Modeling Multiple Sclerosis-Induced Demyelination with NMDA- and GABA_B-Mediated Synaptic Dysregulation in the Polysynaptic Reflex Arc

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Introduction

Multiple Sclerosis (MS):

- The body's immune system attacks the myelin sheath, which protects and insulates nerve fibers[4]

Spasticity:

- Characterized by disruptions in the spinal reflex circuit that stem from an excitatory/inhibitory imbalance caused by both inflammation and demyelination
  - Inflammatory chemicals induce glutamatergic excitotoxicity and decrease GABA receptor expression
  - Demyelination causes fewer GABAergic signals to reach motor neurons[5]
  - Inflammation also alters synaptic connectivity, weakening inhibitory pathways and reinforcing aberrant excitatory loops.[7]

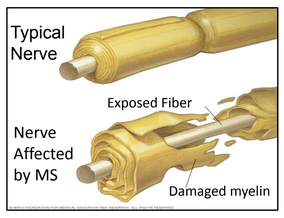


Fig. 1: Comparison of a healthy myelin sheath and a myelin sheath affected by MS[2]

Baclofen:

- Most commonly prescribed drug for spasticity symptoms in MS patients[3]
- Acts as a $GABA_B$ receptor agonist, enhancing inhibitory signals in the CNS, therefore reducing excitatory transmission and dampening motor neuron hyperexcitability[6]

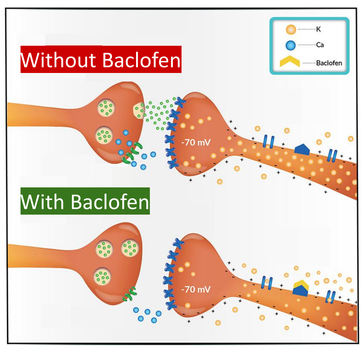


Fig 2: Comparison of neurotransmitter release with and without Baclofen[4]

Goal: We modeled how demyelination and inflammation disrupt spinal circuits in MS, examining the roles of NMDA-mediated excitotoxicity and impaired GABAergic inhibition in spasticity.

Methods

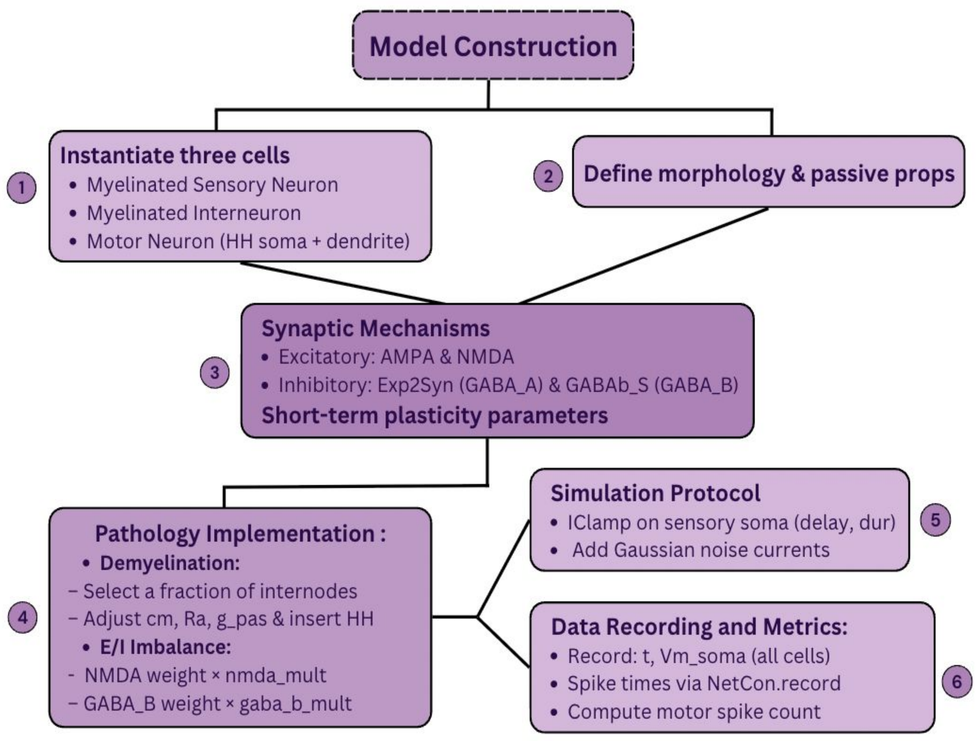


Fig 3: Flowchart of the computational pipeline: model instantiation, synaptic integration, pathology application, simulation execution, and analysis.

