Master thesis : Investigation of Homeostatic Compensatory Mechanisms to Maintain Slow and Regular Pacemaking in Midbrain Dopamine Neurons

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Investigation of Homeostatic Compensatory Mechanisms to Maintain Slow and Regular Pacemaking in Midbrain Dopamine Neurons

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Midbrain dopaminergic neurons are cells capable of spontaneously generating a slow and regular rhythmic electrical activity, known as pacemaking activity. This property is essential for maintaining a basal concentration of dopamine in the striatum and plays a central role in motor control and reward-related behaviors. In the context of Parkinson's disease, the progressive degeneration of these neurons is directly linked to mitochondrial oxidative stress triggered by the continuous influx of calcium through L-type calcium channels ($Ca_v1.3$), which are active during pacemaking. The pharmacological blockade of these channels using isradipine had been proposed as a neuroprotective strategy, supported by promising results in mice. However, the clinical trial conducted in 2020 demonstrated no significant benefit in humans, suggesting an incomplete understanding of the underlying biophysical mechanisms such as the homeostatic compensatory mechanisms. Furthermore, the precise identity of the current responsible for pacemaking remains debated, and a recent hypothesis proposes the existence of a current called I_{XG} or I_{Pace} as the primary engine of the autonomous rhythm.

This work aims to investigate, through numerical simulation, the homeostatic compensatory mechanisms that allow dopaminergic neurons to maintain their pacemaking activity when faced with targeted pharmacological perturbations. To this end, a homeostatic controller based on intracellular calcium dynamics is integrated into two distinct conductance-based models: the Yu model, a classical reference model, and the Fyon model, which incorporates the $\bar{g}_{Pace}$ conductance representing the hypothesized I_{XG} current. Simulations are first conducted on a single average neuron and then extended to heterogeneous populations of 200 neurons, in order to account for the biological variability observed in vivo.

The results reveal a fundamental difference in robustness between the two models. The Fyon model faithfully reproduces known physiological characteristics: the blockade of HCN channels or A-type potassium channels does not significantly disrupt pacemaking activity at the population scale, in agreement with experimental data. In contrast, the Yu model fails to maintain this activity when faced with the same perturbations, illustrating its intrinsic fragility linked to non-physiological activation parameters. Upon the blockade of $Ca_v1.3$ channels, the homeostatic controller drives the calcium concentration back toward its target value in both models, but only the Fyon model preserves rhythmic electrical activity in a large majority of neurons (79%), thanks to the presence of $\bar{g}_{Pace}$ which provides the residual depolarizing current required to cross the excitability threshold. This long-term calcium recovery, observed across the entire population, directly neutralizes the reduction in calcium influx initially induced by the blockade, thereby undermining the neuroprotective effect that was sought. This observation furthermore highlights a fundamental distinction between calcium homeostasis and electrical rhythm homeostasis: the recovery of the calcium signal does not, on its own, guarantee the restoration of pacemaking. At the population scale, blocking L-type channels in the Fyon model reveals a trend toward frequency deceleration and the emergence of bursting activities, suggesting that chronic homeostatic compensations could further counteract the desired neuroprotective effect. Finally, the complete blockade of $\bar{g}_{Pace}$ leads to a loss of activity in 96.5% of the neurons in the population, validating the indispensable role of this conductance as the engine of the autonomous rhythm.

Ultimately, this work provides two complementary computational perspectives on the reasons behind the failure of the isradipine clinical trial: first, the long-term homeostatic recovery of calcium influx directly neutralizes the intended neuroprotective effect; second, the compensatory mechanisms drive a subset of neurons toward bursting discharge regimes that are potentially less neuroprotective. These findings underscore the importance of a detailed understanding of the biophysical mechanisms of pacemaking for designing therapeutic strategies capable of anticipating long-term homeostatic compensations.

