Intracellular Material Transport Simulation in Neurons Using Isogeometric Analysis and Deep Learning

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Abstract. The intracellular material transport plays a crucial role in supporting a neuron cell's survival and function. The disruption of transport may lead to the onset of various neurodegenerative diseases. Therefore, it is essential to study how neurons regulate the material transport process and have a better understanding of the traffic jam formation. Here, we present to model the neuron material transport process and study the traffic jam phenomena during transport using isogeometric analysis (IGA) and deep learning. We first develop an IGA-based platform for material transport simulation in complex neuron morphologies. A graph neural network (GNN)-based deep learning model is then proposed to learn from the IGA simulation and provide fast material concentration prediction within different neuron morphologies. To study the traffic jam phenomena, we develop a PDE-constrained optimization model to simulate the material transport regulation within neuron and explain the traffic jam caused by reduced number of microtubules (MTs) and MT swirls. A novel IGA-based physics-informed graph neural network (PGNN) is proposed to quickly predict normal and abnormal transport phenomena such as traffic jam in different neuron morphologies. The proposed methods help in discovering several spatial patterns of the transport process and provide key insights into how neurons mediate the material transport process within their complex morphology.

Keywords: Neuron material transport · Isogeometric analysis · Deep learning · Graph neural network · PDE-constrained optimization.

1 Introduction

Neurons exhibit striking complexity and diversity in their morphology, which is essential for neuronal functions and biochemical signal transmission. However, it also brings challenges to mediate intracellular material transport since most essential materials for neurons have to experience long-distance transport along axons and dendrites after synthesis in the cell body. In particular, the neuron relies heavily on molecular motors for the fast transport of various materials along the cytoskeletal structure like microtubules (MTs). The disruption of this long-distance transport can induce neurological and neurodegenerative diseases

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like Huntington's, Parkinson's, and Alzheimer's disease. Therefore, it is essential to study the intracellular transport process in neurons. There have been several mathematical models proposed to simulate and explain certain phenomena during transport but limited to simple 1D or 2D domains without considering the complex neuron morphology [18, 4, 7]. Here, we present to simulate the intracellular material transport within complex neuron morphologies using isogeometric analysis (IGA) and deep learning (DL). IGA was proposed based on the conventional finite element method (FEM) to directly integrate geometric modeling with numerical simulation [6]. By using the same smooth spline basis functions for both geometrical modeling and numerical solution, IGA can accurately represent a wide range of complex geometry with high-order continuity while offering superior performance over FEM in numerical accuracy and robustness. Therefore, IGA has been successfully applied in shell analysis [2, 19], cardiovascular modeling [25, 23], neuroscience simulation [15], as well as industrial applications [22, 21]. With the advances in IGA, we first develop an IGA-based simulation platform to reconstruct complex 3D neuron geometries and obtain high-fidelity velocity and concentration results during material transport. Though IGA can accurately solve PDEs in complex neuron morphologies, the high computational cost of 3D simulations may limit its application in biomedical field where fast feedback from simulation is necessary. In recent years, DL has been proven successful in solving high-dimensional PDEs [5] and learning the physics behind PDE models [17]. DL also becomes popular in building surrogate model for PDEs since it can provide efficient prediction for complex phenomena [3, 9]. To address the limitation of our IGA platform, we develop a DL-based surrogate model based on the simulation platform to improve its computational efficiency. We also propose to solve a PDE-constrained optimization (PDE-CO) problem to study the transport control mechanisms and explain the traffic jam phenomenon within abnormal neurons. We then develop a novel IGA-based physics-informed graph neural network (PGNN) that learns from the PDE-CO transport model and effectively predicts complex normal and abnormal material transport phenomena such as MT-induced traffic jams. Our results provide key insights into how material transport in neurons is mediated by their complex morphology and MT distribution, and help to understand the formation of complex traffic jam.

2 Methodology and Results

We first develop an IGA-based simulation platform for modeling the intracellular material transport within the complex morphology of neurons. The platform consists of two modules: geometric modeling and an IGA solver. In the geometric modeling module, we apply a skeleton-based sweeping method [24–26] to generate all-hexahedral control mesh for the complex neuron morphology. We then construct truncated hierarchical tricubic B-splines (THB-spline3D) [20] on the control mesh to represent the geometry for IGA. Regarding the IGA solver module, we simulate the transport process by generalizing the motor-assisted transport model to 3D and couple the model with Navier-Stokes equations to

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obtain the accurate velocity field in neurons. Using our IGA solver, we simulate material transport in the complex neuron morphologies from NeuroMorpho.Org [1] and one example is shown in Fig. 1. Our simulation reveals that the geometry of neurons plays an important role in the routing of material transport at junctions of neuron branches and in distributing the transported materials throughout the networks. It provides key insights into how material transport in neurons is mediated by their complex morphology. Our IGA solver can also be extended to solve other PDE models of cellular processes in the neuron morphology. More information about this work can be found in [8].

