The Virtual Patch Clamp: Imputing *C. elegans* Membrane Potentials From Calcium Imaging Data

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TL;DR

- Infer neural activity of *C. elegans*
- Learn simulator parameter values

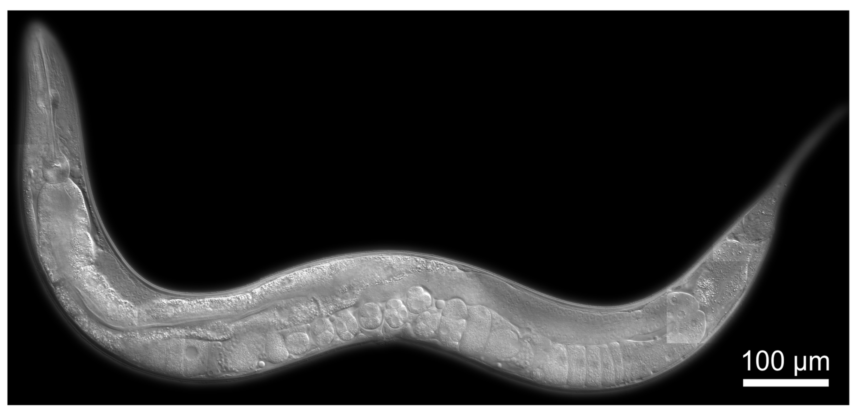

Figure 1a: *Caenorhabditis elegans*. Image courtesy of Chin-Sang laboratory.

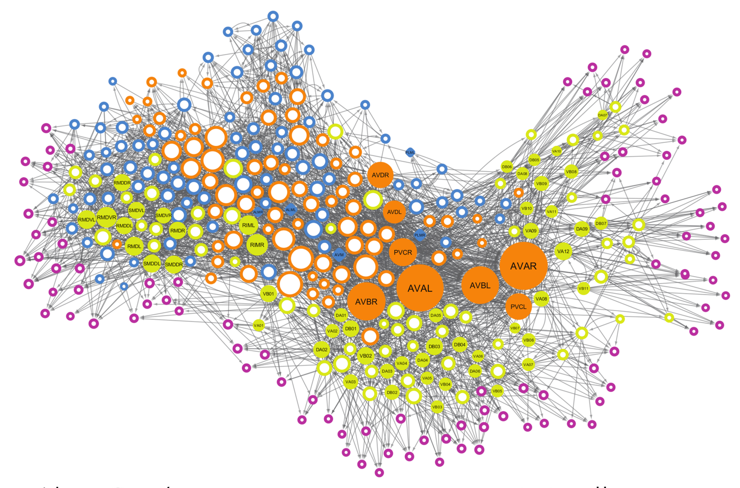

Figure 1b: *C. elegans* connectome, originally mapped by White et al. [1]. Image from Yan et al. [2].

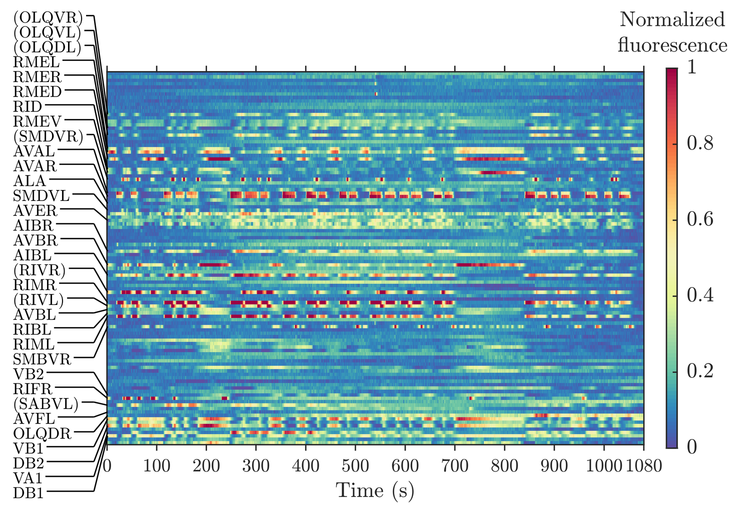

Figure 1c: Calcium imaging data, Kato et al. [3].

```
# Sample state from prior.
params = sample(Ask friendly neuroscientist)
x[0] = sample(Ask friendly neuroscientist)
# Iterate worm.
for t in range(1, T):
    x[t] = sample(x[t-1], params)
    observe(y[t], x[t])  # (Optional fluorescence).
return x
```

Figure 1d: *C. elegans* as a program.

