Computationally Simulating Opioid-Induced Alterations in VTA–NAc Circuits: A Hybrid Biophysical-Reinforcement Model of Reward Prediction Error

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Introduction

Mesolimbic Pathway

- Regulates reward processing in the brain
- Signal generation in the Ventral Tegmental Area (VTA) regulates the release of dopamine into the Nucleus Accumbens (NAc) through a cascade of dopaminergic excitatory and inhibitory neurons

Opioids

- Modulate activity in the mesolimbic pathway
- Bind to Mu/μ Opioid Receptors (MORS), inhibiting gamma-aminobutyric acid (GABA) release throughout the pathway, in turn disinhibiting dopamine release in VTA and NAc dopaminergic neurons
- Increased dopamine release in VTA, causing a neuron firing chain resulting in increased dopamine in NAc

Dopamine Dynamics

- Dopamine levels in the mesolimbic pathway are tightly regulated by the body
  - Dopamine is cleared from synapse with dopamine transporter-mediated reuptake through negative feedback

Reward Prediction Error (RPE)

- Measurement of the difference between the expected and actual reward, taking into account time as a third variable; physically processed in the NAc
- Approaches zero as brain matches expected with actual

Objectives

- Simulate a hybrid biophysical and reinforcement learning model based on existing research and literature
- Portray opioid-induced biological and behavioral changes in the mesolimbic pathway in the brain

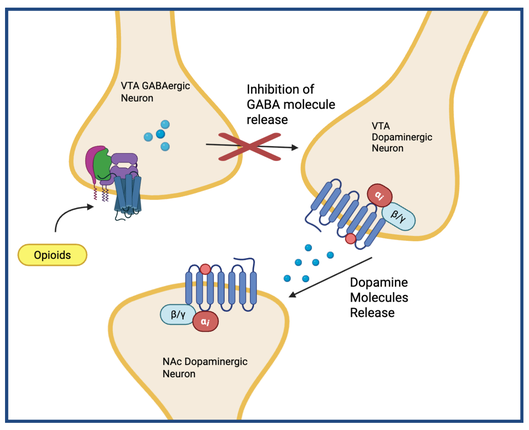

Fig 1. Opioid binding inhibits GABA molecule release, increasing dopaminergic release from VTA to NAc dopaminergic neurons,

Methods

Biophysical Model

- 100 simulated neurons (50 VTA, 50 NAc) in NEURON framework
- Membrane Dynamics Equation

$$C_m \cdot \frac{dV}{dt} = -\Sigma I_{ion} - I_{syn} + I_{ext}$$

  - C_m = membrane capacitance, dV/dt = rate of voltage change, and I = current
  - Neuron's membrane potential (V) changes over time due to ionic, synaptic, and external currents. Through variations of this equation, we simulated NAc and VTA neurons.
  - High membrane potential trigger neuron activation and dopamine release
- Opioid to MOR binding reduces GABAergic Voltage/GABA release
- Output: Dopamine release
  - Synaptic and extrasynaptic DA (Dopamine) pools with distinct kinetics
  - Negative feedback modulation; inhibit further dopamine release

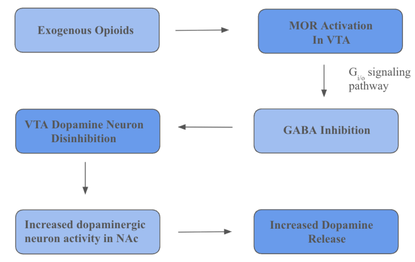

Fig 2. Flow chart of the Biophysical Model

Reinforcement Learning (RL) Model

$$\delta_t = r_t + \gamma V(S_{t+1}) - V(S_t)$$

$r_t \rightarrow$ actual reward received at time t,

$\gamma \rightarrow$ discount factor $(0 \leq \gamma \leq 1)$,

$V(S_{t+1}) \rightarrow$ estimated value of the next state,

$V(S_t) \rightarrow$ estimated value of the current state.