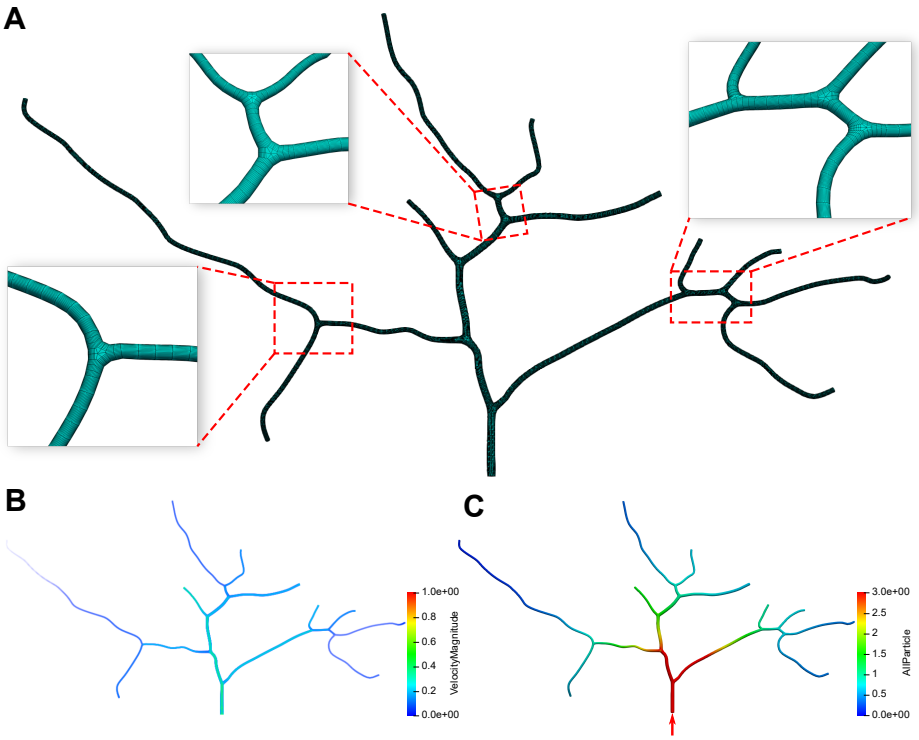

Fig. 1. Simulation of material transport in the neuron morphology of NMO_134036. (A) Hexahedral control mesh of the network with zoom-in details. (B) Velocity field. (C) Concentration distribution of transport materials at 10 s, and the red arrow points to the inlet of material. Unit for color bars: (B) $\mu m/s$ and (C) $mol/\mu m^3$.

Though we can obtain high-fidelity simulation results from the IGA solver, its expensive computational cost limits its application in the biomedical field which needs fast feedback from the simulation. To address this issue, we then develop a DL-based surrogate model to learn from IGA simulation data and provide fast transport prediction in any complex neuron morphology [10]. Instead of using the standard convolutional neural network (CNN) [9], we employ graph neural network (GNN) to tackle the extensive unstructured neuron topologies. Given any neuron geometry, we build a graph representation of the neuron by

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decomposing the geometry into two basic structures: pipe and bifurcation. We train different GNN simulators for these two basic structures to take simulation parameters and boundary conditions as input and output the spatiotemporal concentration distribution. The residual terms from PDEs are used in training to instruct the model to learn the physics behind simulation data. To reconstruct the original neuron geometry, we train another GNN-based assembly model to connect all the pipes and bifurcations following the graph representation. The well-trained GNN model can predict the dynamical concentration change during the transport process with an average error less than 10% and $120 \sim 330$ times faster compared to IGA simulations. The performance of the proposed method is demonstrated on several 3D neuron trees and one testing example is shown in Fig. 2. The interested reader is referred to [10] for more information of this work.