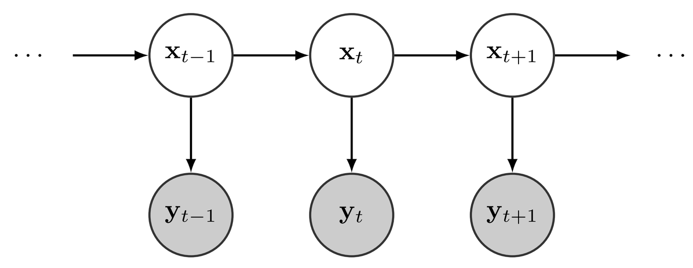

Figure 1e: *C. elegans* as a graphical model.

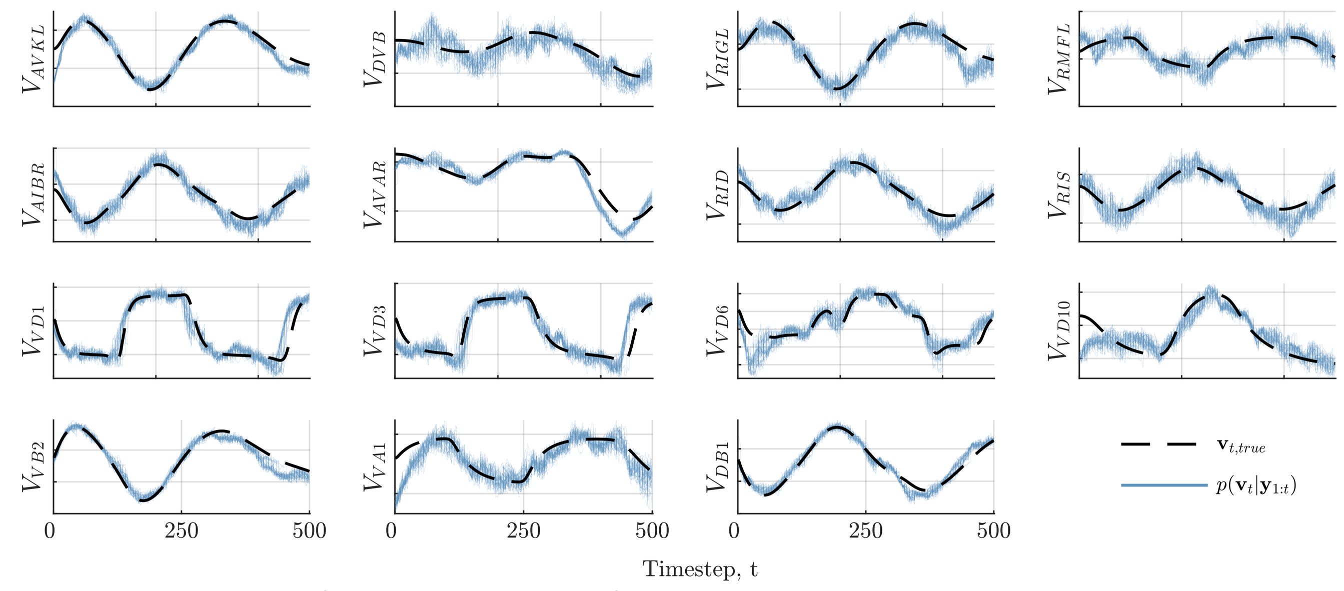

Figure 1f: Neural activity inferred using sequential Monte Carlo.

