Computationally Modelling NMDA Blockages Within a Neural Network

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Introduction

The **N-Methyl-D-Aspartate (NMDA) Receptor** is fundamentally important to memory formation within the brain due to its control of calcium entry into the cell. When NMDA is "closed" due to magnesium bonding to the NMDA receptor, the calcium ions are blocked from entering the transmembrane ion channel, which affects **central nervous functions**. (1)

In recent years, there has been an increased interest in **long-term effects** of NMDA blockages on the brain, due to the "re-wiring" of communication channels (synapses) between neurons. An example of a NMDA-receptor antagonist (acts as a blocker of NMDA) is **Ketamine**, which is often used as an anti-depressant.

This project aims to **model the effects of drugs** such as Ketamine on the brain, and how the blocking of NMDA receptors affects firing rates, which can then be applied to studying **long-term plasticity within the neural hierarchies.**

Methodology

I utilized the Nest Simulator in Python to create a **50x50 2-D grid of neurons**, where 80% of the neurons were **excitatory** (with NMDA and AMPA synapses), leaving the other 20% to be **inhibitory** (with GABA synapses). To create my inhibitory neurons, I utilized python's built in random number generator to generate 500 random numbers between 1-25000. I then selected the neurons with those positions and turned their NMDA and AMPA receptor weights to 0.

For each trial, I ran the simulation for a total of 10000 milliseconds (ms), and the only neurons that had external stimuli were the neurons on the top row. They were randomly spiked at a rate of 50 hZ per second using a **Poisson generator**. All other spikes were generated from neuron to neuron.

All parameters stayed the same from trial to trial, except for the weight and duration of NMDA within the system.

Parameters

The connections between neurons are calculated using a **distance based gaussian probability**. (2)

d(x) = 0.005 + .08 *p(x)

$$p(x) = e^{-\frac{\frac{(x-\text{mean\_x})^2}{\text{std\_x}^2}+\frac{(y-\text{mean\_y})^2}{\text{std\_y}^2}+2\rho\frac{(x-\text{mean\_x})(y-\text{mean\_y})}{\text{std\_xstd\_y}}}{2(1-\rho^2)}}$$

std_x = .025 and std_y = .025,

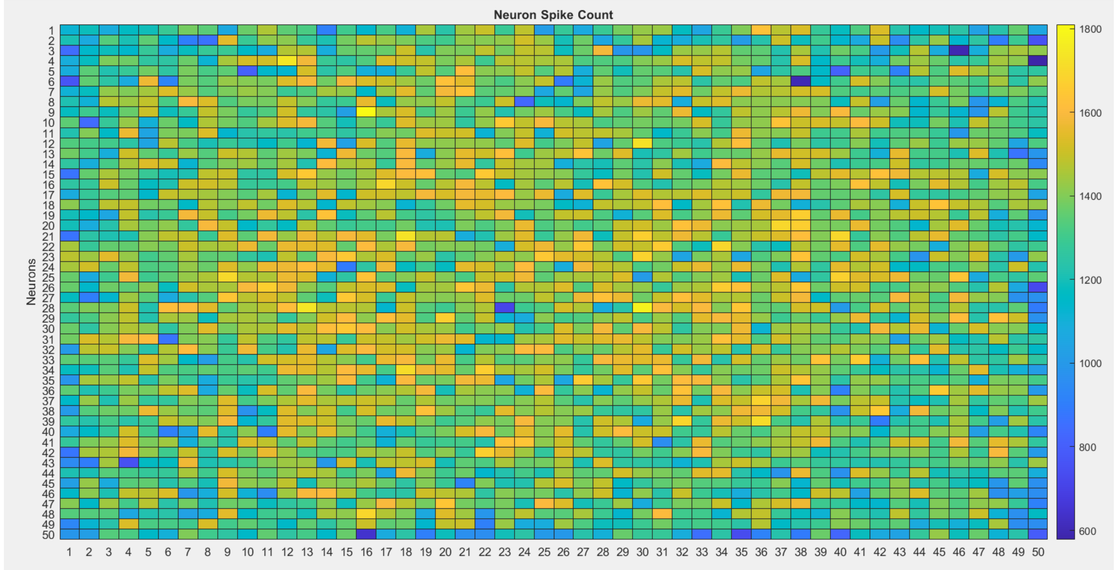
The **strength of synaptic input currents** between neurons are calculated using the same p(x), with variance between NMDA and AMPA parameters.

ampa_d(x) = 2 + 6 * p(x) with std_x = .25 = std_y
nmda_d(x) = 15 + 25 * p(x) with std_x = .25 = std_y

