# Modeling the effect of clozapine on firing rates of dopaminergic neurons in the midbrain

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## Introduction

- **Schizophrenia** is a mental disorder that causes psychosis, abnormal thinking, and strong emotions.
- **Elevated dopamine levels** in the midbrain have been linked to schizophrenia.

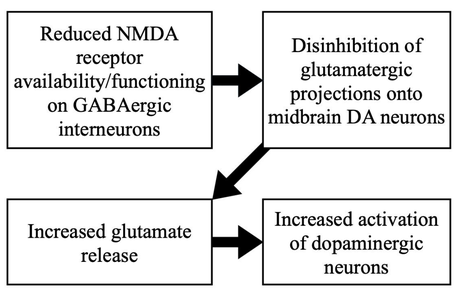



**Figure 1.** Dopamine dysregulation in schizophrenia (Howes et al., 2015, *Journal of Psychopharmacology*).

- **Clozapine (Fig. 2)** is an atypical antipsychotic used to treat schizophrenia in patients with severe symptoms who have not responded to other medications.

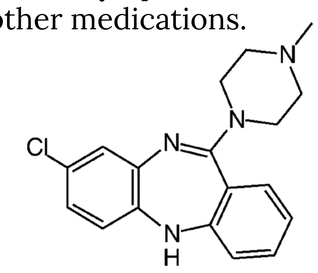


**Figure 2.** Chemical structure of clozapine (Choi et al., 2009, *European Journal of Pharmacology*).

- The drug mechanism works by **inhibiting** both serotonin 5-HT2A receptors and **dopamine receptors**, specifically D2 and D4.
- Clozapine is also known to activate **N-methyl-d-aspartate (NMDA) receptors**, which are essential for health brain function.
- This research focuses primarily on how clozapine regulates **dopaminergic (DA)** neurons in the **basal ganglia**, which is located in the midbrain.
- Though DA neurons and their correlation with schizophrenia have been investigated in previous studies, there has been little research into modeling the effects of clozapine on DA neurons.

### Important Terms:

- A series of recorded times at which a neuron spikes and fires an action potential is called a **spike train**.
- **Synaptic weight** is a measurement of how much influence the firing of one neuron has on another neuron.
- **Fast-Fourier Transforms (FFT)** is a method of describing signals in relation to frequency, rather than time.

## Methods

- We updated a model **(Fig. 3)** that simulates the **firing frequency of a** substantia nigra pars compacta **DA neuron** in the midbrain.
  - The single cell model is composed of a soma connected to 4 proximal dendrites, which are each connected to 2 distal dendrites.
- Constant spiking patterns were applied to inhibitory and excitatory synapses while bursting patterns were only applied to excitatory synapses on the soma and dendrites.
  - The synapses are connected with **NMDA** and **AMPA receptors**.

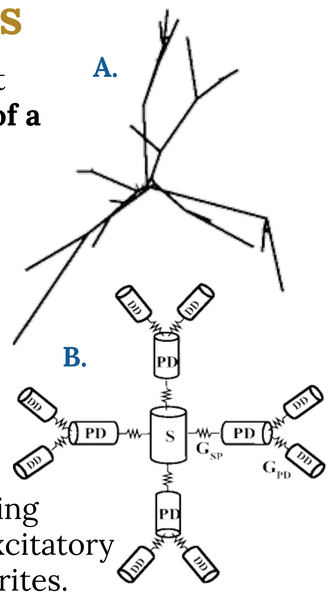



**Figure 3.** A. Neuron rendered by NEURON. B. Schematic model (Kuznetsova et al., 2010, *Journal of Computational Neuroscience*).

- We created a **spike train** with bursting and constant patterns connected to inhibitory and excitatory synapses using the synaptic weights defined above.
- As a result, synaptic current was lowered, which resulted in the DA neuron having **different spiking patterns**, showing how clozapine affects the neuron's behavior.
- To emulate clozapine's mechanism of action, we **adjusted the synaptic weight** (both burst and constant) of the DA neuron based on designated clozapine doses.

$$synweight_c = synweight_b * (1 - clozapine)$$

For burst synaptic weight:

$$synweight_b = 0.75$$

For constant synaptic weight:

$$synweight_b = 0.2$$

| Clozapine dosage (mg) | Burst synweight$_c$ | Constant synweight$_c$ |
|---|---|---|
| 900 | 0.01 | 0.01 |
| 600 | 0.25 | 0.066 |
| 300 | 0.5 | 0.132 |
| 150 | 0.63 | 0.168 |

**Figure 4.** Burst synaptic weight and constant synaptic weight adjusted for specific clozapine doses.

## Discussion/ Conclusions

- By simulating a known mechanism of action that leads to less excitatory dopamine levels, this model provides **insight** into the **effectiveness of clozapine** for treatment-resistant schizophrenia.
  - Based on our data, **increasing doses** of clozapine led to **greater constant firing** within an extended range of time.
    - 900 mg (max. dosage): constant firing for 2000 ms
    - 600 mg (high dosage): high frequency of constant; bursts at 2700 ms and 3000 ms
    - 300 mg (standard dosage): constant firing paired with bursts
    - 150 mg (low dosage): closest to control with rapid burst firing
- Further, during burst firing, **membrane potential is elevated** compared to our control data.
- FFT data shows lower doses of clozapine creates increased amounts of slower frequency data.

