Short-term sensory memory mediates paradoxical neural-behavioral transformation

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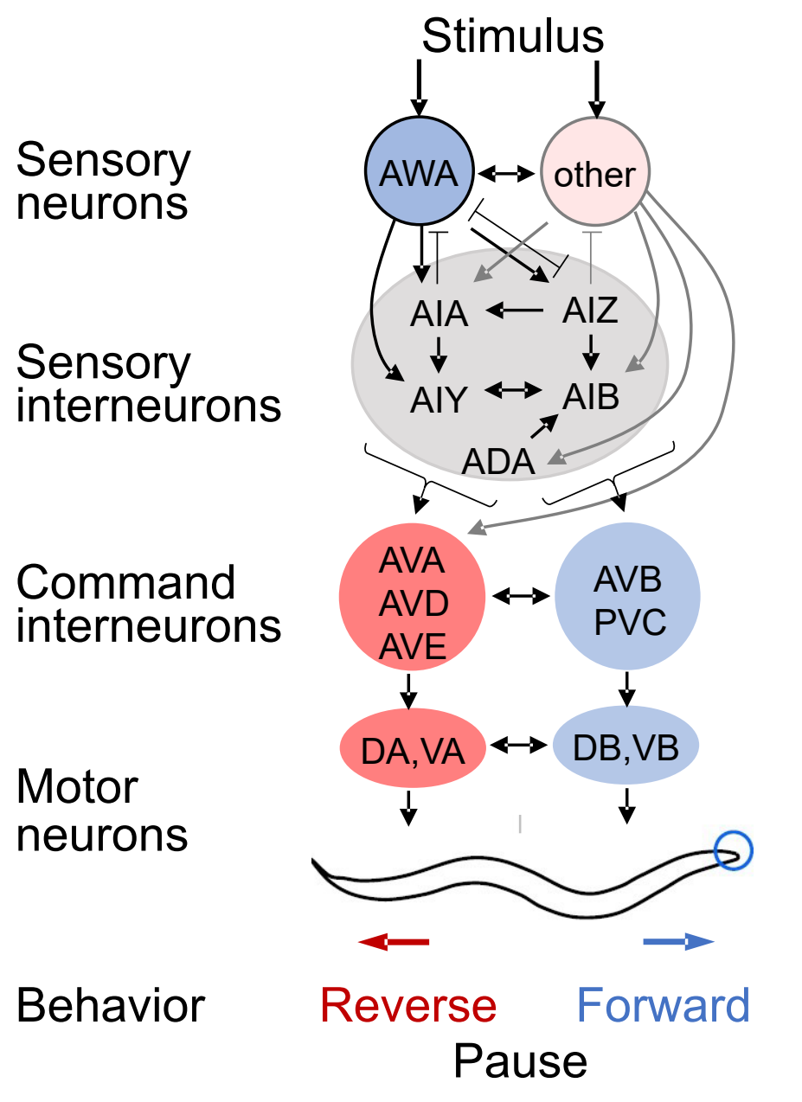
Introduction & Objectives

- 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 (reduce) their responses to repetitive stimuli, while retaining their ability to respond to a novel stimulus[1,2]. **Neural adaptation** can lead either to **invariant** (consistent) behavior, or **habituation** (reduced behavior response).
- We aim to investigate neural adaptation and its flexible translation into behavioral decision-making in the nematode *C. elegans*.
- *C. elegans* contains 302 neurons and ~7000 synapses. Each neuron is individually addressable via genetic expression. Repetitive stimulation elicit characteristic adaptation and habituation responses[2-4].