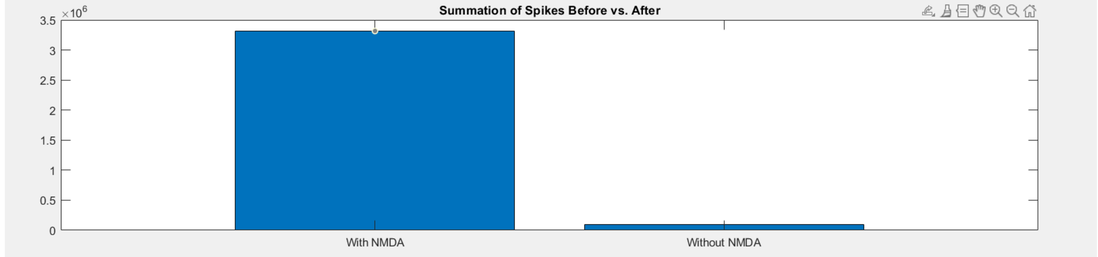
GABA synapses had a weight of -8.0 pico amperes (pA), and the spike generator had a weight of 40 pA.

Graphical Analysis of Pattern Formation (Firing Rates)

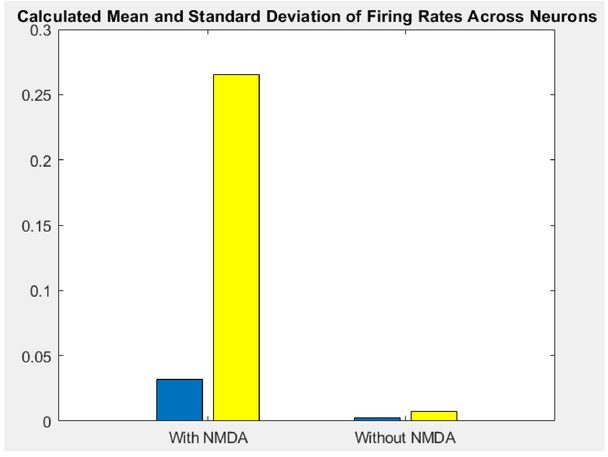
Total Spike Count Per Neuron over 10000 ms when NMDA was blocked at 5000 ms



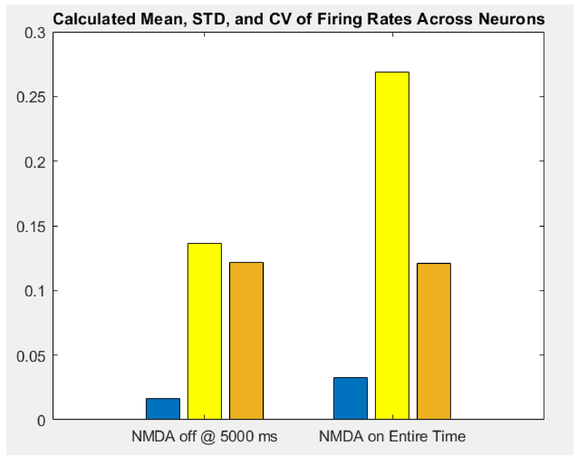
Difference in Total Spikes in System During First 5000 ms and Last 5000 ms



CV over 10000 ms total, NMDA cut off at 5000 ms



CV sim 1 vs sim 2



Results

Calculated **Coefficient of Variance (CV) of Firing Rate Across Neurons** = std(firingrate) / mean(firingrate), where the higher the CV, the more of a "pattern" emerges within the system. A lower CV means that the firing rate becomes more uniform (eventually **dying out**), with less "dips" and "bumps" within the system.

In this situation, the CV with NMDA is **smaller** than the CV without NMDA, but that can be explained by the low number of total spikes without NMDA.

CV w/ NMDA = .0320 / .2650 = .1207
CV w/0 NMDA = .0021 / .0072= .2917

Changes from Pre-Post

93.4375% decrease in STD
97.2830% decrease in mean firing rate

Spike Differences: Pre-Post: 97.26% decrease

3,302,962 in pre
90,499 in post

Future Goals

Now that a dependence has been shown between NMDA receptors and firing rates of neurons, future goals include:

- Modelling **long-term plasticity**
  - Investigating different **models, parameters, and source code** within NEST to eventually create a model to best show the goals
- Modelling the effects of NMDA blockages using drugs such as Ketamine to understand how **short-term effects can be created and applied long-term**
- Understanding how Ketamine and other NMDA blockers **change communication channels** within a neural network
- Furthering a **deeper understanding** of the Nest Simulator

Acknowledgements and References

Mark Lyon – Advisor

(1) Jewett, B. E., & Thapa, B. (2022, December 11). *Physiology, NMDA Receptor*. PubMed; StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK519495/

(2) Terhorst, D., Zajzon, B., Vogelsang, J., Korcsak-Gorzo, A., Lober, M., Espinoza Valverde, J. A., Rechl, M., Jiang, H.-J., Linssen, C., Kunkel, S., Graber, S., Müller, E., Trensch, G., Skaar, J.-E. W., Mitchell, J., Spreizer, S., Benelhedi, A., Serenko, A., Lee, A. Y., … Plesser, H. E. (2025). NEST 3.9. Zenodo. https://doi.org/10.5281/zenodo.17036827