Multilane model of axonal intracellular traffic dynamics considering the influence of Tau Protein in Alzheimer's disease.

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Abstract

Axonal transport mediated by molecular motors along the microtubule (MT) structure is fundamental for proper neuronal function; its inhibition by Tau protein is linked to Alzheimer's disease. Given the limitations of in vivo studies, in silico models emerge as a viable alternative. However, current approaches are often restricted to a single type of motor, omit Tau as an obstacle, simplify MT geometry to a one-dimensional representation, and employ computationally expensive Monte Carlo simulations. This project proposes a multilane model that captures MT geometry, Tau dynamics, and multiple types of molecular motor. To reduce simulation times, a parallelization strategy is implemented. From the simulations, a synthetic dataset will be generated to analyze emergent patterns and phase transitions, correlating the results with Alzheimer.

Keywords: Tau protein, molecular motors, microtubules, axonal intracellular transport, cellular automata, multidimensional.

Introduction

Axonal transport driven by molecular motors along multi-protofilament microtubules (MTs) is vital for neuronal survival. In Alzheimer's disease, hyperphosphorylated Tau protein accumulates, physically obstructing these pathways. Traditional cellular automata models simplify MTs into a one-dimensional lattice, discarding multi-lane dynamics.

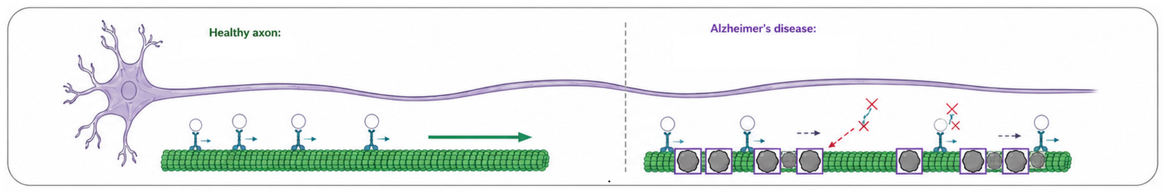


Figure 1. Tau Protein accumulation and its impact on axonal transport.

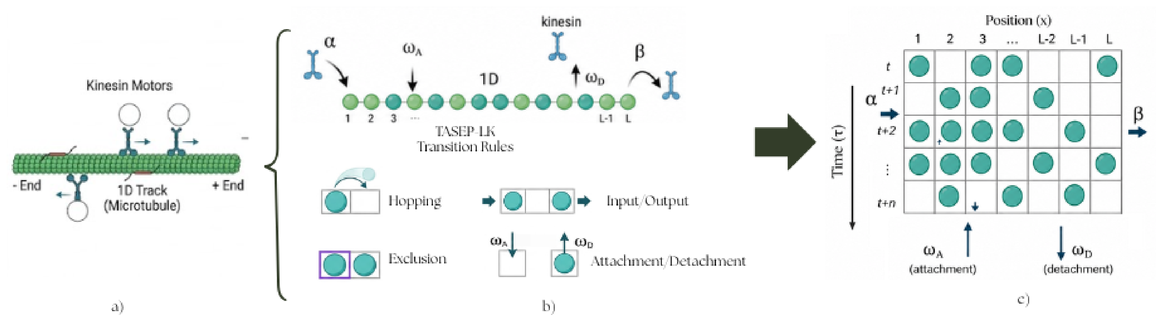
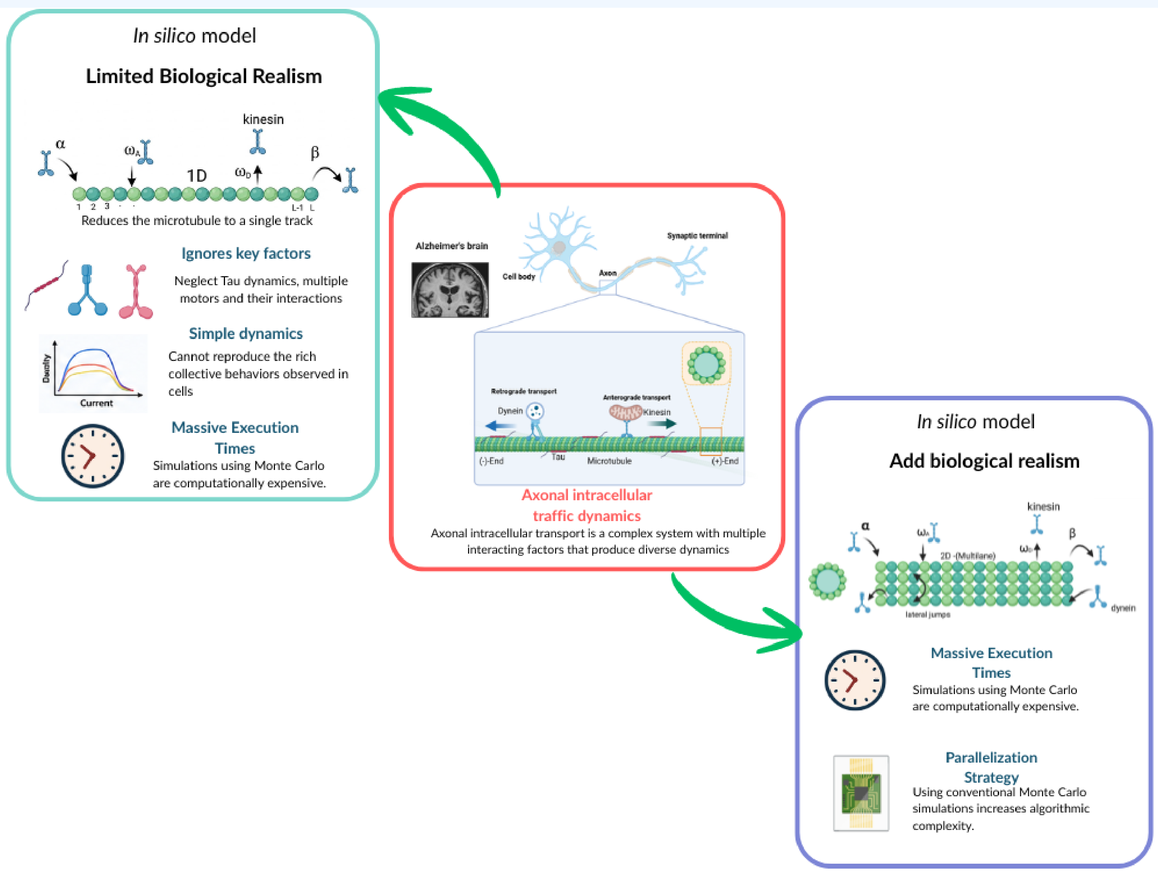


