Inferring Synaptic Update Rules in a Neural Simulator

Honours Thesis

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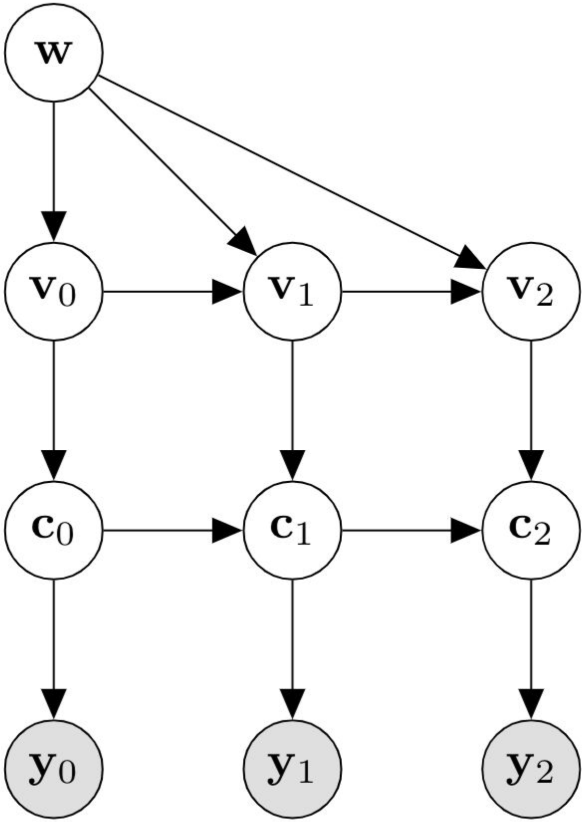
HMM for static neural circuit

Synaptic Weight Matrix $\mathbf{w} \in \mathbb{R}^{n \times n}$

Membrane Potential $\mathbf{v}_t \in \mathbb{R}^n$

Intracellular [Ca^{2+}] $\mathbf{c}_t \in \mathbb{R}^n$

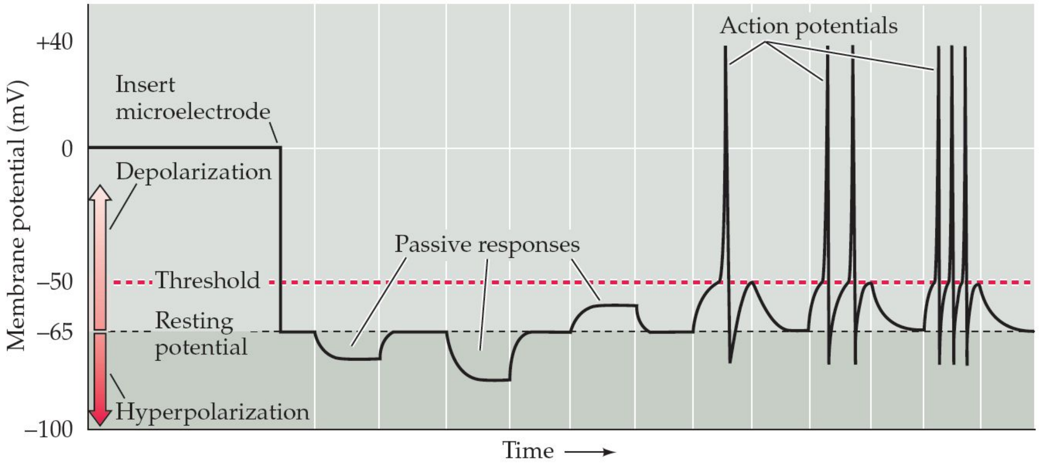
Calcium Fluorescence $\mathbf{y}_t \in \mathbb{R}^n$



Neuroscience Background

Membrane Potential $\mathbf{v}_t \in \mathbb{R}^n$

- determines neuron's activity (depolarization = active, hyperpolarization = suppressed)
- membrane potential = electrical potential inside neuron - electrical potential outside neuron
- electrical potentials determined by concentrations of charged ions (e.g. Na^+, K^+, Cl^-)



