Simulating a Novel Use of Fluoxetine for Enhancing Neuronal Excitability in Demyelinated Axons Present in Multiple Sclerosis

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Introduction

Multiple Sclerosis (MS): A neurodegenerative disorder affecting 2.8 million people worldwide in which immune cells attack and destroy the myelin sheath surrounding axons (demyelination), hindering neuronal signaling and causing inflammation in the brain[1]

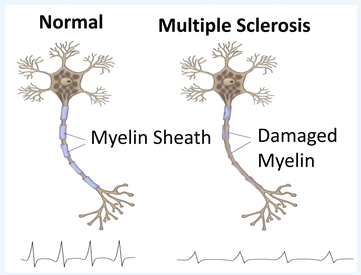

Fig. 1
Comparison of a healthy neuron to a demyelinated one

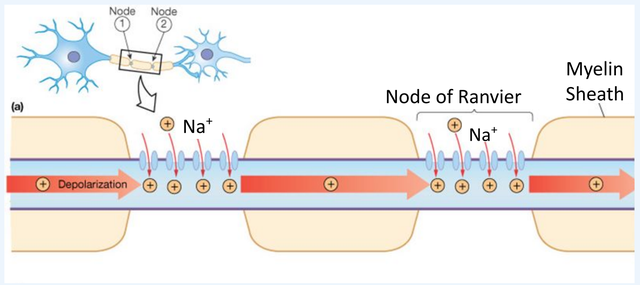

Fig. 2
Diagram demonstrating how sodium ion channels function in a myelinated axon

- **Symptoms:** fatigue, vision problems, numbness/tingling, weakness, pain

Action Potentials: When a neuron sends a message down its axon, a change in voltage is detected to propagate the signal down the cell

Ion Channels: Voltage-gated sodium and potassium channels in a neuron are essential in the continuation of action potentials down an axon

- **Demyelination causes an imbalanced membrane dynamic ratio of sodium to leak channel conductance (g_{Na}/g_L), a biomarker for MS[2]**
- The potential of potassium leak channels as a drug target remains relatively unexplored

Fluoxetine: A drug most commonly used as an antidepressant, however is also a potassium leak channel antagonist (inhibitor)[3]

Objectives: To investigate the potential of Fluoxetine as a pharmacological intervention to mitigate the sodium and potassium leak channel conductance imbalance induced by demyelination

- Focus on if closing potassium leak channels using Fluoxetine can increase the ratio of membrane dynamics
- Determine if spiking frequencies in the demyelinated neuron increase as a result of adding varying doses of Fluoxetine

Methods

- A multicompartmental Hodgkin-Huxley (HH) neural model was constructed using the Xolotl framework:
  - Includes 4 major ion channels: voltage gated sodium (NaV), voltage gated potassium (KV), persistent sodium (NaP), and leak channel (L)
  - Geometrically simplified using cable theory to understand the behaviors in a neuron with reduced complexity
    - Consists of the compartments: soma, axon hillock, initial segment, and nodes of ranvier
  - The model contained 5 nodes of ranvier and simulated partial demyelination by extending the length of the middle node from 80 to 8,000 μm^2
  - Action potentials were evoked by injecting a continuous current of 0.2 nA into the soma to assess its propagation across the demyelinated region and the following nodes
  - Varied NaV and L channel conductances to explore a wide range of ratio combinations on neuron spiking rates
- To calculate the percentage of inhibition against Fluoxetine dosages, the Hill equation was employed with an IC-50 of 19±2 µm and a Hill coefficient of 0.9[3]
  - Parameter for potassium leak channel conductance (g_L) was adjusted in the demyelinated node based on the level of inhibition for varying standard dosages

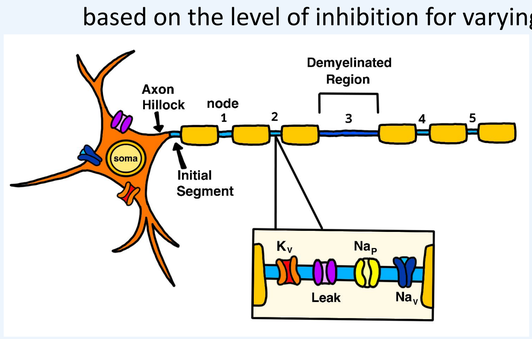

Fig. 3
A labeled visual of our model for a demyelinated neuron
Illustration by Irene Yicheng Jiang

NaV

$$m_\infty = \frac{1}{1+e^{\frac{V+25.5}{-5.29}}}$$

$$h_\infty = \frac{1}{1+e^{\frac{V+48.9}{5.18}}}$$

$$\tau_m = 1.32 - \frac{1.26}{1+e^{\frac{V+120.0}{-25.0}}}$$

$$\tau_h = \frac{0.67}{1+e^{\frac{V+62.9}{-10.0}}} * (1.0 + e^{\frac{V+34.9}{3.6}})$$