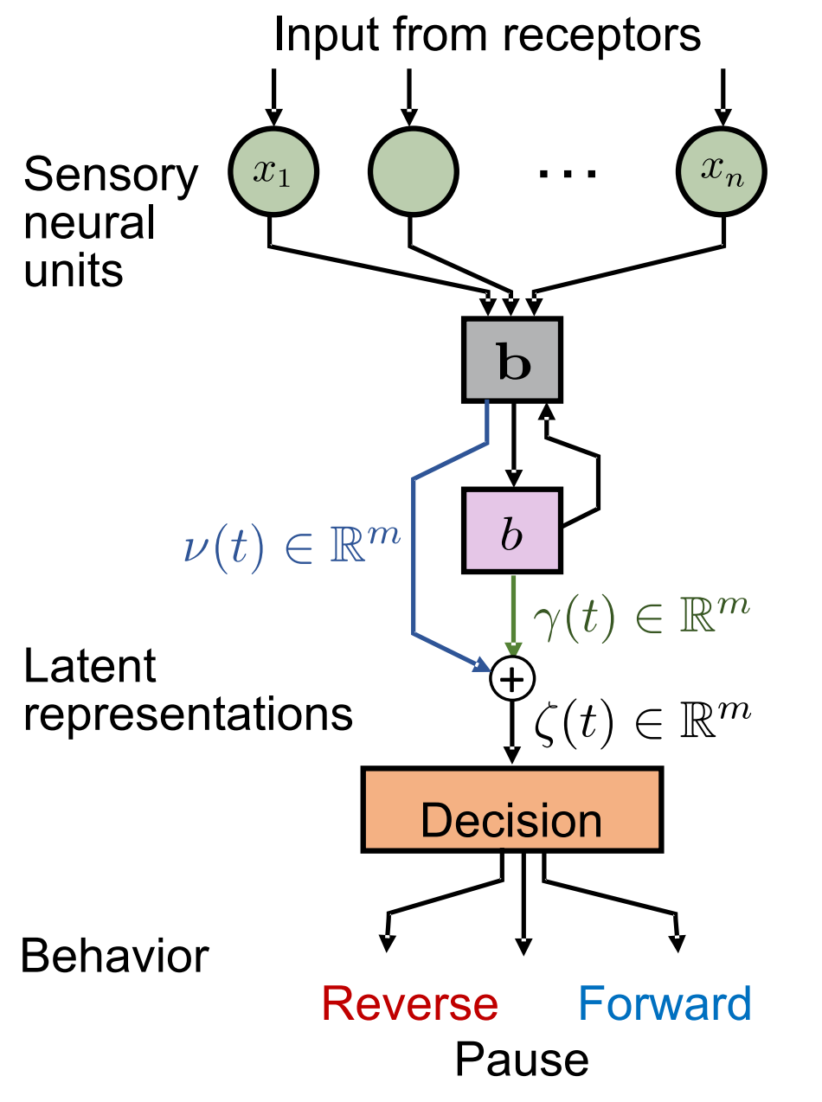


Methods

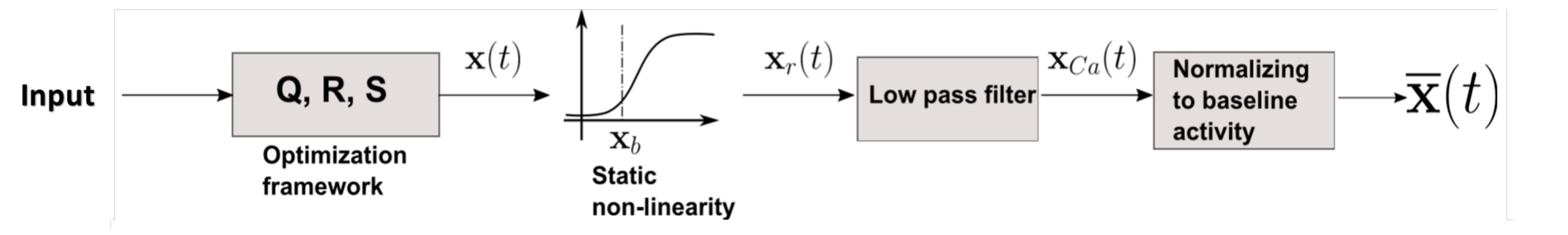
Computational Model:

- Two timescales of information are embedded in the neural response.
  - $\nu(t)$ – "fast" latent representation
  - $\gamma(t)$ – "slow" residual memory
- An optimization-based framework converts odor cues to neural responses.

