A Computational Investigation of Ionic Transport and Gating Due to Electrical Stimulation Treatments

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Background

Parkinson's disease (PD)

A *neurodegenerative disorder* that affects predominately dopamine-producing (dopaminergic) neurons

Symptoms

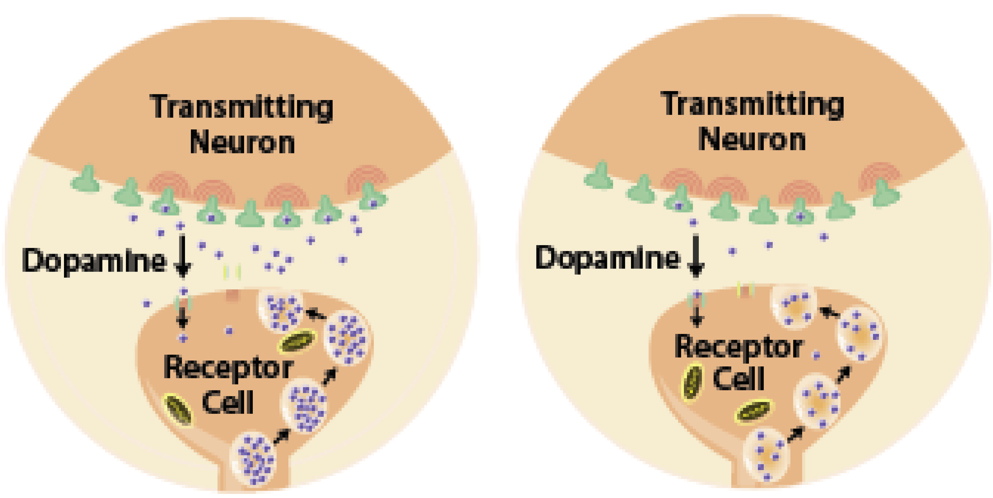
- Tremors
- Limb rigidity
- Gait and balance problems

Treatment

Deep brain stimulation (DBS) is an effective treatment that delivers electrical impulses to targeted brain regions that *disrupt the abnormal activity* causing the symptoms

Calcium (Ca^{2+})

Facilitates cellular communication by activating an intra-cellular signaling cascade that enables vesicles to release their neurotransmitters into the synaptic cleft for *neuronal communication*



Healthy Patient **Parkinson's Patient**

Motivation

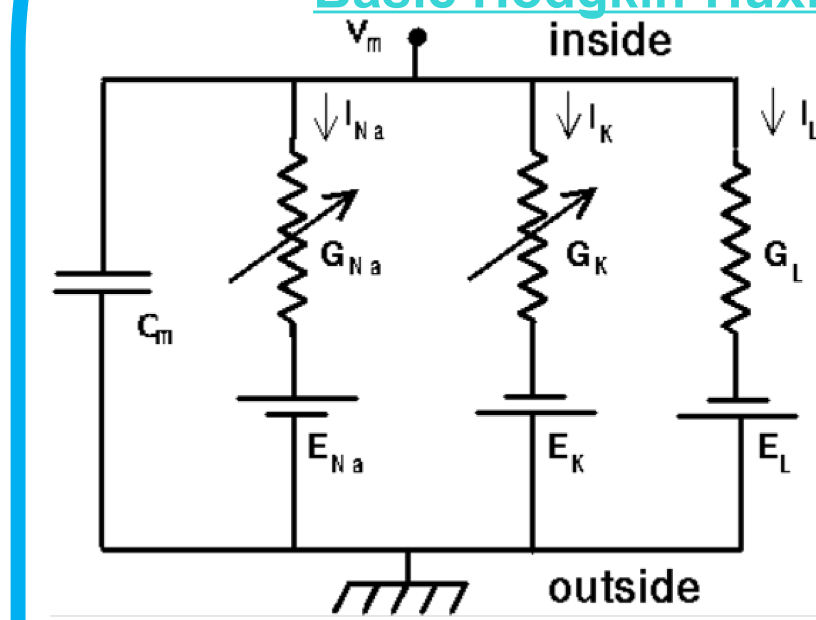
- The precise mechanisms of DBS on ion flow is poorly understood and proves difficult to assess experimentally
- This is an ideal area to investigate with Mathematical Modeling and Computational Simulation
- Research suggests that DBS has an impact on ionic flux
- We hypothesize that Ca^{2+} ionic flow is enhanced by electrical stimulation treatments such as DBS

