# Mechanistic Modeling of Neuropeptide Release in Line Attractor Networks

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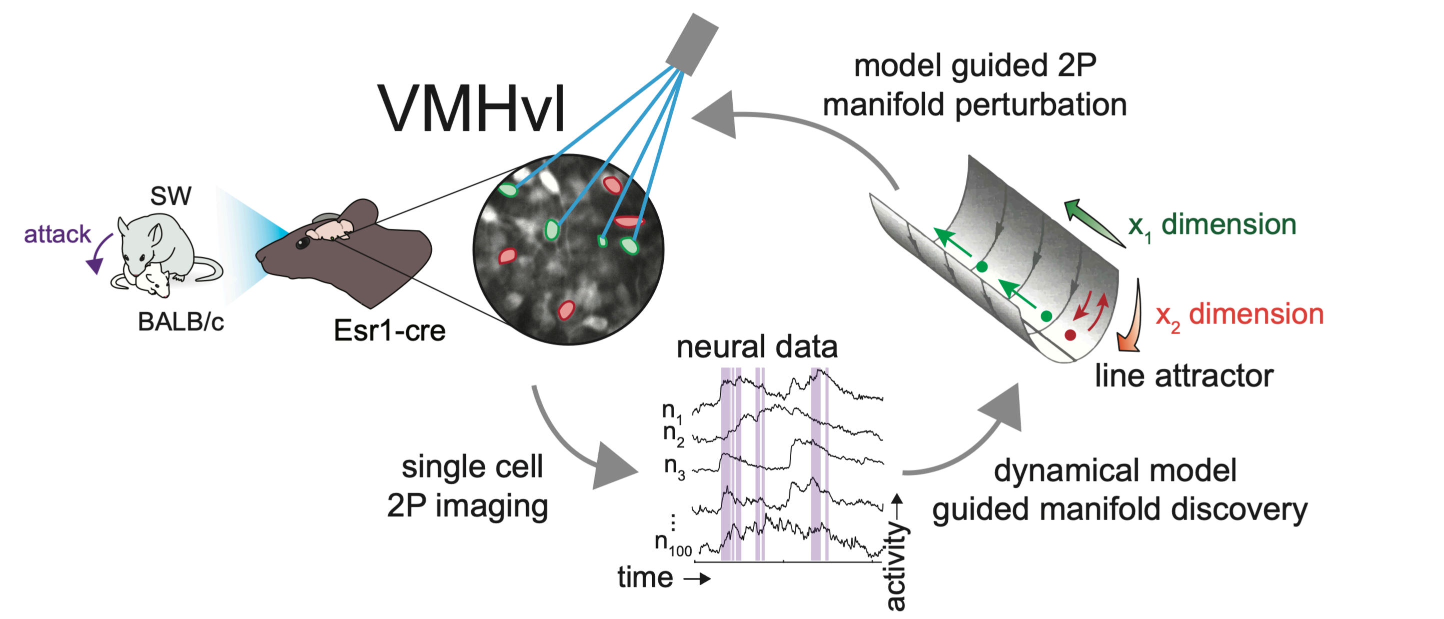
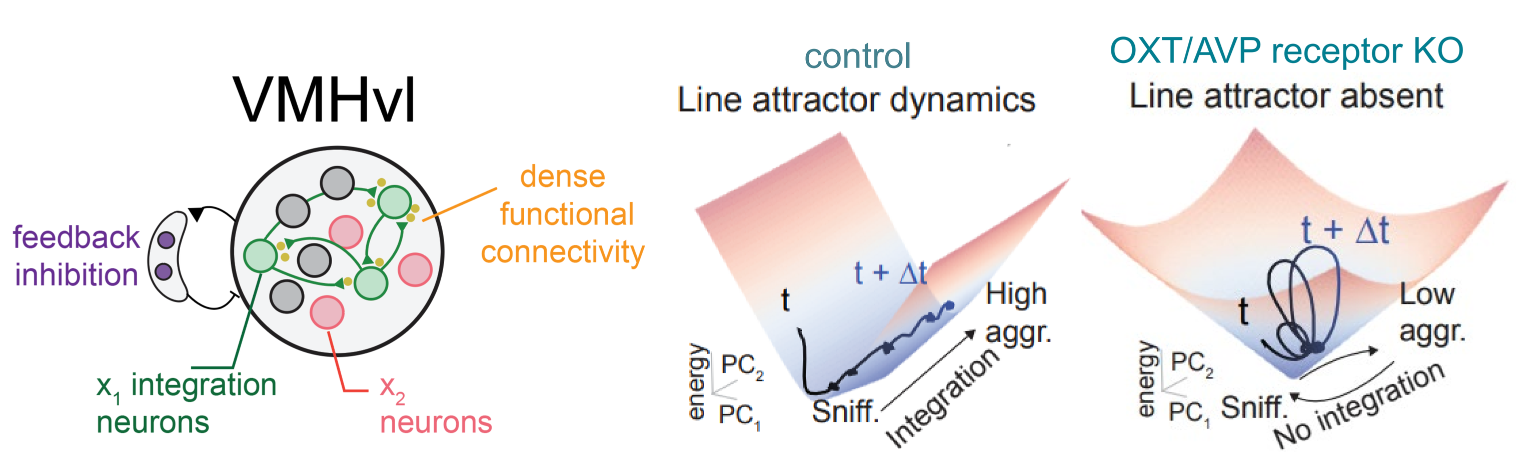
## Background: line attractor networks