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



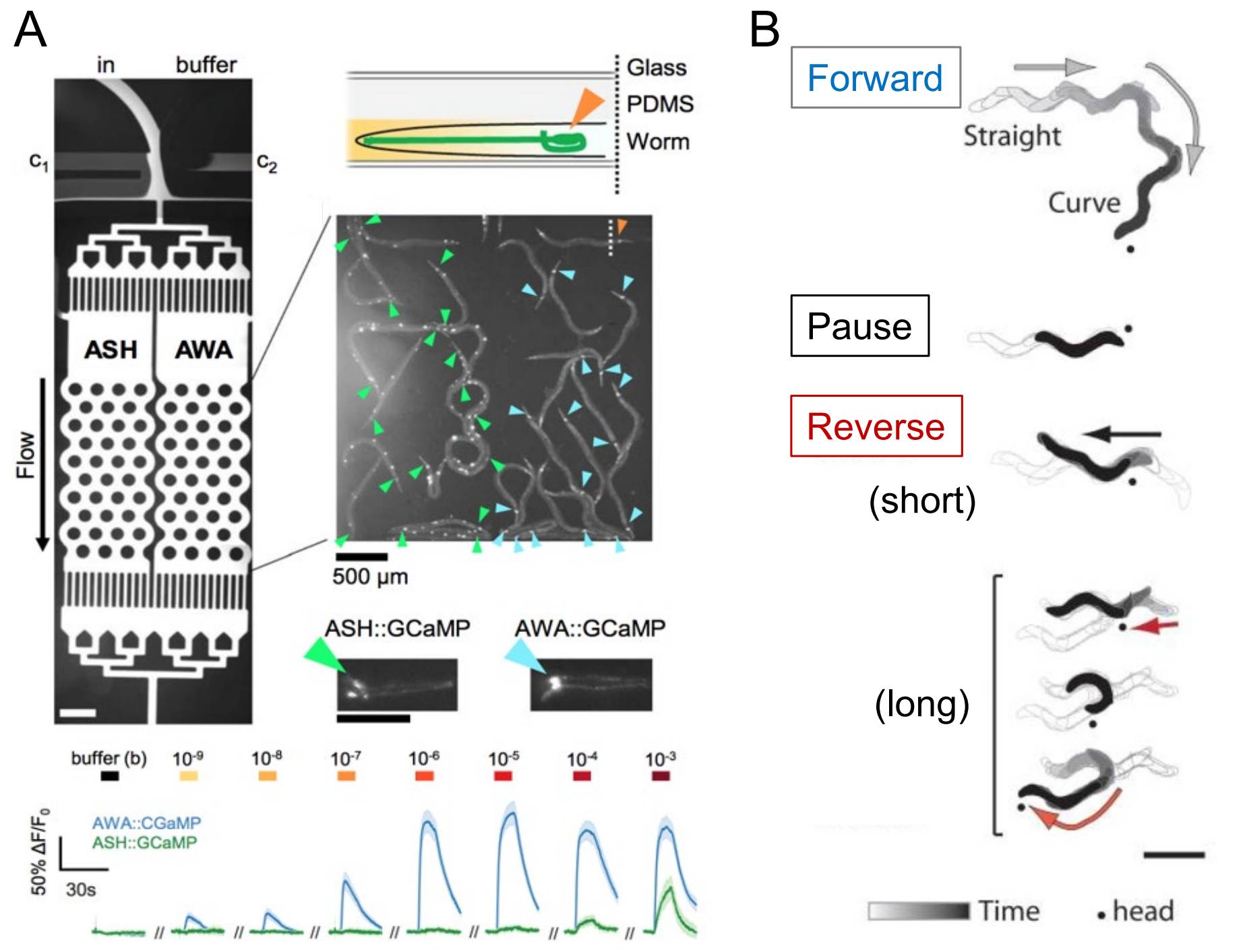
- Calcium dynamics are obtained from the optimal motif as follows:



- A Bayesian decoder generates behavioral decision probability.
- Model allows for non-monotonic stimulus intensity encoding[5].