$t \rightarrow$ individual time steps

- PyTorch framework for model support
- TD (Temporal Difference) Learning
  - At each timestep, the reward processing error δ_t is updated using temporal-difference learning, taking into account previous predictions and the actual reward
- Dopamine levels from previous biophysical simulation fed into model as input
- Output: Reward Prediction Error/RPE

Results

Part 1: Biophysical Model Output

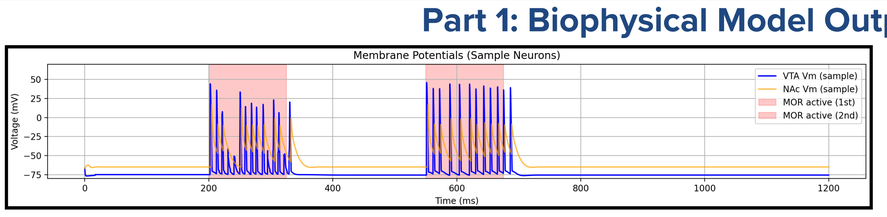

Fig 3. Membrane potential recordings from 50 sample VTA and 50 sample NAc neurons during the MOR-active period (200-325 ms and 550-675 ms), with VTA neurons exhibiting characteristic burst firing patterns.

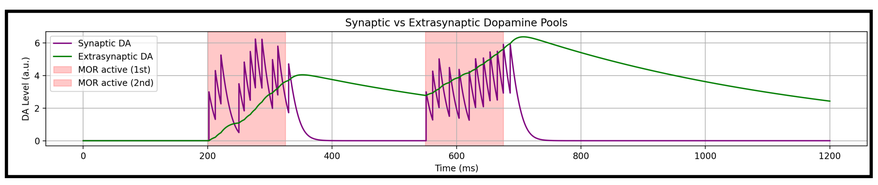

Fig 4. Corresponding synaptic and extrasynaptic dopamine levels, showing elevated DA release that peaks during the MOR-active periods and slowly returns to baseline.

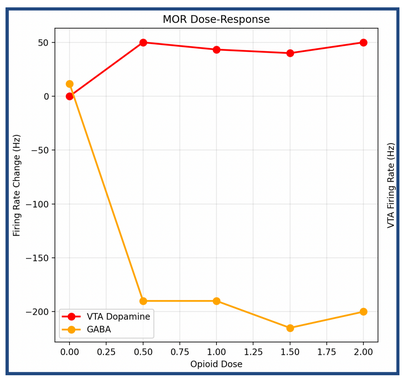

Fig 5. MOR activation corresponding to heightened opioid concentration levels. VTA dopamine increases, whereas GABA levels decrease.

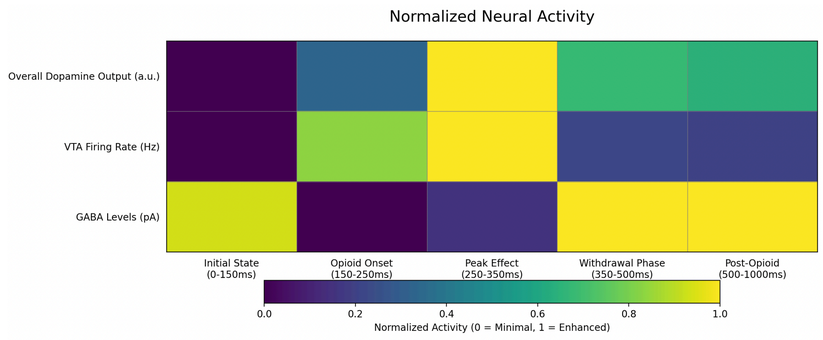

Fig 6. Activity states of GABA levels in post synaptic space, VTA firing, and dopamine release, split by phases. High GABA levels leads to low VTA firing and dopamine output. Low GABA levels activity stimulates VTA firing activity, which consequently leads to high dopamine output.

