Journal of Theoretical Biology 382 (2015) 81–90

Contents lists available at ScienceDirect

Journal of Theoretical Biology

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

Microtubule patterning in the presence of moving motor proteins

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HIGHLIGHTS

- We model the dynamic interactions between microtubules and motor proteins.
- We describe microtubule patterns that can be formed in the presence of motors.
- For single motor types, we show that asters and vortices can form.
- For two opposing motors, we find that anti-parallel microtubule bundles form.

ARTICLE INFO

Article history:
Received 20 June 2014
Received in revised form
31 October 2014
Accepted 24 June 2015
Available online 6 July 2015

Keywords:
Microtubule
Motor protein
Patterning
Partial differential equations

ABSTRACT

Cytoskeletal polymers such as microtubules (MTs) interact with motor proteins to form higher-order structures. *In vitro* experiments have shown that MT patterns such as asters, bundles, and vortices can form under the influence of a single type of dynamic motor protein. MTs also can form anti-parallel bundles, similar to bundles that form the mitotic spindle during cell division, under the influence of two types of moving motors with opposite directionality. Despite the importance of MT structures, their mechanism of formation is not yet understood. We develop an integro-partial differential equation model to describe the dynamic interactions between MTs and moving motor proteins. Our model takes into account motor protein speed, processivity, density, and directionality, as well as MT treadmilling and reorganization due to interactions with motors. Simulation results show that plus-end directed motor proteins can form vortex patterns at low motor density, while minus-end directed motor proteins form aster patterns at similar densities. Also, motor proteins with opposite directionality are able to organize MTs into anti-parallel bundles. Our model is able to provide a quantitative and qualitative description of MT patterning, providing insights into possible mechanisms of spindle formation.

1. Introduction

Microtubules (MTs) and motor proteins interact *in vivo* and *in vitro* to form a variety of patterns. *In vivo*, the organization of MTs is directly connected to the cellular process that a cell is carrying out (Dogterom and Surrey, 2013), such as cell division, cell motility, and cell polarization (Karp, 1996). For example, during cell division, MTs form two asters (as in Fig. 1 (a)) at the spindle poles of the cell, that are separated by an anti-parallel bundle of MTs (as in Fig. 1(b)). It should be noted that for these processes to be carried out, it is not only motor proteins that contribute to moving MTs into their proper organizations, but also many other cellular components and proteins. For example, the motor protein dynein attaches itself to the surface (with the aid of other cellular proteins), and it is thought to help in creating the pushing and pulling forces on MTs that are required to properly align the MT asters at the cell's poles during cell division (Ma et al., 2014). *In vitro*, experiments show that in systems comprised *solely* of MTs and motor proteins (Nedélec et al., 1997; Surrey et al., 2001; Nedélec and Surrey, 2001), MTs can organize into asters, vortices, and bundles, as shown in Fig. 1. Here, we develop a mathematical framework to describe the interactions between moving motors and MTs. Our goal is to describe the patterns found *in vitro*, and to gain insight into how motors contribute to MT patterning *in vivo*.

Previously, partial differential equation (PDE) models have been developed to describe MT patterning in MT/motor systems (Aranson and Tsimring, 2006; Jia et al., 2008; Kim et al., 2003; Lee and Kardar, 2001). Such models have been successful at describing some of the MT patterns found *in vitro* by incorporating many of the important mechanisms required for MT patterning. Some of these mechanisms include motor density, speed, directionality, processivity, as well as MT reorientation, caused by interactions

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http://dx.doi.org/10.1016/j.jtbi.2015.06.040
0022-5193/

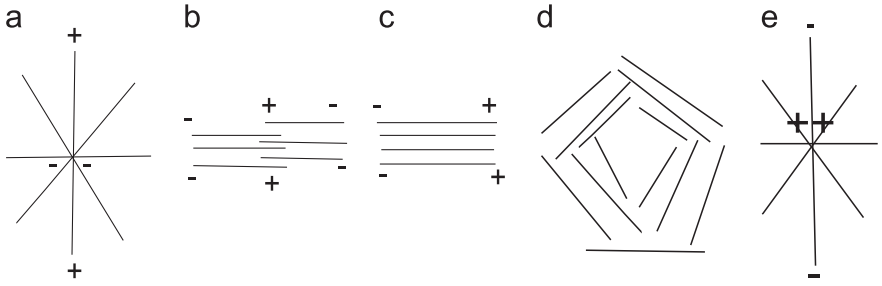

Fig. 1. Examples of MT organization *in vivo* and *in vitro*. *In vivo* organizations include (a) an aster with minus ends at the center (typical of a centrosomal configuration found in non-dividing cells and moving cells), (b) an anti-parallel bundle (similar to the mitotic spindle of a typical dividing cell), and (c) parallel bundles (similar to those found along the axon of a neuron). *In vitro* examples of MT patterns formed in systems comprised of only MTs and motor proteins include those described in (a), (b), and (c), but also include (d) vortices, and (e) an aster with plus ends at the center (Nedélec et al., 1997; Surrey et al., 2001).

with motor proteins. Here, we expand this list of mechanisms to include MT treadmilling, motor activity (the cross-linking capability of a motor), as well as the effect of two opposing motor types.