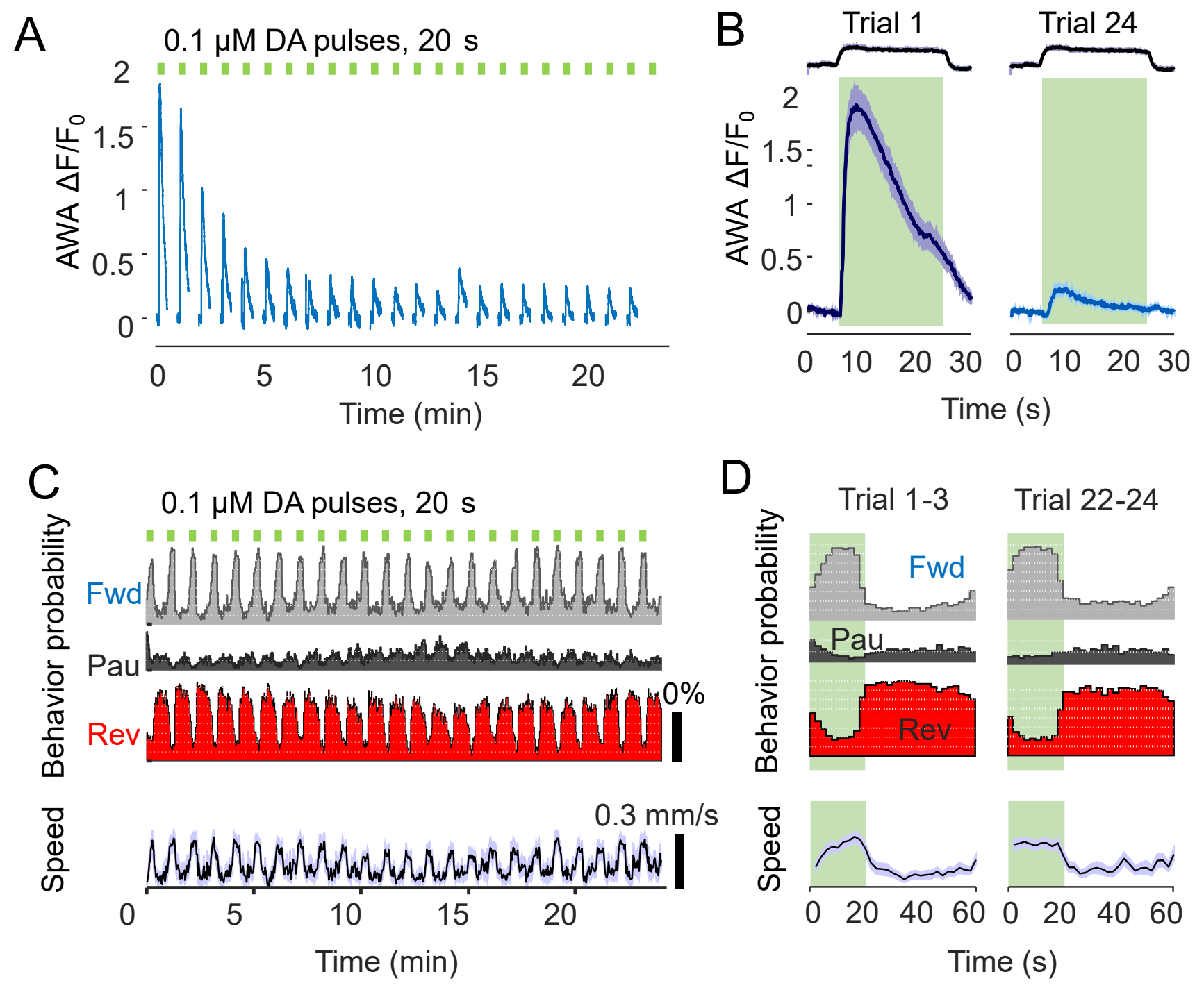
Experimental Data:

- Microfluidic experiments measure *C. elegans* neural responses to precise chemical stimulation by fluorescent calcium imaging and the sensor GCaMP[3-5] (A).
