Modeling the Effects of Buprenorphine during Morphine Withdrawal in Ventral Tegmental Area Dopamine Neurons

Lawrence Long[1, 5], Aiden Kim[2, 5], Luke Shao[3, 5], Oviya Kalaivanan[4, 5], Andrew Looka[5], Marianne Bezaire[5]

BASIS Independent Silicon Valley, 1290 Parkmoor Ave, San Jose, CA 95126[1]; Okemos High School, 2800 Jolly Rd, Okemos, MI 48864[2]; West Windsor-Plainsboro High School North, 90 Grovers Mill Rd, Plainsboro, NJ 08536[3]; Indus International School, Sarjapur- Attibele Rd, Bangalore, KA 562125[4]; Boston University, Boston, MA 02215[5]

Introduction

- Opioids, including morphine (MOR), are an addictive class of drugs that act on the brain's opioid receptors, causing sedation, euphoria, drowsiness, nausea, slowed breathing, and more.
- The ventral tegmental area (VTA) of the midbrain is responsible for producing and sending dopamine (DA) to other parts of the brain through dopaminergic neurons. It is a key part of the brain's reward system, and contributes to the development of drug addiction.
- Buprenorphine (BUP) is a partial opioid agonist that has high-affinity binding to μ-opioid receptors. It is used for the treatment of severe opioid addiction and leads to milder withdrawal symptoms for the patient.

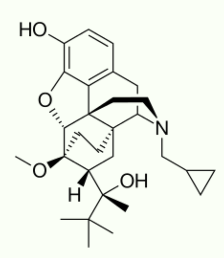


Fig. 1 Molecular structure of BUP.

- We explored the effects of BUP and MOR on the firing patterns and DA output of a VTA neuron undergoing withdrawal.

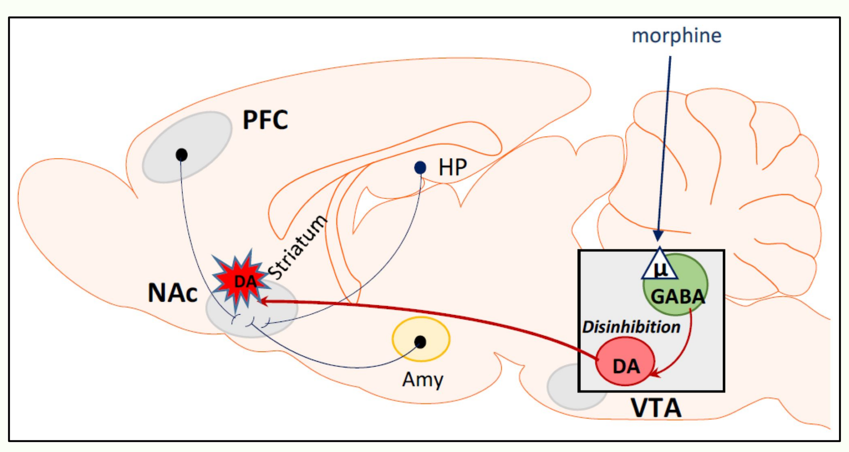


Fig. 2 Mechanisms of morphine induced rewarding effects. MOR inhibits GABA, which disinhibits DA.

Methods

1 **VTA DA Neuron Model**. We modified a NEURON model[1] of a single VTA DA releasing cell. Model cell stimulation resulted from the random activation of the excitatory inputs on second-order dendrites. The simulation models 10 seconds of neuronal activity.

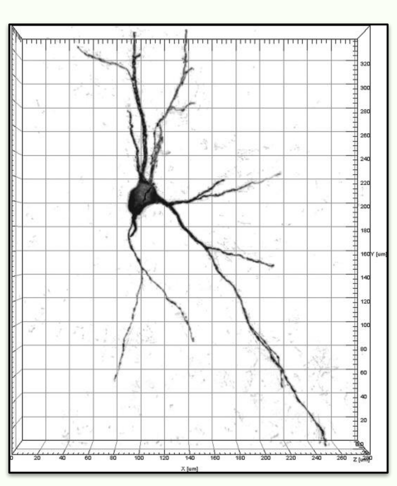


Fig. 3 Morphology of VTA neuron used in model.

