# Scalable Mechanistic Modeling in Neuroscience
## Numerical Methods, High-Performance Computing, and Biological Applications

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Mechanistic computational models provide a means of connecting molecular and cellular processes to the emergent behavior of complex biological systems. In neuroscience, however, the biological detail needed to investigate these connections creates substantial computational challenges. Morphological complexity, spatially distributed signaling, and interactions between electrical and biochemical processes can make detailed simulations prohibitively expensive over biologically relevant timescales or across large networks. Consequently, models often sacrifice spatial resolution, mechanistic detail, or computational scale, limiting their ability to capture the interactions that give rise to neuronal function. My research develops mathematical and computational methods to overcome these limitations, bringing mechanistic modeling together with experimental research to investigate neuronal function and dysfunction and expand the range of biological questions that can be addressed.

**SPINE and Mechanistic Neuronal Modeling**

My research integrates mathematical modeling, numerical analysis, and high-performance computing (HPC) to address questions of increasing biological complexity. I develop numerical methods and scalable algorithms for neuronal models that couple membrane voltage with spatially distributed intracellular calcium dynamics, as well as simulations of interacting neurons in large networks. These strongly coupled systems pose substantial computational challenges, particularly when biological detail must be preserved across complex cellular geometries and extended timescales. This work has led to SPINE (Simulator for Plasticity and Integrated Neuronal Events), a scalable, Python-native framework for detailed neuronal simulations across modern CPU and GPU architectures. Its extensible design supports the integration of new mathematical and computational techniques. Alongside this work, I investigate physics-informed neural networks (PINNs) as an alternative approach to improving the efficiency of mechanistic simulation. Together, these efforts expand the range and complexity of biological systems that can be investigated through mechanistic modeling.

**Biological Applications**

My research brings mathematical and computational modeling together with experimental neuroscience to examine how neuronal structure and activity shape signaling within cells and across networks. In collaborative work on dendritic spines, we examine how endoplasmic reticulum organization and spine geometry influence calcium transport and biochemical compartmentalization. Similar interactions between calcium signaling and neuronal activity are central to our collaborative studies of Purkinje cells, where a mechanistically detailed model incorporating intracellular calcium stores and an SCA1 variant provides a means to investigate disease-related changes in neuronal function. In a separate collaboration on transcranial magnetic stimulation (TMS), we examine how externally induced neuronal activation affects intracellular calcium signaling and synaptic plasticity, and how these cellular responses shape activity across neuronal networks.

**Future Directions**

Looking forward, I will extend these investigations across scales, examining how molecular and cellular mechanisms give rise to coordinated network activity and how their disruption contributes to neurological disease. I will bring mathematical modeling, computational neuroscience, experimental research, and emerging machine learning approaches together to address increasingly complex questions about neural function and its modulation.

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## 1 SPINE and Mechanistic Neuronal Modeling

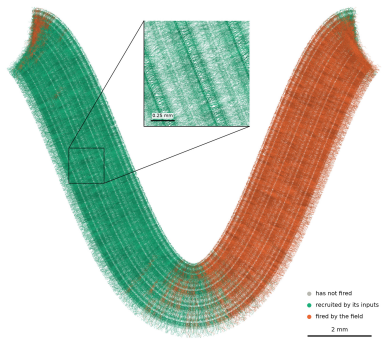



**Figure 1:** 10 000 CA1 pyramidal neurons (25 million compartments, 2.5 million synapses) in a folded network activated by an external field.

A neuron's electrical activity is accompanied by complex changes in intracellular calcium. These signals interact throughout the cell, from the propagation of membrane voltage to calcium exchange with intracellular stores. Their different spatial and temporal scales make them difficult to capture in realistic neuronal geometries, much less across networks. My research combines mathematical modeling, numerical analysis, and high-performance computing to extend mechanistic simulations to increasingly complex biological systems.

This work has produced SPINE (Simulator for Plasticity and Integrated Neuronal Events), a Python-native framework I developed for mechanistic modeling from intracellular signaling to large neuronal networks [4]. SPINE integrates membrane electrophysiology, spatial calcium dynamics, and synaptic signaling, including voltage-gated ion channels and intracellular calcium stores. Its extensible and efficient architecture supports execution across CPU and GPU systems and the incorporation of new mathematical and computational methods.

Making these simulations tractable requires advances in both mathematical representation and computational implementation. My work on Fick–Jacobs reductions of diffusion derives one-dimensional models that retain key effects of complex geometries [1]. These reductions enable transport simulations over longer timescales than would be practical with higher-dimensional models. I also implement efficient time-integration and linear-solver methods and develop parallel algorithms for distributed CPU and GPU execution. Together, these approaches extend detailed cellular models to networks of tens of thousands of neurons and millions of synapses [2] (Fig. 1). I am also investigating physics-informed neural networks (PINNs) as an alternative for solving coupled calcium dynamics, with the goal of reducing computational costs while retaining the mechanistic structure of the models [3].

SPINE also calculates the electric fields generated by external stimulation and incorporates them into neuronal simulations, allowing their effects to be traced from membrane voltage through intracellular signaling to synaptic processes. I apply this capability to transcranial magnetic stimulation (TMS) to investigate how stimulation-induced voltage changes influence calcium dynamics and, ultimately, synaptic plasticity.