Approach

- To examine the impact of DBS on Ca^{2+} transport, we have implemented a Hodgkin-Huxley-based model of a neuron by which we simulate DBS *in silico*, and analyze its impact on Ca^{2+} flow
- We focus on both T-type and L-type calcium channels: *"The diverse expression patterns of the L-type and T-type channels show that these channels are pharmacologically important in Parkinson's disease."*

Mathematical Model

Basic Hodgkin-Huxley Model



- The Hodgkin-Huxley model is a set of nonlinear differential equations that describes how action potentials in neurons are initiated and propagated
- The model was originally used in 1952 to explain action potentials in the axon of a giant squid and has since been widely used

$$C_m \frac{dV_m}{dt} = G_{Na}(E_{Na} - V_m) + G_K(E_K - V_m) + G_L(E_L - V_m) + I_{Inject}$$

$$I_{Na} = (G_{Na_l} + G_{Na} * m^3 * h) * (V - E_{Na}) \qquad \frac{dm}{dt} = \alpha_m * (1.0 - m) - \beta_m * m$$

$$I_K = (G_{K_l} + G_K * n^4) * (V - E_K) \qquad \frac{dn}{dt} = \alpha_n * (1.0 - n) - \beta_n * n$$

$$I_{Cl} = (G_{Cl_l} + G_{Cl}) * (V - E_{Cl}) \qquad \frac{dh}{dt} = \alpha_h * (1.0 - h) - \beta_h * h$$

Our Model Extension

$$\frac{dV}{dt} = (I_{Inj} - I_{Na} - I_K - I_{Cl} - I_{Ca_T} - I_{Ca_L})/C_m$$

$$I_{Ca_T} = G_{Ca_l} + G_{Ca} * m_t^3 * h_t(V - E_{Ca}) \qquad I_{Ca_L} = G_{Ca_l} + G_{Ca} * m_l^2 * h_l(V - E_{Ca})$$

$$\frac{dm_t}{dt} = \frac{m_{t\infty} - m_t}{\tau_{m_t}} \qquad \frac{dh_t}{dt} = \frac{h_{t\infty} - h_t}{\tau_{h_t}} \qquad \frac{dm_l}{dl} = \frac{m_{l\infty} - m_l}{\tau_{m_l}} \qquad \frac{dh_l}{dl} = \frac{h_{l\infty} - h_l}{\tau_{h_l}}$$

$$m_{t\infty} = \frac{1}{1.0 + e^{-\frac{-0.047 - V}{0.005}}} \qquad m_{l\infty} = \frac{1}{1.0 + e^{-\frac{V - (-19.0)}{8.0}}}$$