2 **Simulations**. We ran simulations of the model for control withdrawal conditions, withdrawal plus morphine (-46% GABA, +30% GLU) and withdrawal plus buprenorphine (+47% GABA, +57% GLU). We measured firing patterns and dopamine output. We repeated the simulation 10 times for each condition with a different random seed relating to model cell stimulation.

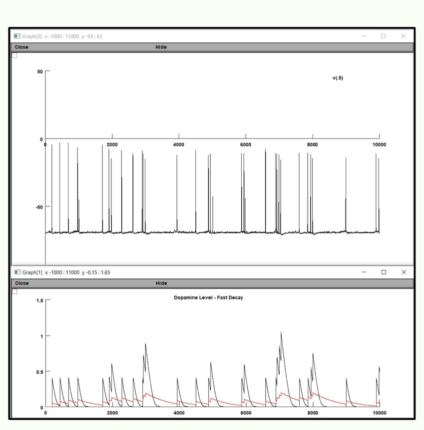


Fig. 4 Sample firing rate and DA output graphs obtained from the NEURON GUI. We re-graphed our simulation data using matplotlib in Python.

3 **Data Analysis**. We wrote our own python code to count single spikes, burst firing, spikes/burst, and DA output over the 10s simulation for all three conditions. We used a t-test to infer the significance of the differences in these four variables for the three conditions.