KV

$$m_\infty = \frac{1}{1+e^{\frac{V+12.3}{-11.8}}}$$

$$\tau_m = 7.2 - \frac{6.4}{1+e^{\frac{V+28.3}{-19.2}}}$$

NaP

$$m_\infty = \frac{1}{1+e^{-0.12(V+39)}}$$

$$\tau_m = 10 + \frac{200}{1+e^{0.4(V+57)}}$$

Leak

$$I_L = g_L(V_m - E_L)$$

Fig. 4
Equations used for the various conductance channels[4]

Results

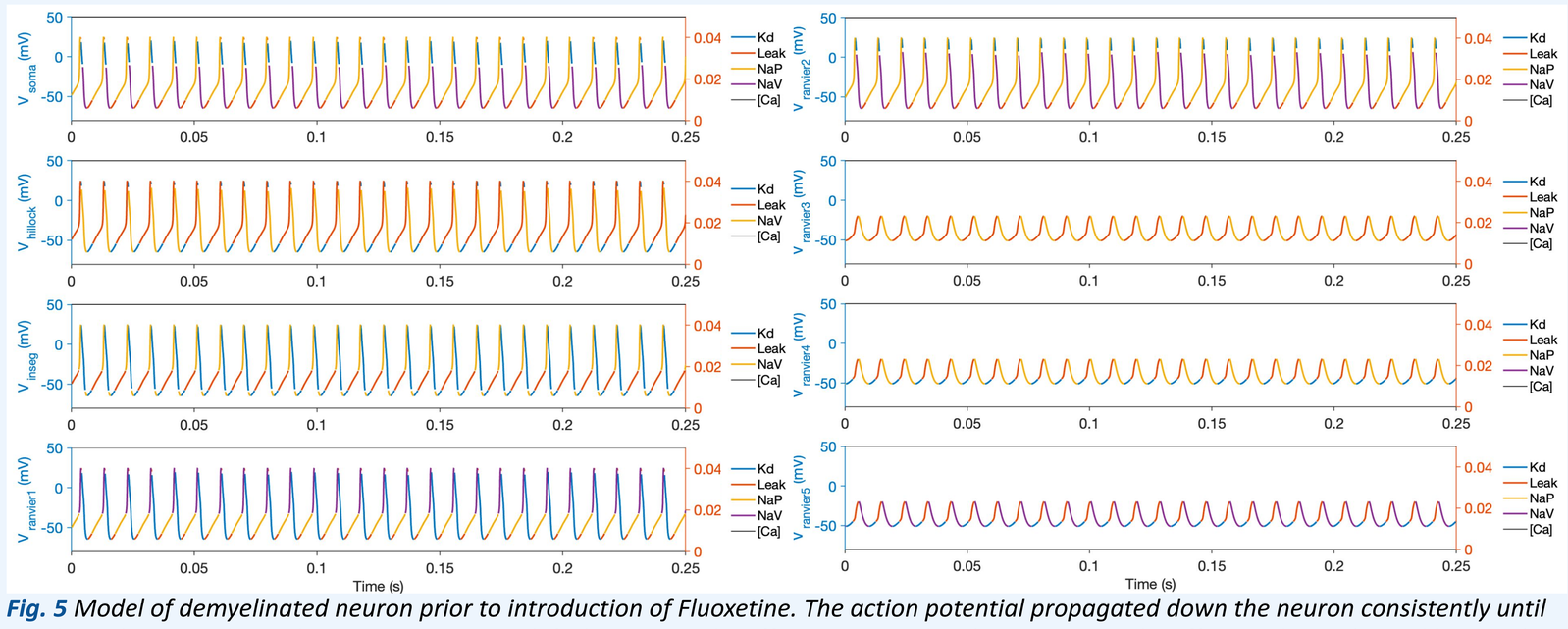

Fig. 5 Model of demyelinated neuron prior to introduction of Fluoxetine. The action potential propagated down the neuron consistently until reaching the demyelinated region. Even once it left this region, the effects remained. Colors represent the effect each ion channel has on the overall waveform: Voltage-gated Potassium (blue), Leak (red), Persistent Sodium (yellow), Voltage-gated Sodium (purple/yellow).

