Multiple Mechanisms of Gain Modulation in the Serotonin System

Emerson Harkin

Richard Naud
Jean-Claude Béïque

University of Ottawa

March 30, 2020

Introduction

A Hub of Behavioural Regulation

- The dorsal raphe nucleus (DRN) is a major source of serotonergic (5HT) input to the forebrain

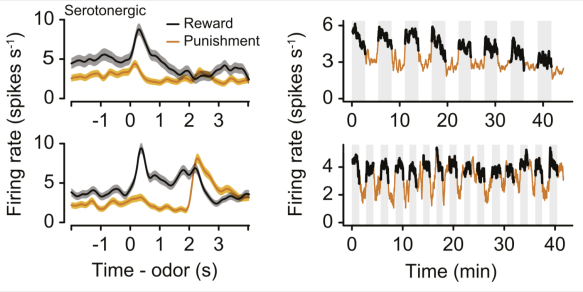
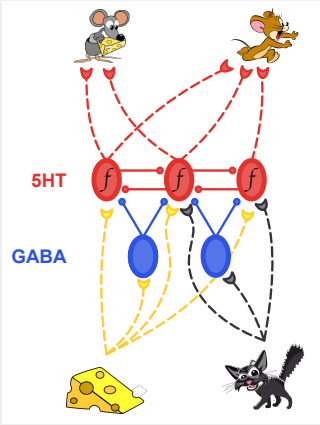
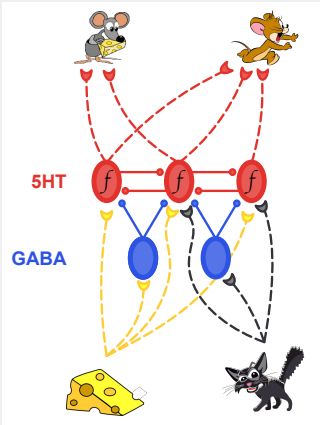


Figure: *In vivo* extracellular electrophysiological recordings of 5HT neurons in awake mice (Cohen et al., eLife 2015).



Motivation

Connection between microcircuitry and function is not well understood.

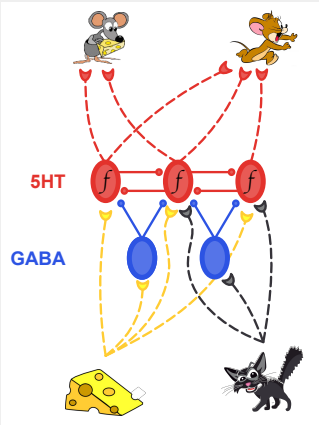


Motivation

Connection between microcircuitry and function is not well understood.

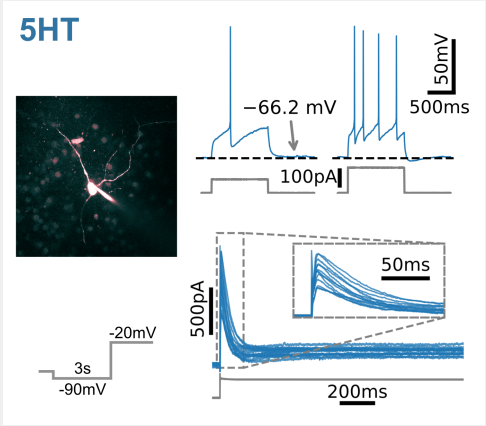
Key Question

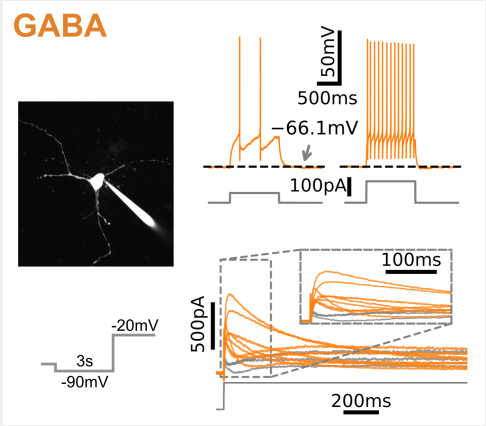
How does the physiology of the DRN support input processing over short timescales?