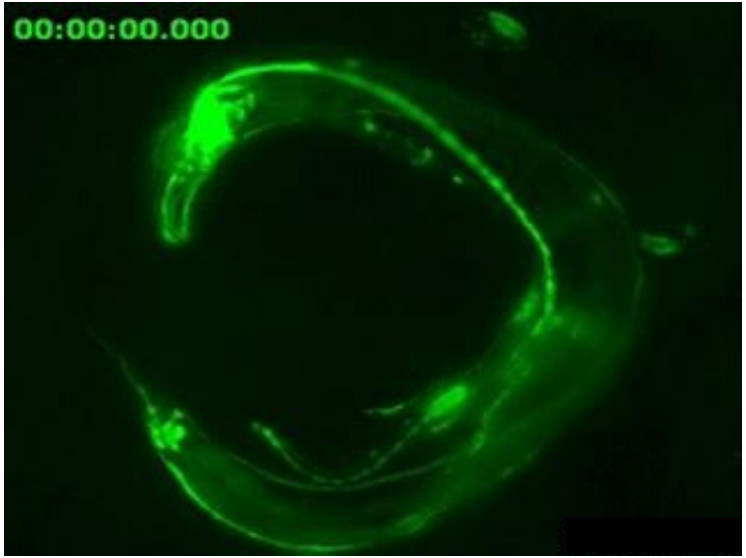
Neuroscience Background

Intracellular [Ca^{2+}] $\mathbf{c}_t \in \mathbb{R}^n$

- increases when neuron's membrane is depolarized

Calcium Fluorescence $\mathbf{y}_t \in \mathbb{R}^n$

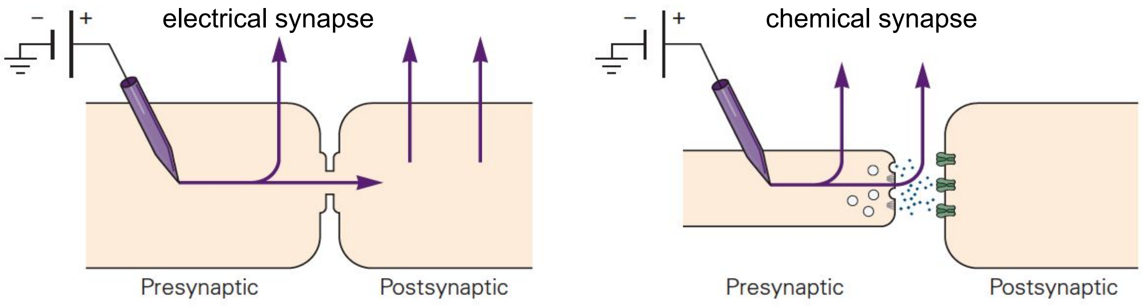
- measures intracellular [Ca^{2+}] using molecules which fluoresce when they bind calcium
- indirect measure of neuron activity



Synaptic Plasticity

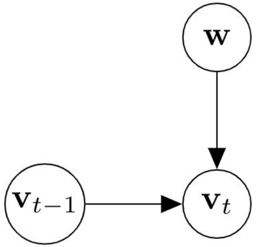
Synaptic Weight Matrix $\mathbf{w} \in \mathbb{R}^{n \times n}$

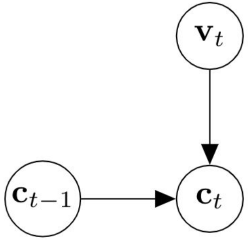
- Synapse: junction where membrane potential of one neuron influences membrane potential of another

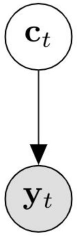


- Synaptic Weight: abstraction denoting influence exerted by one neuron on the other
    - Synaptic weight determined by receptor, channel, presynaptic vesicle density, etc.