## 2 Biological Applications

A central goal of my research is to understand how the organization and interaction of neuronal processes give rise to cellular and network function. This involves examining how neuronal structure shapes electrical and biochemical signaling, how these signals interact within individual cells, and how their effects extend across networks. At the subcellular level, my work on calcium signaling in dendritic spines investigates how endoplasmic reticulum (ER) continuity and spine geometry influence calcium transport and biochemical compartmentalization [5]. By combining detailed models of calcium diffusion with dimensionally reduced descriptions of complex spine geometries, I examine how ER organization regulates signaling over biologically relevant timescales.

These interactions also shape how neurons respond to synaptic input and generate electrical activity. Purkinje cells provide an important setting for studying these mechanisms because their activity integrates distinct synaptic pathways with intracellular calcium dynamics. This is particularly relevant to spinocerebellar ataxia type 1 (SCA1), in which altered Purkinje-cell activity contributes to motor dysfunction. I developed a mechanistically detailed Purkinje-cell model incorporating parallel-fiber and climbing-fiber inputs, intracellular calcium stores, and an SCA1 variant. The model captures key features of experimentally observed responses to climbing-fiber stimulation, including complex-spike duration and subsequent firing pauses in healthy and SCA1 cells. I use the model to investigate how changes in calcium-

handling mechanisms and ion-channel conductances contribute to disease-associated electrical activity. Because intracellular calcium and membrane excitability are closely coupled, changes in either can alter the other. I use the model to investigate how disruptions in calcium handling and membrane conductances interact to produce abnormal firing patterns and contribute to the loss of normal Purkinje-cell function in SCA1.

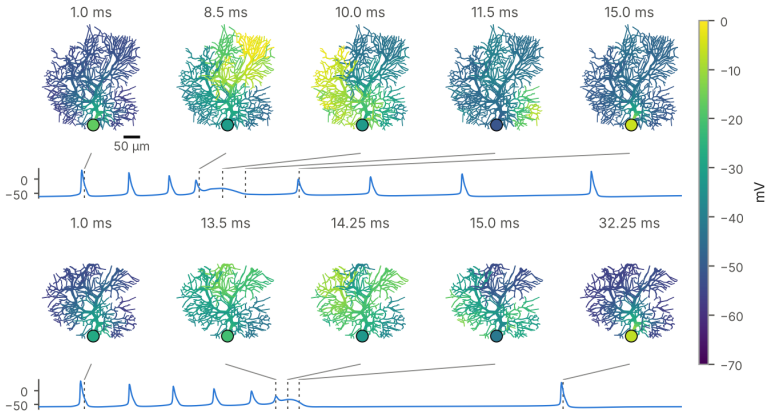



**Figure 2:** A healthy Purkinje cell (top) and its SCA1 (82Q) variant (bottom) responding to climbing-fiber input in an experimentally calibrated model.

At the network level, my work on transcranial magnetic stimulation (TMS) investigates how external stimulation alters neuronal activation patterns, intracellular calcium signaling, and synaptic plasticity. By examining how these cellular responses interact across interconnected neurons, I investigate how external stimulation can reshape coordinated network activity.

## 3 Future Directions

My long-term research vision is to advance our understanding of how complex neural systems function through the interactions of their underlying biological mechanisms. I will investigate how processes at the molecular and cellular levels combine to shape neuronal activity, how these interactions give rise to network behavior, and how their disruption contributes to neurological disease. A central direction of this work will be extending mechanistic investigations beyond individual cells to interconnected neural systems, examining how coordinated activity emerges and responds to changing conditions and external interventions. I will bring together mathematical modeling, computational neuroscience, experimental biology, and emerging machine learning approaches to address questions that are difficult to study through any one approach alone. Through this work, I will expand the scope of mechanistic neuroscience and develop new ways to investigate neural function, dysfunction, and modulation.

## References


[1] **Z. M. Miksis** and G. Queisser. "A Convergent Geometry-Aware Reduction for Diffusion in Branched Tubular Networks". In: *arXiv:2501.08247 [math.NA]* (2026).

[2] **Z. M. Miksis** and G. Queisser. "A Hybrid MPI+Multi-GPU Solver for Coupled Voltage-Calcium Dynamics in Neuronal Networks". In: *2026 IEEE High Performance Extreme Computing Conference (HPEC)*. 2026. URL: https://ieee-hpec.org/2026-hpec-proceedings-0918/.

[3] **Z. M. Miksis** and G. Queisser. "A Physics-Informed Neural Network For Coupled Calcium Dynamics in a Cable Neuron". In: *ICLR 2024 Workshop on AI4DifferentialEquations In Science*. 2024. URL: https://openreview.net/forum?id=TpOyZwImbp.

[4] **Z. M. Miksis** and Gillian Queisser. *SPINE: Simulator for Plasticity and Integrated Neuronal Events*. Version 1.0.0. 2026. DOI: 10.5281/zenodo.24226059.

[5] J. Saarikangas, L.-S. Kontturi, **Z. M. Miksis**, H. Vihinen, M. Serrano López, T. Fatima, E. Elomaa, T. Mäki-Marttunen, E. Jokitalo, and G. Queisser. "Dynamic gating of ER continuity promotes biochemical compartmentalization of dendritic spines". In: (2026). Submitted.




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