Emergence of axonal microtubule patterns through self-organization: a computational study

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INTRODUCTION

Microtubule (MT) arrays serve as the cytoskeleton and cellular cargo transport structures for developing and established axons. Disruptions to axonal MT arrays are observed in conjunction with neurodegenerative diseases such as Alzheimer's. We use experimentally motivated computational simulations of molecular-scale interactions to explore the maintenance and recovery of axonal MT arrays.

BACKGROUND

In axons, most microtubules are oriented with their plus ends away from the cell body. This polarity orientation is referred to as a plus-end-out polarity pattern.

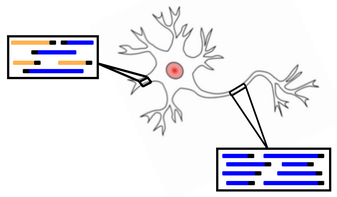


Figure 1. A neuron with MTs shown in two regions: a dendrite (left) and the axon (right). The plus-end of the MT is indicated by the black rectangle. MTs are colored based on the orientation of their plus end: their polarity. Blue MTs are plus-end-out, where 'out' means pointing away from the cell body. Orange MTs are minus-end-out.

Polarity corruption from minus-end-out microtubules arise from a variety of cellular activities and processes including branched nucleation, mechanical bending and breaking, or protein severing that results in microtubule flipping.

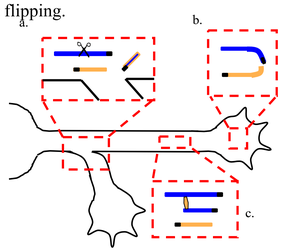


Figure 2. The plus-end-out polarity pattern is threatened by (a.) severing by katanin and spastin, enabling rotation; (b.) bending induced severing at the growth cone, creating terminal-end minus-end-out MTs; (c.) local nucleation of potentially misoriented or short MTs.

In a hypothetical mechanism known as "polarity sorting", cytoplasmic dynein transports minus-end-out MTs toward the cell body through a combination of cargo transport and filament sliding. By pushing minus-end-out MTs into the cell body, thus "clearing" them from the axon, a predominantly uniform plus-end-out pattern is maintained.

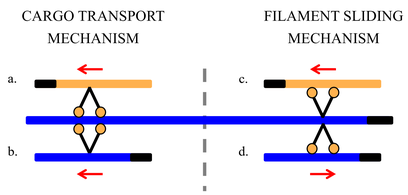


Figure 3. Molecular motor dynein exerts forces, indicated by red arrows, on MTs based on relative orientations. To the left is the cell body and to the right is the distill end. Orange circles indicate the motor domains of dynein. If the center MT is minus-end-out the cargo transport mechanism carries MTs toward the distill end.

AGENT-BASED COMPUTATIONAL SIMULATIONS OF POLARITY SORTING MODEL

We use agent-based simulations to characterize baseline polarity sorting model. Our ongoing goal is to investigate interplay with additional dynamic features.

Polarity Sorting Model, baseline features:
- Random distribution of initial MT length, position, and polarity
- Stochastic binding and load-dependent unbinding of cytoplasmic dynein
- Dynein slides adjacent MTs in polarity-dependent manner (Fig. 3)

Additional dynamic mechanisms that regulate MT polarity pattern:
- Nucleation of MTs along axons
- MT dynamics (rescue and catastrophe)
- Severing of long MTs
- Rotational diffusion ("flipping")
- Plus-directed motor proteins (kinesin-1), non-motile cross-linking proteins

Mechanical input parameters including load-velocity characteristics of motor proteins and load-dependent detachment are experimentally constrained [1].