Experimentally-Constrained Single Neuron Models

Physiology of DRN Neurons



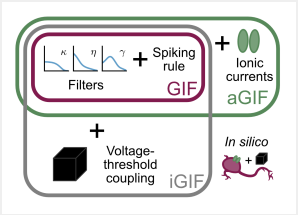


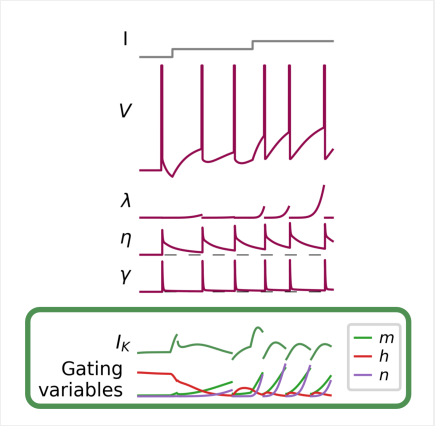
Generalized Integrate-and-Fire Models

$$C\frac{dV}{dt} = -g_l(V(t) - E_l) - \eta(t) + I(t)$$

$$p(\text{spike}) = 1 - \exp(-\lambda(t)\Delta t)$$

$$\lambda(t) = \lambda_0 \exp\left(\frac{V(t) - (\theta + \gamma(t))}{\sigma}\right)$$





Extended GIFs Capture Behaviour of DRN Neurons

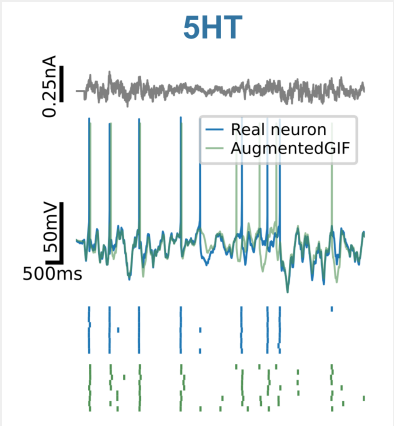


Figure: aGIF predictions on test data for a representative 5HT neuron.

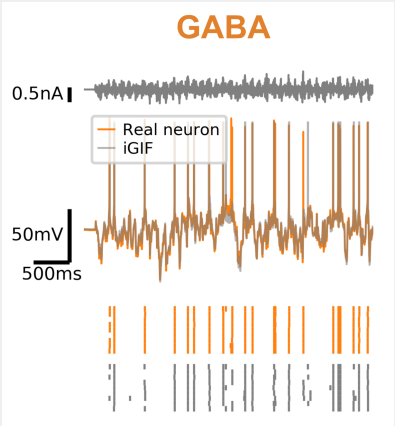
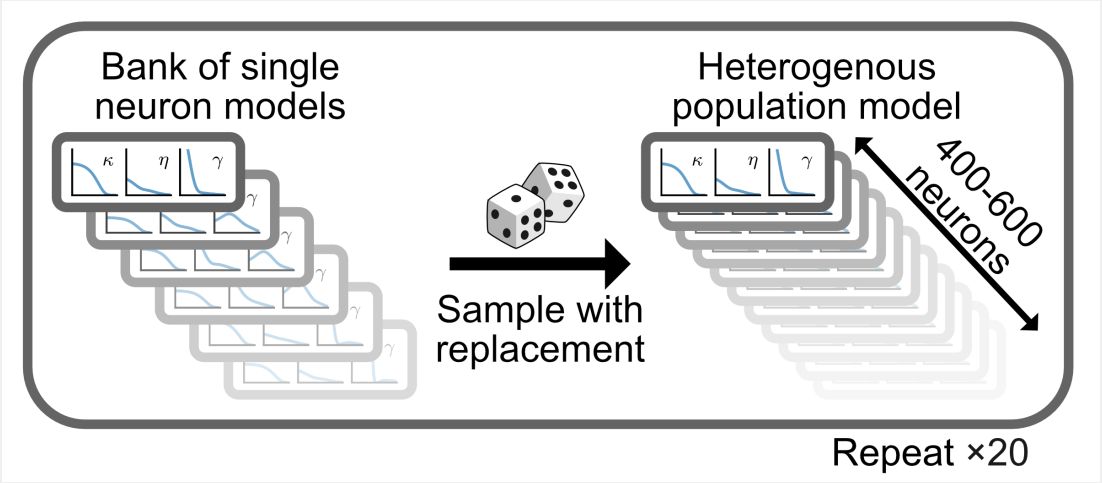