Results

Firing Rates and Dopamine Release of Withdrawal Neurons

Fig. 5 Withdrawal Neuron, Firing Rate over Time

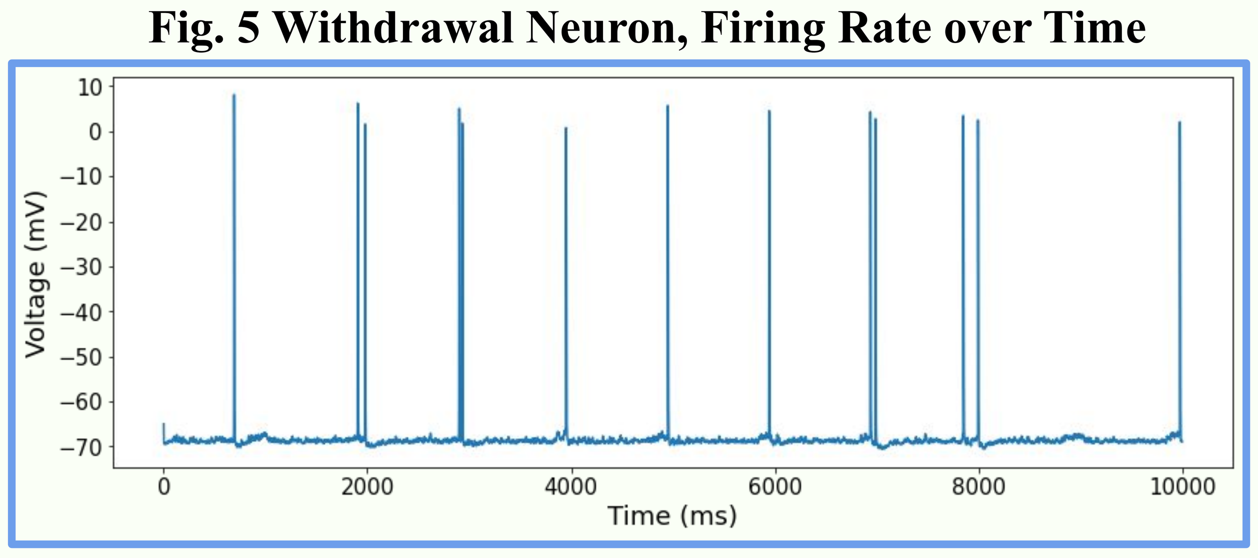


Fig. 6 Withdrawal Neuron with MOR, Firing Rate over Time