The Anderson Lab studies the neural basis of emotions, particularly aggression. Emotions are scalable and persistent, with the hypothalamus regulating innate social behaviors like aggression.[1] In the ventromedial hypothalamus (VMHvl), a dynamic landscape reveals a trough that functions as a line attractor for aggression. This approximate line attractor keeps neural activity within the trough during aggressive behavior, with movement along the trough corresponding to escalating aggressive actions, from sniffing to dominant mounting, culminating in an attack.[1]

## Paradox in Neuropeptide Release




VMHvl possesses dense functional connectivity

vs.

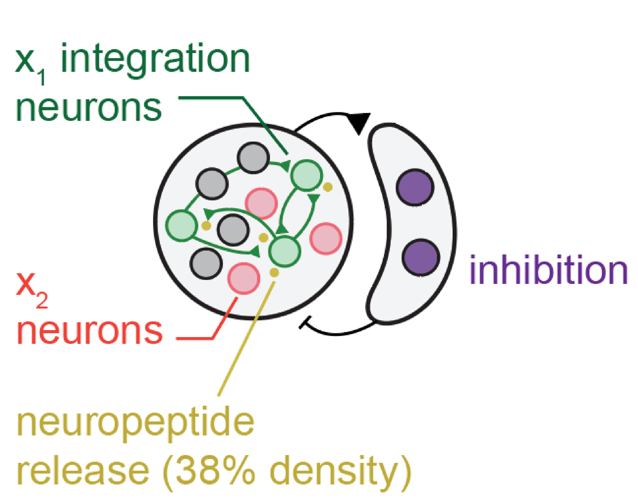
VMHvl line attractor requires OXT/AVP signaling

Contrast between both experiments suggests a complex and unexplained role for OXT and AVP neuropeptides in maintaining the line attractor dynamics beyond what functional connectivity alone can achieve.

## Goal

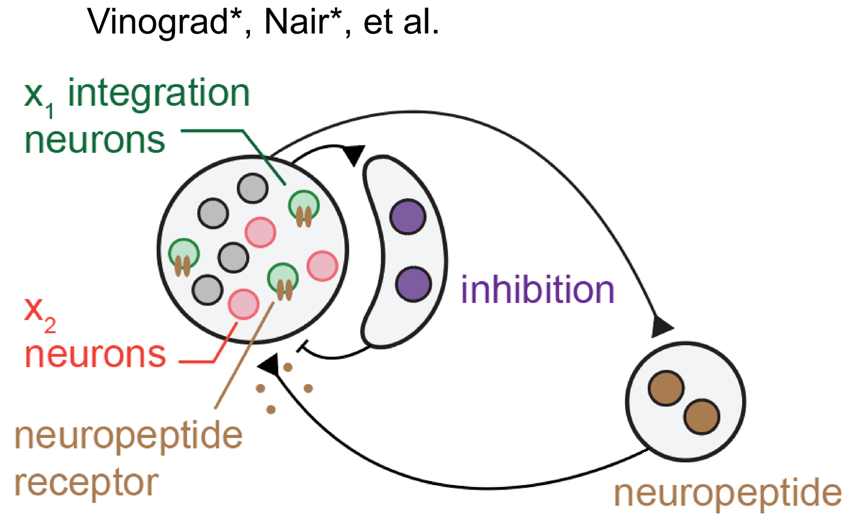
1. Model local release of neuropeptide

Focuses on synaptic interactions and local network structure, with a connection density of 38%.[2]




2. Model long-range release of OXT/AVP

Requires receptor specificity on $X_1$ neurons,[3] other parameters as per Vinograd*, Nair*, et al.




