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Surfing at wave fronts: The bidirectional movement of cargo particles driven by molecular motors

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Abstract We examine the properties of intracellular transport of particles (vesicles, organelles, virus, etc.) in the realm of models that describe the dynamics of interacting molecular motors moving along microtubules. We use a continuum description of motor distribution and argue that certain features of cargo movement have their origins on its ability to perturb the existing motor profile and to *surf* at the resulting shock wave fronts that separate regions of different motor concentrations. In this case, the observed bidirectionality of cargo movement is naturally associated with reversals of shock direction. Comparison of the quantitative results predicted by this model with available data suggests that the geometrical characteristics of cargo may be related to the extension and intensity of the perturbation they produce and thus, to their kinetics. Possible implications of these ideas to understand features of the movement of virus particles within the cell body are discussed in connection with their distinguished morphological characteristics.

Introduction

The active transport of particles (organelles, vesicles, virus) inside the cells is mediated by motor proteins such as myosin, kinesin and dynein [1]. The unidirectional motion of a single motor along protein filaments or microtubules is well characterized experimentally and it was first modeled at a microscopic level by a stochastic dynamics describing the behavior of a Brownian particle in the presence of a time-dependent asymmetric potential field [2—5]. The idea is based on the mechanism of ''ratchet and paw'' introduced by Feynman to discuss the meaning of the second law of thermodynamics [6]. Since then, this model has been used as a prototype to explain why and in what conditions Brownian particles are able to do work against external potential gradients.

More recently, it appeared in the literature attempts to describe the properties resulting from the movement of many interacting Brownian motors with particular interest on the nature of the observed *bidirectional movement* accomplished by *cargo* for which the combined action of many motors appears to be crucial [7—10]. The non-diffusive *bidirectional* movement is characterized by inversions of cargo direction after

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processive runs [1] that may be preceded by relative long *resting times* (intervals within which the particles remain at the same position on the microtubule). Quantitative models that describe the movement of relative extensive objects such as filaments in motility assays suggest that bidirectionality arises in this case from the collective behavior of considered grafted motors acting on a same cargo [11]. It is not clear, however, how to extend these models to describe the observed bidirectional movement of relative small particles, as vesicles or virus, that happens at microtubules where the carrying motors are free to move (not grafted).

The most accepted explanation in this case comes from the referred *coordination model* [7,9]. According to this, the bidirectional movement would result from the coordinated action of two types of motors — plus-ended and minus-ended motors — attached simultaneously to cargo. The reversal of its direction would just reflect the fact that one or other type of motor, but not both simultaneously, happens to be active during the respective time intervals. Motor coordination, that is, the control of each motor activity, would be accomplished by an external non-motor protein complex that should be able to coordinate the movement and timing of many motors of different nature and distinct characteristics — certainly a very non-trivial job. Up to now, such an external complex still needs to be identified in real systems [12]. Another possibility within the same lines is based upon the existence of a *tug-of-war* competition mechanism between two types of motors that may happen, according to a recent analysis [13], in the absence of a coordinator. In any case, however, it remains the problem to explain how and in what conditions the transport can get into effect, avoiding the traffic-jam that may be expected as a consequence of the presence of many motors and cargoes dividing space on a single microtubule and, eventually, moving to opposite directions [14]. It is thus accurate to attribute to the bidirectional transport of cargo the status of a ''major puzzle in the context of *in vivo* intracellular transport'', as in a recent work by Kulic and co-worker [15].

At certain scales of interest, phenomena related to the collective behavior of interacting Brownian motors have also been considered using models to describe dynamic aspects of continuum motor distributions. Such approach is generally justified upon evaluation of the characteristic sizes and time scales where these molecules operate at very low Reynolds numbers [16] and it is based on the continuum versions of ''asymmetric exclusion processes'' (ASEP) [17—20] for studying the *long-time* behavior of motors interacting through short-range interactions as excluded volume [16,21—23]. From this perspective, the (microscopic) asymmetric movement of individual motors is assumed *a priori*. The general interest in this context consists in analyzing the *steady-state* behavior of a defined motor density distribution. These are obtained as the solutions to the corresponding non-linear differential equation — the viscous Burgers equation, that describes the dynamics of the system in these limits — with *open boundary conditions*. It is also possible to superimpose to the ASEP a non-conservative Langmuir process that allows the system to exchange motors with the exterior bulk at any position of the microtubule [22]. Apparently, however, questions related to cargo transport, have not been considered in this context.

Here, we make a proposal in this direction based on considerations about interactions among cargoes and motors. It relies on the idea that a cargo is able to produce local changes onto *a priori* motor density distribution, as it approaches the microtubule at a defined initial time. Thereafter cargo shall take advantage of the gradients of motor density, induced by this initial perturbation, to move along microtubule by *surfing* at the density shock waves formed as the motor system relaxes back to the original profile. Shock waves separate regions of different motor densities and evolve in this case according to the *transient* solutions to the Burgers equation for the considered initial conditions (or initial perturbation). Within this view, bidirectional movement of cargo particles would follow as a direct consequence of the reversals in shocks propagation directions.

Surfing of *bacteria* along thin nanotubes [24] and *surfing* of *virus* along the surface of filopodia [25] have been observed and are examples of systems where bidirectional movement happens in the presence of a single motor type.

It is also noticeable in this respect the experimental data published recently showing the occurrence of vectorial transport of small floating objects moving at the fronts of chemical waves produced in a Belousov—Zhabotinsky (BZ) type of chemical reaction [26]. This strongly supports the ideas presented here and suggests that, although the motor/cargo system is rather distinct from that considered in these experiments, it may exhibit an equivalent mechanism to that responsible for the transport within the BZ medium. In Section 4 we discuss one possibility.

We use data from the movement of vesicles in Drosophila embryo [27] to perform a phenomenological analysis of our model considering the explicit expressions predicted for shock velocities. As we shall see, this allows one to associate geometrical characteristics of cargo with the extension and magnitude of the considered initial perturbation it produces on motor density profile. In view of this, we discuss on possibility to use these results to understand aspects of the virus movement within the cell body.

From the microscopic potential models to the macroscopic motor density profile

In order to present our ideas in the context of the related works in the literature, it is convenient to review some aspects of the existing theoretical studies intended to describe the dynamics of interacting motor particles. In particular, we consider the usual procedure to obtain the continuum limit in the mean field approximation (the macroscopic limit) of an ASEP model representing the stochastic dynamics of motors that move by jumping from one site to another in a one-dimensional lattice. Within this

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[1] Here, processive run makes reference to the movement accomplished towards a definite direction before inversion or detachment from microtubule.