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Axonal transport cargo motor count versus average transport velocity: Is fast versus slow transport really single versus multiple motor transport?

Robert H. Lee *, Cassie S. Mitchell

Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, Atlanta, GA, USA

HIGHLIGHTS

- We develop a model of kinesin and dynein motors suitable for use at the cargo level.
- We propose that motor "pausing" is obstruction/ensnarement followed by detachment.
- We find that motor count can potentially explain fast versus slow transport.
- We make several experimentally testable predictions based on this result.

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ABSTRACT

Cargos have been observed exhibiting a "stop-and-go" behavior (i.e. cargo "pause"), and it has generally been assumed that these multi-second pauses can be attributed to equally long pauses of cargo-bound motors during motor procession. We contend that a careful examination of the isolated microtubule experimental record does not support motor pauses. Rather, we believe that the data suggests that motor cargo complexes encounter an obstruction that prevents procession, eventually detach and reattach, with this obstructed-detach–reattach sequence being observed in axon as a "pause." Based on this, along with our quantitative evidence-based contention that slow and fast axonal transport are actually single and multi-motor transport, we have developed a cargo level motor model capable of exhibiting the full range of slow to fast transport solely by changing the number of motors involved. This computational model derived using first-order kinetics is suitable for both kinesin and dynein and includes load-dependence as well as provision for motors encountering obstacles to procession. The model makes the following specific predictions: average distance from binding to obstruction is about 10 μm; average motor maximum velocity is at least 6 μm/s in axon; a minimum of 10 motors is required for the fastest fast transport while only one motor is required for slow transport; individual in-vivo cargo-attached motors may spend as little as 5% of their time processing along a microtubule with the remainder being spent either obstructed or unbound to a microtubule; and at least in the case of neurofilament transport, kinesin and dynein are largely not being in a "tug-of-war" competition.

1. Introduction

What lies behind "fast" versus "slow" axonal transport? While in-axon data abounds for the existence of these two modes of transport, there is no isolated microtubule data to support two separate modes. Of course, it is possible that one or more as of yet unknown assistive proteins play a role. But, what if there are not two modes but instead, one very long range of transport speeds. We recently showed quantitative evidence that slow axonal transport might be equated to single motor axonal transport based solely on an analysis of cargo loading forces and single motor stall forces(Mitchell and Lee, 2009). This suggestion begs the question, "Is fast axonal transport simply multi-motor transport?" That is, the only difference between slow and fast transport the number of motors involved?

In the work presented here, we quantitatively examine what it would theoretically take to make this proposition true. That is, what assumptions must we make to transform slow and fast transport into a single/multimotor transport theory? Many of the presented

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* Corresponding author. Tel.: +1 404 894 4484.
E-mail address: rlee2@emory.edu (R.H. Lee).

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assumptions have strong experimental support, some are controversial, and the remainder are presented here as model predictions, as they go beyond the current experimental record.

The most contentious assumption that we examine in this theoretical study is also one for which we believe there is strong experimental support: there is no motor equivalent to “stop and go” cargo transport. That is, the experimental evidence supports a cargo-level multi-second “pause” in axon, but not a motor-level multi-second pause in otherwise nominal procession. Instead, we suggest that, at the motor level, cargo pause events are really stop, detach, and reattach events. It is interesting to note that this concept is in line with the original model developed by (Brown et al., 2005), which simply had “on track” and “off track.” However, subsequent models (Craciun et al., 2005), introduced the “pause” as a means to explain the longer time constants observed in the original data (Wang and Brown, 2001).

Furthermore, we contend that the experimental evidence supports the notion that the stop in cargo movement (i.e. cargo “pause”) is due to obstruction. Thus, nominal motor procession is halted because further stepping is physically impeded (e.g. the motor has either reached the end of the microtubule or another complex is blocking further microtubule access). Eventually, this motor detaches and subsequently binds to a microtubule again in a different location. For example, while motor events in isolated microtubule experiments are often characterized as “pause” (e.g. Dixit et al., 2008; Ross et al., 2008), examination of the supplemental data shows that these events are terminated, not by the motor starting to process after not moving for an extended period, but by the end of the experimental recording. In short, observed motor “pauses” are classified as such because they were not observed detaching before recording time ran out.

The product of our theoretical examination of the experimental literature is a unified computational model capable of producing the entire spectrum of axonal transport velocities. Utilizing this model, we make specific predictions regarding the specifications of the transport infrastructure required for the model and its theoretical assertions to be true in axon.

