Master thesis : Modeling and dynamical analysis of dopaminergic neuron activity and its role in reward quantification

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Modeling and dynamical analysis of dopaminergic neuron activity and its role in reward quantification

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Abstract

Dopamine is a chemical released by the brain which has long been associated with the pleasant feeling that accompanies a reward. The neurons that release such chemical, called dopaminergic neurons, have therefore been the subject of research and study for years. In fact, understanding the behaviour of the neurons that drive the regulation of dopamine levels and their interactions with the other entities that compose the brain is necessary for the understanding of a larger entity called the reward circuit. This circuitry which drives multiple phenomenona such as motivation, emotions, etc. Impairment and alterations in the circuitry is also known to lead to psychiatric disorders and addiction.

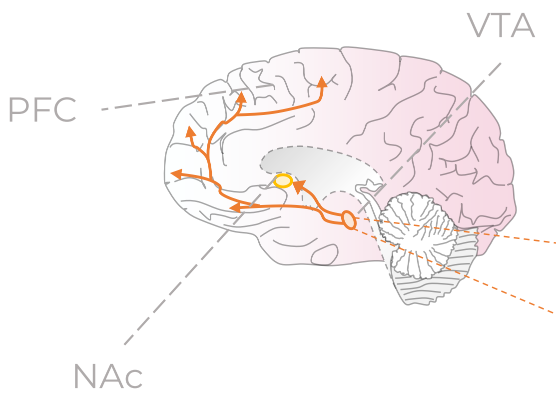
Dopaminergic neurons present a specific behaviour as they actually fire in different modes which are imbricated together. On one hand, when unsolicited, they fire at a slow and robust rate. On the other hand, when they are triggered, their frequency of firing increases which also increases the dopamine release. This variability allows to regulate the dopamine in the brain.

This thesis focuses on the study of a model developed by G. Drion on the dynamics of dopaminergic activity.

The first part of this thesis aims to reproduce experimental results that were obtained to validate the model. Using engineering tools such as model reduction and phase plane analysis, a deeper study of the dynamics of the model is performed in order to understand the mechanisms that drive the behaviour of the model.

As a second part, the aim is to use the model in order to develop a hypothesis on the regulation of the firing frequency of dopaminergic neurons according to physiological properties of the neurons and linking it to the quantification of reward in the brain.

Stucture and motivations



Understanding the dynamics of dopaminergic neurons in reward

Part 1 : Backgound

→ *Reward dopaminergic pathway*

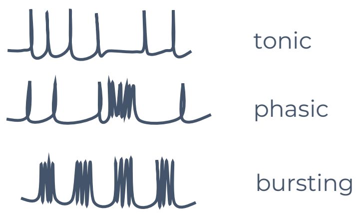
Nucleus accumbens (NAc), Prefrontal cortex (PFC) and Ventral Tengmental Area (VTA)

Components

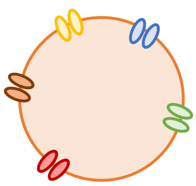
Addiction, depression,...

