A Diffusion-Based Model of Kinesin Recycling in Neurons

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Introduction
The axon terminal of neuronal cells has complex signaling and metabolic demands. Transmitting signals to neighboring neurons through synapses involves macromolecules, presynaptic vesicles, and organelles (such as mitochondria), many of which are synthesized in or near the cell body [1]. Diffusion of large molecular complexes over long distances is slow, and neuronal axons can be meters long, so supplying the synapse with cargo synthesized in the soma through diffusion would be inefficient. There are motor proteins that actively transport cargo.

One motor protein is kinesin, which consumes energy down to the microtubule (MT) tracks of the axon, pulling cargo along and thus supplying the proteins that actively transport cargo.

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Continuing this line of exploration, we propose a "bucket-brigade" mechanism, in which cargos "chase" kinesins during active transport and diffusion of unbound kinesin motors is restricted by cargo jams and therefore no longer a limiting step in kinesin recycling. The cargo jams occur when active transport is disrupted by spatial inhomogeneities due to MT discontinuities or occlusion of MTs by other microtubule associated proteins (MAPs).

Investigate, by formulating and solving a mathematical model of axonal transport in the presence of spatial inhomogeneities, whether the bucket-brigade mechanism of kinesin recycling results in cargo transport that is efficient over long distances.

Objective

Bucket Brigade Model

- Passive kinesin (diffusion)
  - kinesin bound to cargo (advection)
- Free kinesin (diffusion)
- Bound kinesin

It has been shown that particles in the presence of obstacles have a slower diffusion rate. This is the excluded volume effect. This decrease is given by the power law below (see, e.g., [5–6] and references therein):

\[ D_{\text{eff}} = D_0 \left( 1 - \frac{C_{\text{ex}}}{C} \right) \]

and \( C_\text{ex} \) is the preclusion limit: as total cargo approaches this limit, \( D_{\text{eff}} \) goes to 0, and \( C \) is a constant related to the shape of the obstacles.

Methods

Partial Differential Equations (PDEs)

- \( \partial C / \partial t = D_{\text{eff}} \partial^2 C / \partial x^2 \) (diffusion)
- \( \partial C / \partial t = C \partial V / \partial x \) (advection)

- \( \partial V / \partial t = -k_{\text{aff}} C + k_{\text{diss}} V \) (equilibrium)

- \( R = k_{\text{aff}} / (P \cdot C + k_{\text{diss}} \cdot V) \)

Boundary Conditions

- zero flux

Mathematical Interpretations of Assumptions

- MAPs, e.g., tau, can cause slowdowns in kinesin advection and decrease binding [5]
- MTs are discontinuities

Results

Figure 3a: Kymograph of the cargo concentration of the 5-barrier bucket-brigade model. The horizontal axis corresponds to the length of the axon, while the vertical axis is time. The cross hairs through the fourth pile are shown in Fig. 3b and Fig. 3c, the horizontal and vertical, respectively.

Figure 4 & 5: Variables \( Q \) (Fig. 4) and \( P \) (Fig. 5) at steady state of the 5-barrier model.

Figure 6: Excluded Volume Effect

\[ D_{\text{eff}} = D_0 \left( 1 - \frac{C_{\text{ex}}}{C} \right) \]

Spatial inhomogeneities

- Free kinesin (diffusion)
- Bound kinesin

Discussion

To test competitiveness of the bucket-brigade mechanism of kinesin recycling, we compared active steady-state fluxes of the bucket-brigade model and the model with no barriers with the same model parameter values. In doing this, we confirmed that the unrestricted kinesin diffusion is inefficient for long axons (Fig. 9), but the bucket brigade maintains a virtually constant flux, even though it is limited by several processes. Theoretically, we confirm our hypothesis that the bucket brigade is more efficient in longer neurons (Fig. 9). For a definitive answer, we must run long-length simulations. But reaching a steady state by solving the time-dependent PDEs becomes computationally expensive, because for all lengths, we must use a small spatial step to avoid errors. Since these simulations are computationally expensive, our current numerical solver has yet to complete the simulations needed to confirm our hypothesis.

The bucket brigade model takes longer time to reach a steady state (Fig. 7). This is because the flux in this model is limited by the rate with which kinesin is pursued (over the cargo jams, or the latter rely on cargo diffusion which is slow). This rate can be increased by increasing the diffusion of cargo within the jam, but this will lower the diffusion barriers for kinesin, and the model becomes more like the no-barrier model. We can also reconstrue the definitions of "steady state" for the bucket-brigade model. After an initial peak, the flux stays steady, which is a functional steady state (Fig. 7). The initial steady value corresponds to fluctuations in the cargo jams, which is similar to the environment in real neurons. Considering this to be an actual steady-state flux would make the comparison of the models less challenging.

Future Directions

We would like to complete the currently-running long-length simulations to see if our hypothesis holds. This computational problem might be solved more efficiently by a time-independent PDE solver, however implementation of a stable and fast-converging time-independent solver is a challenge in and of itself.

As described above, emergence of cargo jams and movements of cargo in the vicinity of the cargo jams is a limiting factor. To model these processes more realistically, one could treat a multi-scale hybrid deterministic-stochastic model, in which the kinesin-adsorption and diffusion over areas with no barriers are described contiguously, as we do now; but the processes in the vicinity of the cargo jams, and the piles themselves, are modeled stochastically. Resolving the piles statistically on a small spatial scale would more accurately depict the collisions of molecules and excluded volume effect. By allowing the piles to statistically appear, disappear, and reappear in different places, the model would better describe the dynamics of the axon and the cellular environment. We hope to use the results of our model to make testable hypotheses for our experimental collaborators.

References


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