Deterministic Simulator







$$c_T \frac{dv_i}{dt} = I_i^{(s)} - I_i^{(c)} - I_i^{(e)} - g_m(v_i - V_L)$$

$$I_i^{(e)} = \sum_{j=1}^{N_n} g^{(e)} W_{ji}^{(e)} (v_j - v_i)$$

$$I_i^{(c)} = \sum_{j=1}^{N_n} g^{(c)} W_{ji}^{(c)} s_j (v_i - E_j)$$

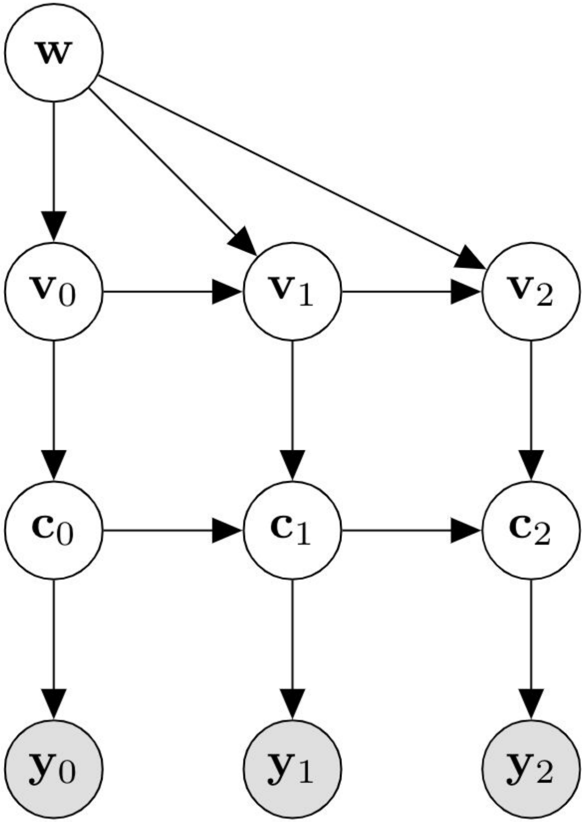
$$s_i = \left(1 + \exp\left\{K \frac{v_i - V_i^{Eq}}{V_{Range}}\right\}\right)^{-1}$$

$$\frac{dc_i}{dt} = -\kappa_{Ca} I_i^{(Ca)} - \frac{c_i - c^{Base}}{\tau_{Ca}}$$

$$I_i^{(\mathrm{Ca})} = g_{Ca} s_\infty (v_i - E_{Ca})$$

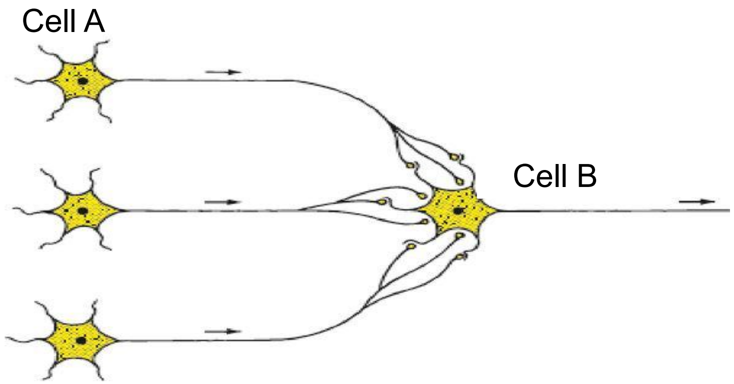
$$s_\infty(v) = \left(1 + \exp\left\{\frac{-(v - v^H)}{\rho}\right\}\right)$$

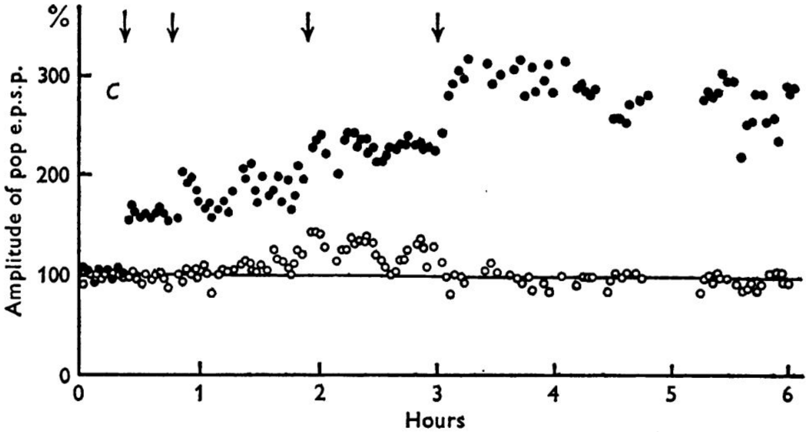
$$F_t = \kappa_F \frac{c_i}{c_i + K_d} + d_F$$



Synaptic Plasticity

Donald Hebb (1949): When cell A “repeatedly or persistently” takes part in firing cell B, the efficiency of A’s signal to B (weight of synapse) is increased by some physiological process





Bliss & Lomo, 1973

Most learning theories incorporate the idea that synaptic plasticity is a fundamental mechanism by which behavioural response is modified.