### Limitations:

- One limitation of this model is that it assumes all channels and pumps are **evenly distributed** along the neuron.
- The model we based our research on is of a healthy DA neuron, **not a schizophrenic cell**. As a result, our results operate under the assumption that a schizophrenic cell would fire similarly to a healthy cell.
- Clozapine units are not well-defined given that our conversion was somewhat arbitrary.
- The 600mg data point does not follow the general trend in our FFT data.

### Future Research:

- Future studies can apply this method to simulate the effect of **different antipsychotics** on receptors in midbrain DA neurons.
- Clozapine also binds at **α-adrenergic, muscarinic, and histamine receptors**. As a result, clozapine's impact on neurons through these receptors can also be modelled and studied.
- Modelling calcium currents in dopaminergic neurons in relationship to antipsychotic drugs can be studied.

## Results

### Control:

**Figure 5.** Neuron firing rate without clozapine.

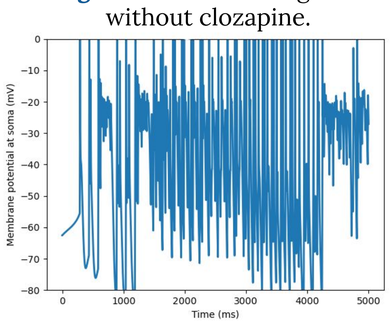
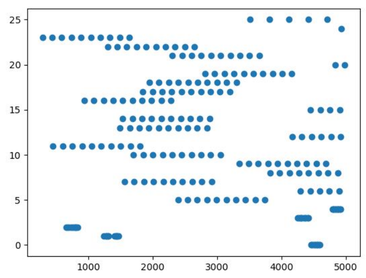



**Figure 6.** Upstream stimulation spike train.



### With Clozapine:

**Figure 7.** Neuron firing rate (left) and FFT (right) with 900 mg clozapine.

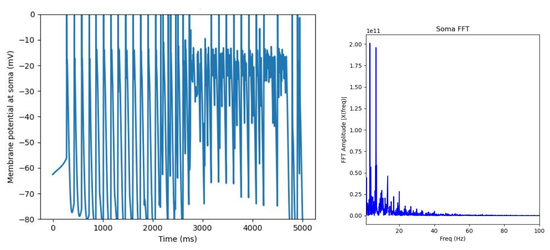



**Figure 8.** Neuron firing rate (left) and FFT (right) with 600 mg clozapine.

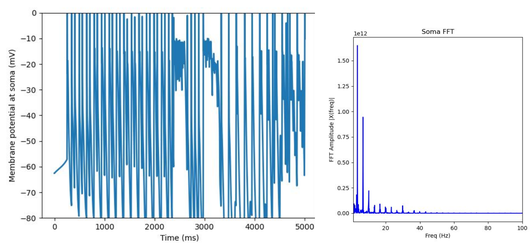



**Figure 9.** Neuron firing rate (left) and FFT (right) with 300 mg clozapine.

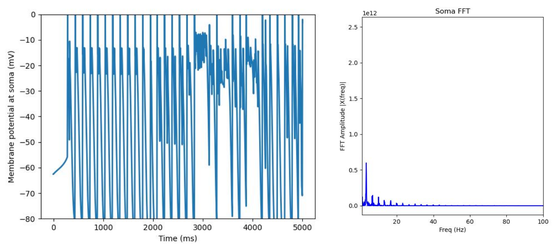
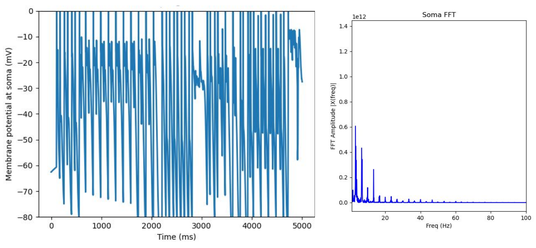



**Figure 10.** Neuron firing rate (left) and FFT (right) with 150 mg clozapine.




## References

1. Chiodo, L. A., & Bunney, B. S. (1985). Possible mechanisms by which repeated clozapine administration differentially affects the activity of two subpopulations of midbrain dopamine neurons. *The Journal of Neuroscience*, 5(9), 2539–2544. https://doi.org/10.1523/jneurosci.05-09-02539.1985
2. Howes, O. D., Williams, M., Ibrahim, K., Leung, G., Egerton, A., McGuire, P. K., & Turkheimer, F. (2013). Midbrain dopamine function in schizophrenia and depression: A post-mortem and positron emission tomographic imaging study. *Brain*, 136(11), 3242–3251. https://doi.org/10.1093/brain/awt264
3. Kuznetsova, A. Y., Huertas, M. A., Kuznetsov, A. S., Paladini, C. A., & Canavier, C. C. (2010). Regulation of firing frequency in a computational model of a midbrain dopaminergic neuron. *Journal of Computational Neuroscience*, 28(3), 389–403. https://doi.org/10.1007/s10827-010-0222-y. These network models used in the present study were obtained from ModelDB (accession number 127507).
4. Subramanian, S., Völlm, B. A., & Huband, N. (2017). Clozapine dose for schizophrenia. *Cochrane Database of Systematic Reviews*, 2017(6). https://doi.org/10.1002/14651858.cd009555.pub 2

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