Part 2: Reinforcement Learning Output

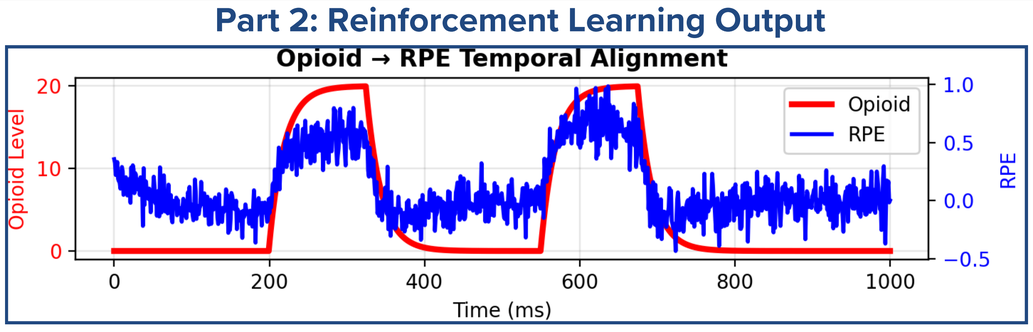

Fig 7. Opioid and RPE levels in the body with arbitrary units. RPE displays a sharp increase in response to opioid injection from approximately the 200-325 ms and 550-675 ms ranges.

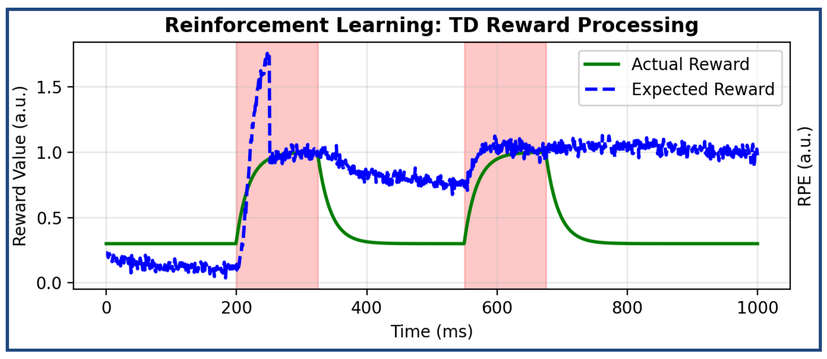

Fig 8. Actual and expected rewards upon consuming opioids. The brain undergoes a sharp increase in reward during the 200-325 ms and 550-675 ms time stamps due to indirect opioid triggering of dopaminergic neurons. The brain expects additional reward after initial opioid consumption due to the previous actual experienced reward.

Discussion

Conclusions

- The biophysical model found that, during the MOR activation period, there were:
  - Elevated VTA and NAc dopaminergic neuron amplitude and rate of firing levels
  - Increased synaptic and extrasynaptic dopamine release
- RL model showcased how increased MOR and dopaminergic activity leads to:
  - An immediate increase in expected reward perception
  - A positive RPE, triggering a desire for more opioid consumption

Applications

- Potential development of pharmacological interventions targeting specific components of the pathway or modeled biological mechanisms
- Our model helps explain how opioids distort reward processing through the mesolimbic pathway, encouraging future opioid consumption
- Further development of this model could help personalize strategies for individual differences in opioid levels, dopaminergic activity, or RPEs

Limitations/Future Steps

- A one to one correlation between opioid levels and "actual reward" levels is not accurate
  - The actual correlation is more complex
- Low quantity of neurons
  - Our models work with merely 100 neurons, which does not reflect the ~100 billion neurons in the human brain
  - A general influx of opioids into the simulation was the input
    - The model does not utilize a specific class of opioids: different opioids will likely have diverse effects on RPE
  - Not all human behavioral aspects were accounted for
    - Other factors affecting mesolimbic pathway and RPE
- Baseline data does not reflect natural levels of opioids and normal dopaminergic neuron firing in a healthy individual

References

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