- Behavior responses were quantified as locomotory state probability[6] (B).



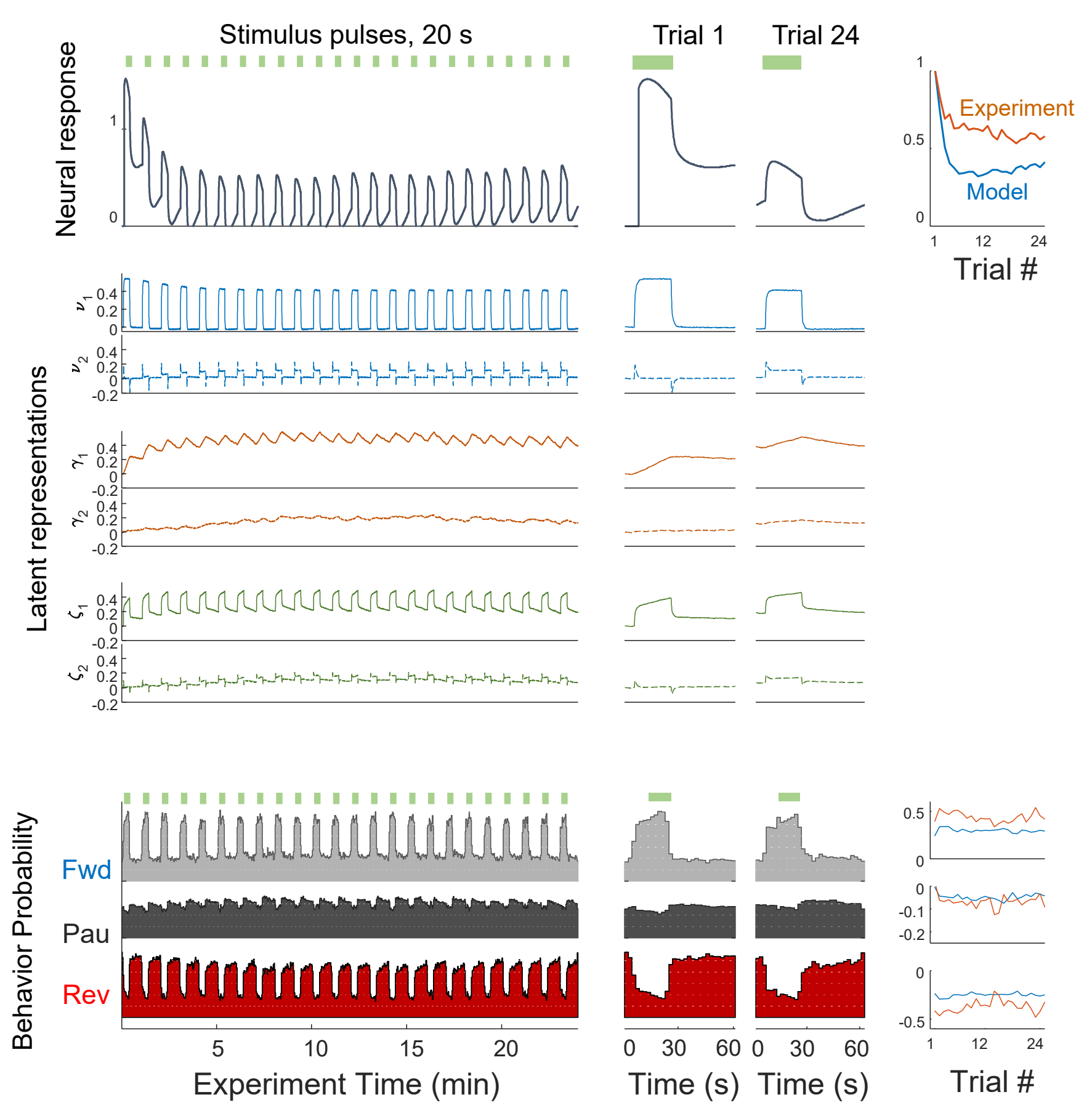
Experiment: Adaptation without habituation

