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Effect of fuel concentration on cargo transport by a team of Kinesin motors

Anjneya Takshak [1], Nirvantosh Mishra [1], Aditi Kulkarni, Ambarish Kunwar *

Department of Biosciences and Bioengineering, Indian Institute of Technology Bombay, Mumbai 400076, India

HIGHLIGHTS

- A team of Kinesin motor proteins transports cellular cargos using ATP as fuel.
- How fuel concentration affects transport by the team largely remains unexplored.
- Mechano-chemical models of cargo transport developed here fill up this knowledge gap.
- Mechano-chemical models include effect of both force and fuel on cargo transport.
- Models predict very large cargo travel distances at limiting fuel concentrations.
- Models predict Michaelis-Menten dependence of cargo velocity on fuel concentration.
- These predictions from modeling can be directly tested by in-vitro experiments.
- Our results may be used to regulate and fine-tune transport by motor-based shuttles.

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ABSTRACT

Eukaryotic cells employ specialized proteins called molecular motors for transporting organelles and vesicles from one location to another in a regulated and directed manner. These molecular motors often work collectively in a team while transporting cargos. Molecular motors use cytoplasmic ATP as fuel, which is hydrolyzed to generate mechanical force. While the effect of ATP concentration on cargo transport by single Kinesin motor function is well understood, it is still unexplored, both theoretically and experimentally, how ATP concentration would affect cargo transport by a team of Kinesin motors. For instance, how does fuel concentration affect the travel distances and travel velocities of cargo? How cooperativity of Kinesin motors engaged on a cargo is affected by ATP concentration? To answer these questions, here we develop mechano-chemical models of cargo transport by a team of Kinesin motors. To develop these models we use experimentally-constrained mechano-chemical model of a single Kinesin motor as well as earlier developed mean-field and stochastic models of load sharing for cargo transport. Thus, our new models for cargo transport by a team of Kinesin motors include fuel concentration explicitly, which was not considered in earlier models. We make several interesting predictions which can be tested experimentally. For instance, the travel distances of cargos are very large at limited ATP concentrations in spite of very small travel velocity. Velocities of cargos driven by multiple Kinesin have a Michaelis–Menten dependence on ATP concentration. Similarly, cooperativity among the engaged Kinesin

* Corresponding author.
E-mail address: akunwar@iitb.ac.in (A. Kunwar).

[1] First Co-authors.

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motors on the cargo shows a Michaelis–Menten type dependence, which attains a maximum value near physiological ATP concentrations. Our new results can be potentially useful in controlling artificial nano-molecular shuttles precisely for targeted delivery in various nano-technological applications.

1. Introduction

Molecular motors are specialized proteins which perform the long-range and short range transport of cargo particles (vesicles, mitochondria, mRNA particles, liposomes, pigment granules, etc.) along cytoskeletal filaments in eukaryotic cells [1]. The commonly employed proteins which perform this cargo trafficking inside cells belong to three families: Kinesin superfamily, Dynein and Myosin families [1,2]. Most Kinesin superfamily members are (+) end directed, which means that they carry cargo from the cell interior to the cell periphery. Several in-vitro single molecule studies have revealed the details about the mode of action of Conventional Kinesin (Kinesin-1) [2,3]. It is a highly processive motor which takes several steps on the microtubule [4] prior to detaching. It has two motor domains through which it attaches to the microtubule and travels in discrete steps of 8 nm in a coordinated hand over hand mechanism. During the process of cargo transport, a single Kinesin motor can move processively against an opposing force (load) in the range of up to 5 to 7 pN [5]. Additionally, Kinesin motors can also detach from microtubule with load-dependent unbinding rate and reattach [6–8].

Since the amount of force generated by a single Kinesin motor is usually insufficient for effective long-range intra-cellular transport, multiple Kinesin motors often work together as team to achieve this [9,8]. Several models have been proposed to study cargo transport by a team of molecular motors [10–16]. Klumpp et al. [6] proposed a model considering that the applied load on the cargo is distributed equally among all engaged motors. Models later developed by Kunwar et al. [17,18] incorporated stochastic load sharing among multiple motors engaged on a cargo. However, these models cannot be used to understand the effect of fuel concentration on cargo transport by a team of motors, as underlying single motor characteristics do not incorporate fuel dependence.

In this paper, we use an experimentally-constrained model of single Kinesin motor to study cargo transport by a team of multiple Kinesin motors using earlier developed Mean-field [6] and Stochastic models [17,18] of load sharing. Hereafter, we shall refer to Mean-field model of load sharing [6] as Mean-field model, and Stochastic model of load sharing [17,18] as Stochastic model.

2. Experimentally-constrained model of single Kinesin motor

Schnitzer et al. [5] proposed a load dependent Composite State Model to describe the stepping behavior of a single Kinesin motor over a microtubule which incorporates effect of both load and fuel (ATP) concentration. When an ATP molecule is bound to one of the two heads of a Kinesin motor, the motor is said to be in Composite State. According to this model, Kinesin head can detach from the microtubule, with a smaller ATP concentration-dependent probability, before ATP binding (State I). Kinesin head can also undergo detachment with a greater load-dependent probability, after ATP binding (State II).

The experimental velocity curves of single Kinesin motors can be fitted using a Michaelis–Menten equation [5] as a function of ATP concentration (denoted by $[ATP]$), at different loads as given by the following relation

$$v\left(F,[ATP]\right)=\frac{V_{max}[ATP]}{[ATP]+K_M}=\frac{\mathrm{d}K_{cat}\left(F\right)[ATP]}{[ATP]+\frac{K_{cat}(F)}{K_b(F)}} \tag{2.1}$$

where V_{max} $(= dK_{cat})$ is the velocity at saturating ATP concentration in nm/s, d is the step size of a single Kinesin motor in nm, $K_{cat}\left(F\right)$ is the load-dependent catalytic turnover constant, and $K_b\left(F\right)$ is the load dependent second order rate constant for ATP binding to the Kinesin motor. Both the rate constants exhibit an inverse exponential type Boltzmann relationship with load as follows:

$$K_{cat}\left(F\right)=\frac{K_{cat}^{o}}{p_{cat}+q_{cat}\exp\left(\frac{F.\delta_{cat}}{k_BT}\right)}$$

$$K_b\left(F\right)=\frac{K_b^{o}}{p_b+q_b\exp\left(\frac{F\delta_b}{k_BT}\right)}$$

where K_{cat}^{o} and K_b^{o} are the respective rate constants, measured in s^{-1} and $\mu M^{-1}s^{-1}$ respectively, in the absence of external load. k_BT is the thermal energy at temperature T, δ_{cat} and δ_b represent the characteristic motor distances in nm over which the load acts during catalysis and binding respectively. p_{cat} and q_{cat} $(= 1 - p_{cat})$ are the fractions of the unloaded catalytic