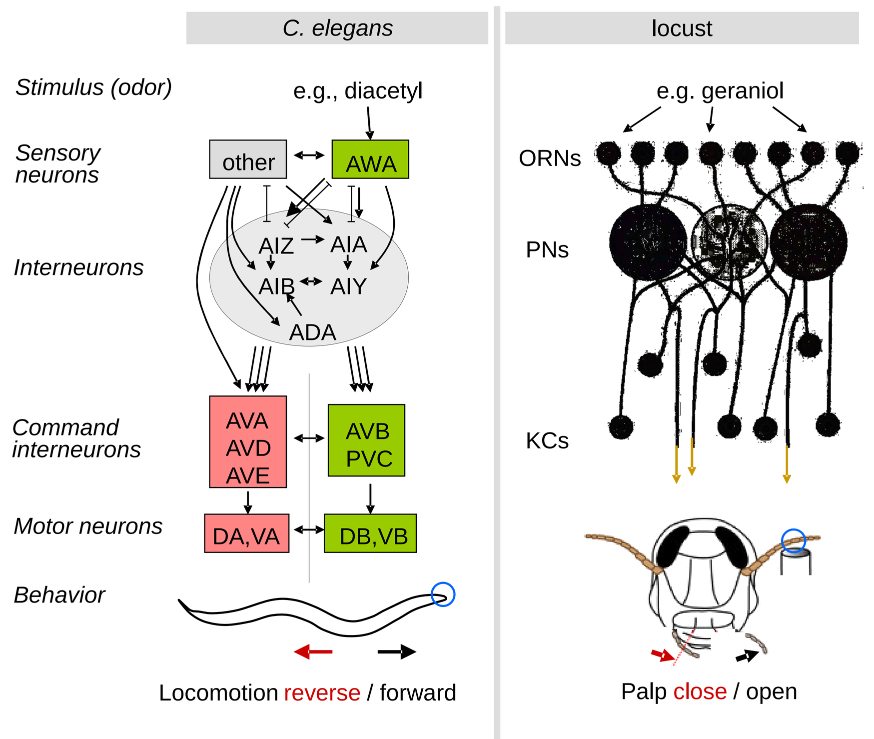
# Multiple time-scale normative circuit model of *C. elegans* sensory adaptation and behavior

Hamilton White[1,3], Sruti Mallik[4], ShiNung Ching[4], Baranidharan Raman[5], Dirk R. Albrecht[1,2]

[1]Department of Biomedical Engineering, [2]Department of Biology and Biotechnology, Worcester Polytechnic Institute
[3]Worcester Polytechnic Institute – University of Massachusetts Medical School Joint PhD Program
[4]Department of Electrical and Systems Engineering, [5]Department of Biomedical Engineering, Washington University at St Louis

## Introduction & Objectives

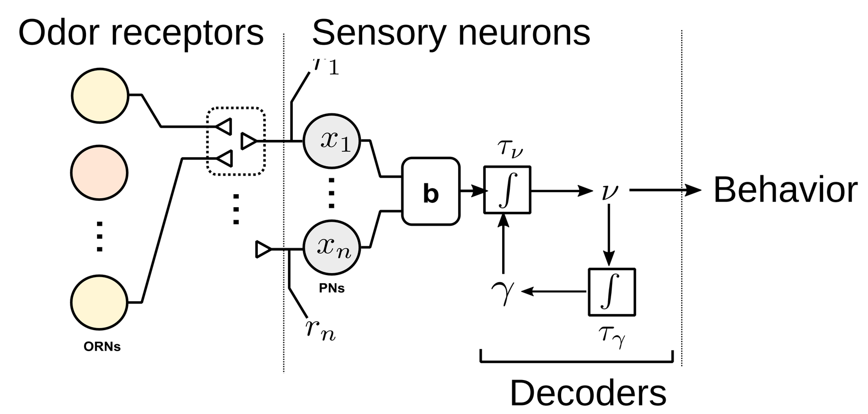
- Sensory neural networks mediate state-dependent transformations from external stimuli to behavioral response, allowing dynamic adjustment to the environment and organism needs.
- We seek to uncover rules that govern these neural computations and how emergent phenomena arise in normal and disease conditions.
- For example, neurons in early olfactory networks adapt their responses to repetitive stimuli, while retaining their ability to respond to a novel stimulus[1,2].
- The general olfactory system architecture is conserved across species[3].
- Characteristic adaptation responses to repetitive stimulation are observed in locust and *C. elegans*[4-6].
- We aim to investigate inter-species similarity in neural adaptation, and extend observations to behavior.
- *C. elegans* contains 302 neurons and ~7000 synapses. Each neuron is individually addressable via genetic expression.




