# Modeling Sensitivity of Neuronal Firing to L-Type Calcium Channel Activity


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## Introduction

**The substantia nigra (SNc) is a part of the brain associated with learning, movement, addiction, and more. Within the substantia nigra, there are different subpopulations of dopaminergic neurons which project to different areas of another part of the brain called the striatum. These different subpopulations are believed to have different functions and effects on behavior. In particular, DLS (dorsolateral striatum) projecting neurons of the SNc that have been shown to be involved with movement refinement and initiation and are most vulnerable to Parkinson's show a linear response to inhibitors of the L-type $Ca^{2+}$ channel $Ca_V1.3$.**

**In this experiment, the goal was to investigate how $Ca_V1.3$ acts as a linear amplifier in the DLS projecting neurons through the simulation of the L-type channel-specific blocker isradipine (ISR).**

## Motivation

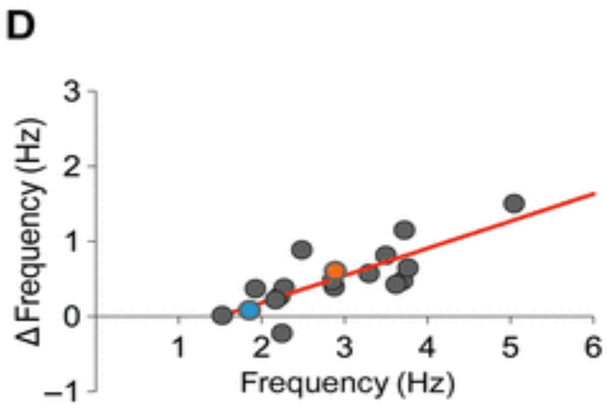


**Figure 1. Published data from identified DLS-projecting neurons (Shin et. Al 2022 *Science Advances*) show a linear relationship between the baseline frequency and decrease in frequency when $Ca_V1.3$ is blocked with ISR.**

## Methods

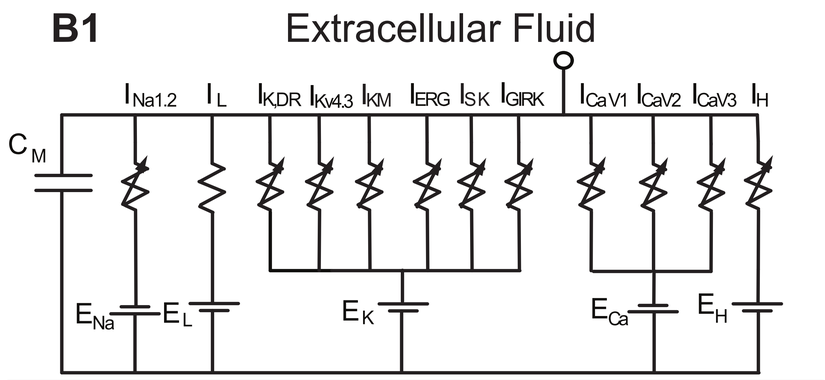


**Figure 2. The Hodgkin-Huxley equivalent circuit model of a neuron represents it as a nonlinear RC circuit: $C_m dV/dt = \sum I$, where $I$ are the currents. $g_{CaV1}$ is the conductance of the L-type calcium current and $g_L$ is the leak conductance. The NEURON software package was used for the simulated neural activity.**

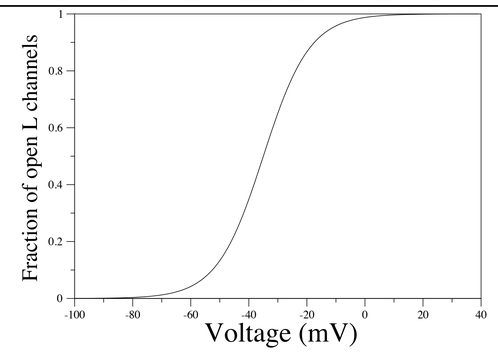


**Figure 3. The conductance for $Ca_V1.3$ is nonlinear. The sigmoid represents the steady state open fraction of the $Ca_V1.3$ channels (m) as a function of voltage. The L-type calcium current is $I_{CaV1} = g_{CaV1}*m*(E_{Ca} - V)$, where m is the voltage and time-dependent gating variable. The leak is just $I_L = g_L*(E_{Ca} - V)$ with no nonlinear term.**