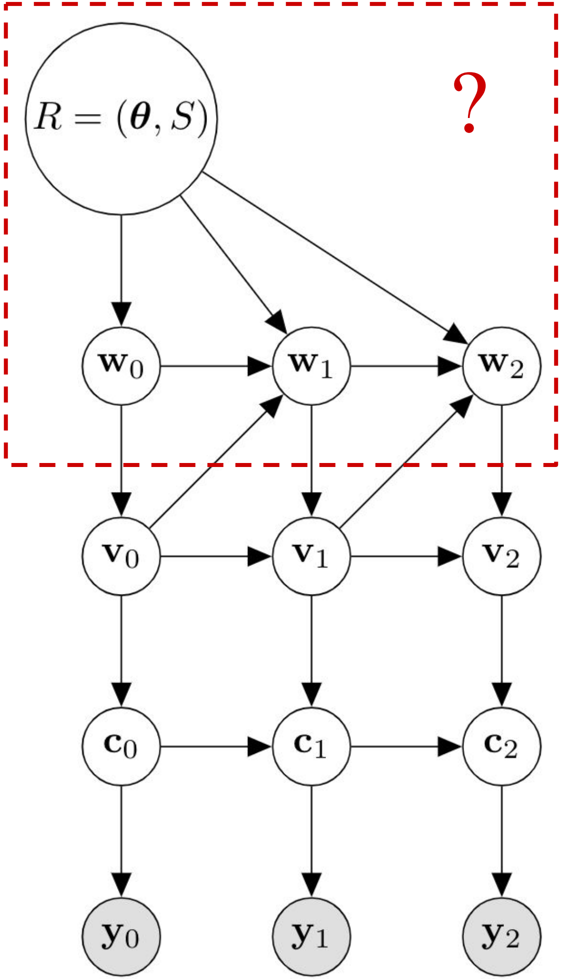
Synaptic Plasticity

A Physiological Basis for a Theory of Synapse Modification

Mark F. Bear, Leon N Cooper, Ford F. Ebner

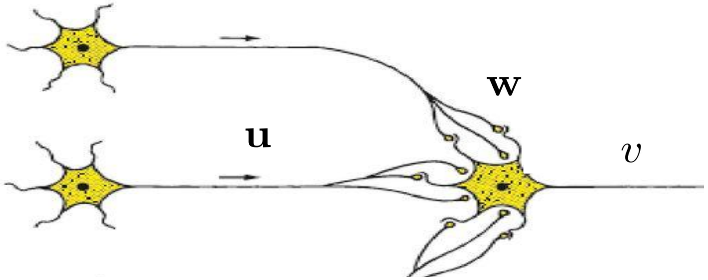
Science, New Series, Vol. 237, No. 4810 (Jul. 3, 1987), pp. 42-48

. A basic problem becomes how these synapses adjust their weights so that the resulting neural network shows the desired properties of memory storage and cognitive behavior.



Formalizing Synaptic Update Rules

Donald Hebb (1949): When cell A “repeatedly or persistently” takes part in firing cell B, the efficiency of A’s signal to B (weight of synapse) is increased by some physiological process



$$\tau_w \frac{d\mathbf{w}}{dt} = v\mathbf{u}$$

$\mathbf{w} \in \mathbb{R}^n$	upstream synaptic weights
$\mathbf{u} \in \mathbb{R}^n$	presynaptic firing rates
$v \in \mathbb{R}$	postsynaptic firing rate
$\tau_w \in \mathbb{R}$	rate constant

Compositional structure:

S = div({}, mul({}, {}))

Continuous parameter(s):