3. Hybrid models that feature both

Combines elements from both local and long-range models, suggesting that all mechanisms may work synergistically.

## Implementation of a line attractor model with long-range release of neuropeptides

equation for synaptic current (1)

$$\tau_s \frac{dp_i}{dt} = -p_i(t) + r_i(t)$$

equation for membrane potential (2)

$$\tau_m \frac{dx_i}{dt} = -x_i(t) + g\Big(\sum_{j=1}^{N} J_s * p_j(t) - g_{inh} * I(t)\Big) + w_i * s(t)\Big)$$

equation for inhibition (3)

$$\tau_i \frac{dI_{inh}}{dt} = -I_{inh}(t) + \frac{1}{N}\sum_{n=1}^{N} r_n(t)$$

equation for neuropeptide inhibition (4)

$$\tau_{NP} \frac{dI_{NP}}{dt} = -I_{NP} + \frac{1}{N}\sum_{i=1}^{N} r_n(t)$$

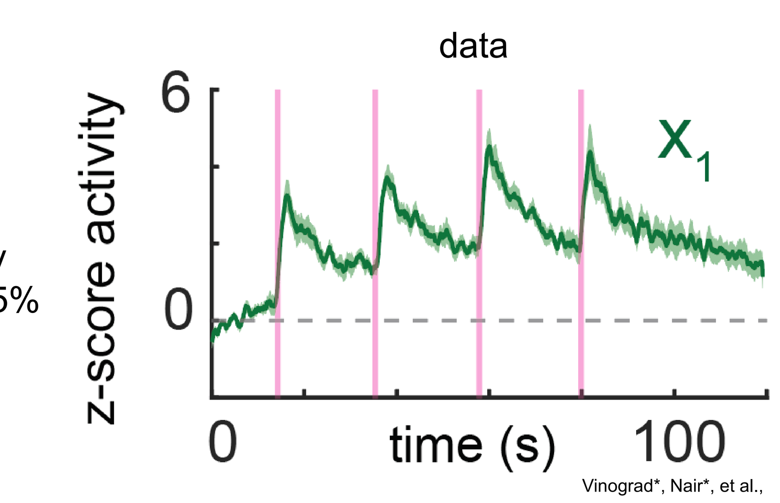
$\tau_s$ is the synaptic time constant
$\tau_m$ is the membrane potential time constant
$x(t)$ is the membrane potential of each neuron
$g$ is the general gain?
$J_s$ is the function of every single cell (connectivity matrix)
$p(t)$ is the recurrent inputs
$g_{inh}$ is the gain associated with input
$I(t)$ ?
$w$ is the weights of the input
$s(t)$ is the input? Optogenetic impulses?
$\tau_i$ is the inhibition time constant
$I_{inh}(t)$ is an inhibitory population
$N$ is the number of neurons
$\tau_{NP}$ is the neuropeptide time constant
$r(t)$ is the instantaneous spiking rate

1. original model has differential equations 1-3
2. We added equation 4
3. a key parameter to tune is $g_{NP}$: gain of peptide release in VMHvl
4. parameters are tuned to match integration time constant from data using simulations in Caltech HPC (high-perf. computing center)