## Results

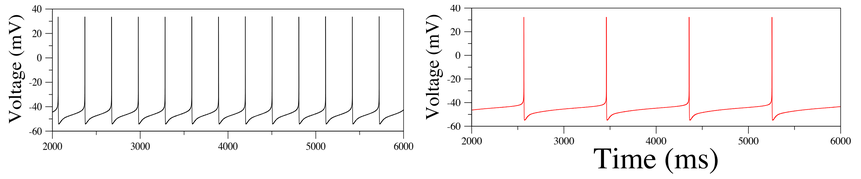


**Figure 4. Representative voltage traces at baseline frequency (left) and with simulated ISR applied (right). Consistent with Shin et al, blocking gCaL reduces frequency.**

## Results

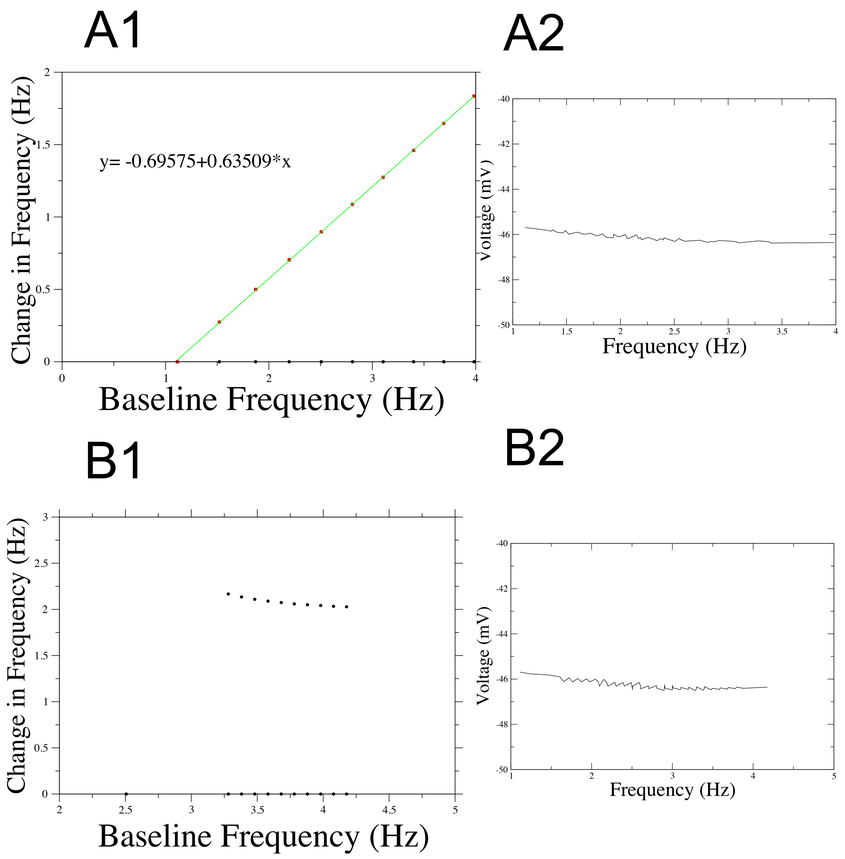


**Figure 5. A. Frequency was varied by increasing $g_{CaV1}$. A1. Faster frequencies had a higher value of $g_{CaV1}$, so blocking $g_{CaV1}$ produced a greater decrease in frequency. A2. This was not accounted for by an increase in mean inter-spike membrane potential. B. Specifically the sodium component of the leak $g_L$ was varied, so increasing $g_L$ also increased the frequency. B1. In this case the change in frequency with $g_{CaV}$=0 was not strongly dependent on baseline. B2. No increase in mean inter-spike membrane potential.**

## Conclusion

- **When the baseline frequency was controlled only by the conductance of the L-type channel, the change in frequency with $g_{CaV}$=0 was linear, consistent with the effect of ISR in Fig. 1.**
- **However, the linear dependence was lost when the baseline frequency was controlled by the sodium leak conductance instead.**
- **The explanation in Shin et. Al 2022 was that at higher frequencies, more $Ca_V1.3$ was recruited because of the nonlinearity in Fig. 3 and the higher mean inter-spike membrane potential at higher frequencies. Fig. 5A2 and B2 did not replicate that phenomenon, more study is required..**


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