- Neural responses **adapt** ~7-fold over 24 repeated pulses of 0.1 μM diacetyl (DA) for 20 s every minute (A,B).
- Behavioral responses remain **invariant** to repeated pulses and do **not** habituate (C,D).
- *How do behavior responses remain constant during sensory adaptation?*



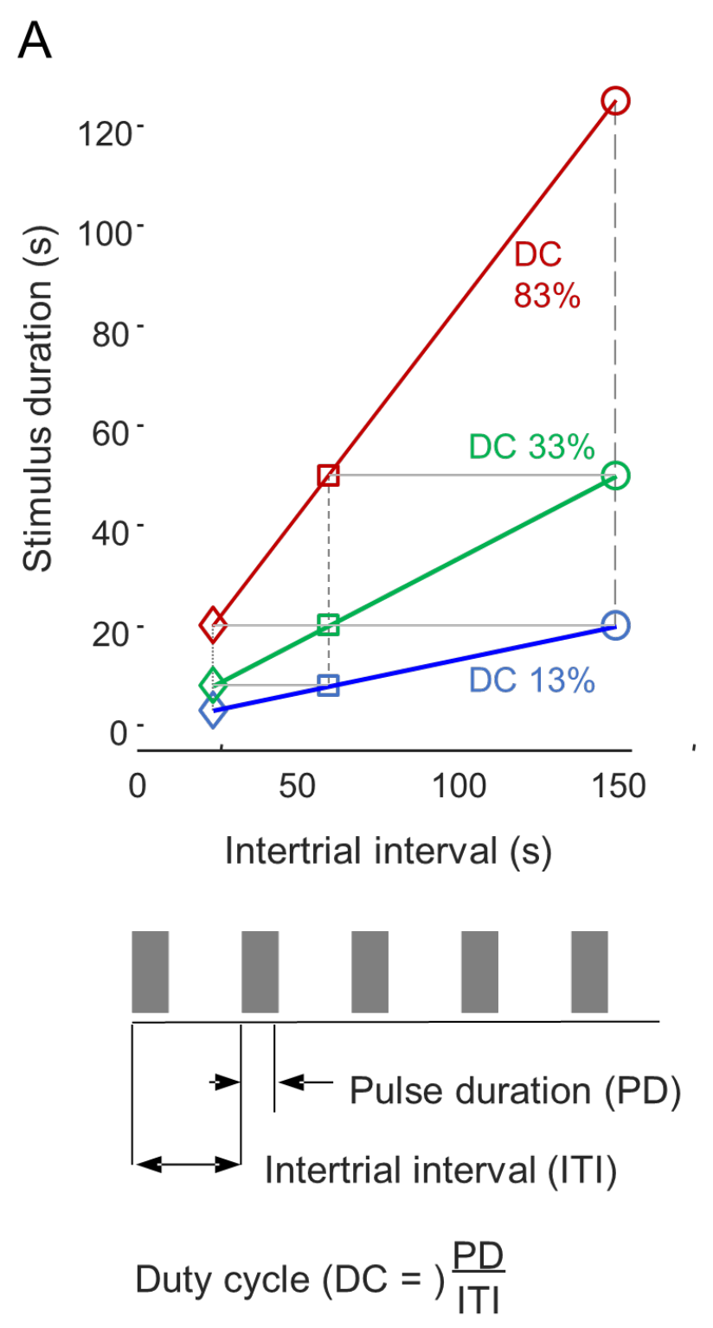
Model: Adaptation without habituation

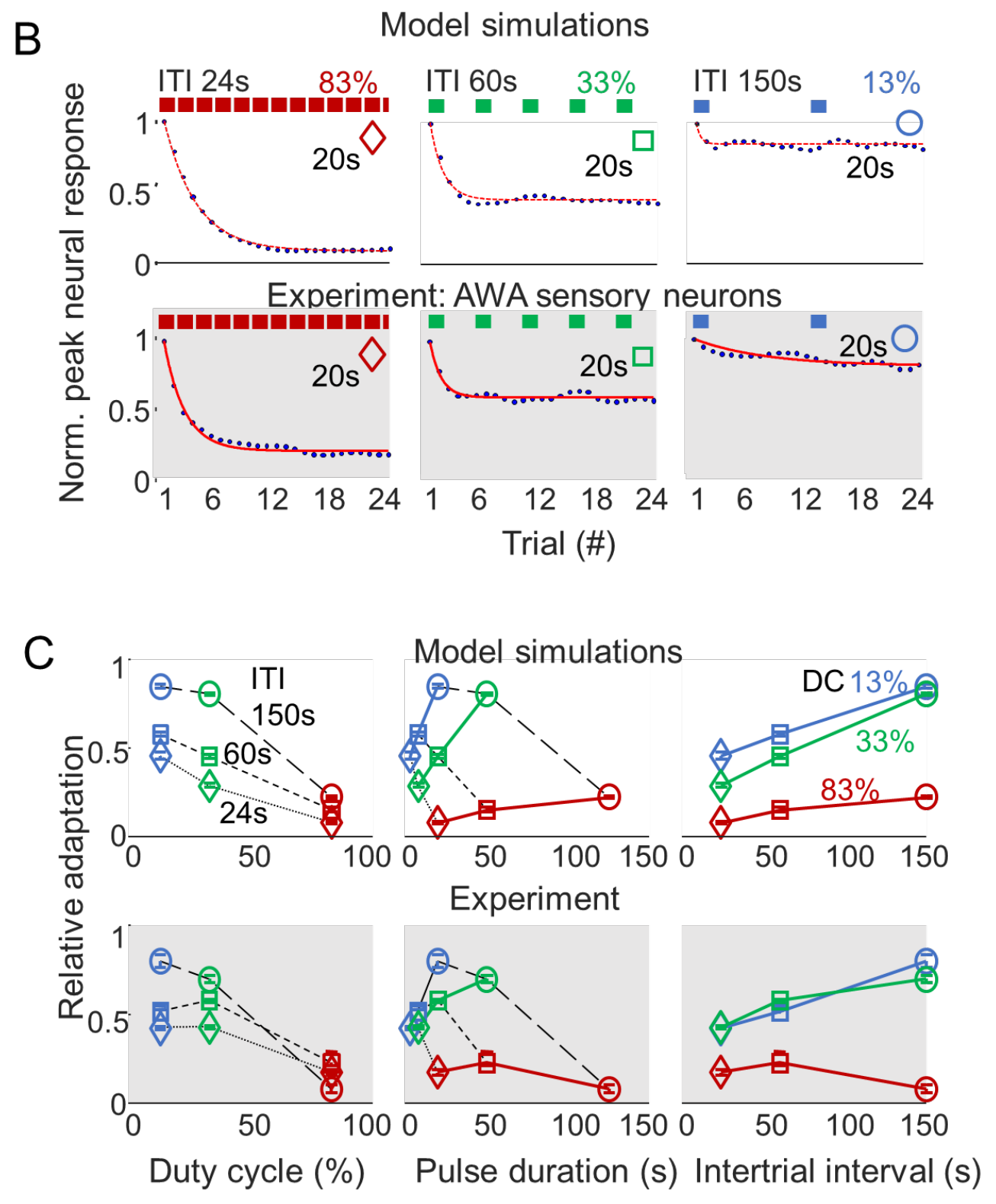
- Model simulations of neural output with optimized parameters demonstrate neural adaptation without habituation.
- Parameters include:
  - τ_v and τ_γ – rate of decay for "fast" and "slow" latent states
  - $drift\_v$ and $drift\_\gamma$ – rate of forgetting prior input and history
  - b – scaling factor input to memory
  - Gaussian mixture components modeling behavior from latent states
- Sensory memory $\gamma(t)$ accumulates over repeated stimulation.