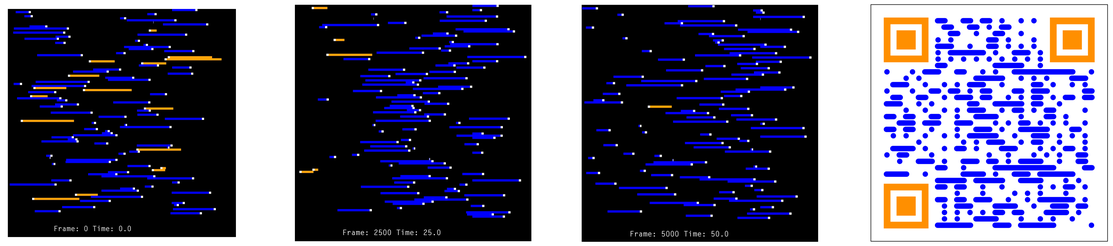
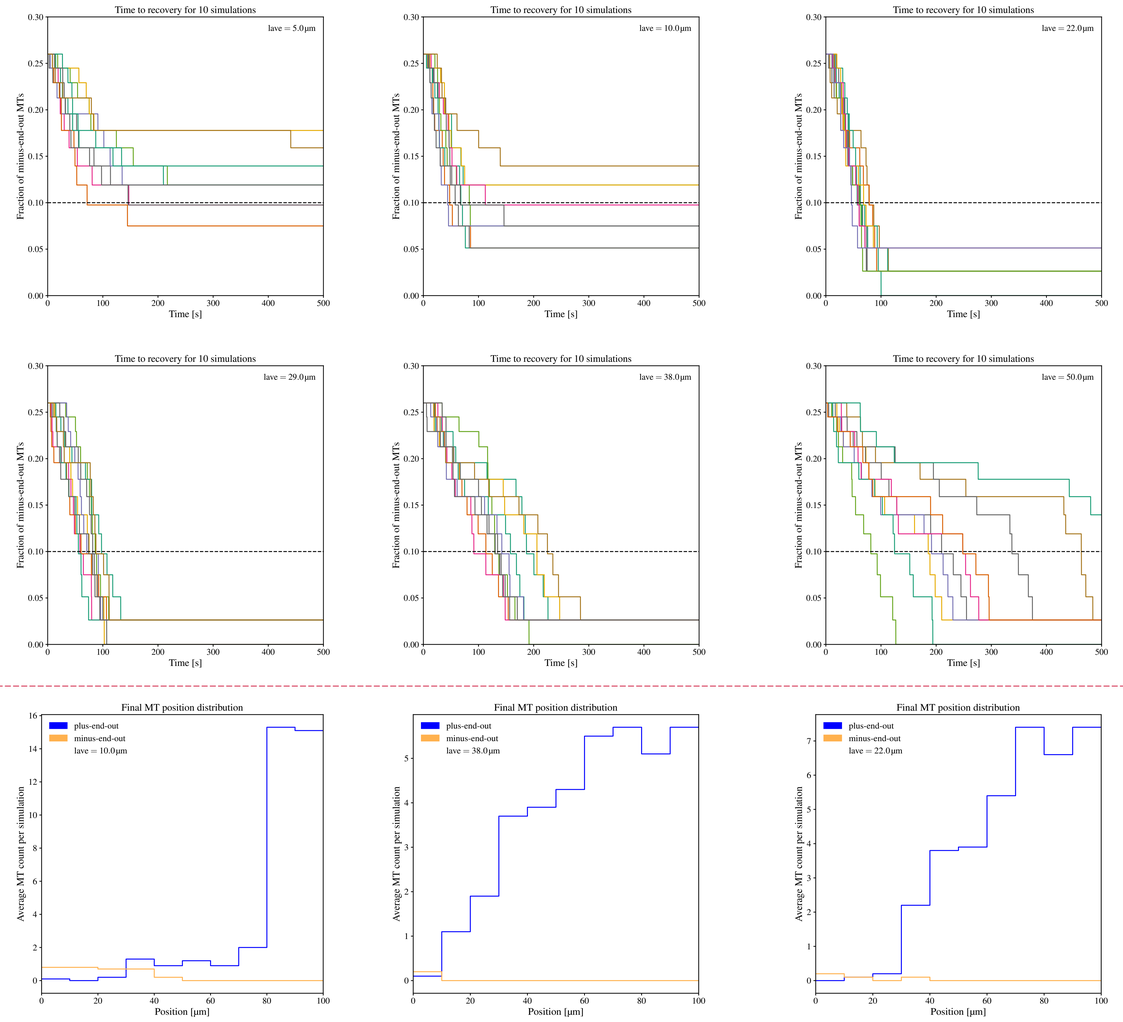


Figure 4. A 50 second simulation of successful polarity sorting starting with a 32% polarity flaw. The QR-code (d) directs to **cwu-computational-biophysics.github.io/** where the animation can be viewed in full.

Successful or ideal polarity sorting means the recovery of the axon from some flawed state, Figure 4a, to a nearly pure pattern, Figure 4c. A polarity flaw like Figure 4a may arise from disease or injury. The simulations demonstrate the efficacy of the dynein-based polarity sorting model in recovering a plus-end-out polarity pattern.

RECOVERY OF UNIFORM POLARITY PATTERN: TIME DYNAMICS

To compare the effect of varying simulation parameters we say an axon is recovered when less than 10% of MTs are minus-end-out. By this metric, the animation in Figure 4 has a recovery time of approximately 10 seconds. The proportion of minus-end-out MTs does fluctuate past the recovery time due to stochastic processes but such fluctuations are well within a healthy axons sorting capability.



RECOVERY IS FASTEST FOR INTERMEDIATE LENGTHS

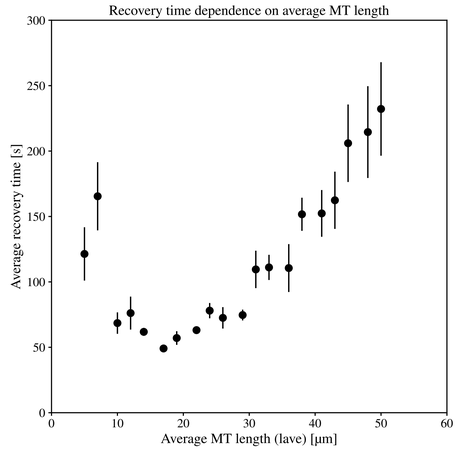


Figure 7. The relationship between recovery time and average MT length. Each point is found by averaging the recovery time of 10 simulations at identical parameters and starting conditions.

FUTURE WORK

- Systematically investigate impact of additional dynamic factors, including MT dynamics, nucleation, and severing. Determine conditions where polarity flaws accumulate and plus-end-out pattern is not recovered.
- Quantify mechanical forces on growth cone arising from dynein-based MT sliding in the distal axon; Investigate role of axonal MT sliding on axon growth.

ACKNOWLEDGEMENTS

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REFERENCES

1. Craig et al. (2017), Polarity sorting of axonal microtubules: a computational study, Mol. Biol. Cell, 28(23):3271–3285.