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Modeling bidirectional transport of quantum dot nanoparticles in membrane nanotubes

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ABSTRACT

This paper develops a model of transport of quantum dot (QD) nanoparticles in membrane nanotubes (MNTs). It is assumed that QDs are transported inside intracellular organelles (called here nanoparticle-loaded vesicles, NLVs) that are propelled by either kinesin or dynein molecular motors while moving on microtubules (MTs). A vesicle may have both types of motors attached to it, but the motors are assumed to work in a cooperative fashion, meaning that at a given time the vesicle is moved by either kinesin or dynein motors. The motors are assumed not to work against each other, when one type of motors is pulling the vesicle, the other type is inactive. From time to time the motors may switch their roles: passive motors can become active motors and vice versa, resulting in the change of the vesicle's direction of motion. It is further assumed that QDs can escape NLVs and become free QDs, which are then transported by diffusion. Free QDs can be internalized by NLVs. The effects of two possible types of MT orientation in MNTs are investigated: when all MTs have a uniform polarity orientation, with their plus-ends directed toward one of the cells connected by an MNT, and when MTs have a mixed polarity orientation, with half of MTs having their plus-ends directed toward one of the cells and the other half having their plus-ends directed toward the other cell. Computational results are presented for three cases. The first case is when organelles are as likely to be transported by kinesin motors as by dynein motors. The second case is when organelles are more likely to be transported by kinesin motors than by dynein motors, and the third case is when NLVs do not associate with dynein motors at all.

1. Introduction

MNTs, also called tunneling nanotubes, first described in [1], are recently discovered structures that connect different types of animal cells, including peripheral blood NK cells, macrophages, immune cells, neurons as well as other types of cells [2–5]. These structures are formed from plasma membrane [6]. MNTs provide highways for transport of membrane vesicles; there is also data indicating that they may impede transfer of small molecules [7].

Biological importance of MNTs is related to their possible role in intercellular communication and signaling [8–11], including long-distance interaction between natural killer cells and target cells [4]; there are also indications that MNTs can provide tunnels for spreading of prions [12], bacteria [13], and viruses [6], including the HIV virus [14,15].

There are two structurally distinct types of MNTs: thin MNTs contain only F-actin cables while thicker MNTs contain both F-actin cables and MTs [13]. Recently, He et al. [16] reported experimental evidence demonstrating that QD nanocrystals are actively transported in membrane nanotubes. QDs are semiconductor nanocrystals whose excitons are confined in all three spatial directions, which explains their unique electronic properties. QDs have potential applications in molecular and cellular imaging, they show promise as probes for investigating vesicular transport in living cells, as well as in targeted drug delivery systems [17–19].

Active transport in living cells is accomplished by molecular motors. Members of kinesin and dynein families run on MTs while myosin motors move along F-actin filaments [20–22]. The purpose of this paper is to continue the work began in [23] and, based on experimental evidence reported in [16], utilizing a different kinetic model than that used in [23], to develop a mathematical model describing nanoparticle transport in MNTs. He et al. [16] hypothesized that the difference in the QD concentration in neighboring cells may act as a driving potential for nanoparticle transport. The developed model is used to quantify this hypothesis and also to elucidate the effect of the MT polarity orientation in MNTs on nanoparticle flux. To the best of the author's knowledge, this is the first attempt to develop a model of nanoparticle transport in MNTs. The proposed model can be used for the development of sampling strategies for future experiments by utilizing the approach suggested in [24].

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2. Mathematical model and governing equations

According to Ref. [9], in MNTs that contain F-actin fibers alone, transport of cellular components is unidirectional. This fact suggests that actin fibers inside MNTs have the same polarity orientation. However, in MNTs containing both F-actin fibers and MTs (this is the type of MNTs studied in [16]) constant shuttling of QDs that reversed direction every few seconds was observed. Since the average rate of QD transport was 1.23 μm/s, which is close to velocities of kinesin and dynein motors moving on MTs, He et al. [16] hypothesized that bidirectional transport of QDs was mediated by kinesin and dynein motors moving on MTs. Also, He et al. [16] found that QDs were colocalized or encapsulated in some cellular organelles (other than early endosomes), called here NLVs. In addition, situations where QDs exhibited Brownian diffusion were observed. Frequent reversal of QDs motion when they are transported by kinesin or dynein motors can mean one of the two things. It could be an indication that the MT polarity orientation in an MNT is mixed, as in dendrites [25], and NLVs switch between MTs with opposite orientation while being propelled by the same type of molecular motors (kinesin or dynein motors, this situation is displayed in Fig. 1b). Alternatively, it could mean that the MT polarity orientation in an MNT is uniform (as in axons) but an NLV contains both kinesin and dynein motors attached to it and these motors take control of NLV motion from time to time. In other words, consider an NLV that is moving along an MT. The reversals of NLV direction could indicate that the NLV is propelled by kinesin motors for some time while all dynein motors are disconnected from the MT, then dynein motors take over while kinesin motors disconnect from the MT. In fact, results reported in [26] support coordination between kinesin and dynein motors since no apparent inhibition by the opposite motors was observed.