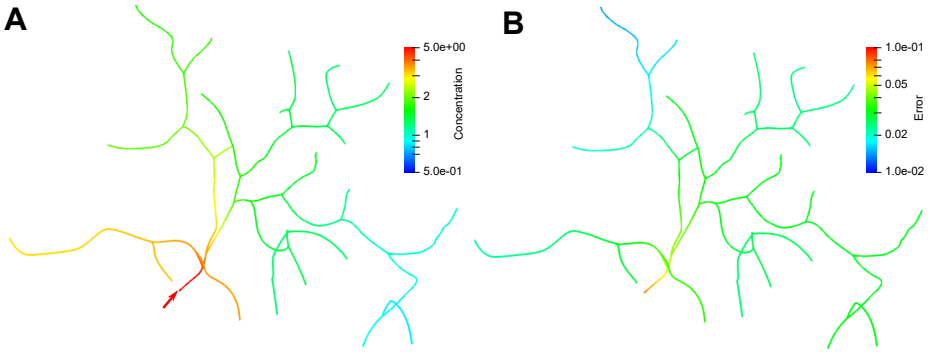

Fig. 2. The concentration prediction of material transport in the neuron morphology of NMO_06846. (A) The predicted concentration result of steady state at $t = 15\ s$. The red arrow points to the inlet of material. Unit for color bars: $mol/\mu m^3$. (B) The nodal error between the ground truth (IGA simulation result) and predicted concentration. Logarithmic scale is used to highlight the distribution pattern.

In addition, we improve the motor-assisted transport model by considering the active transport control from neuron. We present to solve a novel IGA-based PDE-CO problem that effectively simulates the material transport regulation and investigates the formation of traffic jams and swirls during the transport process in complex neuron structures [12, 11]. In particular, we design a new objective function to simulate two transport control mechanisms for (1) mediating the transport velocity field; and (2) avoiding the traffic jam caused by local material accumulation. The control strength can be adjusted through two penalty parameters in the objective function and the impact of these parameters is also studied. We also introduce new simulation parameters to describe the spatial distribution of MTs, which can be used to simulate traffic jams caused by abnormal MTs. In Fig. 3, we present the traffic jam simulation caused by the reduction of MTs in a single pipe geometry. The MT distribution is reduced in the red dashed rectangle region, which leads to a decrease of velocity and the accumulation of material in this local area. The proposed IGA optimization framework is transformative and can be extended to solve other PDE-CO models of cellular

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processes in complex neurite networks. See more information about this work in [12, 11]. Our simulation reveals that the molecular motors and MT structure play fundamental roles in controlling the delivery of material by mediating the transport velocity on MTs.

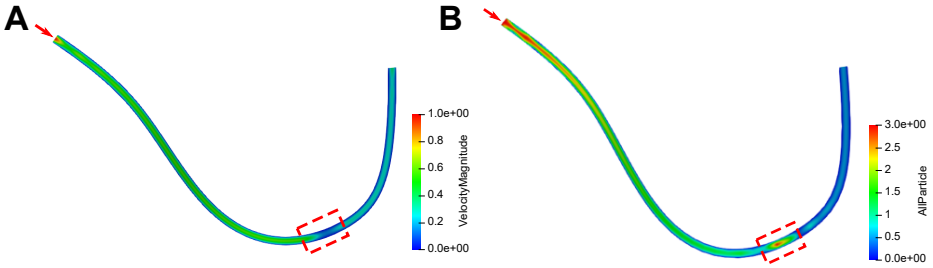

Fig. 3. Traffic jam simulation in a single pipe geometry extracted from NMO_06840. The traffic jam is introduced by reducing MTs in the red dashed rectangle region. (A) Velocity field. (B) Concentration distribution. The red arrows point to the inlet of material. Color bars unit for velocity field: $\mu m/s$ and concentration: $mol/\mu m^2$.