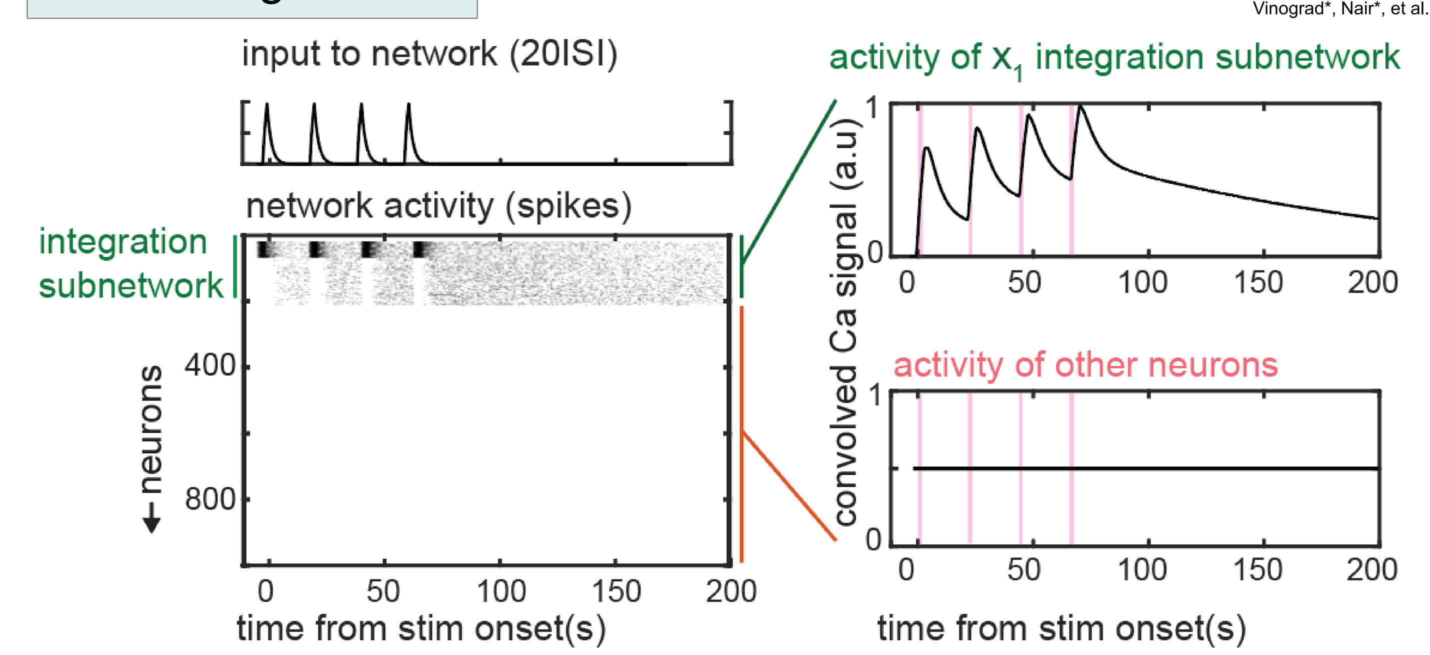
## Preliminary Results

activation of $x_1$ ensemble

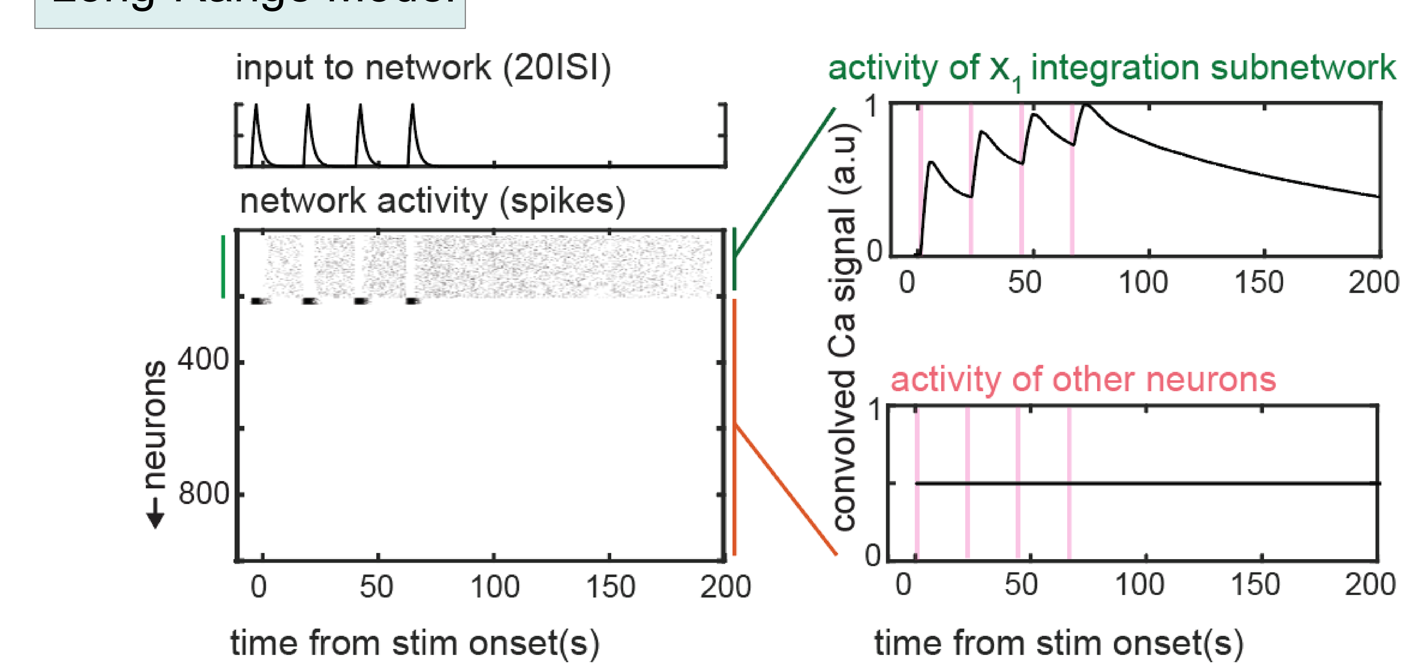
Pulse-like inputs were given to the simulations to emulate the experimentally optogenetic activation of 5 $x_1$ neurons (25% of the network).