Implications

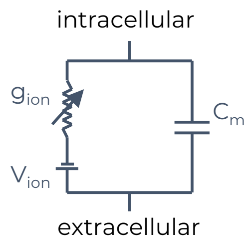
→ Focus on *Slow pacemakers* DA neurons



Firing patterns



Identifying main ionic currents



Modeling with conductance-based model

Part 2 : Experiments and reproduction of results

→ Focus on the role of SK channels and L-type calcium channels

Experiments

→ Computational reproduction

→ Dynamical analysis

→ Model validation

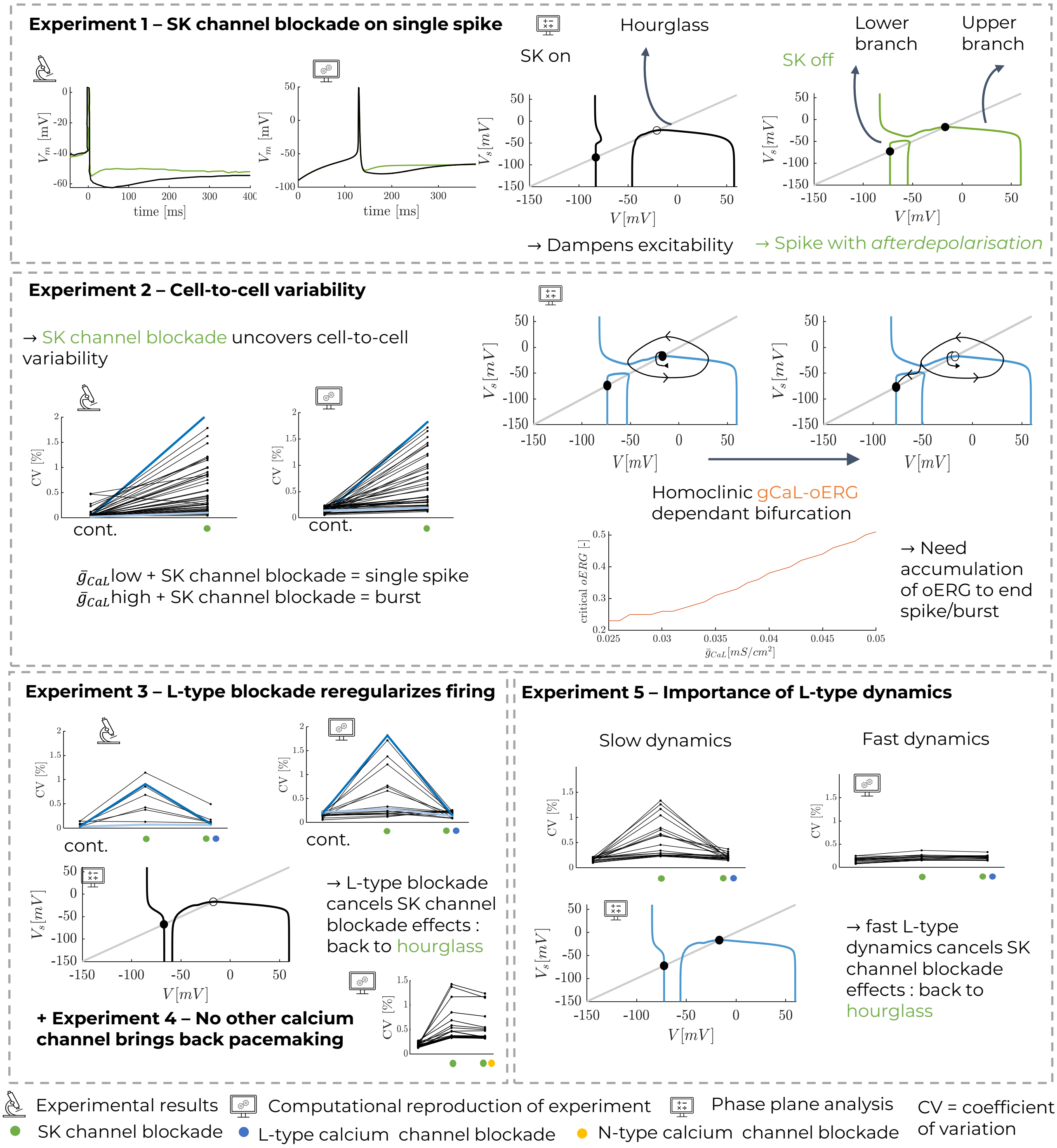
Part 3 : Effect of NMDA

→ NMDA is known to drive changes in firing for DA neurons. Effect of adding it to experiments of Part 2 ?