## Methods

### Computational Model:

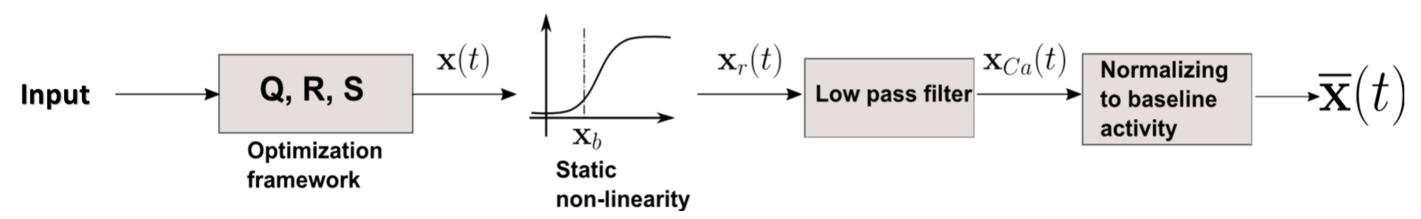
- Multiple timescales of information are embedded in the neural response.
  - $\gamma$ – residual memory
  - $\nu$ – latent representation




- An optimization based framework converts odor cues to neural responses.

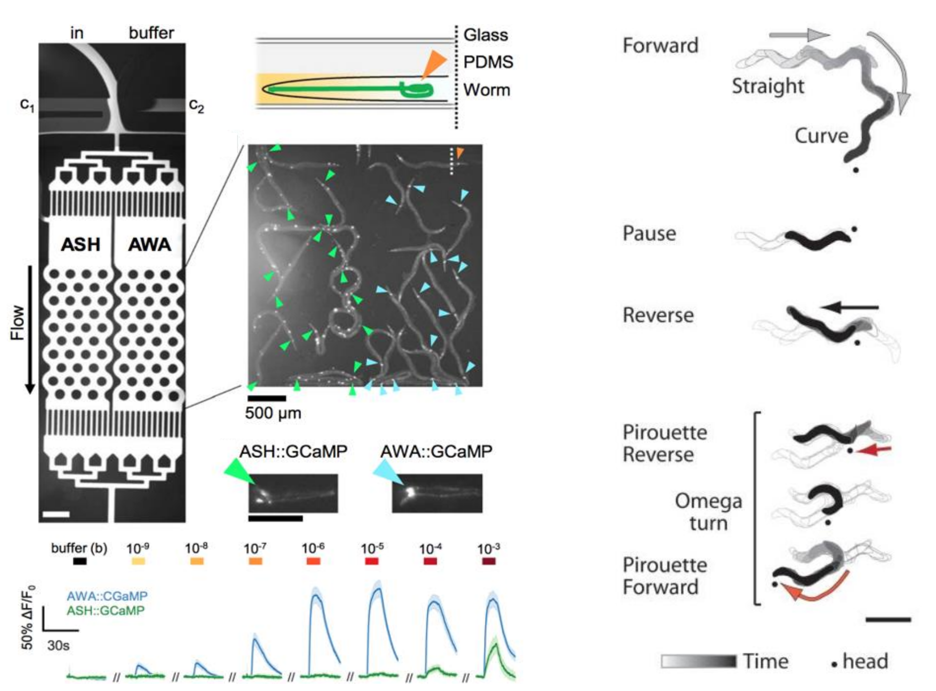
$$\mathbb{J}(\mathbf{x}) = \int_0^t \frac{1}{2}[\underbrace{(\nu - \mathbf{z})^T\mathbf{Q}(\nu - \mathbf{z})}_{\text{Accuracy of representation}} + \underbrace{\mathbf{x}^T\mathbf{S}\mathbf{x}}_{\text{Energy efficiency}} + \underbrace{\dot{\mathbf{x}}^T\mathbf{R}\dot{\mathbf{x}}}_{\text{Avoid rapid fluctuations}}]dt$$