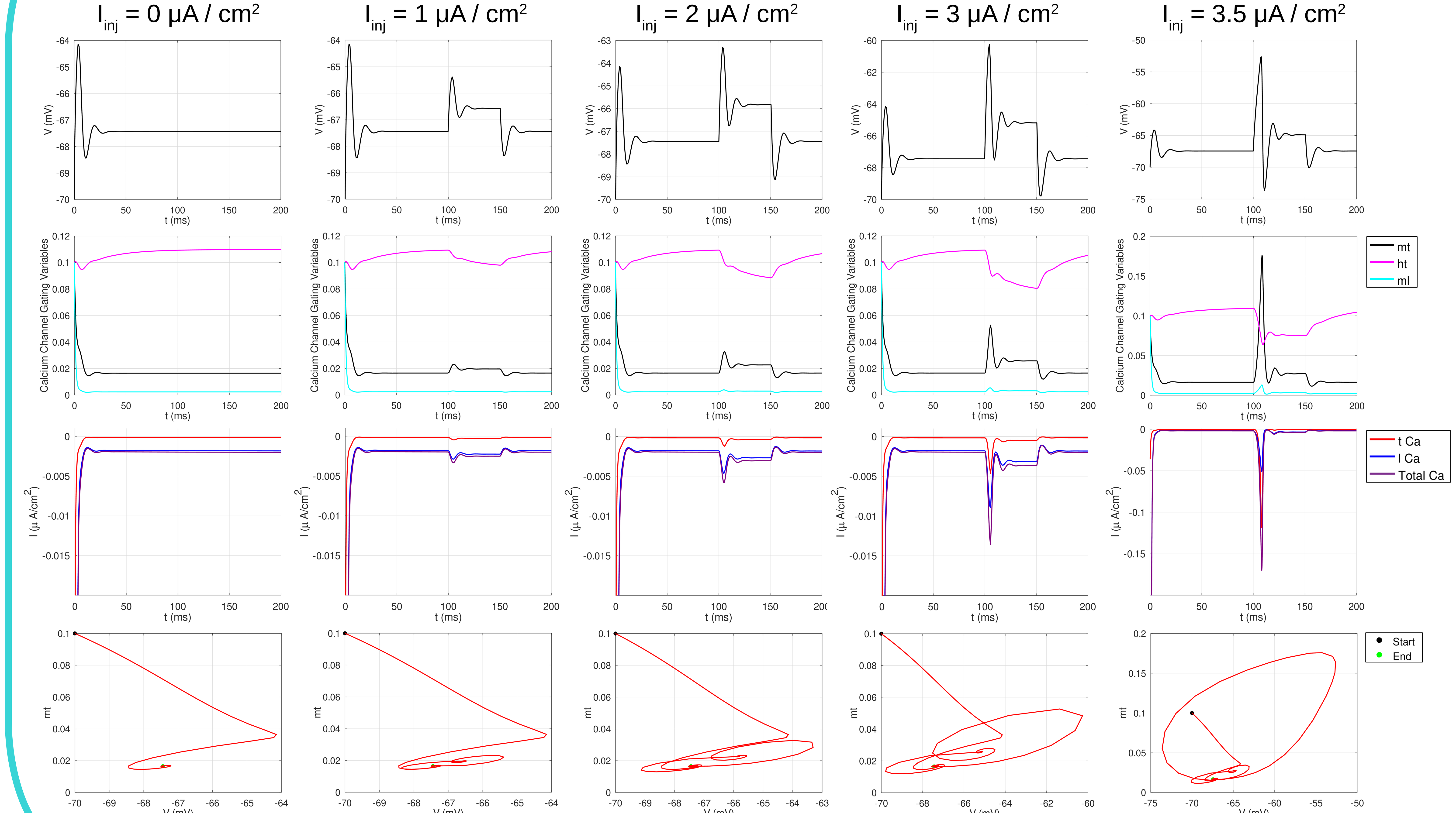
$$h_{t\infty} = \frac{1}{1.0 + e^{\frac{-0.080 - V}{-0.006}}} \qquad h_{l\infty} = \frac{1}{1.0 + e^{\frac{V - (-42.0)}{8.0}}}$$