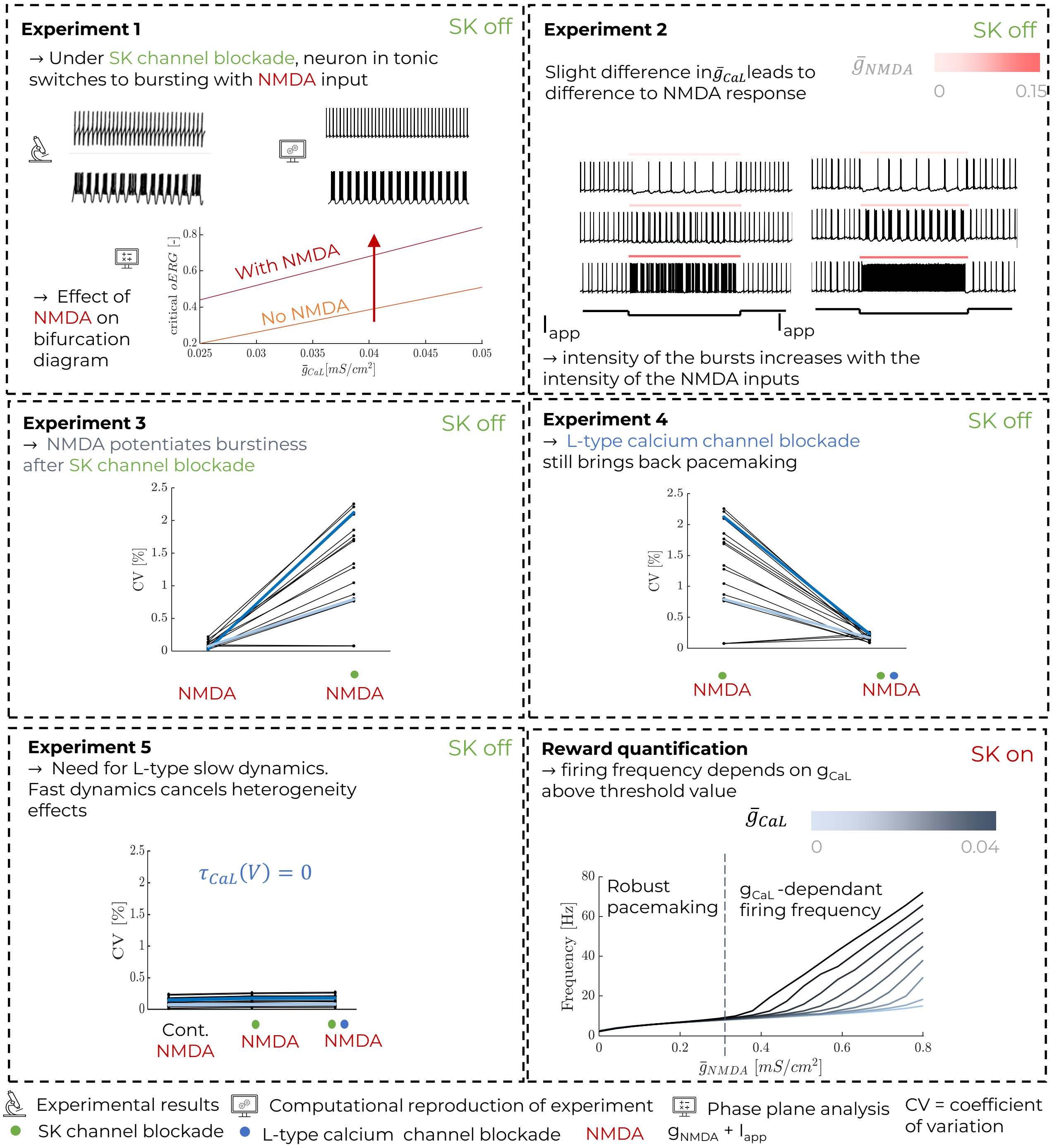
Computational simulation

→ Dynamical analysis

→ NMDA hypothesis of reward quantification



Experiment 1 – SK channel blockade on single spike
Hourglass
SK on
SK off
Lower branch
Upper branch
time [ms]
V [mV]
→ Dampens excitability
→ Spike with afterdepolarisation
Experiment 2 – Cell-to-cell variability
→ SK channel blockade uncovers cell-to-cell variability
cont.
$\bar{g}_{CaL}$low + SK channel blockade = single spike
$\bar{g}_{CaL}$high + SK channel blockade = burst
Homoclinic gCaL-oERG dependant bifurcation
critical oERG [-]
→ Need accumulation of oERG to end spike/burst
Experiment 3 – L-type blockade reregularizes firing
→ L-type blockade cancels SK channel blockade effects : back to hourglass
+ Experiment 4 – No other calcium channel brings back pacemaking
Experiment 5 – Importance of L-type dynamics
Slow dynamics
Fast dynamics
→ fast L-type dynamics cancels SK channel blockade effects : back to hourglass
Experimental results
Computational reproduction of experiment
Phase plane analysis
CV = coefficient of variation
SK channel blockade
L-type calcium channel blockade
N-type calcium channel blockade


Experiment 1
SK off
→ Under SK channel blockade, neuron in tonic switches to bursting with NMDA input
→ Effect of NMDA on bifurcation diagram
With NMDA
No NMDA
critical oERG [-]
Experiment 2
SK off
Slight difference in $\bar{g}_{CaL}$ leads to difference to NMDA response
$\bar{g}_{NMDA}$
0
0.15
I_{app}
I_{app}
→ intensity of the bursts increases with the intensity of the NMDA inputs
Experiment 3
SK off
→ NMDA potentiates burstiness after SK channel blockade
CV [%]
NMDA
NMDA
Experiment 4
SK off
→ L-type calcium channel blockade still brings back pacemaking
CV [%]
NMDA
NMDA
Experiment 5
SK off
→ Need for L-type slow dynamics. Fast dynamics cancels heterogeneity effects
$\tau_{CaL}(V) = 0$
CV [%]
Cont.
NMDA
NMDA
NMDA
Reward quantification
SK on
→ firing frequency depends on g_{CaL} above threshold value
$\bar{g}_{CaL}$
0
0.04
Robust pacemaking
g_{CaL} -dependant firing frequency
Frequency [Hz]
$\bar{g}_{NMDA}$ $[mS/cm^2]$
Experimental results
Computational reproduction of experiment
Phase plane analysis
CV = coefficient of variation
SK channel blockade
L-type calcium channel blockade
NMDA
g_{NMDA} + I_{app}