- Calcium dynamics are obtained from the optimal motif as follows:




### Experimental Data:

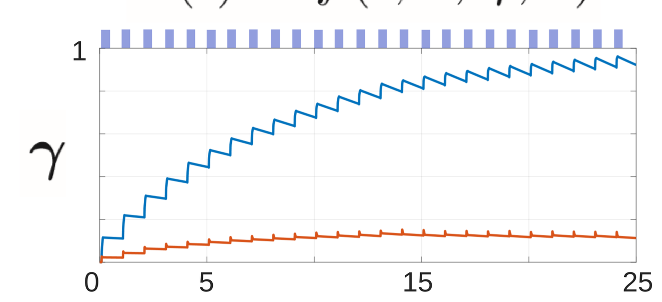
- Microfluidic experiments measure *C. elegans* neural responses to precise chemical or optogenetic stimulation via fluorescent calcium imaging[4,5,7].
- Behavior responses were quantified as locomotory state probability[8].

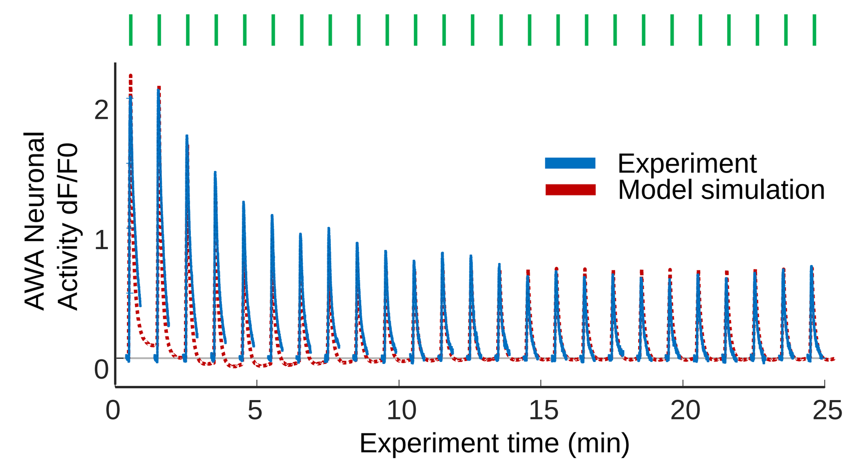



## Results: Model Parameterization

$$\dot{\mathbf{x}}(t) = f(t, \mathbf{x}, \gamma, \boldsymbol{r})$$

- Neural responses adapt to repeating stimulus due to slow but steady build-up of memory during successive encounters.
- Parameters of the computational model were fit to AWA neuron calcium responses **using a single stimulation pattern**:
  - 4 s pulse of 1 µM diacetyl every 60 s