Figure 2. **One-dimensional TASEP-LK lattice model abstraction.** **a**)Abstraction of the complex microtubule cylinder into a discrete one-dimensional lattice of length L. **b**) Local kinetic transition rules determined by entry (α), exit (β), attachment (ω_A), and detachment (ω_D) probabilities. **c**)Spacetime occupation matrix generated through time iterations mapping particle positions over time $t + n$.

Problem statement



Related Work

Table 1. Comparison between previous TASEP-based models for intracellular transport and the proposed model.

Author(Year)	Computational Model	Lanes	Tau	Lane Change	Motors	Bi-dir.	Resolution method
Chandel et al.(2015)	TASEP-LK+NNN	1	✗	✗	1	✗	MF/MC
Gupta (2016)	TASEP-LK	2	✗	✓	1	✗	MF/MC
Ryan et al.(2021)	TASEP-LK	1	✓	✗	1	✗	MF/MC
Mendez (2023)	TASEP-LK	1	✓	✗	1	✗	MC
This Work	Multi-lane TASEP-LK	M	✓	✓	2	✓	MC

Abbreviations: TASEP = Totally Asymmetric Simple Exclusion Process; LK = Langmuir Kinetics; NNN = Next-Nearest-Neighbor; MF = Mean Field; MC = Monte Carlo; M = Multiple lanes; Bi-dir. = Bidirectional transport.

Research questions

- How do the dynamics caused by Tau protein hyperphosphorylation affect the collective behavior of molecular motor traffic?
- How does the inclusion of multidimensional geometry capture the dynamics of molecular motor shock fronts when encountering Tau obstacles compared to one-dimensional models?
- How can a multilane cellular automata computational model characterize and contrast axonal transport properties between a healthy system and emerging obstruction patterns in early-stage Alzheimer's disease?