2. Methods

As a basis for the presented computational models, we conducted an extensive review of in vitro mechano-chemical procession of kinesin and dynein, as well as what is known about cargo level transport in vivo. This review is summarized in Supplementary Information. The key findings of this review, which subsequently become the basis for the models presented, are

1) There is no evidence for motor-level “pausing.” It is true that motor procession is step-wise and therefore there is a time lag between steps. However, these time lags are substantially shorter in duration than the multisecond pausing of cargos observed in vivo.
2) There is no evidence of a delay between binding to microtubule and procession.
3) Motor encounters with potential obstructions result in immediate pass, immediate reversal or a halt that ultimately resolves with detachment (Dixit et al., 2008; Ross et al., 2008).
4) In addition to typical obstructions, there is support for motors becoming more severely entangled in a manner that results in prolonged unbinding delays (Brown et al., 2005; Dixit et al., 2008; Ross et al., 2008).
5) In vitro (isolated microtubule) binding rates and in vivo binding rates are the result of very different constraints and are therefore not meaningfully comparable (Craciun et al., 2005; Dixit et al., 2008).
6) In vitro (isolated microtubule) maximum procession velocities are possibly as much as an order of magnitude slower than in vivo maximum procession velocities (Dixit et al., 2008; Kural et al., 2005). We suggest that this may be due to unavoidable bulk flow disturbances in vitro.
7) Unbinding and procession rates are load-dependent in a roughly linear manner (Coppin et al., 1997; Mallik et al., 2004).
8) Cargo load on processing motors is velocity dependent (Mitchell and Lee, 2009)

Based on these key findings, as well as other experimental observations, we developed a generalized kinetic model of single motor movement along a microtubule intended to encapsulate all possible scenarios (Fig. 1a). This generalized kinetic model was subsequently reduced into an in-axon cargo level motor model (Fig. 1b; See Supplement for development details).

The model consists of four states: Moving, Obstructed, Free and Ensnared. Moving represents nominal procession along the microtubule and as such actually represents two of the generalized model states (anterograde poised and straddled). Note that the rate of procession is load dependent. Obstructed represents all conditions that result in an otherwise functioning motor being prevented from

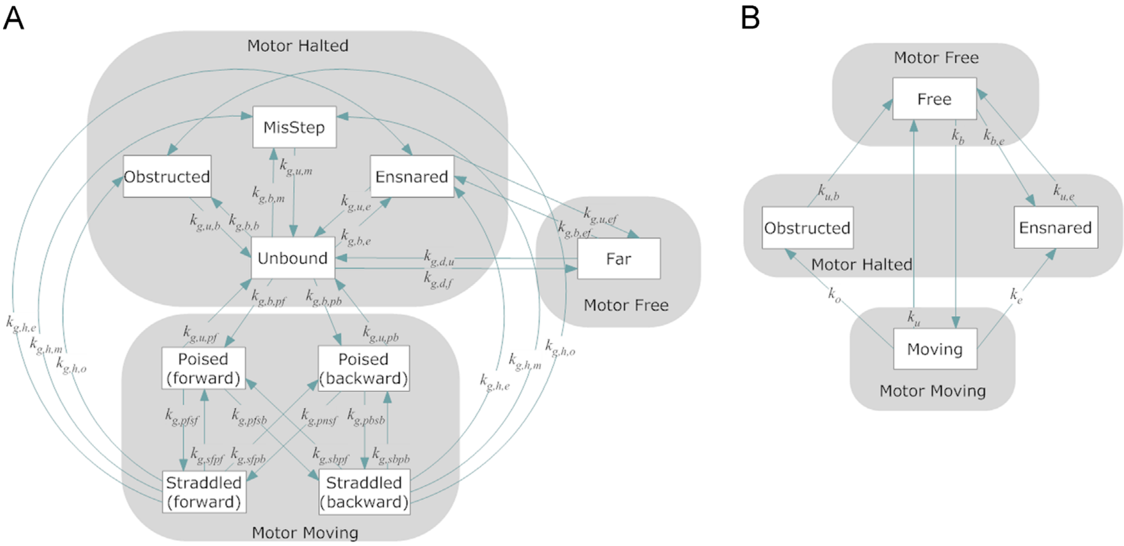

Fig. 1. Development of motor model. (A) Generalized model with all possible transitions included. (B) simplified model generated by merging states.