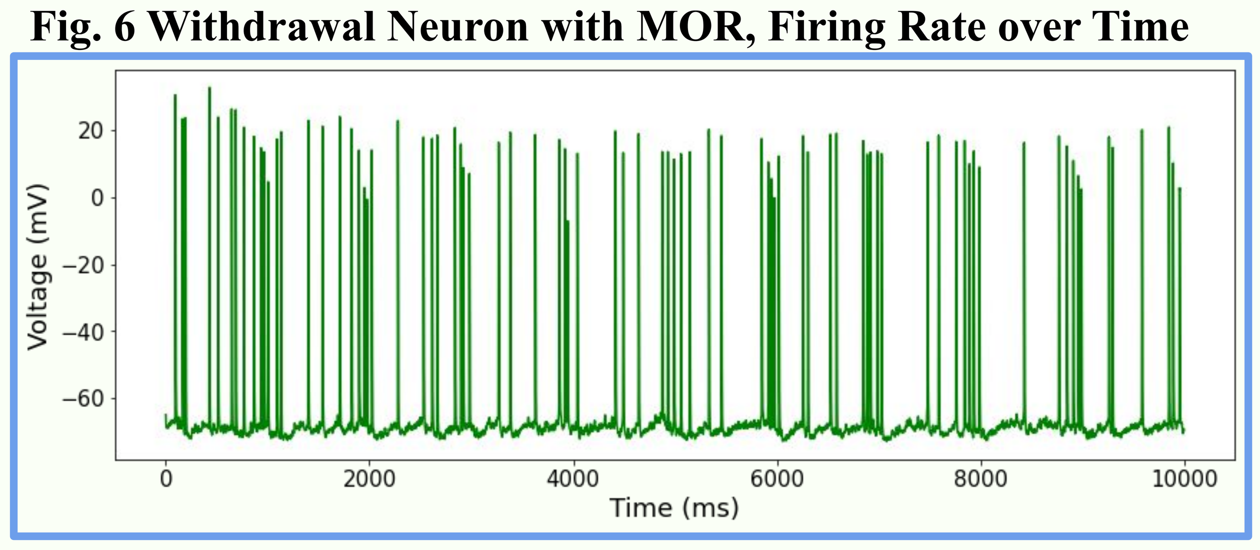


Fig. 7 Withdrawal Neuron with BUP, Firing Rate over Time

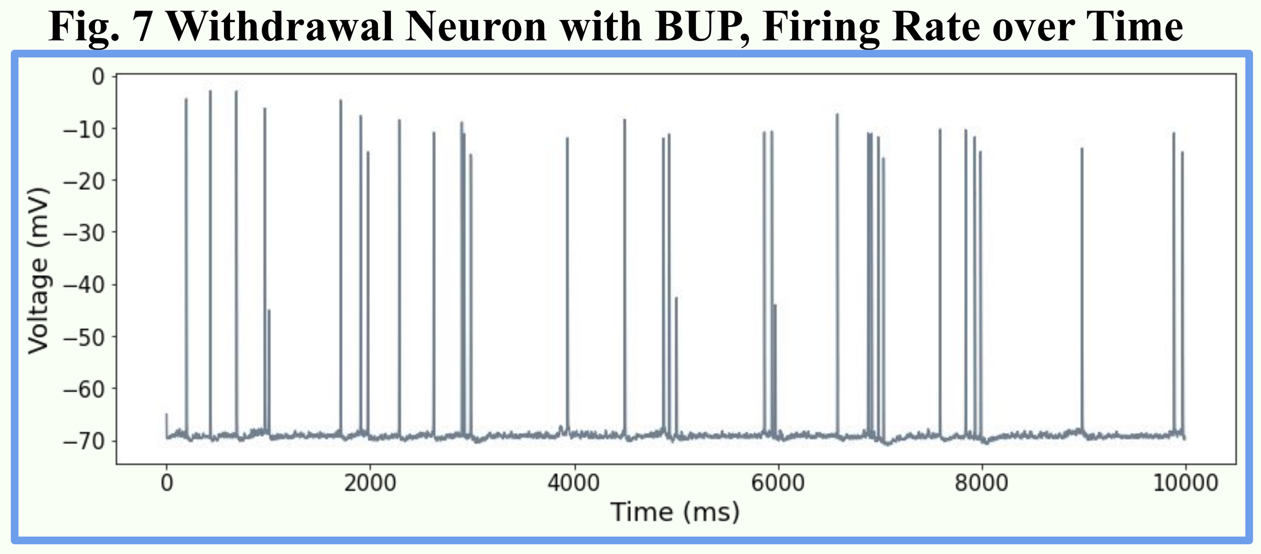


Fig. 8 Withdrawal Neuron, DA Release over Time