### Short-Range Model




### Long-Range Model

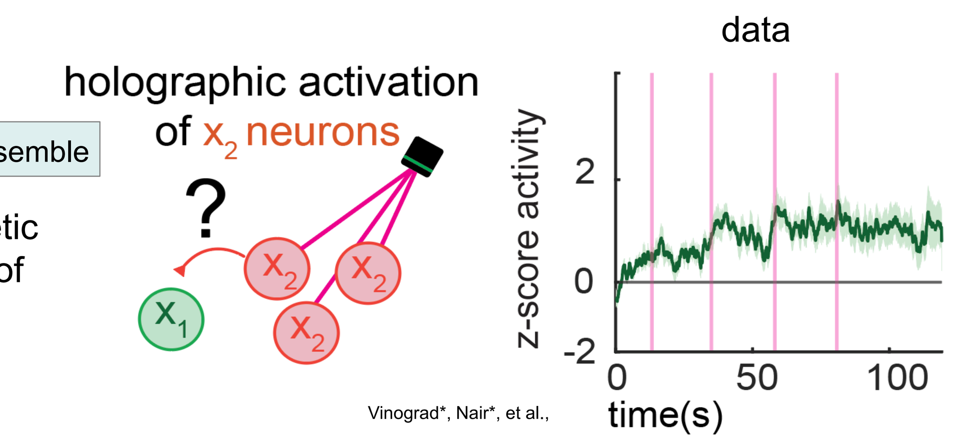



Both models captures integration due to $x_1$ ensemble activation. The activation led to the recruitment of additional neurons, reflecting the integration seen in experiments.