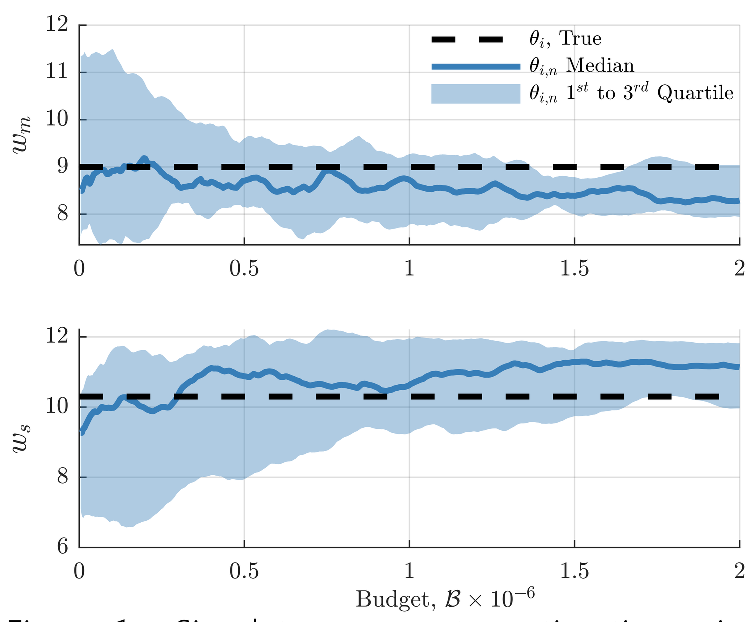

Figure 1g: Simulator parameter estimation using variational optimization of pseudo-marginal evidence approximation.

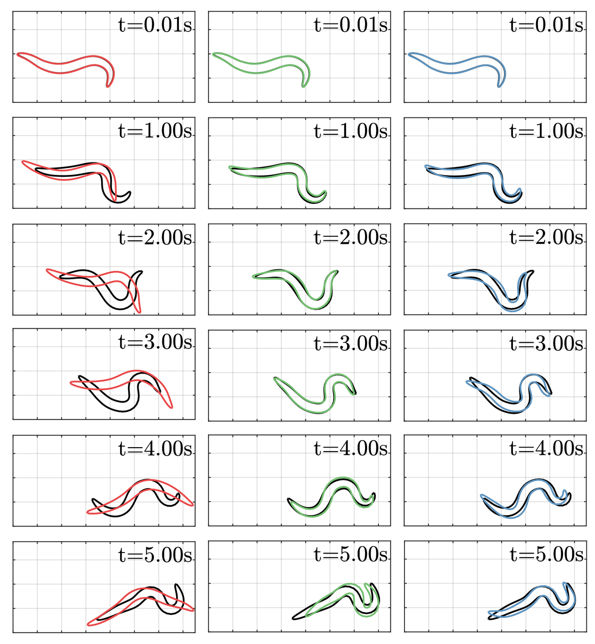

Figure 1h: Behavior simulation, inferred without being conditioned on.

Simulator

$$\frac{dV_i}{dt} = \frac{V_{r_i} - V_i}{C_i R_i} + \sum_{j=1}^{N} \left(I_{ij}^{gap} + I_{ij}^{syn} + I_i^{stim}\right)$$

$$I_{ij}^{gap} = n_{ij}^{gap} g_m^{gap} (V_i - V_j)$$

$$I_{ij}^{syn} = n_{ij}^{syn} g_{ij}^{syn} (E_j - V_i)$$

$$g_{ij}^{syn} = \frac{g_m^{syn}}{1 + \exp\left(k \frac{V_j - V_j^{eq}}{V_{range}}\right)}$$

Figure 2a: Governing relationships for neural dynamics, Wicks et al. [5].

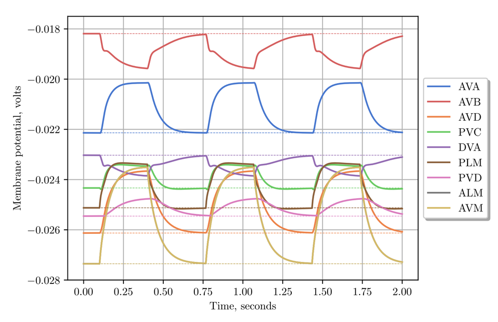

Figure 2b: Simulation of 9 neuron subsystem (see Wicks et al. [5]).