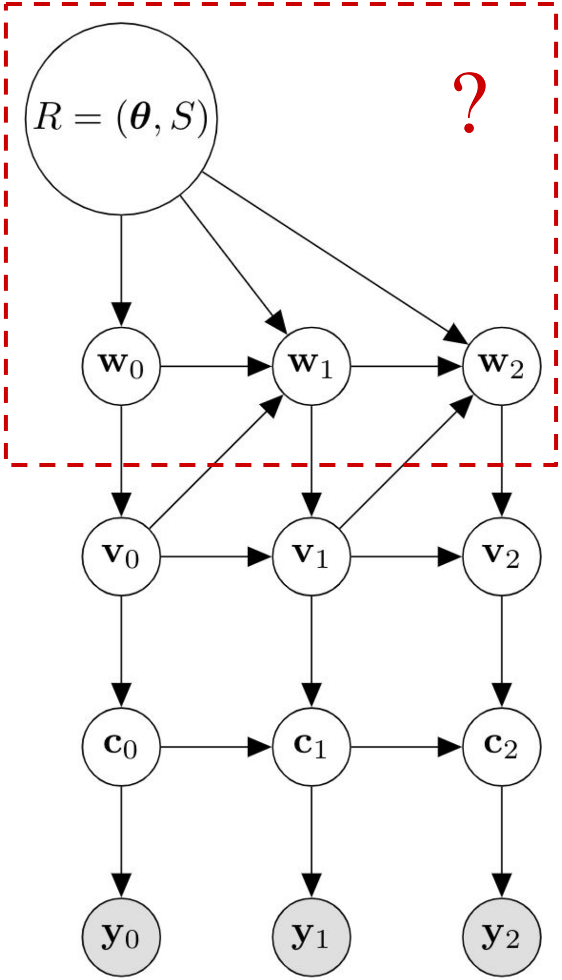
$\boldsymbol{\theta}$ = τ_w

SURF Goal

Model synaptic weight dynamics underlying plasticity in a given behaviour

Big picture: infer $p(\mathbf{w}, R|\mathbf{y})$ given

observations $\mathbf{y}$ of neural activity in circuit underlying behaviour, during learning



Simplifying Assumptions

1) Deterministic simulator and R :

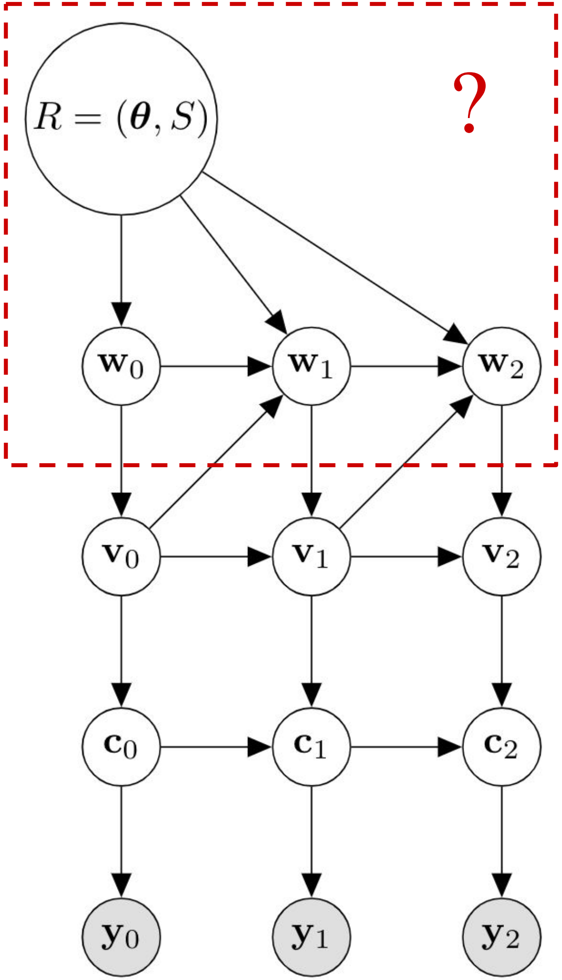
- only need $\mathbf{w}_0$ and R
- maximum a posteriori estimate $\mathbf{w}_0^*, R^* = \underset{\mathbf{w}_0, R}{\operatorname{argmax}}\ p(\mathbf{w}_0, R|\mathbf{y})$

  is decent approximation of $p(\mathbf{w}, R|\mathbf{y})$

2) Finite set of candidate structures $\{S_1, \ldots, S_k\}$:

- first step towards difficult search over infinite discrete structure space

$$\mathbf{w}_0^*, \boldsymbol{\theta}_k^* = \underset{\mathbf{w}_0, \boldsymbol{\theta}_k}{\operatorname{argmax}}\, p(\mathbf{w}_0, \boldsymbol{\theta}_k|\mathbf{y})$$

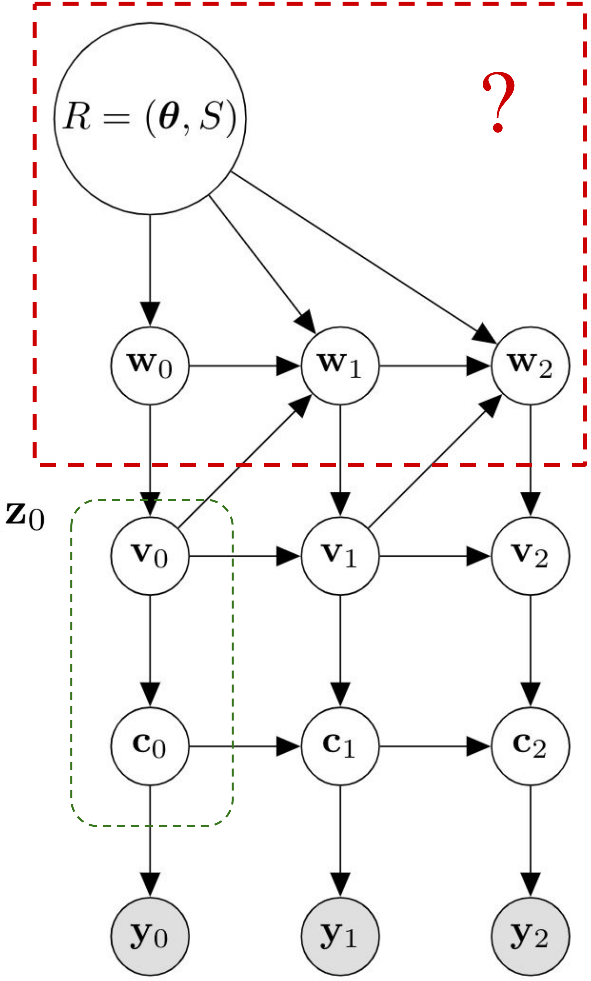


Continuous Optimization Objective

$$\mathbf{w}_0^*, \boldsymbol{\theta}_k^* = \underset{\mathbf{w}_0, \boldsymbol{\theta}_k}{\operatorname{argmax}}\, p(\mathbf{w}_0, \boldsymbol{\theta}_k | \mathbf{y})$$

$$= \underset{\mathbf{w}_0, \boldsymbol{\theta}_k}{\operatorname{argmin}} - \log(\mathbb{E}_{\mathbf{z} \sim p(\mathbf{z}|\mathbf{w}_0, \boldsymbol{\theta}_k, S_k)}[p(\mathbf{y}|\mathbf{z})])$$

$$- \log(p(\mathbf{w}_0 | \boldsymbol{\theta}_k, S_k)) - \log(p(\boldsymbol{\theta}_k | S_k))$$