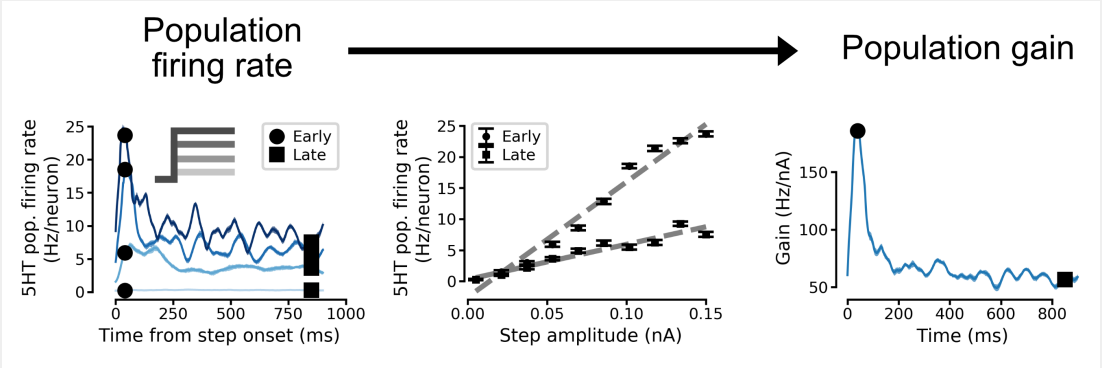
Figure: iGIF predictions on test data for a representative GABA neuron.