Results: Model predicts adaptation levels for all stimulation patterns

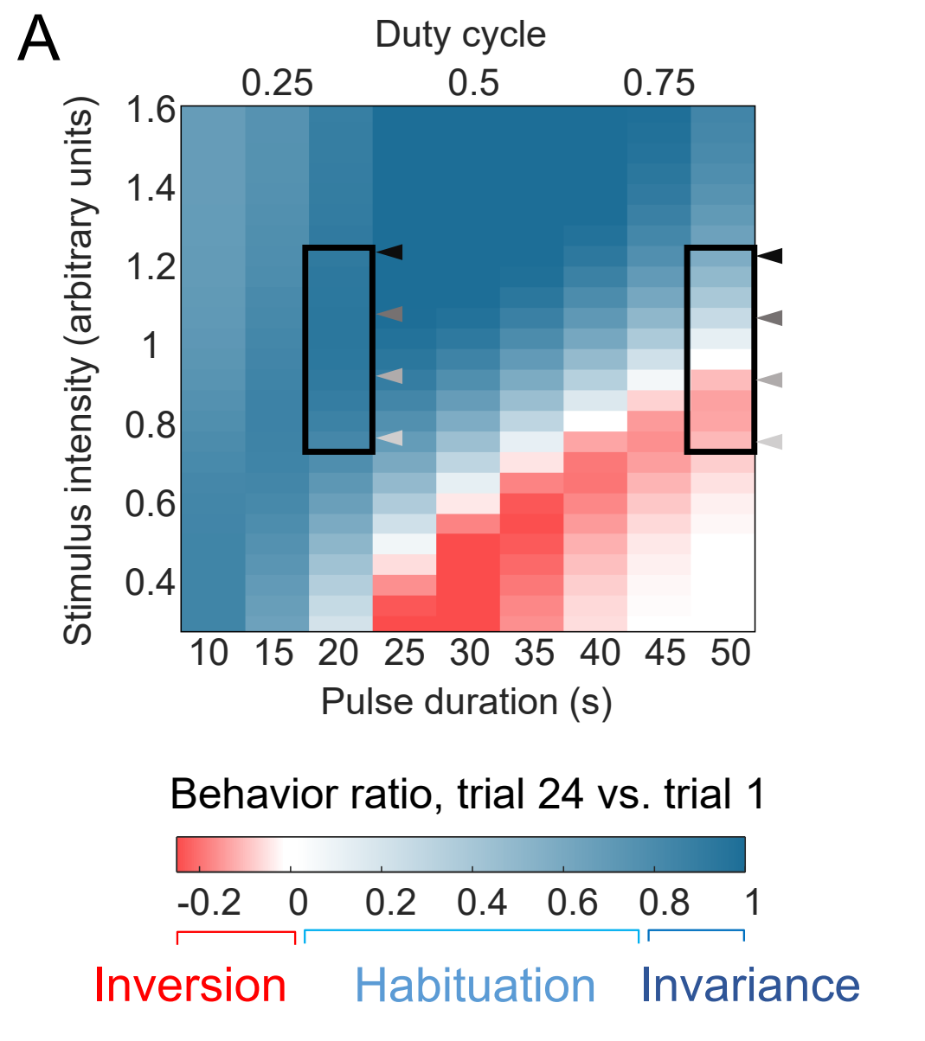
- Using model parameters optimized with one experimental dataset (20s every 60s, 1 μM), neural responses were simulated to varying stimulus pulse duration (PD), inter-trial interval (ITI), and duty cycle (DC = PD / ITI).
- Nine stimulus patterns explored higher and lower PD, ITI, and DC.
- Adaptation in peak neural responses was predicted to be **greater for higher duty cycle and shorter inter-trial interval.**
- Experimental recordings in *C. elegans* show close correspondence to simulations.