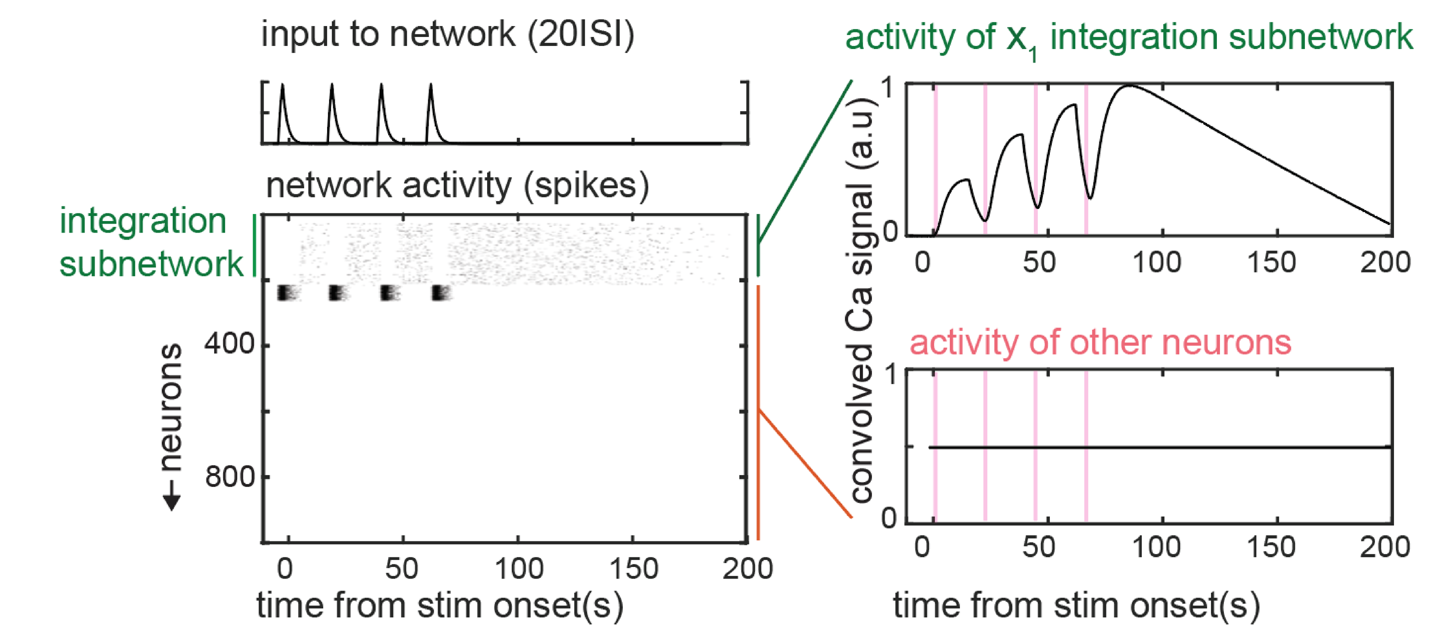
## Long-range model overshoots

activation of $x_2$ ensemble

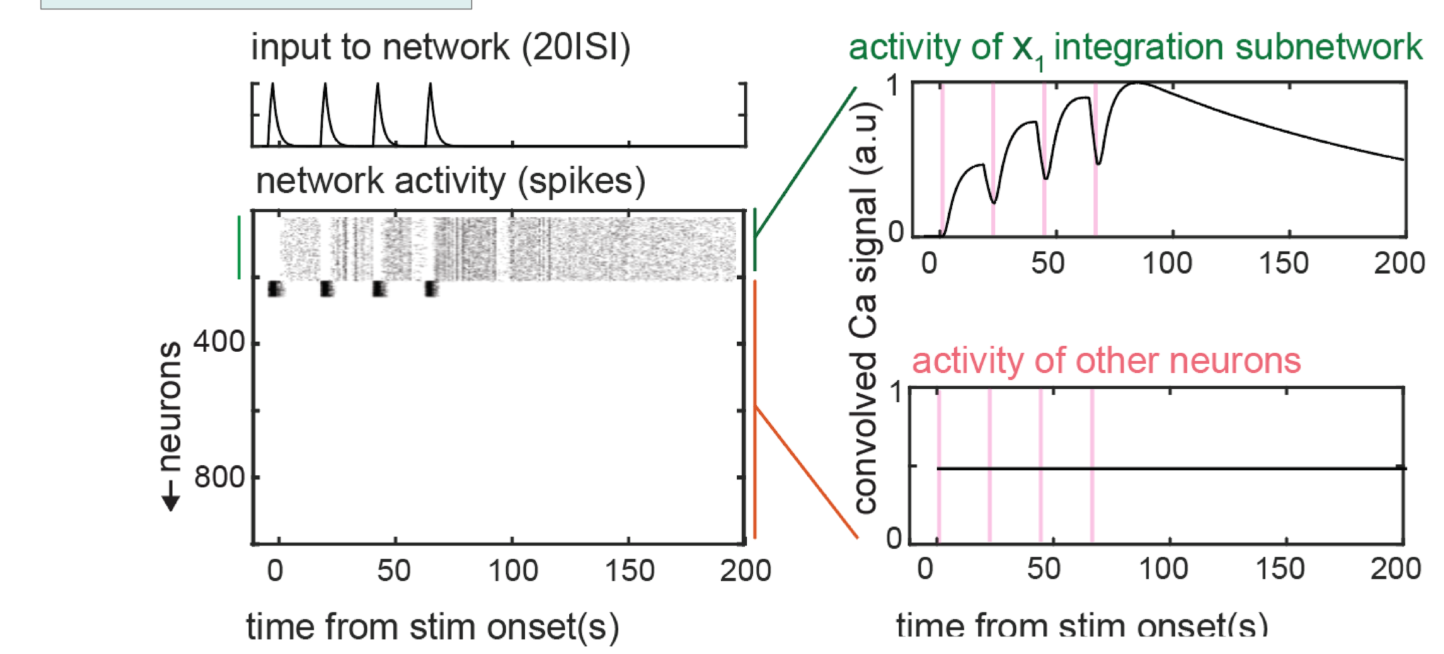
Models also simulated optogenetic activation of 5 $x_2$ neurons (25% of the network).