Predicting the Behaviour of Populations

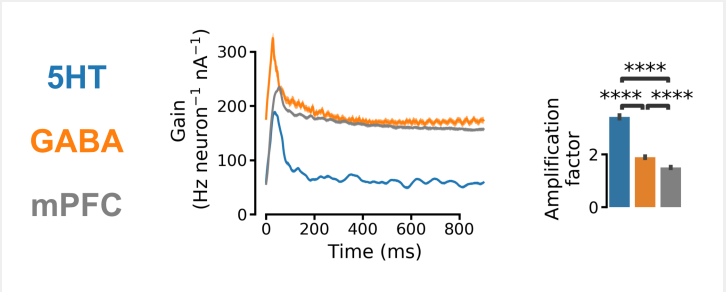
From Single Neurons to Populations



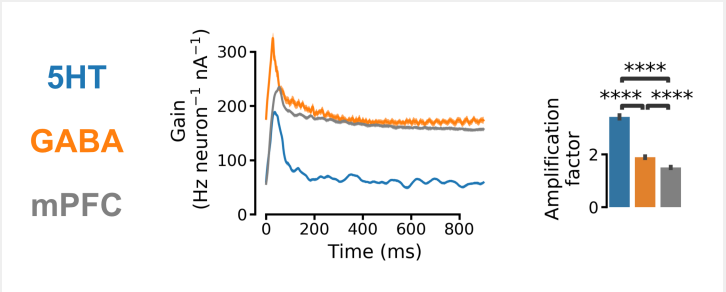
Quantifying Population Responses



5HT Neurons Amplify Fast Inputs

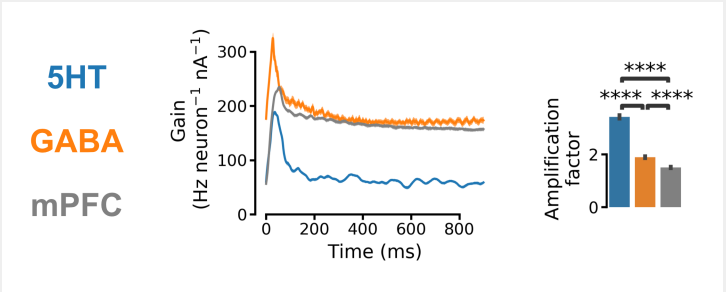


5HT Neurons Amplify Fast Inputs



- “Amplification” is due to suppression of slow inputs by strong adaptation mechanisms

5HT Neurons Amplify Fast Inputs



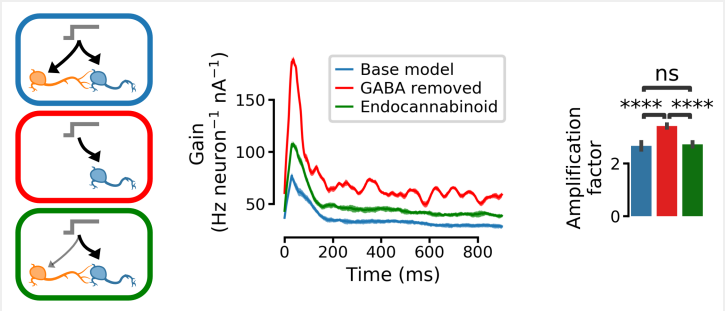
- "Amplification" is due to suppression of slow inputs by strong adaptation mechanisms

Question

How might the output gain of the DRN be regulated?

Potential Physiological Mechanisms of Gain Modulation

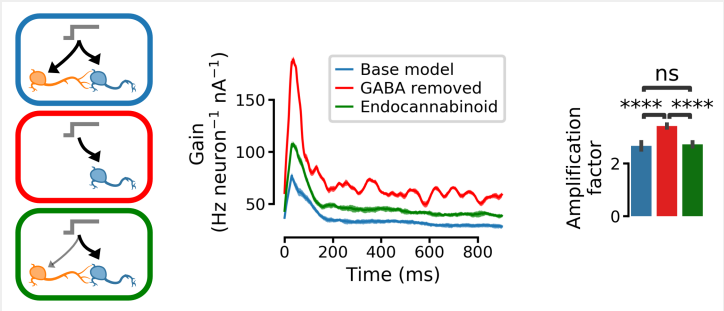
Mechanism #1: Feed-Forward Inhibition



- 5HT neurons receive feed-forward inhibition from GABA neurons in the DRN
- Endocannabinoids preferentially weaken synapses onto GABA neurons

(Geddes et al., PNAS 2016)

Mechanism #1: Feed-Forward Inhibition



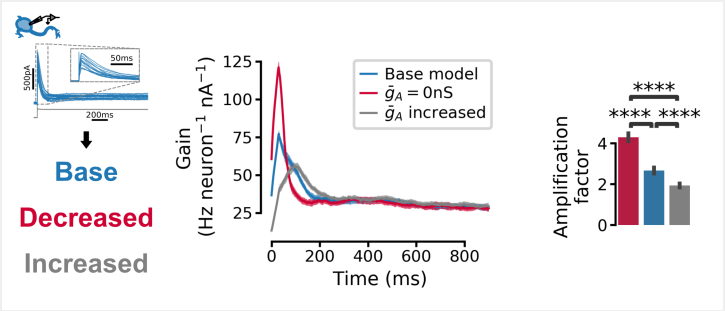
- 5HT neurons receive feed-forward inhibition from GABA neurons in the DRN
- Endocannabinoids preferentially weaken synapses onto GABA neurons