Based on the PDE-CO model, we develop a novel IGA-based physics-informed graph neural network (PGNN) to quickly predict normal and abnormal transport phenomena such as traffic jam in different neuron geometries. The proposed method learns from the IGA simulation of the intracellular transport process and provides accurate material concentration prediction of normal transport and MT-induced traffic jam. The IGA-based PGNN model contains simulators to handle local prediction of both normal and two MT-induced traffic jams in pipes, as well as another simulator to predict normal transport in bifurcations. Bézier extraction is adopted to incorporate the geometry information into the simulators to accurately compute the physics-informed loss function with PDE residuals. The well-trained model effectively predicts the distribution of transport velocity and material concentration during traffic jam and normal transport with an average error of less than 10% compared to IGA simulations. Using our IGA-based PGNN model, we study abnormal transport processes in different geometries and discover several spatial patterns of the transport process. In Fig. 4, we present the traffic jam predictions caused by the reduction of MTs in a 2D neuron tree. Compared to the IGA simulation results, the sudden decrease of velocity and increase of concentration in the traffic jam region (red dashed circle region) are accurately captured by the PGNN model. The PGNN model is also employed to study traffic jam caused by MT swirls in 3D neuron geometries and successfully captures the unique spatial patterns of transport velocities during traffic jam, such as vortex and reversing streamlines, which explains how the non-uniform MT distributions affect the transport velocity and hinder the smooth delivery of the material. The interested reader is referred to [13] for more information of this work.

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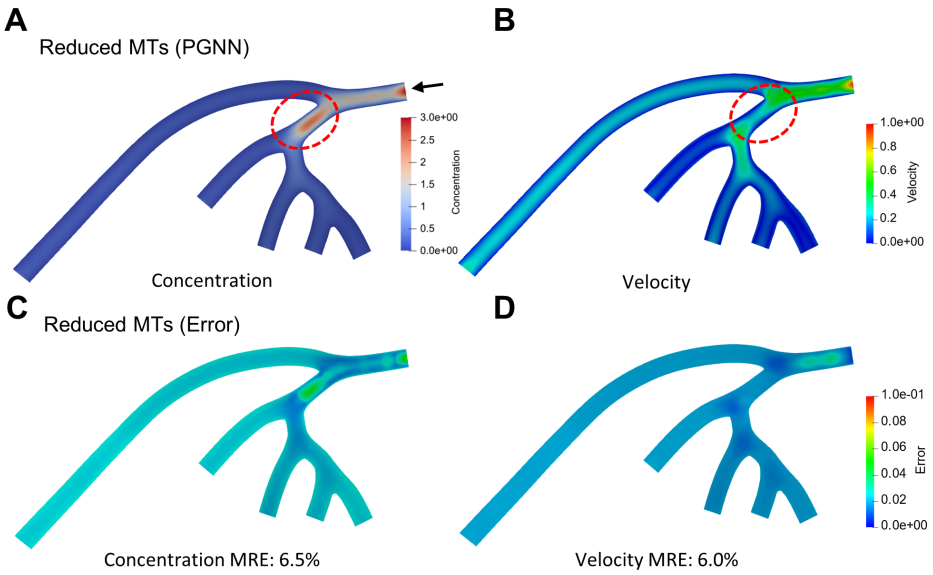

Fig. 4. The comparison between IGA simulation and PGNN prediction of the traffic jam caused by reduced MTs in a 2D neuron tree extracted from NMO_54504. (A, B) The predicted (A) concentration distribution and (B) velocity of the traffic jam. Black arrow points to the material inlet and the red dashed circle labels the traffic jam region. (C, D) The nodal errors of (C) concentration and (D) velocity between IGA and PGNN results. Unit for color bars: Velocity: $\mu m/s$ and Concentration: $mol/\mu m^3$.

3 Conclusion

In summary, we study the intracellular material transport within complex neuron morphologies using IGA, DL, and PDE-constrained optimization. Our developed computational packages utilize high-performance computing clusters and provide high-fidelity velocity and concentration results within complex neuron morphologies. These results provide references for the comparison with actual transport in real neurons to further answer the question of how neurons deliver the right material to the right destination in a balanced fashion with their complex neurite networks and how the transport may be affected by disease conditions. In the future, there are several interesting directions to extend this work. The current PDE-CO model only considers the influence of traffic jams on the material concentration but neglects its effect on the deformation of neuron geometries. To address this limitation, we can couple the transport model with a structural model and solve a fluid-structure interaction problem to simulate the geometry deformation during traffic jam. It is also necessary to verify our mathematical models by designing comparable biological experiments. For instance, the photoactivation technique can be used to visualize the material transport process and extract the velocity or concentration distribution to compare with simulation results. Employing the proposed transport model to study other biological processes with material transport involved would be a natural extension of this work as well. For instance, neuron elongation relies on the tubulin trans-

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ported from the cell body to the neurite tip. The coupling between the material transport model with a neuron growth model [16, 14] can provide a better understanding of the neuron growth process and neurodegenerative diseases.

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