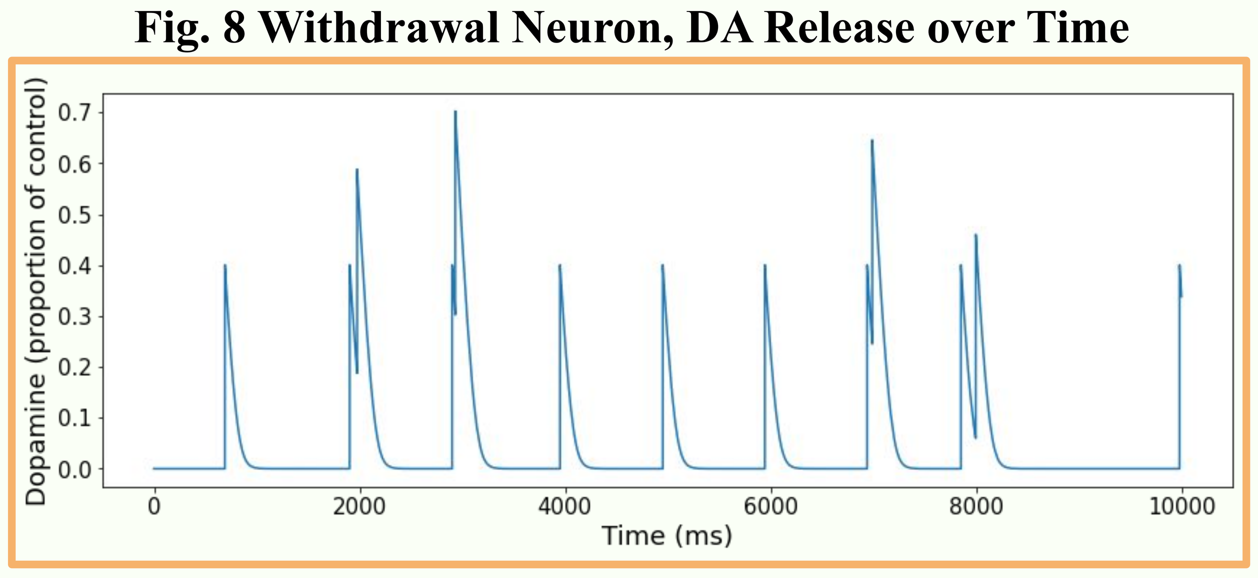


Fig. 9 Withdrawal Neuron with MOR, DA Release over Time

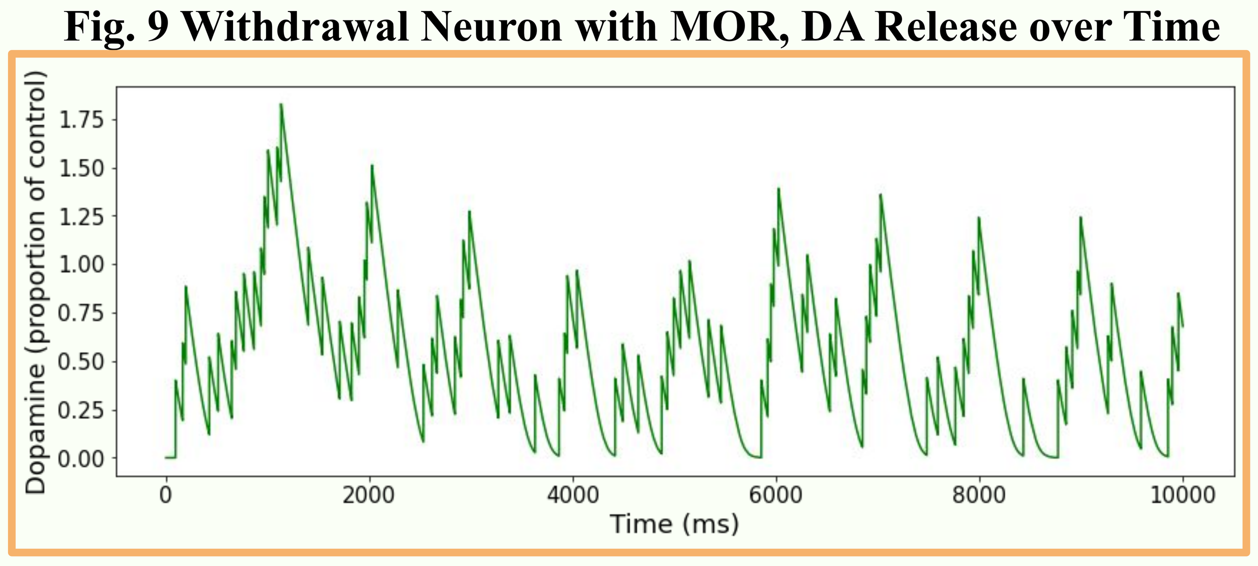
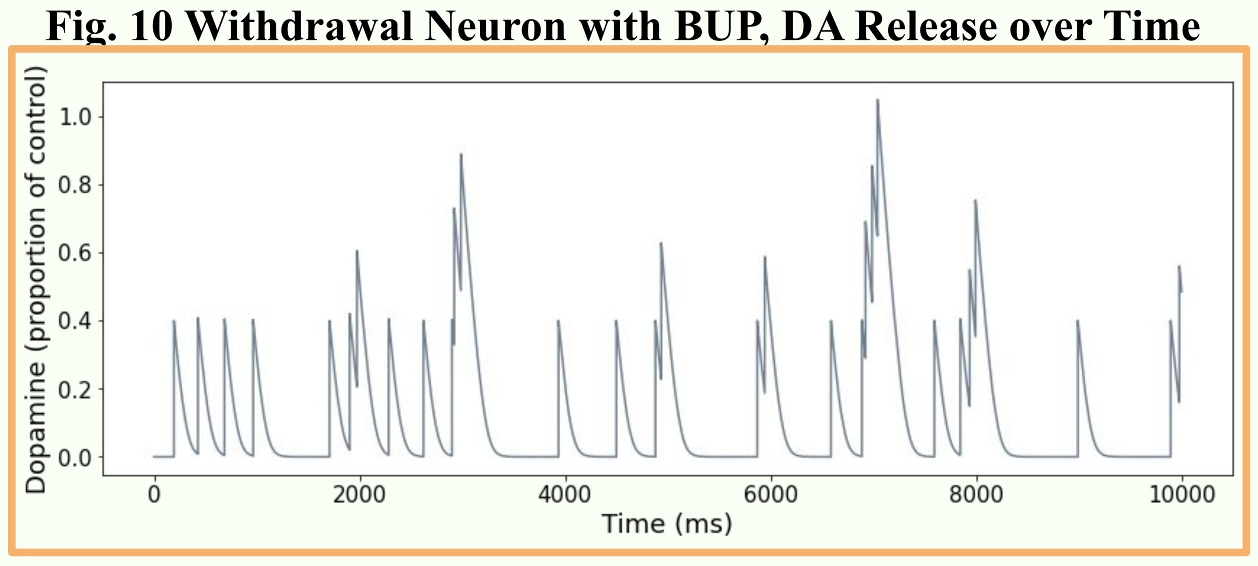