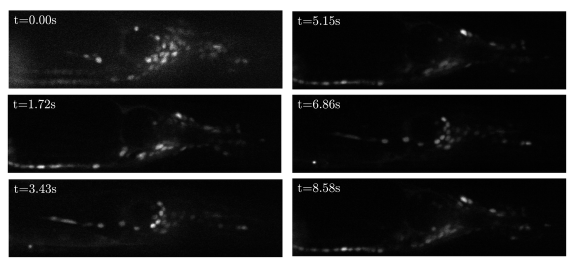

Figure 2c: Raw fluorescence images, from Kato et al. [3].

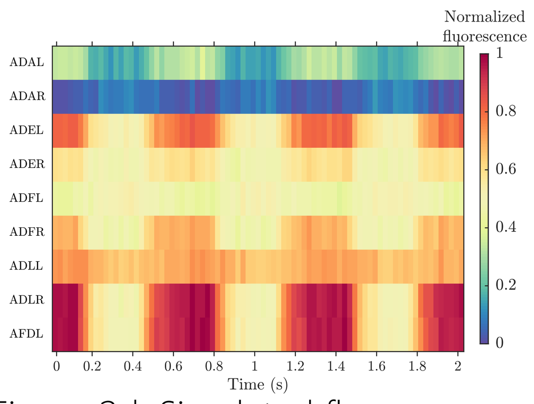

Figure 2d: Simulated fluorescence traces using calcium dynamics from Rahmati et al. [6]

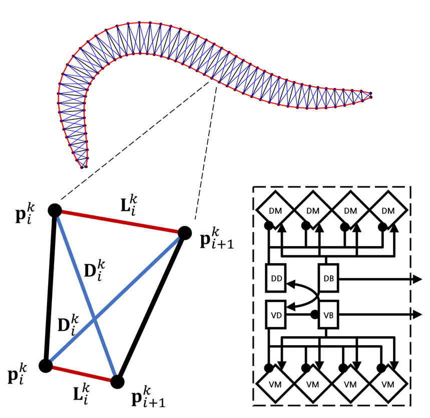

Figure 2e: WormSim locomotion model from Boyle et al. [7].

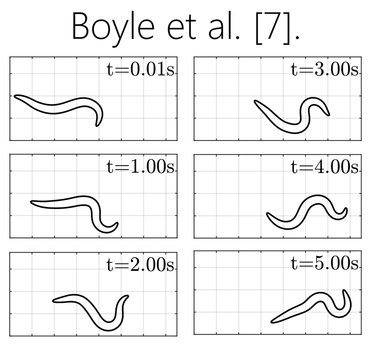

Figure 2f: Simulated body locomotion.

State Space Inference

- Wish to recover posterior distribution over neural activations, calcium concentrations, body pose, and proprioceptive feedback, conditioned on partial calcium imaging observations.
- Of 302 neurons, approximately 50 have corresponding positively identified fluorescence traces.
- Use SMC [8] to compute model evidence and posterior predictive distribution over neural activations and body pose.

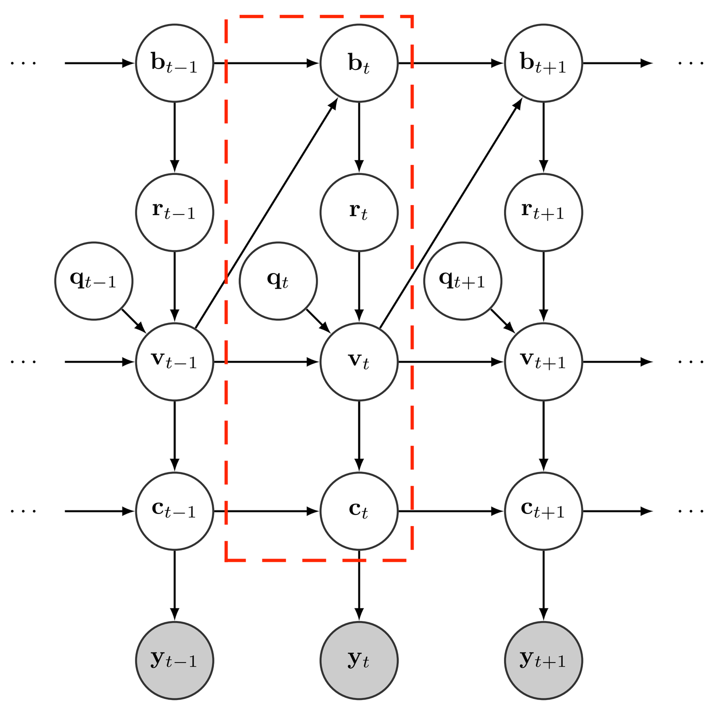

Figure 3: Graphical model of the full simulator corresponding to *C. elegans*.