Category	Sensory Neuron	Interneuron	Motor Neuron
Ion Channels	HH Sodium (g_Na = 0.03 S/cm²) HH Potassium (g_K = 0.01 S/cm²) Slow K (km)	Same as sensory neuron	Same as sensory neuron
Membrane Properties	C_m = 1.0 µF/cm² (nodes), 0.3 µF/cm² (internodes) R_a = 100 Ω·cm (nodes), 50 Ω·cm (internodes)	Same as sensory neuron	Same as sensory neuron
Demyelination Model	Convert X% of internodes to: g_pas = 1e–3 S/cm² adjusted C_m and Ra based on X (X = 21%, 24%, 40% for PPMS, RRMS-R, RRMS-A)	Same as sensory neuron	Same as sensory neuron
Synaptic Inputs	N/A	AMPA + NMDA from sensory neuron	NMDA + AMPA from sensory neuron GABA_B from interneuron
Stimulation	IClamp: delay = 2 ms, dur = 2000 ms, amp = 0.7 nA	N/A	N/A
Noise	Gaussian noise (σ = 0.05 nA)	Gaussian noise (σ = 0.05 nA)	Gaussian noise (σ = 0.05 nA)

Results

Comparison	T-statistic	P-value	Significant (< 0.05)	Interpretation
Control vs PPMS	-23.70739914	7.30E-32	TRUE	PPMS > Control
Control vs RRMS_R	-12.94546665	1.89E-19	TRUE	RRMS_R > Control
Control vs RRMS_A	-30.62000136	9.43E-38	TRUE	RRMS_A > Control
PPMS vs RRMS_R	10.2559675	4.75E-17	TRUE	PPMS > RRMS_R
PPMS vs RRMS_A	-5.548578404	2.45E-07	TRUE	RRMS_A > PPMS
RRMS_R vs RRMS_A	-16.1340419	7.58E-29	TRUE	RRMS_A > RRMS_R

Fig 4: Pairwise t-tests show significant differences in spike counts across all MS conditions ($p < 0.05$).
The results highlight how demyelination severity and synaptic imbalance distinctly shape motor neuron excitability in the model.

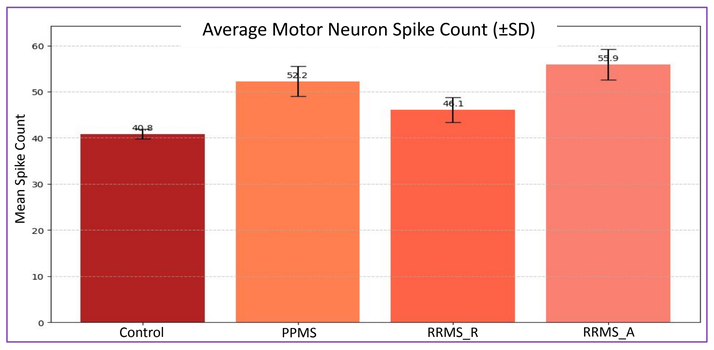


Fig 5: Motor neuron spike counts (mean ± SD) across conditions. Hyperexcitability is elevated in PPMS and RRMS attack phases compared to Control and RRMS remission.

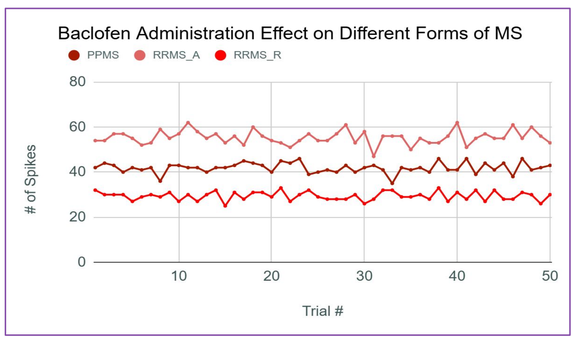
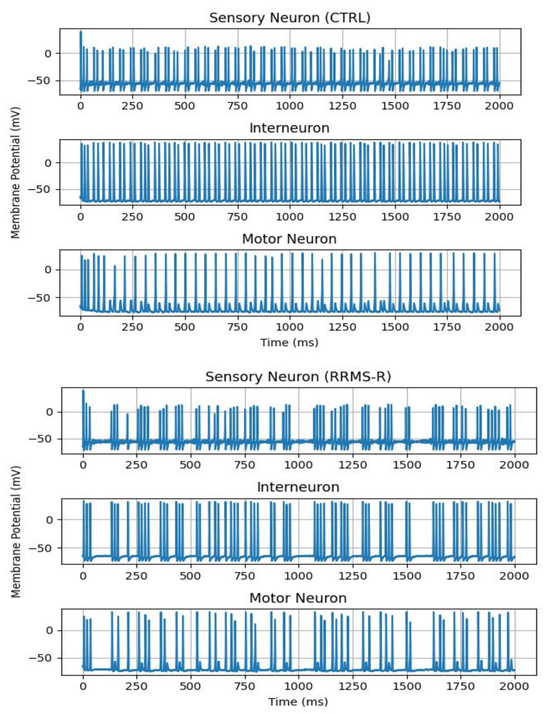


Fig 6: Effect of Baclofen on neural spike activity across MS subtypes. Baclofen reduced spike counts in all groups, with the greatest reduction in RRMS_R, followed by PPMS and RRMS_A. This suggests varied treatment response based on MS subtype and activity.



