Modeling Substantia Nigra Pars Reticulata Responses to Pallidal and Striatal Inputs Using a Two Compartment Model

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\section*{Introduction}

\begin{itemize}
\item In the brains of vertebrates, a subcortical region called the \textit{basal ganglia} (BG) is thought to be involved in decision making and action selection.
\item Within the rodent brain, the \textit{substantia nigra pars reticulata} (SNr) serves as the primary output nucleus of the basal ganglia.
\item The SNr receives converging GABA\textsubscript{A} mediated inputs from the direct and indirect pathways within the BG.
\item We modeled the integration of these converging GABA dynamics by SNr neurons.
\end{itemize}

\section*{Methods}

\begin{itemize}
\item We devised and analyzed a computational model of an SNr neuron that includes somatic and dendritic compartments, relevant GABAergic inputs, and other pertinent factors including intracellular chloride dynamics.
\item Our model is built upon the Hodgkin-Huxley framework, where $I_{\text{APP}}$ is the applied current, $I_\text{s}$ is the current generated by a channel for the ion $x$, and $V_S$ and $V_D$ are the membrane potentials and $C_S$ and $C_D$ are the capacitances for the somatic and dendritic compartments respectively:
\begin{align*}
\frac{dV_S}{dt} &= -\left(\sum_{n} I_n \right) + I_{\text{APP}}, \\
S^* &= \{\text{Na, NaP}, \text{K, Ca, SK, Leak, GABA, DS}\} \\
C_D \frac{dV_D}{dt} &= -\left(\sum_n I_n \right) + (\sigma)_{\text{Tonic}} \text{Cl}^\text{Tonic}, \\
D^* &= \{\text{TRPC3, GABA, SD}\}
\end{align*}
\item Parameters and their values, as well as gating equations and additional differential equations are not included.
\end{itemize}

\section*{Two Compartment SNr Model Neuron Produces Appropriate Dynamics}

\begin{itemize}
\item These two plots show the model exhibits the expected behavior of an action potential.
\item In the membrane phase plot, the white dot is the point afterhyperpolarization (AHP). The black dot is spike height (AP Peak).
\end{itemize}

\section*{GPe Stimulation Affects Firing Rate Based on $E_{\text{GABA}}$ & $\text{Cl}^-$}

\begin{itemize}
\item The \textit{globus pallidus} (GPe) is a segment of tissue within the BG that connects to the soma of SNr neurons and is responsible for the indirect pathways in the BG.
\item We simulated optogenetic stimulation of the somatic synapses of the SNr neurons by the GPe for the duration of one second at 40 Hz.
\item The effect of this stimulation on the SNr neuron’s somatic behavior depended upon the value of $E_{\text{GABA}}$ and the intracellular Cl\textsuperscript{-} levels.
\item $K_{\text{ClC}}$ and $S_{\text{Tonic}}$ are the conductances associated with a tonic chloride load and the extrusion capacity of Cl\textsuperscript{-} respectively. The figure to the right shows the result of low $E_{\text{GABA}}$, small Cl\textsuperscript{-} conductance, and high Cl\textsuperscript{-} extrusion. The neuron is unable to fire.
\end{itemize}

\section*{Future Directions}

\begin{itemize}
\item We are interested in how identical populations of SNr neurons can maintain differing firing rates without continuous input. Our next steps are to add synaptic coupling to this model, specifically looking at two coupled SNr neurons.
\item We will analyze the effects of a shift in $E_{\text{GABA}}$ in the two-neuron model and see whether this results in a difference in firing rate for the two neurons.
\item Validate model by measuring intracellular Cl\textsuperscript{-} and $E_{\text{GABA}}$.
\end{itemize}

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