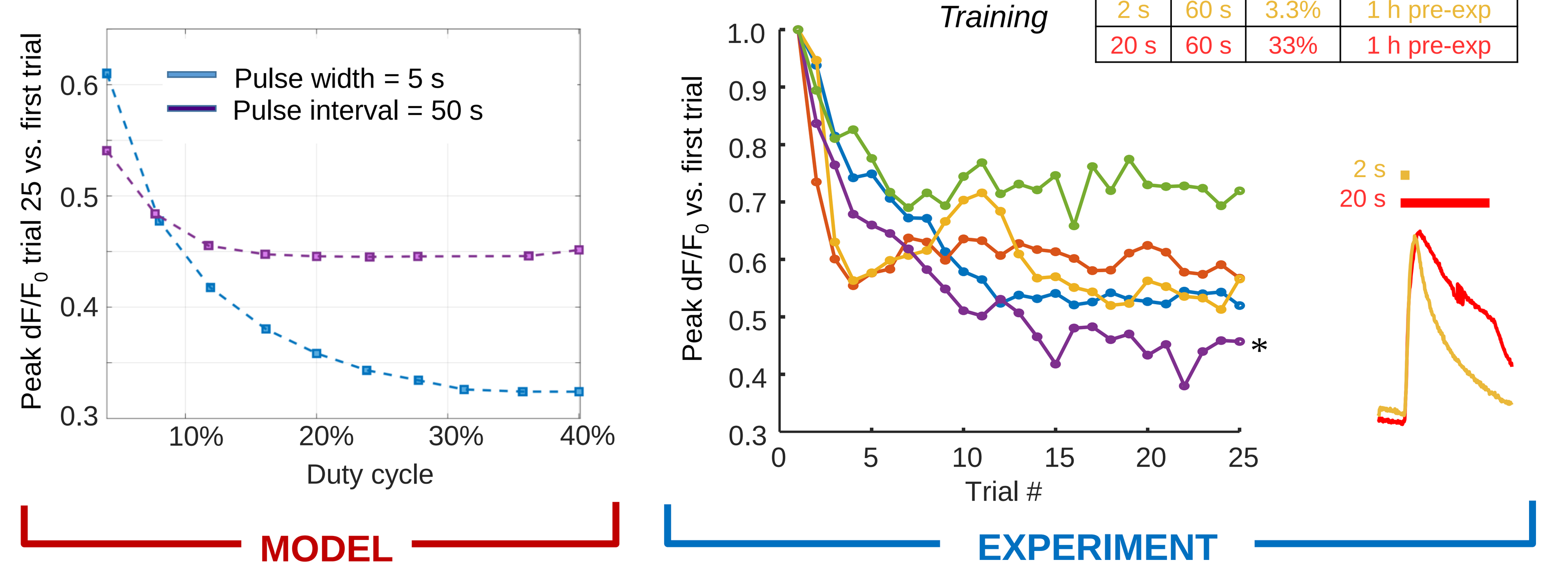




## Results: Predictions & experiment

- Neural responses were simulated to varying pulse patterns: width, inter-stimulus interval (ISI), and duty cycle (width/ISI).
- Adaptation in peak neural responses was predicted to be **more sensitive to stimulus interval than to pulse width**.
- The predictions were verified experimentally in *C. elegans* chemosensory experiments, using both naïve and pre-exposed animals.

| Pulse width | Interval | Duty cycle | Stimulus pre-eposure | |
|---|---|---|---|---|
| 2 s | 60 s | 3.3% | naïve | |
| 4 s | 60 s | 6.7% | naïve | * |
| 4 s | **90 s** | 4.4% | naïve | |
| 2 s | 60 s | 3.3% | 1 h pre-exp | |
| 20 s | 60 s | 33% | 1 h pre-exp | |