Continuous Optimization Objective

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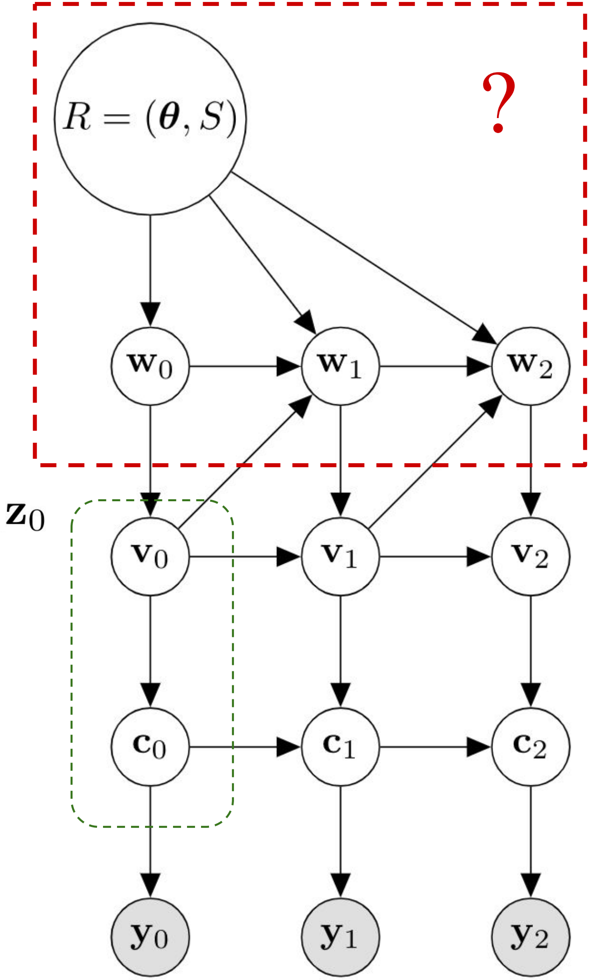
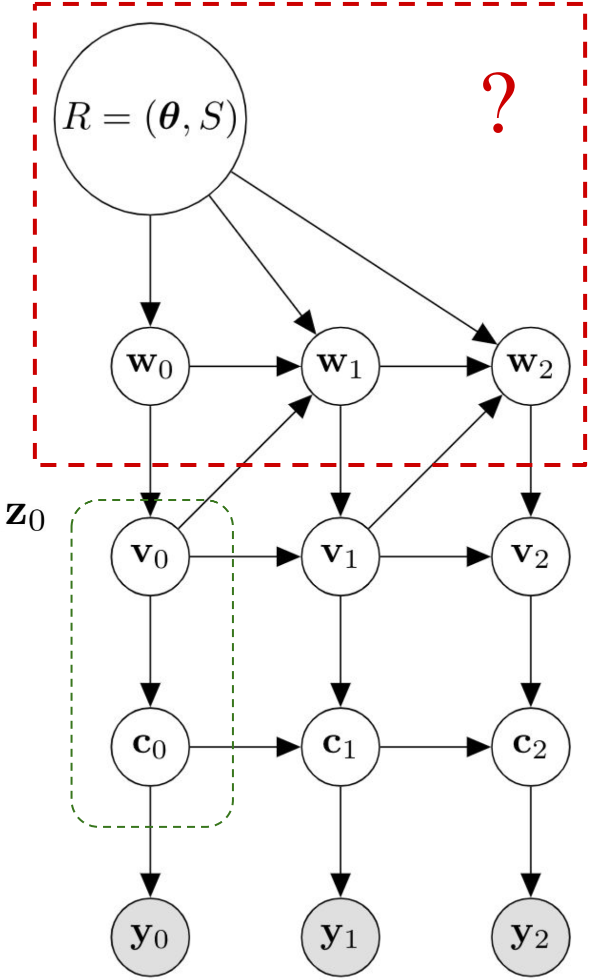


Continuous Optimization Objective

$$-\log(p(\mathbf{w}_0|\boldsymbol{\theta}_k, S_k)) - \log(p(\boldsymbol{\theta}_k|S_k))$$

Rayleigh distribution with scale parameter for each non-zero entry equaling the experimentally determined naive weights