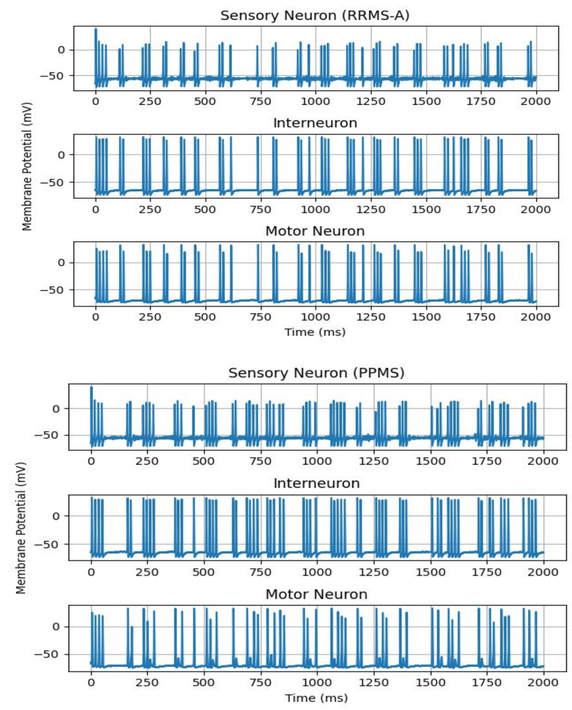


Fig 7: Membrane potential traces of the sensory, interneuron, and motor neurons reveal that increasing NMDA conductance and decreasing GABA_Binhibition drive hyperexcitability in RRMS Attack, partial recovery is seen in RRMS Remission, while chronic demyelination in PPMS disrupts spike transmission despite preserved sensory input.

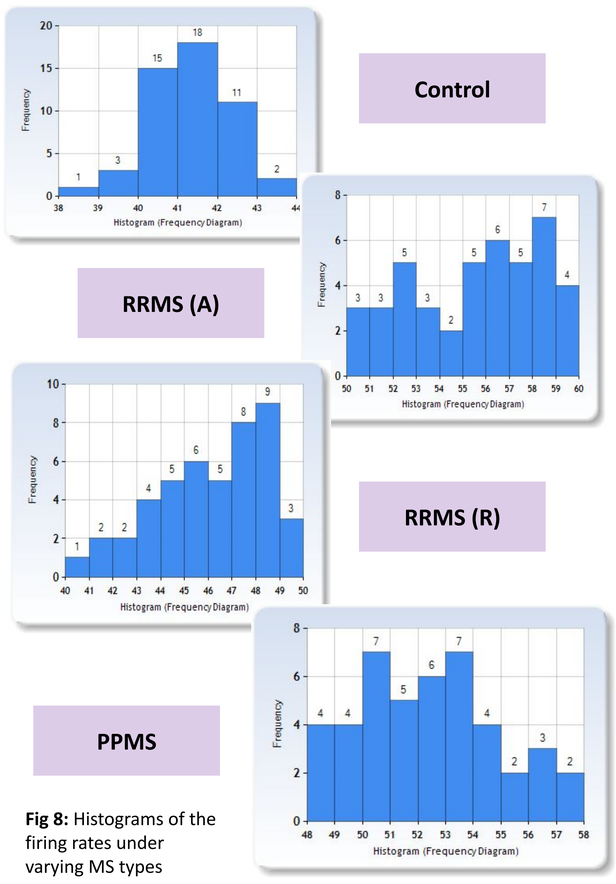


Fig 8: Histograms of the firing rates under varying MS types

Discussion/Conclusions

Key Findings:

- Our model shows that demyelination and inflammation increase firing rates in spinal motor neurons, suggesting a mechanism for understanding spasticity in MS.
- When we simulated baclofen by increasing GABA_B conduction, spiking decreased, demonstrating its role in restoring inhibitory balance.

Interpretation of Results:

- Our findings support the idea that spasticity in MS is driven by an imbalance between excitation and inhibition, not just signal loss from demyelination.
- The model shows how inflammation amplifies motor neuron activity, contributing to the hyperexcitability presenting as spasticity symptoms.
- Baclofen's effect in the model mirrors its clinical use, validating our approach.

Significance:

- This model explains how MS-related cellular changes lead to motor symptoms. It can also test the efficacy of treatments virtually and may guide development of better therapies targeting synaptic imbalance.

Limitations:

- Our model simplifies real spinal circuits, lacking glial cells or full-body responses
- It also relies on estimated parameters for inflammation and neurotransmission, so results are meant to be exploratory, not predictive.[5]

Further Directions:

- Possible next steps include adding astrocyte signaling and simulating muscle activation to better link circuit activity to spasticity.

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Program Files