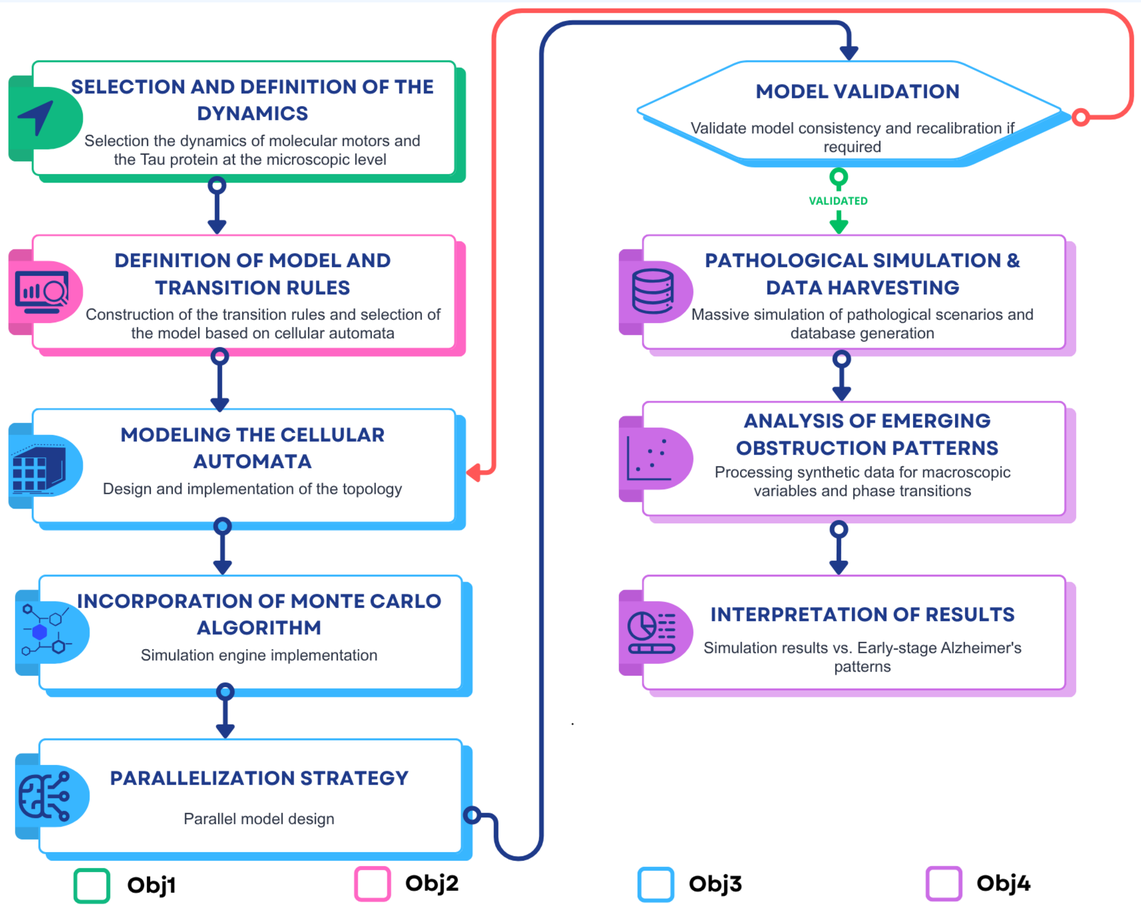
Objectives

General: Design a parallel computational model that integrates microtubule structural geometry and Tau protein dynamics based on cellular automata to analyze the collective behavior of molecular motors traffic and its relationship with Alzheimer's disease.

Specifics:

- **Obj1:** Analyze and select molecular motors dynamics and Tau protein association states.
- **Obj2:** Define and formalize the rules representing molecular motor dynamics and Tau protein association states.
- **Obj3:** Design, implement and validate a parallel computational model based on cellular automata that integrates the interaction rules of molecular motors and Tau protein.
- **Obj4:** Characterize phase transitions and critical density thresholds in the model to correlate emerging obstruction patterns with early stages of Alzheimer's disease development.

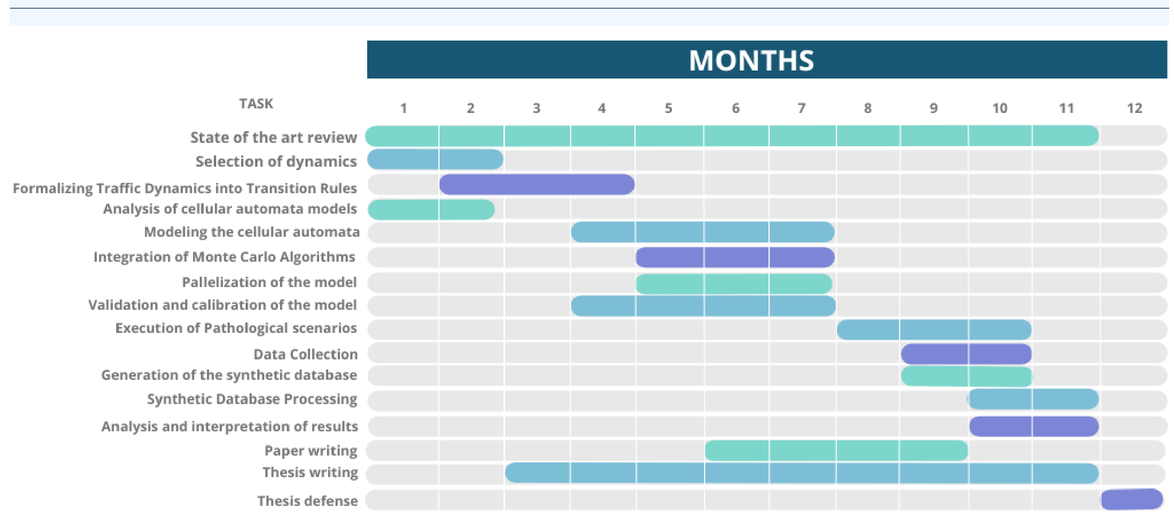
Methodology



Expected Results

- **A Multi-Lane Parallel Computational Model of Axonal Traffic:** Development of a simulator based on cellular automata capable of capturing the realistic multi-lane topology of the microtubule.
- **Parallelization Strategy:** Design and implementation of a parallel solution to optimize the execution of the Monte Carlo algorithm.
- **Characterization of Deterioration and Emerging Patterns:** Analysis of the generated synthetic dataset to determine correlation with Alzheimer's disease.

Schedule



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