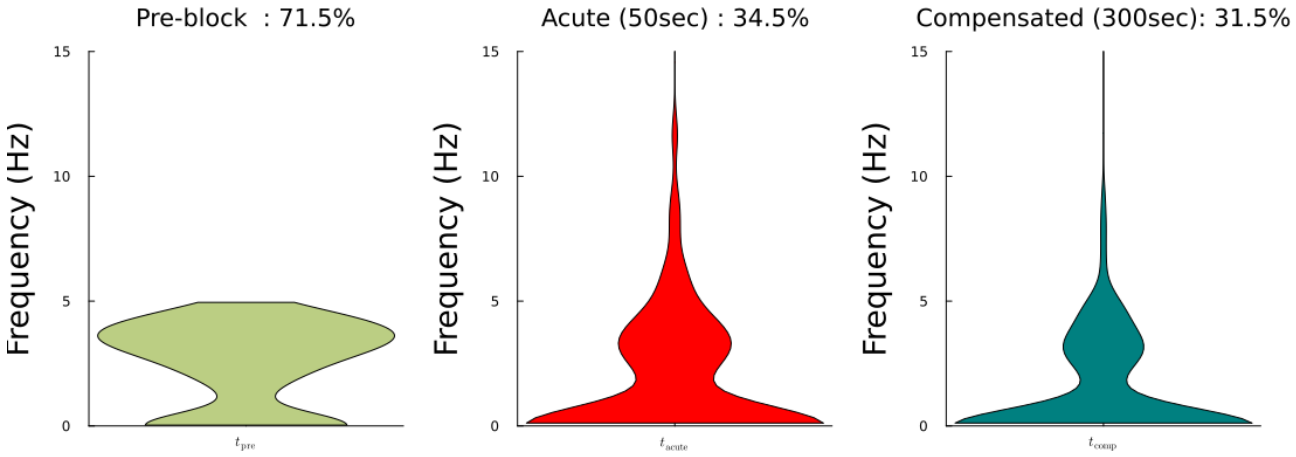

Figure 1: Evolution of firing frequency distributions before, immediately after, and following long-term compensation for L-type calcium channel blockade in the Yu population.

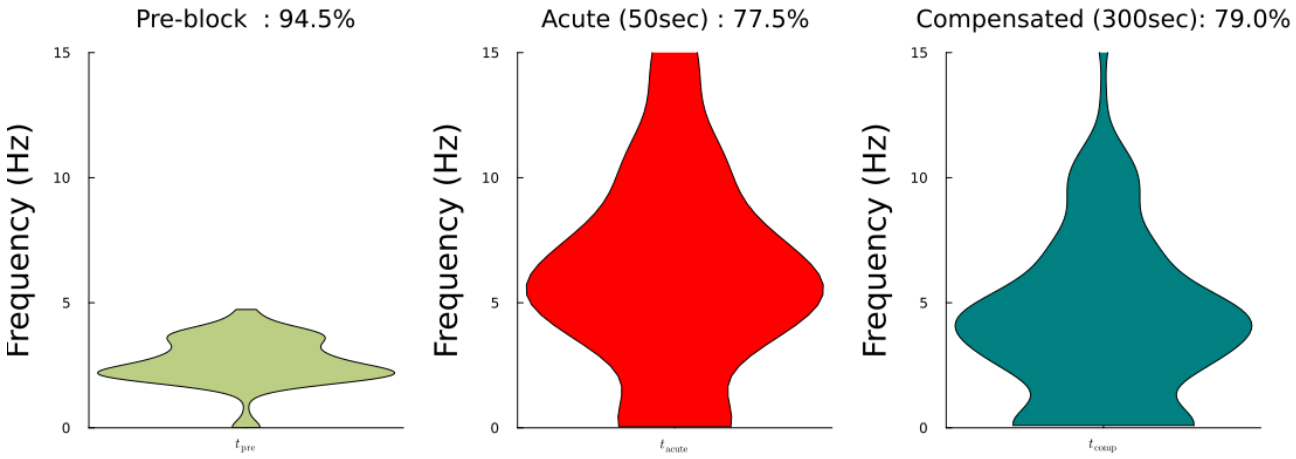

Figure 2: Evolution of firing frequency distributions before, immediately after, and following long-term compensation for L-type calcium channel blockade in the Fyon population.

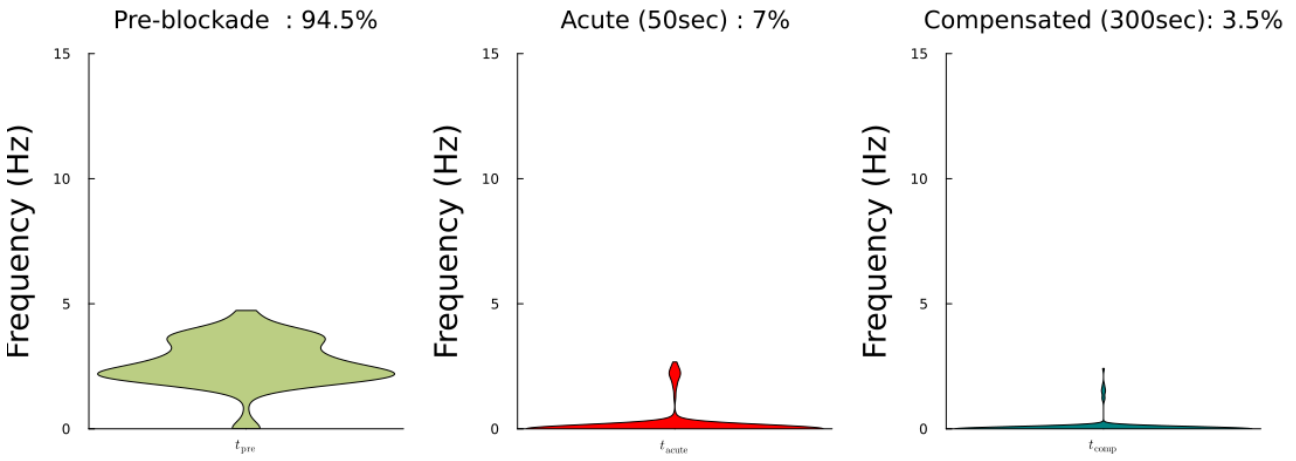

Figure 3: Evolution of firing frequency distributions before, immediately after, and following long-term compensation for $\bar{g}_{Pace}$ channel blockade in the Fyon population.