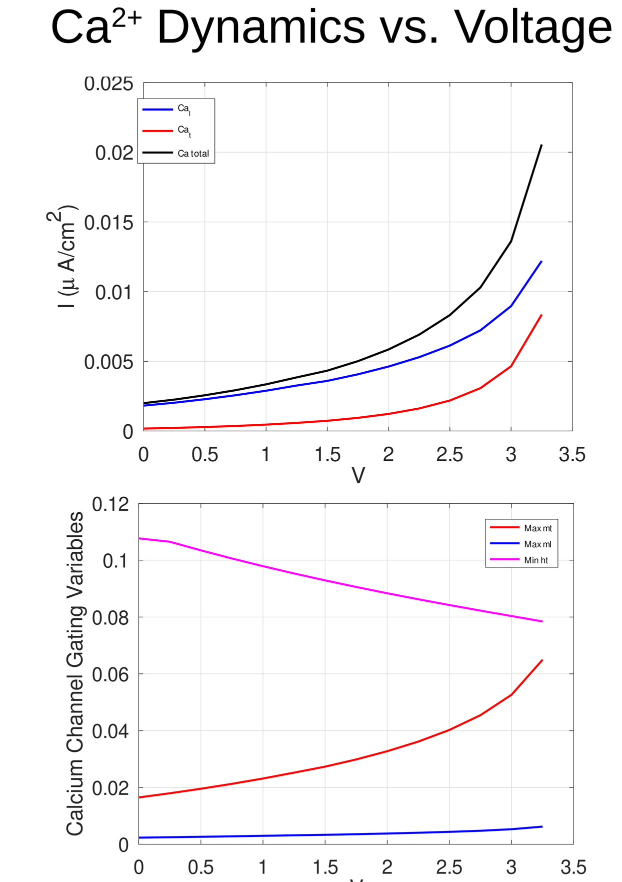
$$\tau_{m_t} = \left(\frac{1.84}{1 + e^{\frac{-0.027 - V}{0.008}}} + \frac{1.19}{1 + e^{\frac{-0.072 - V}{-0.020}}}\right)^{-1} \qquad \tau_{m_l} = 0.6 + \frac{3.0}{e^{-\frac{V - (-19.0)}{24.0}} + e^{\frac{V - (-19.0)}{24.0}}}$$

$$V > -60mV: \quad \tau_{h_t} = \left(0.0076 + \frac{0.177}{1 + e^{\frac{-0.0566 - V}{0.0063}}} + \frac{0.134}{1 + e^{\frac{-0.0995 - V}{-0.0056}}}\right)^{-1} \qquad \tau_{h_l} = 200$$

$$V < -60mV: \quad \tau_{h_t} = 3.10 + \frac{3.683}{1 + e^{\frac{-0.0379 - V}{0.0047}}} + \frac{46.34}{1 + e^{\frac{-0.0706 - V}{-0.0086}}}$$

Simulations and Results



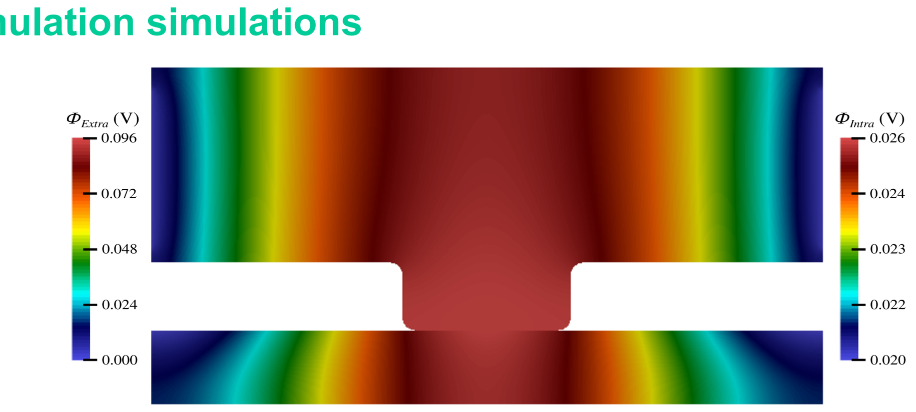


Conclusions

- We observe an exponential increase in calcium flow as the voltage increases
- Phase diagram's steady-state is reached with a consistent, yet increasing complex trajectory
- Inactivation gating variables contribute less relevance to ionic flow than activation gating variables
- There is an inevitable crossover on our extreme values graph, that is ultimately accomplished during action potential
- The ***L-type channel has greater calcium inflow than the T-type channel*** for all injection levels tested
- It is observed that Ca^{2+} ionic flow is enhanced by electrical stimulation treatments such as DBS; this is supported by the exponential relationship between Ca^{2+} and membrane voltage
- It is also observed that though the T-type Ca^{2+} channel has faster kinetics than the L-type, it transports less Ca^{2+}; this further supports the notion that both T and L-type channels are therapeutically vital in PD pathogenesis and treatment

Next Steps

- **Analyze multi-dimensional phase diagrams**
- **Examine model prediction accuracy with comparisons to DBS clinical and medical literature**
- **Integrate Cell Model with larger-scale 3-dimensional electrical stimulation simulations**



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