(Geddes et al., PNAS 2016)

Key Point

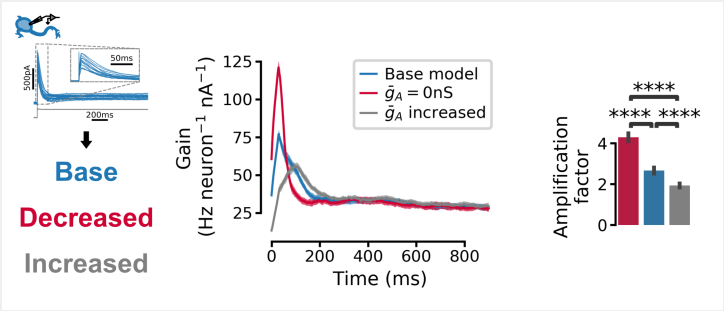
Endocannabinoids might regulate overall output gain of DRN.

Mechanism #2: Regulation of Transient Current in 5HT Cells



- Noradrenergic signalling may reduce this current (Aghajanian, Nat 1985)

Mechanism #2: Regulation of Transient Current in 5HT Cells



- Noradrenergic signalling may reduce this current (Aghajanian, Nat 1985)

Key Point

Transient current may regulate amplification of fast inputs.

Conclusion

Summary

Two empirical results:

1. Electrophysiological properties of GABA neurons are surprisingly diverse
2. Maximum-likelihood models capture the behaviour of DRN neurons

Two predictions:

Summary

Two empirical results:

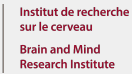
1. Electrophysiological properties of GABA neurons are surprisingly diverse
2. Maximum-likelihood models capture the behaviour of DRN neurons

Two predictions:

1. 5HT neurons fire at low rates, but respond preferentially to fast inputs
2. Feed-forward inhibition and intrinsic currents play complementary roles in regulating output gain of DRN network

Acknowledgements

- Dr. Richard Naud
  - Dr. Alexandre Payeur
- Dr. Jean-Claude Béïque
  - Michael Lynn
  - Jean-François Boucher
  - Léa Caya-Bissonnette
  - David Lemelin
  - Chloe Stewart
  - Dominic Cyr
  - Sean Geddes
- Dr. André Longtin
- Dr. Leonard Maler
- Dr. Mario Tiberi
- Dr. Paul Albert
- Dr. Tuan Bui
- Dr. Simon Chen



Thank you!

Diverse Firing Patterns in GABA Neurons

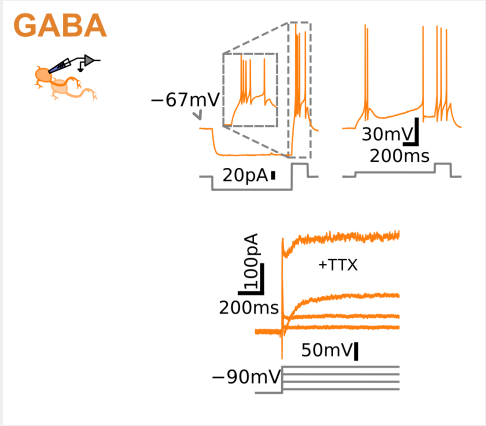


Figure: A burst-firing DRN GABA neuron.

