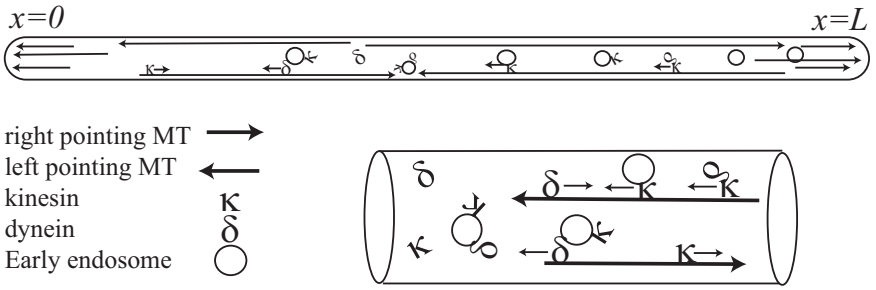

Fig. 1. A diagram of the early endosome (EE) transport system in a long cell of the fungus *Ustilago maydis*. Shown are microtubules (MTs) with plus ends pointing right (left) indicated by long or thick arrows. Note that at the two ends of the cell, MTs have a specific orientation. Early endosomes (circles) are transported by kinesin (towards plus MT end) and dynein (towards minus MT end). The motors can detach from the MT, but kinesin remains bound to an EE. Dynein can either walk or be carried by kinesin. The inset shows an enlarged view with various motor and motor-endosome states, indicating directions of motion relative to the MT track on which they move. Our models describe subsystems in increasing levels of detail. Some (but not all) models allow for cytosolic, freely diffusing states, as illustrated in the inset.