MTs are dynamic protein polymers formed through the self-assembly of α-, β-tubulin dimers (Karp, 1996; Wade, 2009). They grow through the addition of GTP-bound tubulin dimers, generally from the plus end of the MT, and shrink through dissociation of GDP-bound tubulin at this end. The minus end of the MT is generally more stable, being capped by stabilizing proteins. Two primary types of dynamic movement that MTs undergo are treadmilling (Waterman-Storer and Salmon, 1997; Mitchison and Kirschner, 1986) and dynamic instability (Waterman-Storer and Salmon, 1997; Kirschner and Mitchison, 1984). MT treadmilling is a chemical process that is defined as the steady-state, unidirectional flux of subunits through a polymer, as a result of continuous net assembly at one end of a polymer and continuous net disassembly at the other end. This type of dynamics results in the directed (constant) motion of the MT towards its plus end. Treadmilling has been observed *in vivo*, but can be difficult to reproduce *in vitro*. Dynamic instability refers to slow growth of a MT at its plus end, followed by fast depolymerization and has been observed both *in vivo* and *in vitro*.

Motor proteins are ATPases, and so are driven by the hydrolysis of adenosine triphosphate (ATP) (Howard, 2001). By transforming chemical energy into work, they are able to perform a number of important functions such as walking along MTs (either towards their plus end or minus end) and transporting molecular cargo across the cell. Motor proteins affect MT organization by cross-linking adjacent MTs (Nedélec et al., 1997). As motors walk along the cross-linked MTs, they produce pushing and pulling forces that help to reorient the MTs. Motor proteins can also slide MTs. MT sliding occurs when a motor is attached (absorbed) to a non-moving substrate at its cargo domain, where its free legs are able to attach to a MT (Yokota et al., 1995; Gibbons et al., 2001). Since the motor remains stationary, it effectively pushes the MT along its own axis as it walks along it. Sliding has been replicated in *in vitro* experiments (called gliding assays) (Yokota et al., 1995; Gibbons et al., 2001; Tao et al., 2006; Vale et al., 1992) and has been studied mathematically by White et al. (2014), as well as by Aranson and Tsimring (2006) and Aranson and Tsimring (2006). For the model developed and studied here, we do not consider MT sliding. However, translocation of MTs by sliding is shown to be an important mechanism for pattern formation, and is explained briefly in the discussion section of the paper.

The particular properties of motor proteins, such as their speed, directionality, and processivity, as well as their concentrations, determine what types of MT patterns can form. Some motors, such as kinesin-14, are fast (0.1 μm/s) and walk towards the minus end of a MT (and are called minus-end directed), while other motors, like kinesin-5, are very slow (0.04 μm/s), and walk towards the plus end of a MT (and are called plus-end directed). MT processivity refers to the length of time a motor protein attaches to and walks along a MT (without detaching from the MT). Some motors, like kinesin-1 (conventional kinesin), can attach to MTs and walk long distances along them (processive), while others, like kinesin-5, can only walk short distances along MTs before detaching from them (weakly processive motors). Some motors, like kinesin-14, can attach to MTs but cannot walk along them for any significant amount of time (non-processive).

For MTs, both local and non-local models have been proposed to describe how MTs evolve in the presence of motor proteins. Defining a model as local or non-local refers to the treatment of the redistribution part of the model; in our case, this corresponds to MT reorientation (governed by motor proteins). Most models of MT evolution describe MT reorientation using local diffusion-type terms (Jia et al., 2008; Kim et al., 2003; Lee and Kardar, 2001). For example, the model of Lee and Kardar (2001) suggests that MTs undergo small reorientations in the presence of motor proteins. However, we know from recent *in vitro* studies that large reorientations are possible (Nedélec et al., 1997; Nedélec and Surrey, 2001). Thus, models that use integral terms to describe MT angular redistribution, that is, non-local models, are more reasonable from a biological perspective. Non-local models describe redistribution in terms of probabilities, and are referred to as velocity-jump models (Othmer, 2010). Such models have a rich history in the study of large-scale animal movement governed by certain cues that can exist over large distances (Othmer et al., 1988). More recently, such models have been used to describe the evolution of cellular systems (Hillen, 2006). A recent example of such a non-local model used in MT/motor systems is a study by Aranson and Tsimring (2006). This model uses a diffusion term to describe small scale fluctuations of MTs in the absence of motors, and also includes a non-local term to describe alignment of MTs as they collide with one another. The action of the motor proteins is implicit (Aranson and Tsimring, 2006), and suggests that motors are dispersed uniformly throughout space, so that when two MTs interact, they instantaneously align due to motor protein action. A second example of a non-local MT/motor model is that by White et al. (2014), in which MT patterning is examined using a similar integral term as in Aranson and Tsimring (2006) to describe MT redistribution. However, in White et al. (2014), the probability of alignment is based on more complex interactions between MTs and motors. In particular, the probability of alignment depends on the mean MT orientation, as well as the motor density and motor activity. Also in the model of White et al., MT patterning occurs under the influence of stationary motor proteins, as opposed to moving motors. In this paper, we extend the model of White et al. (2014) to take into account the mobility of motors.

To model motor protein dynamics, it is attractive to use a single advection–diffusion equation to account for the combined