Journal of Computational Science 2 (2011) 324–334

Contents lists available at SciVerse ScienceDirect

Journal of Computational Science

journal homepage: www.elsevier.com/locate/jocs

Exact stochastic simulations of intra-cellular transport by mechanically coupled molecular motors

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ARTICLE INFO

Article history:
Received 27 April 2011
Received in revised form 25 August 2011
Accepted 31 August 2011
Available online 14 September 2011

Keywords:
Hybrid stochastic–deterministic model
Hybrid continuous–discrete simulation
Stochastic simulation algorithm
Intra-cellular transport
Motor proteins

ABSTRACT

Numerous processes in live cells depend on active, motor-driven transport of cargo and organelles along the filaments of the cytoskeleton. Understanding the resulting dynamics and the underlying biophysical and biochemical processes critically depends on computational models of intra-cellular transport. A number of motor–cargo models have hence been developed to reproduce experimentally observed transport dynamics on various levels of detail. Computer simulations of these models have so far exclusively relied on approximate time-discretization methods. Using a consensus motor–cargo model that unites several existing models from the literature we demonstrate that this simulation approach is not correct. The numerical errors do not vanish even for arbitrarily small time steps, rendering the algorithm inconsistent. We propose a novel exact simulation algorithm for intra-cellular transport models that is also computationally more efficient than the approximate one. Furthermore, we introduce a robust way of analyzing the different time scales in the model dynamics using velocity autocorrelation functions.

1. Introduction

Many intra-cellular cargos such as large molecules, vesicles, organelles, or virus particles are transported along the filaments of the cytoskeleton by motor proteins. Due to their polarization and highly ordered arrangement in the cell, microtubules can support directed and targeted transport in order to, e.g., shuttle cargo between the plasma membrane and the peri-nuclear region. Complex intra-cellular distributions and motion patterns have been observed for various cargos, including virus particles, lipid droplets, vesicles, and small organelles; see for example Refs. [1–4] and references in Ref. [5].

In order to quantify and explain these patterns, computational studies of intra-cellular transport have been invaluable [6]. These simulations require accurate yet computationally efficient models of single motor–cargo complexes. A number of such models have been proposed in which a motor is described by a few discrete chemical states and its discrete location on a microtubule, rather than its full atomic structure. In these models coarse-grained motors are mechanically coupled to a cargo that is typically modeled as a rigid sphere immersed in a highly viscous medium. Elastic motor–cargo links transmit the forces that drive cargo motion. The chemical state-changes of the motors – such as binding to, stepping on, and unbinding from microtubules – are described by Poisson processes with rates that depend on the environment and on the forces exerted on the motor [7–11].

We combine previous models into a "consensus model" that is formally described by sets of coupled stochastic chemical reactions where binding, stepping, and unbinding of different motors are discrete reaction events. Coupling between different motors is provided through the dynamics of the cargo. Between individual reaction events this dynamics is governed by a deterministic law, hence defining a hybrid stochastic–deterministic model. State-of-the-art studies of intracellular transport simulate such models using iterative algorithms with discrete time steps of size Δt [10–13]. Due to this time discretization, the probabilities of the reactions and the position of the cargo exhibit a truncation error that decreases with some power of Δt. This power is called the *convergence order* of the simulation and it depends on the specific time-discretization scheme used. The computational cost of these approximate simulation methods is inversely proportional to the time step Δt. The choice of Δt hence entails a tradeoff between numerical accuracy and computational performance.

Analytical [8,14] and numerical [9–11,13,15,16] studies of transport models have revealed a number of non-trivial effects, such as cascades of correlated unbinding events and fast switching of motion direction, which are closely related to stochastic barrier crossing. In systems exhibiting such behavior, tiny errors in the probabilities of the basic state transitions (i.e., binding, stepping, unbinding) can be amplified to large errors in the crossing rates and time correlations. Due to their non-linear nature, these errors

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doi:10.1016/j.jocs.2011.08.006

may remain significant even for the smallest feasible time step Δt.

The stochastic kinetics of chemical reactions coupled to a deterministic dynamical system can be simulated exactly with a hybrid variant of Gillespie's stochastic simulation algorithm [17–19]. Unlike approximate time-discretization algorithms, this exact method does not involve any discretization error and hence samples cargo trajectories from the correct probability distribution as defined by the transport model.

In this paper we describe how the consensus transport model can be simulated exactly using a novel hybrid continuous–discrete simulation algorithm. The presented exact simulation algorithm does not require choosing a time step. It is parameter free and does, by construction, not entail any tradeoff between efficiency and accuracy. Nevertheless, any quantity computed from Monte Carlo simulations is uncertain due to finite sample size. We compare the computational performance of the presented exact algorithm to that of the approximate one and study the convergence properties of the approximate method. Hereby, the finite-sample Monte Carlo error naturally defines the scale of an acceptable numerical error for the approximate algorithm. We find that some transport properties simulated using the approximate method are systematically wrong, i.e., the error shows no sign of convergence within feasible bounds for the time step. Moreover, the exact algorithm is typically between one and two orders of magnitude faster than the approximate one for biologically relevant motor numbers.