Parameter Estimation

- Seek $\theta^* = \operatorname{argmax}_{\theta^*} p(\theta|y)$
  $= \operatorname{argmax}_{\theta^*} \int p(y|x,\theta) p(x|\theta) p(\theta) dx$
- y is calcium imaging time series.
- Parameters include synaptic weights, gap junction conductivities, electromagnetic properties etc.
- Simulators are not differentiable.
- Use approximate gradient method variational optimization [4].
- Maximize expectation under proposal:
  $\phi^* = \operatorname{argmax} L(\phi)$
  $= \operatorname{argmax} \mathrm{E}_{\theta^{(i)} \sim q(\theta|\phi)} \left[p(\theta|y) \right]$
  $\nabla_\phi L(\phi) = \mathrm{E}_{\theta^{(i)} \sim q(\theta|\phi)} \left[p(\theta^{(i)}|y) \nabla_\phi \log q(\theta^{(i)} | \phi) \right]$

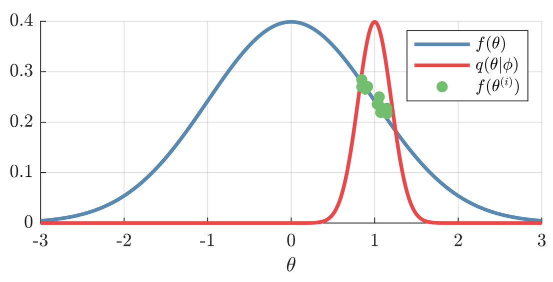

Figure 4a: Illustration of VO

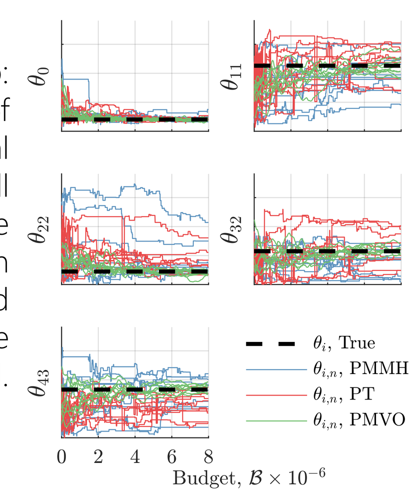

Figure 4b: Comparison of variational optimization to full posterior inference methods on partially observed autoregressive model.

Community

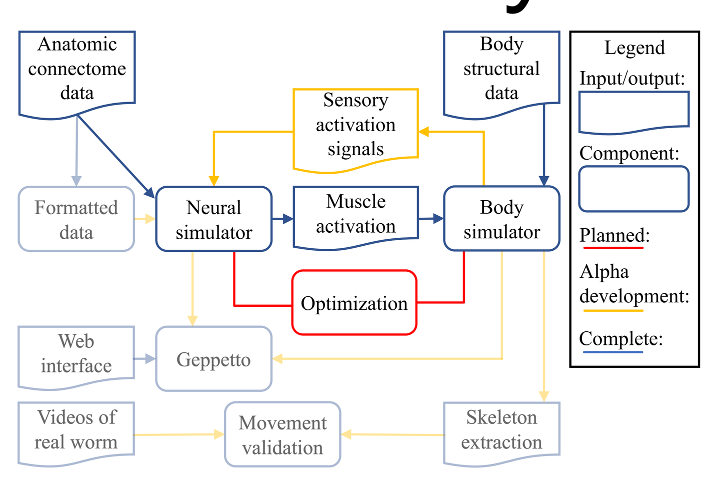

Figure 5: Simulation pipeline proposed by OpenWorm. Adapted from Sarma et al. [9].

Implementation

- Python and C++ implementation using ZeroMQ inter-process communication.
- Particle sweeps parallelized with worker pools intra-node.
- VO parallelized across multiple distributed compute nodes, coordinated using OpenMPI, to >100 nodes.

References

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