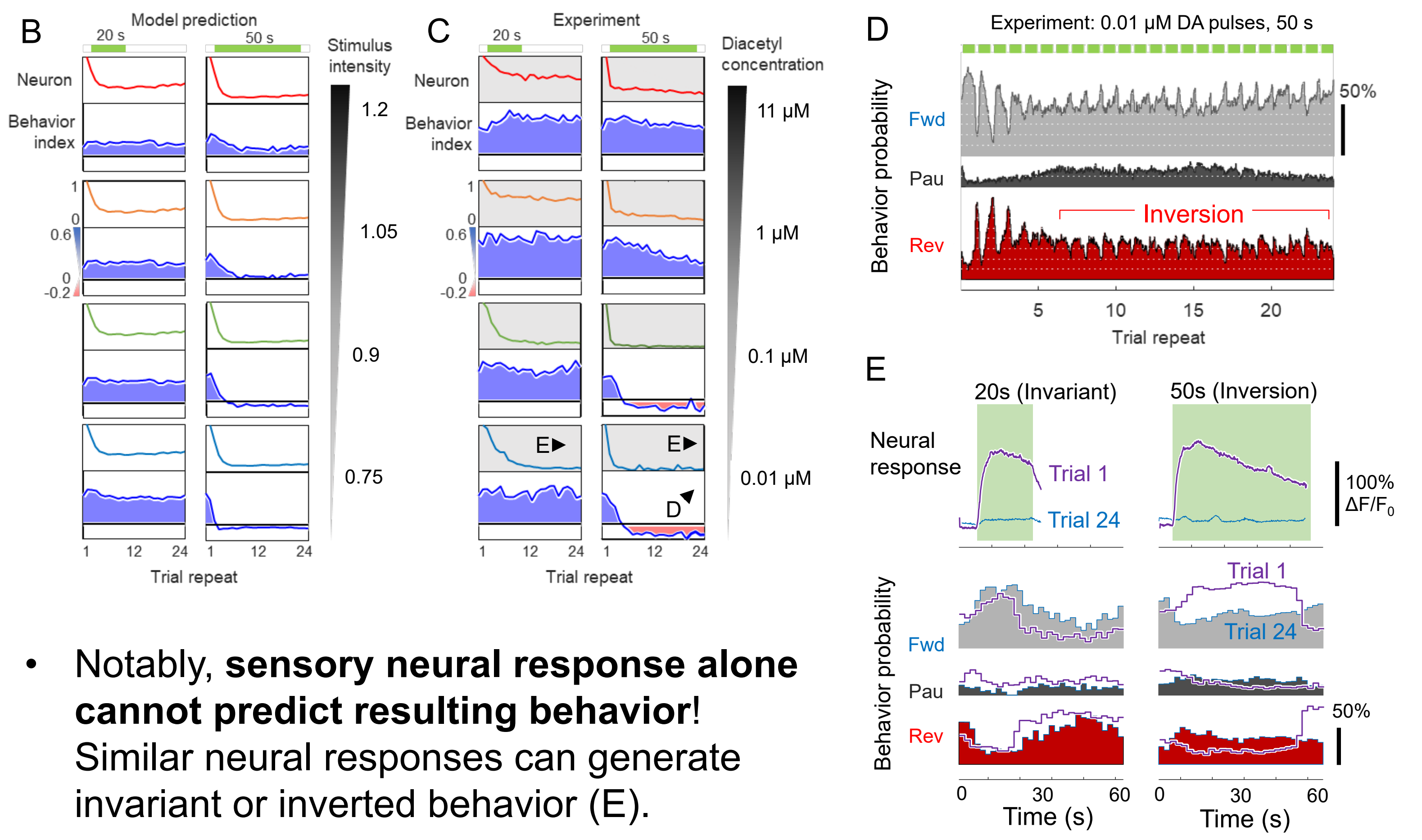




Results: Behavior Invariance, Habituation, and *Behavioral Inversion*

- The model predicts that stimulus concentration and duty cycle determine if behavior responses remain **invariant** or **habituate**.
- A paradoxical regime is predicted, in which behavioral responses habituate below zero response and reverse valence, i.e. attractive stimuli elicit aversive behavior. This **behavioral inversion is predicted to occur at long duty cycle and low stimulus intensity** (A,B).
- Experimental measurements **confirm** this new, unexpected phenomenon (C,D).





- Notably, **sensory neural response alone cannot predict resulting behavior!** Similar neural responses can generate invariant or inverted behavior (E).

Summary & Future directions

- A two time-scale normative model of *C. elegans* sensory responses matched observed neural adaptation without behavioral habituation.
- The model also predicted an *emergent, paradoxical stimulus-to-behavior inversion* that occurs at high duty cycle and low stimulus intensity.
- Behavioral inversion was *indeed observed* in *C. elegans* experimental data. The system enables a rapid model–experiment feedback loop for validation.
- Our integration of theory and modeling affirms the role of dynamical processes, beyond just primary neural response, in mediating behavior.
- How latent representations are encoded in *C. elegans* neural circuitry is currently unknown. Candidates include neuropeptide signaling and interneuron dynamics. Future study with mutants altering these signaling pathways will elucidate these mechanisms.

References & Support

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