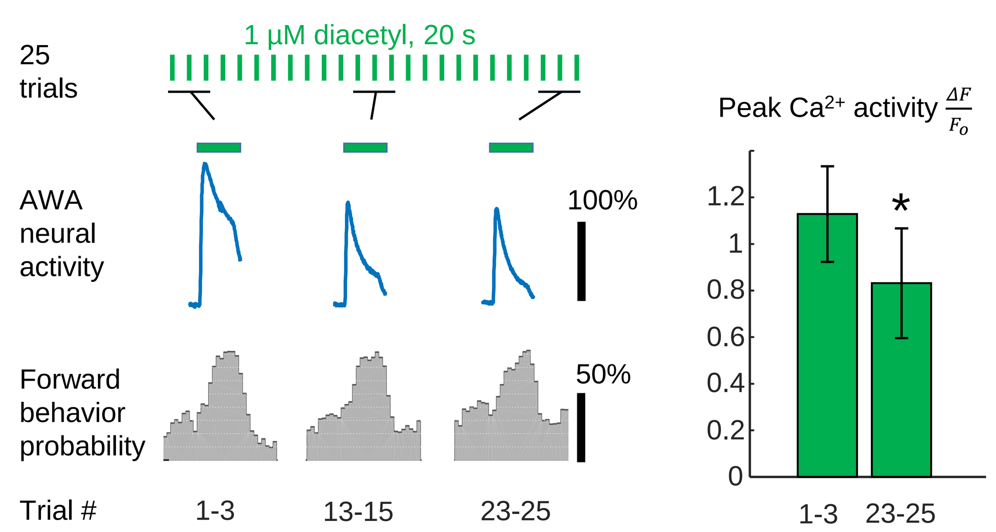
*Training*




- Shorter trial intervals cause more adaptation in peak neural activity than longer intervals.
- Pulse duration does not change adaptation rate or peak height for durations > 2 s, but does alter the calcium waveform.
- Pre-exposure alters adaptation rates at least for 1 hr.

## Results: Sensory adaptation & behavior

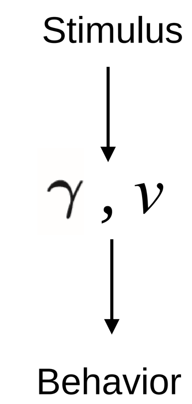
- Repeated odor stimulation results in **adaptation of neural responses**, but **no change in behavior** responses.
- *How do behaviors remain constant during sensory adaptation?*



