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A stochastic model for microtubule length dynamics

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ABSTRACT

In this paper, we use random walk theory to describe the length dynamics of microtubules, one of the principal components of the cytoskeleton. We present a simple two-state model (growing and shrinking) of microtubule length evolution that incorporates a variable rate of switching between the states. Using the generating function technique, we calculate the mean length of microtubule, its variance and diffusion coefficient. We also report analytical and computer simulation results for the mean number of positive monomers in microtubule, and find good qualitative agreement with experimental data.

1. Introduction

Stochastic processes are omnipresent in fields as diverse as physics, biology and economics. "Birth-and-death" processes, or "generation–recombination" processes, also known as "one-step processes" [1], play an important role in modeling various systems, such as photon emission or absorption, chemical reactions, population dynamics. "Random walks" are probably one of the best known one-step processes, with far reaching applications. The random walk problem is well studied, but depending on the question posed, this topic continues to present new and interesting puzzles, and to invite new applications outside of the physics area.

In this paper, we use random walk theory to model the length dynamics of microtubules, one of the principal components of the cytoskeleton [2]. These polar, linear polymers have two major roles in the cell: they form a rigid internal skeleton for some cells and they also act as cellular tracks along which motor proteins can move structures within the cell. These tracks can either grow out from the centrosome towards the periphery of the cell or can be free. Microtubules are dynamic structures that undergo continuous assembly and disassembly within the cell. These polar structures have a fast-growing plus end and a slow-growing minus end. They remain in a non-equilibrium state driven by sudden polymerization changes, switching stochastically from growing to shrinking and vice versa. Microtubules grow by the attachment of *GTP* (guanosine triphosphate tubulin units) at their plus end. However, if the *GTP* cap hydrolyzes into *GDP* (guanosine diphosphate tubulin units), the microtubule is destabilized, the *GDP* complexes are detached and shrinkage ensues. Another interesting aspect of microtubule dynamics is "treadmilling" [3], when free microtubules display persistent growth at one end and shrinking from the other end.

From the point of view of statistical physics, microtubules represent interesting non-equilibrium systems, amenable to a stochastic treatment. In 1984, Mitchison and Kirschner [4] discovered the "dynamic instability" of microtubules (the random transition between states of assembly and disassembly). Mitchison and Kirschner conjectured that this instability is a consequence of competition between assembly and *GTP* hydrolysis; once the stabilizing *GTP* cap is gone, the microtubule dissociates rapidly (process known in the literature as "the microtubule catastrophe"). Despite the large number of

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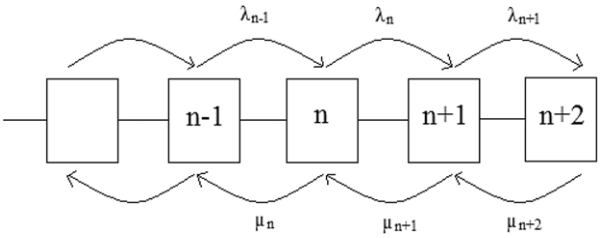

Fig. 1. General definition of a one-step process and its transition probabilities. The process is defined as a Markov process on an integer set $\{n\}$ with jumps allowed only between adjacent sites. Adapted from [1].

theoretical and experimental studies [5–9], there still is no coherent model for the microtubule dynamics able to explain the experimental data fully. On the theoretical front, a variety of models have been proposed: very detailed ones that include all 13 protofilaments that make up the microtubule [10,11] and minimalist models that contain as few parameters as possible, such as the ones proposed by Flyvbjerg et al. [12] and Antal et al. [13].

This paper presents a two-state model of microtubule length dynamics that incorporates a *variable rate* of switching between a growing and shrinking microtubule. This is a novel approach—so far, the theoretical models proposed assumed *constant rates* of transition between states. We do not account for stochastic avalanches or catastrophes that occur as part of *in vivo* and *in vitro* microtubule experiments. Specifically, based on some simple dynamical rules first introduced in Ref. [13], in the context of our model, we calculate the mean length of the microtubule as a function of time, its variance and the diffusion coefficient of the microtubule tip. We compare our analytical and computational results with experimental results reported in Ref. [4], and find good qualitative agreement.

This paper is structured as follows: We first (Section 2) give an overview of "one-step processes", and define our model. Using the generating function technique, we solve the master equation for some particular cases to obtain the probability distribution for the lengths, the average length and the diffusion coefficient (Sections 3 and 4). In Section 5 we discuss the distribution of positive monomers for the case of variable rates. We compare our analytical results with the computer simulations and the experimental biological data and conclude with a summary of our work and some open questions.

2. Model

A starting point for the study of one-step processes is the master equation, which expresses the conservation of configurational probabilities. In general, consider a system in state "r" at time "t". $P_r(t)$ is the probability that this system is in this particular state. The time dependence of P_r is given by the master equation, which states:

$$\frac{\mathrm{d}P_r}{\mathrm{d}t} = \sum_s P_s W_{sr} - \sum_s P_r W_{rs}. \tag{1}$$

This is a balance (continuity) equation. The probability of state "r" increases with time due to states that evolve into state "r", and it decreases with time because of transitions from state "r" to other states. In this equation, W stands for the transition rates to and from state "r". Knowing W allows one to calculate all probabilities P_r as a function of time.

For the special case of one-step processes, transitions happen only between adjacent states, labeled as a set of integers "n" (Fig. 1). The evolution of probability $p_n(t)$ is described by the following master equation:

$$\frac{\mathrm{d}p_n}{\mathrm{d}t} = \mu_{n+1}p_{n+1} + \lambda_{n-1}p_{n-1} - (\mu_n + \lambda_n)p_n \tag{2}$$

where μ_n is the probability per unit time of a transition from state "n" to state "$n-1$", and λ_n is the probability per unit time of a transition from state "n" to state "$n+1$" (see Fig. 1). These quantities can be constants (this is the classical random walk case), or polynomials in n.

In the context of one-step processes, we define the following idealized model for the microtubule (Fig. 2), based on a theoretical model introduced by Ref. [13]. Using Antal et al. notation, treat the microtubule as an ordered set of *GTP* ("+") and *GDP* ("−") monomers. The microtubule evolves according to the following rules:

- *Attachment*. A microtubule grows by attachment of a guanosine triphosphate tubulin unit (GTP^+ monomer) at either end. We define λ_l to be the attachment rate at the left (negative) end of the microtubule, and λ_r the corresponding attachment rate at the right (positive) end of the microtubule.
- *Detachment*. A microtubule shrinks by detachment of a guanosine diphosphate tubulin unit (GDP^- monomer) at either ends. We define μ_l to be the detachment rate at the left (negative) end of the microtubule, and μ_r the corresponding detachment rate at the right (positive) end of the microtubule.
- *Conversion*. Each GTP^+ monomer can convert via hydrolysis into a GDP^- monomer. We assume this rate to be 1.