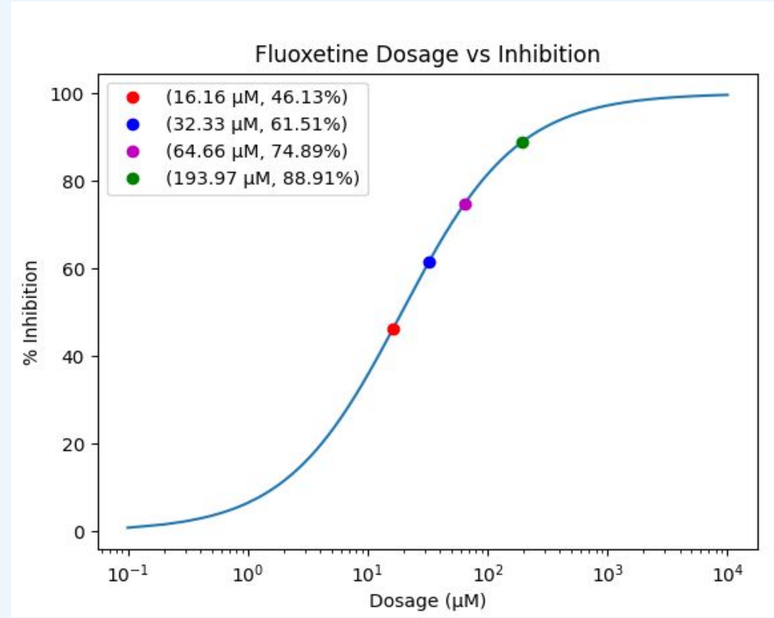

Fig. 6 Concentration-response curve using Hill equation to model percent inhibition against varying doses of Fluoxetine.

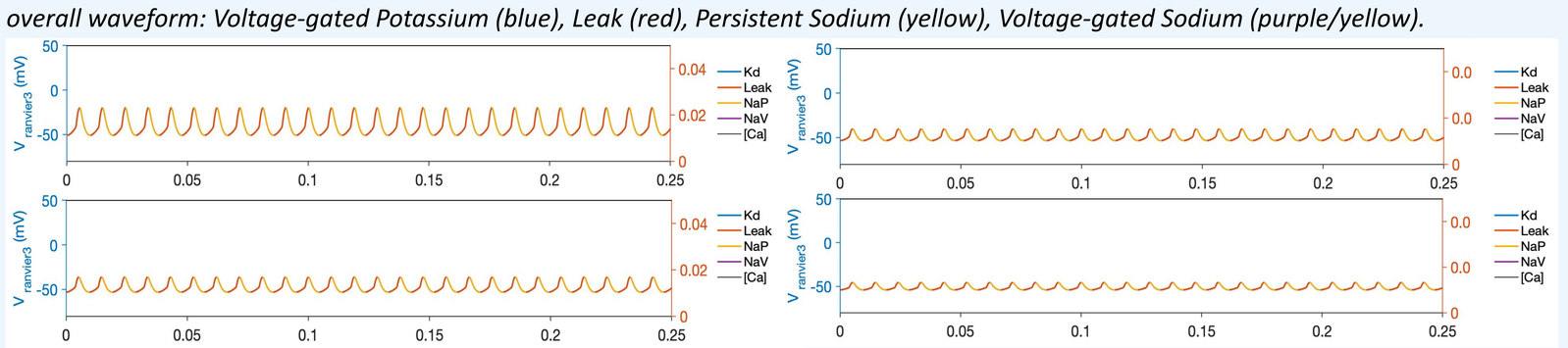

Fig. 7 Effect of the four chosen doses of Fluoxetine on the demyelinated region of the neuron. Although the amplitude of the action potential changed, the frequency did not.

Conclusion & Discussion

Conclusion:

- Inhibition of the potassium leak channel conductance did not have a significant effect on the excitability of the model neuron
- The action potential was unable to be fully revived once it had left the demyelinated region, suggesting that fluoxetine would not have an effect in restoring neuronal excitability in an MS patient
- Our results suggest that potassium leak channels are not effective as targets for drugs to improve symptoms of demyelination

Discussion:

- An alternative way to potentially restore the g_{Na}/g_L ratio would be to increase Na conductance by opening further sodium ion channels
- However, most sodium channel openers are toxic, as the flow of sodium ions into the cell causes extreme depolarization and generates an upstroke of action potentials
- The opening of sodium channels can cause seizures, abnormal and dangerous brain activity, or death

Limitations:

- Geometrically simplified using cable theory with only 4 compartments: soma, hillock, initial segment, and nodes of ranvier
- Assumes all ion channels and potassium leaks are evenly distributed along the axon and that all leak channels in the model are potassium channels
- Effects of Fluoxetine were simulated only on a single neuron, while in reality, drugs affect entire systems of neural networks

Future research:

- Attempt to restore population level neural firing rates, which could be applied to a network of neurons to see if a drug has an effect on a whole brain region compared to a single neuron
- Simulate alternate potassium leak channel antagonists and compare their results to Fluoxetine

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