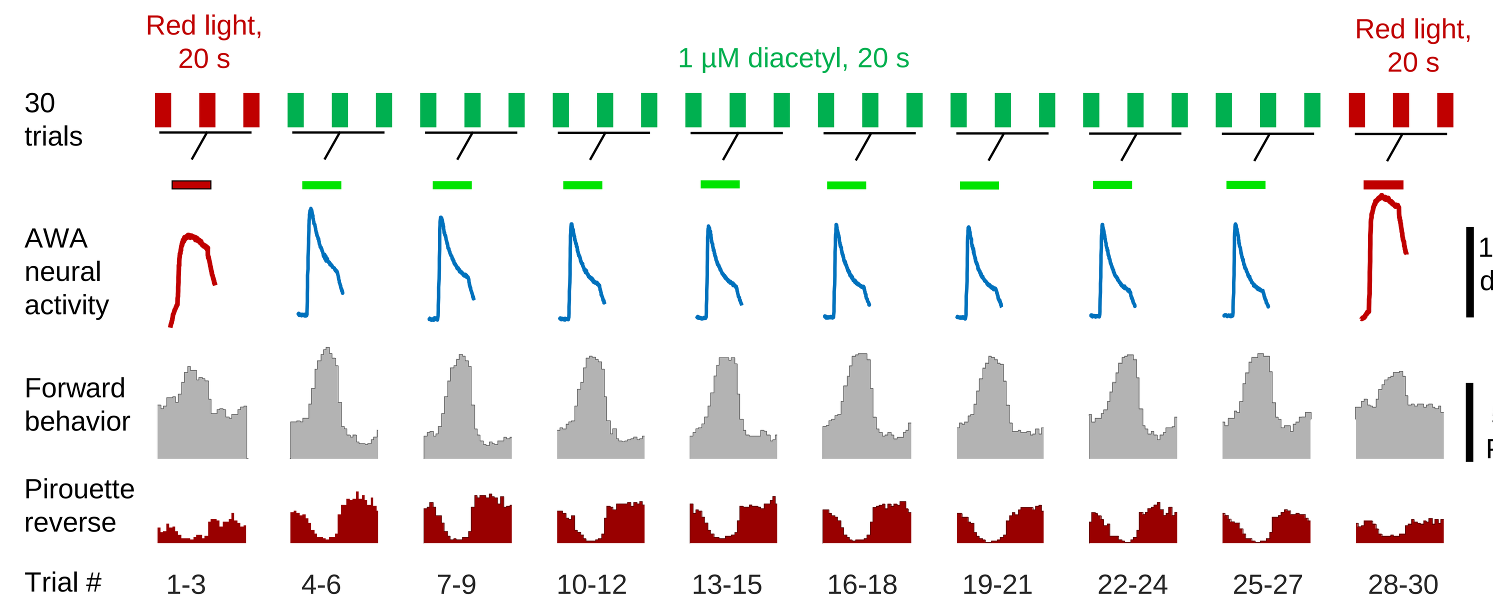

## Results: Optogenetic stimulation

- The transformation between neural representation of sensory information and behavior is unknown.
- Several possible scenarios allow uniform behavior from uniform stimulation, despite neuronal adaptation, such as:

| *Linear compensation:* downstream circuits become equally sensitized to respond to weaker input | *Nonlinear flip-flop*: downstream circuits are insensitive to changes in neural response above inflection | … |
|---|---|---|




- To test these models, optogenically-evoked AWA sensory neural and behavioral responses were compared before and after odor adaptation.
- Animals expressing the ion channel Chrimson[5,7] in AWA neurons **respond consistently** to red light with minimal adaptation (neurons and behavior).




- If downstream circuits become sensitized to weaker sensory neural responses during adaptation, then *behavior responses to optogenetic stimulation should strengthen*. This was **not observed experimentally**, despite some *increase* in optogenetic light response after adaptation.

## Summary & Future directions

- A two time-scale normative model of *C. elegans* sensory neural responses, structured on locust olfaction and parameterized with one stimulus pattern, effectively predicted adaptation to other temporal patterns.
- Current model may benefit from *interaction* among time scales, such as adjustment of fast inactivation during slow adaptation.
- The fast model – experiment feedback loop enables rapid hypothesis testing and model refinement.
- Further experimental data will test alternative sensory – behavior transformations, examine circuit-level feedback from additional neurons, and compare adaptation to mixtures, during starvation, and across species.

## References & Support

1. R.F. Thompson. "Habituation." *International Encyclopedia of the Social & Behavioral Sciences*, (2015): 480-483
2. Rankin, C.H., et al. "Habituation revisited: an updated and revised description of the behavioral characteristics of habituation." *Neurobiology of learning and memory* 92.2 (2009): 135-138.
3. Strausfeld, N. J. and Hildebrand, J. G. "Olfactory systems: common design, uncommon origins?" *Current opinion in neurobiology*, 9.5 (1999): 634-639.
4. Larsch, J., Ventimiglia, D., Bargmann, C.I., and Albrecht, D.R. "High-throughput imaging of neuronal activity in Caenorhabditis elegans" PNAS 110.45 (2013):E4266-E4273.
5. Larsch, J., et al. "A circuit for gradient climbing in *C. elegans* chemotaxis." *Cell Reports* 12.11 (2015):1748-1760.
6. Zhang, L., et al. "Encoding the expectation of a sensory stimulus." *bioRxiv* (2018): 281071.
7. Lagoy, R.L., and Albrecht, D.R. "Automated fluidi delivery from multiwell plates to microfluidic devices for high-throughput experiments and microscopy" *Scientific Reports* (2018): 6217.
8. Albrecht, D.R. and Bargmann, C.I. "High-content behavioral analysis of Caenorhabditis elegans in precise spatiotemporal environments." *Nature Methods* 8.7 (2011): 599-605.

This work was supported by NSF 1724218: *CRCNS Collaborative Research: Studying Competitive Neural Network Dynamics Elicited By Attractive and Aversive Stimuli and their Mixtures*