Fig. 10 Withdrawal Neuron with BUP, DA Release over Time

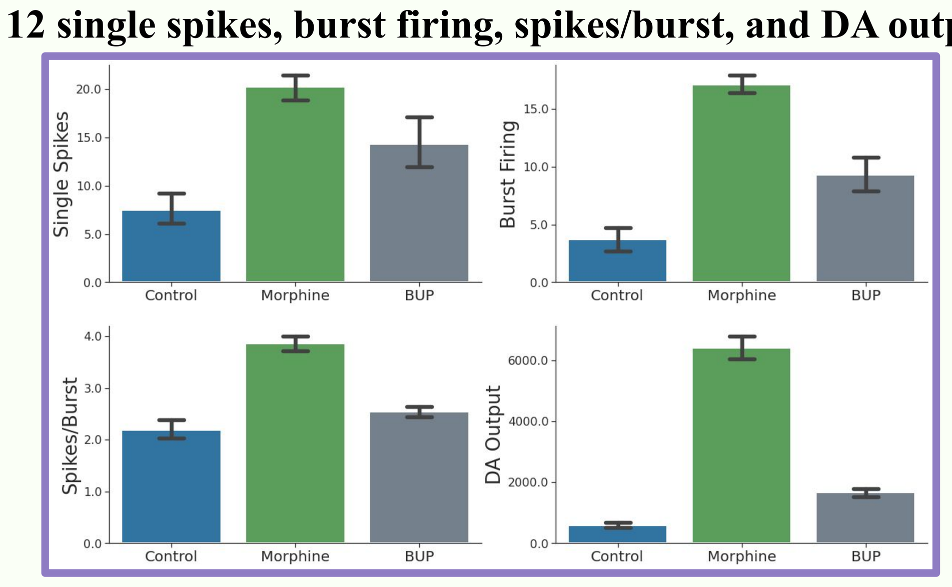


Categories	Single spikes	Bursts	Spikes / burst	DA output
Control vs Morphine	1.18e-9	0	1.14e-10	0
Control vs BUP	5.89e-4	1.504e-5	5.93e-3	1.98e-10
Morphine vs BUP	1.38e-3	6.34e-8	0	0

Fig. 11 P-value table for each test group. $p<0.05$ = statistically significant

Discussion & Conclusions

Fig. 12 single spikes, burst firing, spikes/burst, and DA output



Conclusion

- Based on our model, administering BUP to a VTA neuron undergoing morphine withdrawal significantly increases single spikes, burst firing, spikes/burst, and DA output as compared to a control cell undergoing withdrawal. However, this increase is only intermediate to the levels reached by morphine administration to a VTA DA cell undergoing withdrawal.
- These results support the current use of BUP as a morphine addiction treatment helping relieve the symptoms of morphine withdrawal.

Discussion

- To the extent of our knowledge, this is the first attempt to model the effects of an opioid agonist on a VTA DA neuron.
- By providing a quantitative method of the effects of buprenorphine, our model could support the development of more personalized doses for different stages of morphine withdrawal.

Limitations & Future Work

- GABA and GLU were the two parameters modified in our model. While GABA and GLU have the largest effects on VTA activity, research suggests that other neurotransmitters such as acetylcholine may also have a noticeable impact.
- As more research emerges about the mechanisms behind opioid addiction, this model can serve as a base to study withdrawal, addiction, and existing/future treatments.

References

1. Enrico et al., (2016). Morphofunctional alterations in ventral tegmental area dopamine neurons in acute and prolonged opiates withdrawal. A computational perspective. Neuroscience, 322, 195-207. https://doi.org/10.1016/j.neuroscience.2016.02.006
2. Xhakaza et al., (2021). Alterations in neurotransmitter levels and transcription factor expression following intranasal buprenorphine administration. Biomedicine & Pharmacotherapy, 138, 111515. https://doi.org/10.1016/j.biopha.2021.111515
3. Yang, L., et al, (2020). Morphine selectively disinhibits glutamatergic input from mPFC onto dopamine neurons of vta, inducing reward. Neuropharmacology, 176, 108217. https://doi.org/10.1016/j.neuropharm.2020.108217
4. Kosten, T. R., & George, T. P. (2002). The neurobiology of opioid dependence: implications for treatment. Science & practice perspectives, 1(1), 13–20. https://doi.org/10.1151/spp021113

Acknowledgements

We would like to thank Dr. Marianne Bezaire and Andrew Looka for their unparalleled guidance throughout this project. Special thanks to Kaitlyn Dorst for leading us through foundational neuroscience content, and our parents for their continuous support. Finally, we would like to thank Boston University and the RISE staff for making making this research opportunity possible.