Previous studies have reported high sensitivities of the transport properties to the model parameters within their physiological bounds. Several mobility regimes with qualitatively different behaviors have been identified in the parameter space of intracellular transport models. Refining this picture requires screening the parameter space with high resolution, which critically depends on the availability of computationally efficient and accurate simulation algorithms. The present exact simulation method is computationally efficient and provides full control over the Monte Carlo error.

2. A consensus motor–cargo model

A large number of coarse-grained models of motor–cargo complexes have been proposed in the literature [8–11]. We present here a "consensus model" that unites the concepts, state variables, and the laws for their dynamics that have been used in most related studies.

We consider the situation where a single, rigid cargo is moved by several motors of possibly opposite movement directions. We only resolve the 1D position of the cargo along the microtubule filament; models that resolve the cargo's orientation and its diffusive motion perpendicular to the filament also exist [10]. Motor proteins stochastically step on, bind to, and unbind from microtubules with rates that may depend on the force acting on the motor–filament bond. The physical properties of the motor–cargo links play a key role for the cargo dynamics, as they define the magnitude of forces in the system and their fluctuations in response to stochastic events. Frequently, the motor–cargo links are modeled as linear elastic springs, parameterized by their elasticity κ. In response to the forces transmitted by these springs, the cargo moves in the viscous environment of the cytoplasm. Due to the low Reynolds number, this movement is governed by Stokes' law of drag, parameterized by the drag coefficient γ. Inertial forces and thermal diffusion of the cargo are neglected. The latter is justified since the mechanical energy released by a single motor protein is one order of magnitude larger than the average thermal energy of the cargo [20]. Moreover, thermal fluctuations are already implicitly accounted for in the reaction model where they provide the activation energy for the motor protein reactions, leading to stochastic forces acting on the cargo. Since motors do not directly "see" each other, coupling between different motors is exclusively due to cargo motion. An overview of the model state variables, their relations, and the admissible state transitions is given in Fig. 1.

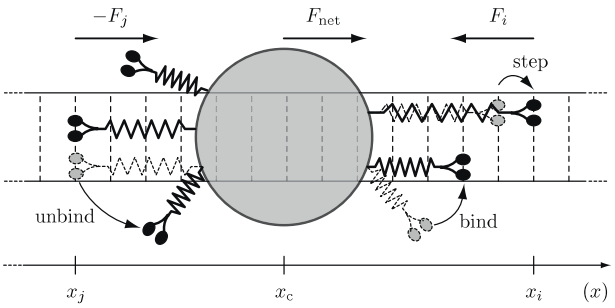

Fig. 1. Illustration of the consensus motor–cargo model. Molecular motors (black) are attached to a rigid cargo (gray disk) through linear elastic springs (zig-zag lines). Motors stochastically bind to, unbind from, and step along discrete binding sites (dashed lines) on a microtubule. The cargo moves in response to the net force F_{net} transmitted by the set of motor–cargo links.

2.1. Time scales

Molecular motors transform chemical energy released by ATP hydrolysis to work in a mechano-chemical cycle [21–23]. In the motor kinesin, this is achieved by a conformational change in the protein structure, pulling the motor forward along the microtubule in discrete steps of 8 nm [7,24]. The time required to complete one such "power stroke" is much shorter than the time between subsequent steps of the same motor and too short for any significant cargo movement to happen meanwhile [7]. Individual steps can therefore be modeled as stochastic events that complete instantaneously at discrete times points. From the perspective of the cargo, these events instantaneously bring the motor–cargo connection to a new state, i.e., the motors jump to the next binding site in their movement direction, elongating the spring. Binding and unbinding of motors are chemical reactions that are also modeled as instantaneous stochastic state changes.

Depending on the properties of the motors and the cargo, the time between individual motor steps and the viscous relaxation time of the cargo position can be of similar order. The cargo dynamics hence has to be explicitly resolved and considered in the stochastic unbinding and stepping processes. Nevertheless, the separation of time scales into instantaneous stochastic events with small rates and slow continuous movement of the cargo allows building a mathematical model from well-known and well-characterized components.

2.2. Mathematical model description

The motion of motors along microtubules is inherently discrete, since the motor–filament interaction responsible for the stable bond is localized to specific parts of the motor and the microtubule. The microtubule consists of α- and β-tubulin dimers, arranged in 13 linear polymer chains called protofilaments. Motors rarely switch between protofilaments. Step lengths of motors are thus integer multiples of the 8 nm distance between two tubulin dimers on the same protofilament. Kinesin almost exclusively makes steps of 8 nm, while cytoplasmic dynein has been observed to also make steps of an integer multiple of that [25,26]. This motivates the use of $L = 8$ nm as the unit of length.

Each motor i is described by the tuple $m_i = (x_i, b_i, d_i)$, where $x_i \in \mathbb{Z}$ is its position, $b_i \in \{\text{bound}, \text{unbound}\}$ its binding state, and the constant $d_i \in \{-1, +1\}$ its movement direction along the filament