There is evidence that organelle transport along MTs powered by kinesin and dynein motors may interact or even cooperate with organelle transport along F-actin filaments powered by myosin motors [27,28]. There is also evidence of force-based interaction and spatial organization between actin- and MT-based cytoskeletons [29]. Models of bidirectional motor-driven transport differ in their resolution and complexity. There are models that are based on statistical physics. In particular, Ashwin and Lin [30] utilized a mean field approximation to analyze coordinated motion of anterograde and retrograde motors sharing a single MT while Zhang [31] developed a model that accounts for intermotors interactions. A stochastic model recently developed in [32] proposes that a diffusing motor (myosin) does not influence motion of a directional motor (kinesin) but rather enhances kinesin processivity by helping it to rebind to MTs. In the context of the model developed in the present paper this enhancement of processivity can be accounted for by increasing values of the kinetic constants characterizing the rates of motor binding to MTs.

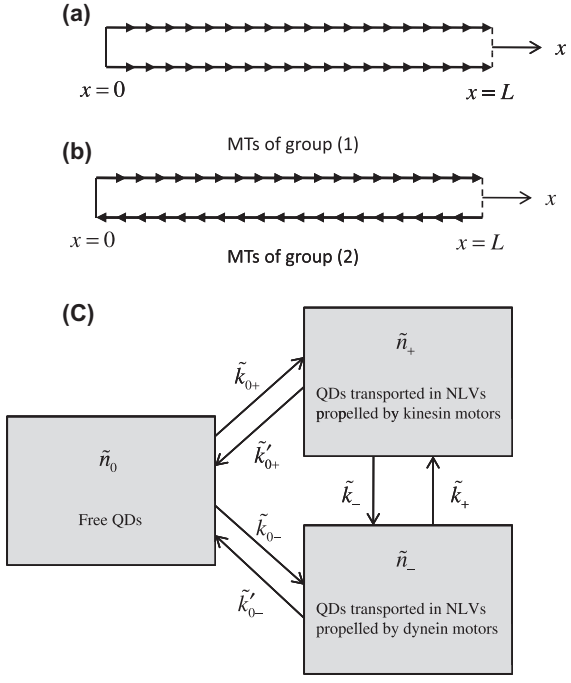

Fig. 1. (a) Schematic diagram for a uniform MT polarity orientation in an MNT, (b) schematic diagram for a mixed MT polarity orientation in an MNT, (c) kinetic diagram showing QD populations and kinetic processes between them.

In what follows, tildes denote dimensional parameters. Three populations of QDs are considered in the model: QDs internalized by NLVs propelled by kinesin motors (the average concentration of such QDs is denoted by $\tilde{n}_+$), QDs internalized by NLVs propelled by dynein motors (the average concentration of such QDs is denoted by $\tilde{n}_-$), and free QDs that are not associated with MTs and are in the state of Brownian diffusion (the average concentration of such QDs is denoted by $\tilde{n}_0$). It is assumed that an NLV may have both kinesin and dynein motors attached to it, but can be propelled by only one type of motors at a given time. There are other models, based on the hypothesis postulating a tug-of-war between the motors [33–36]. It should be noted that whether activation/deactivation of motors is regulated or the motors are in the tug-of-war is not going to affect governing equations developed in this paper. This is because at the level of resolution of the developed model it is only the average NLV velocity that matters and it is not important whether it is produced by a single kinesin motor or (for example) by two kinesin motors opposing one dynein motor.

When kinesin motors are deactivated and dynein motors are activated (as a result, an NLV changes the direction of its motion), the concentration of plus-end-directed QDs, $\tilde{n}_+$, decreases, and the concentration of minus-end-directed QDs, $\tilde{n}_-$, increases. The rate of this process is characterized by the kinetic constant $\tilde{k}_-$ (see the kinetic diagram in Fig. 1c). The rate of the opposite process (when dynein motors propelling an NLV are deactivated and kinesin motors take over) is characterized by the kinetic constant $\tilde{k}_+$. QDs can escape from kinesin and dynein-driven NLVs and become free QDs, the rates of these processes are characterized by kinetic constants $\tilde{k}'_{0+}$ and $\tilde{k}'_{0-}$, respectively. When free QDs are internalized by kinesin or dynein-driven NLVs, concentrations $\tilde{n}_+$ and $\tilde{n}_-$ increase and $\tilde{n}_0$ decreases; the rates of these processes are characterized by kinetic constants $\tilde{k}_{0+}$ and $\tilde{k}_{0-}$, respectively.

Equations governing QDs transport in MNTs are based on Smith–Simmons equations governing molecular motor-assisted transport of intracellular organelles [37], with some modifications due to a more complicated kinetic model (Fig. 1c) and different boundary conditions. Equations are written in the dimensionless form (dimensionless parameters have no tildes); dimensionless variables are defined in Eqs. (9) and (10) below. If MTs have the same polarity orientation in an MNT (as in axons [23], Fig. 1a), equations governing transport of QDs in an MNT are

$$\frac{\partial n_0}{\partial t} = D_0 \frac{\partial^2 n_0}{\partial x^2} - 2(k_{0+} + k_{0-})n_0 + 2k'_{0+}n_+ + 2k'_{0-}n_-, \tag{1}$$

$$\frac{\partial n_+}{\partial t} = -k_- n_+ + n_- + k_{0+}n_0 - k'_{0+}n_+ - \frac{\partial n_+}{\partial x}, \tag{2}$$

$$\frac{\partial n_-}{\partial t} = k_- n_+ - n_- + k_{0-}n_0 - k'_{0-}n_- - v_- \frac{\partial n_-}{\partial x}, \tag{3}$$

Dimensionless kinetic constants used in the model are summarized in Table 1.