### Short-Range Model

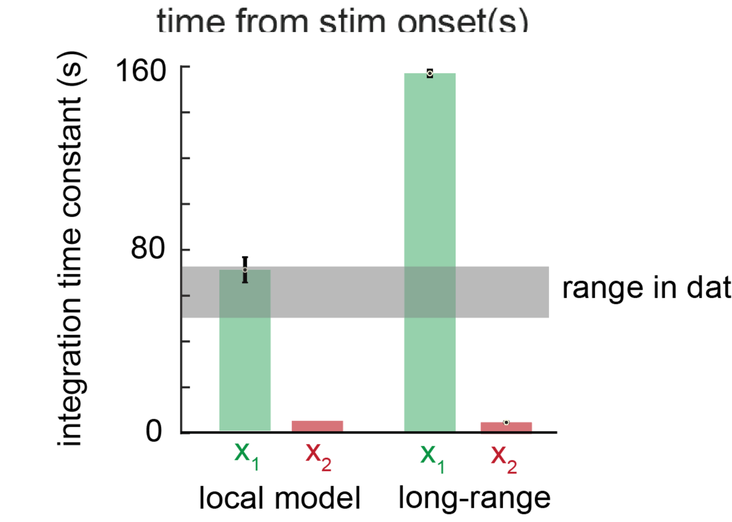



### Long-Range Model

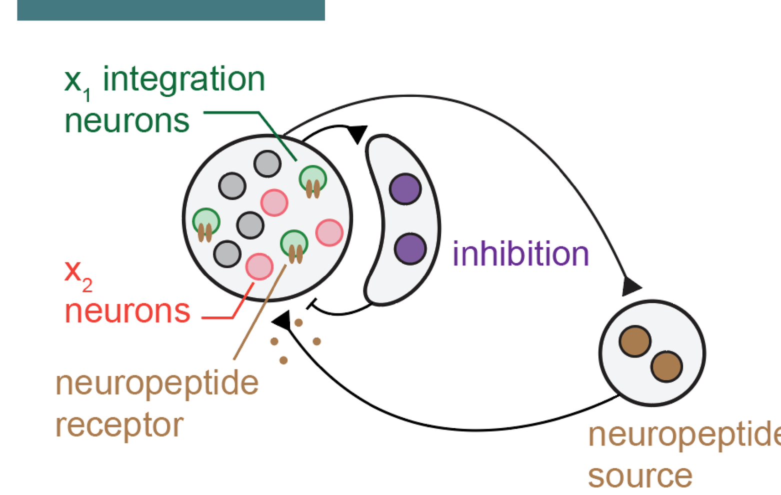



The long-range model's activation of $x_2$ neurons caused excessive neural integration and $x_1$ activation, diverging from experimental data, while the local release model more accurately matched follower cell activity and decay time.

comparison of local and long-range model's integration time constant for activation of $x_2$ ensemble




## Future Work




predictions from long-range model

- requires receptor specificity on $x_1$ neurons
- might require anatomical specificity of connectivity from $x_1$ neurons to neuropeptide source

explore “hybrid” models that integrate local and long-range release mechanisms

explore biophysical models that accurately capture downstream signaling from peptide release

## Acknowledgements

Thank you to my mentor Aditya Nair and PI Dr. David J. Anderson for giving me the opportunity to work on this project. This project was supported by the BrainWAVE program at Caltech.

Citations: [1] Nair et al., Cell 186, 178-193 (2023) [2] Vinograd, A., Nair, A., et al., Nature (2024) [3] Mountoufaris, et al., Preprint (2023)