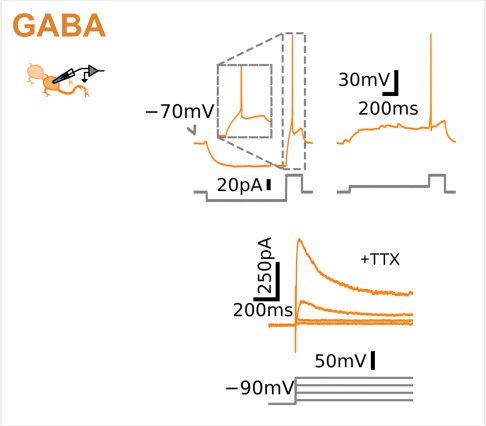
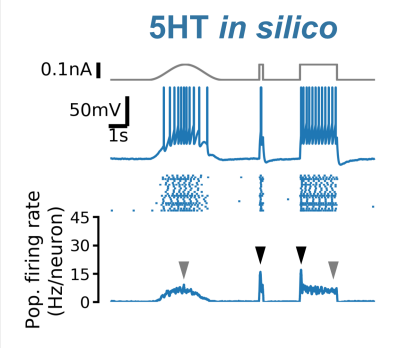
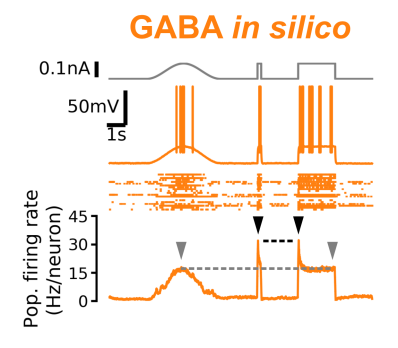


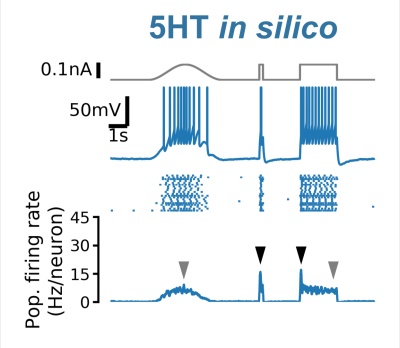
Figure: A non burst-firing DRN GABA neuron.

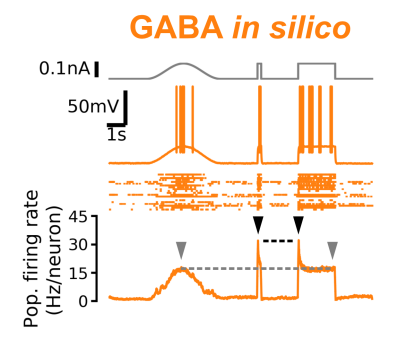
Population Responses to Slow and Fast Inputs





Population Responses to Slow and Fast Inputs





Key Point

Sustained steps reflect input processing on multiple timescales.

5HT Neurons Encode Fast-Changing Variables

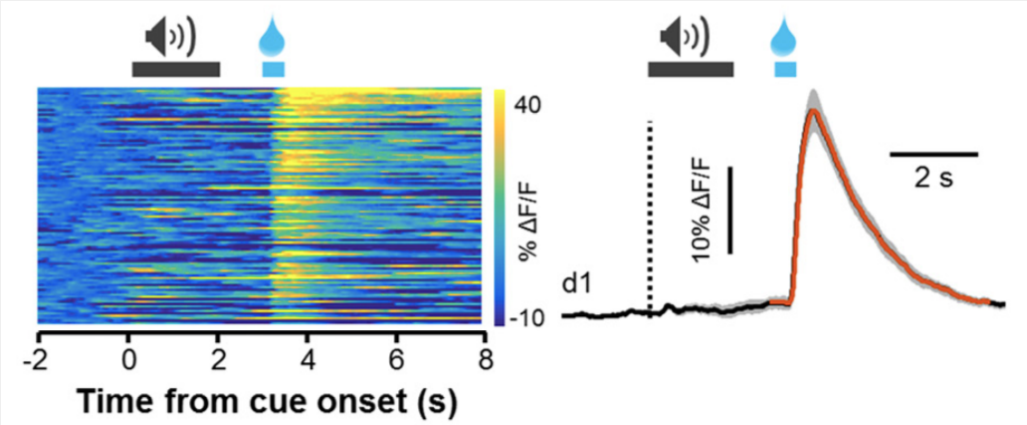


Figure: *In vivo* fluorometric recordings of 5HT population activity in awake mice (Zhong et al., J Neurosci 2017).