$$\mathcal{N}(1, 0.1)$$

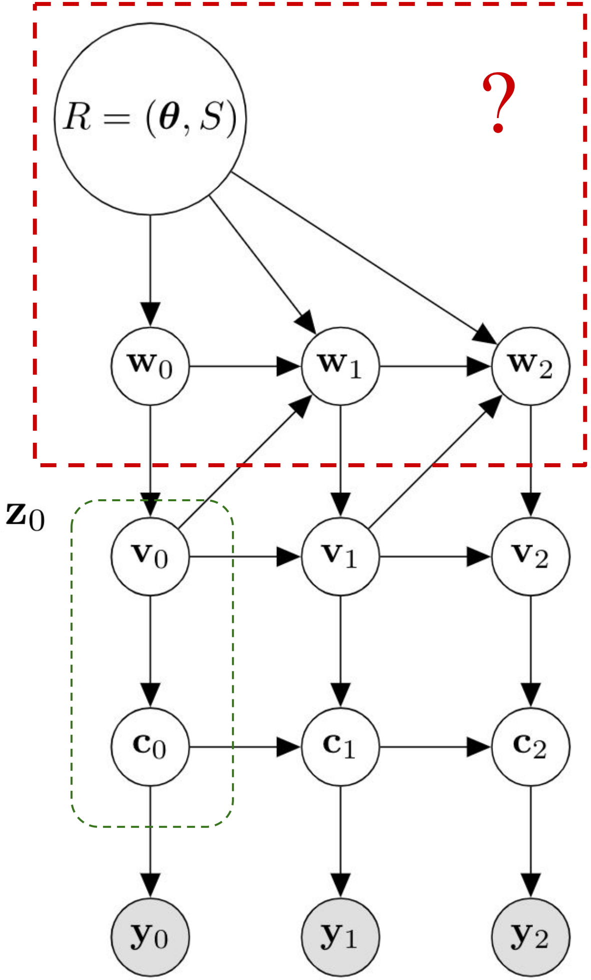


Continuous Optimization Objective

$$\mathbf{w}_0^*, \boldsymbol{\theta}_k^* = \underset{\mathbf{w}_0, \boldsymbol{\theta}_k}{\operatorname{argmax}}\, p(\mathbf{w}_0, \boldsymbol{\theta}_k | \mathbf{y})$$

$$= \underset{\mathbf{w}_0, \boldsymbol{\theta}_k}{\operatorname{argmin}} - \log(\mathbb{E}_{\mathbf{z}\sim p(\mathbf{z}|\mathbf{w}_0, \boldsymbol{\theta}_k, S_k)}[p(\mathbf{y}|\mathbf{z})])$$

$$- \log(p(\mathbf{w}_0 | \boldsymbol{\theta}_k, S_k)) - \log(p(\boldsymbol{\theta}_k | S_k))$$

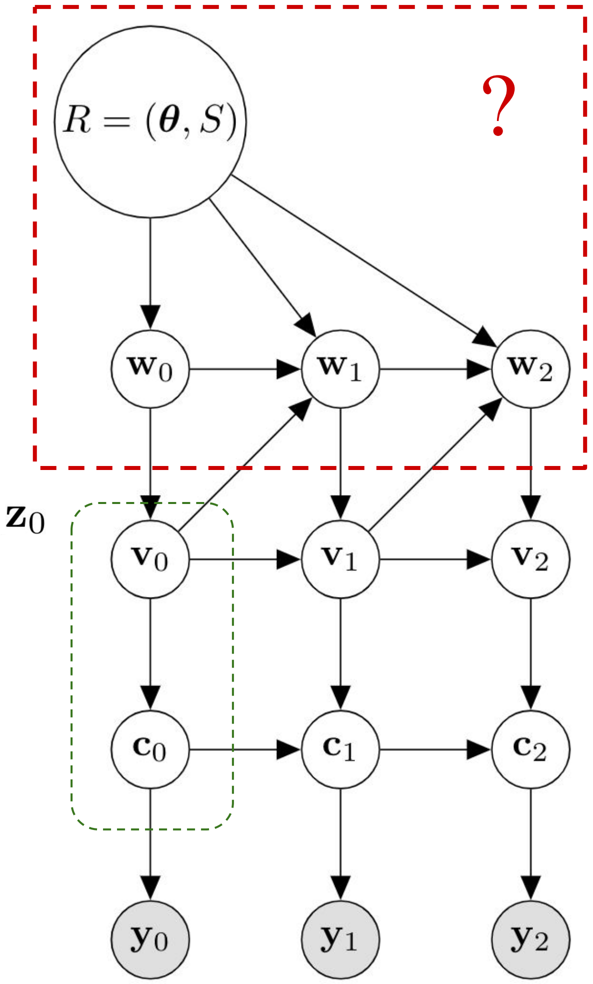


Continuous Optimization Objective

$$-\log(\mathbb{E}_{\mathbf{z}\sim p(\mathbf{z}|\mathbf{w}_0,\boldsymbol{\theta}_k,S_k)}[p(\mathbf{y}|\mathbf{z})])$$

$$= \lim_{N\to\infty}\left[-\log\left(\frac{1}{N}\sum_{i=1}^{N}\prod_{t=0}^{T}p(\mathbf{y}_t|\mathbf{z}_t^{(i)})\right)\right]$$ By LLN

Approximate expectation with Monte Carlo integration



Continuous Optimization Objective

This MC integration requires:

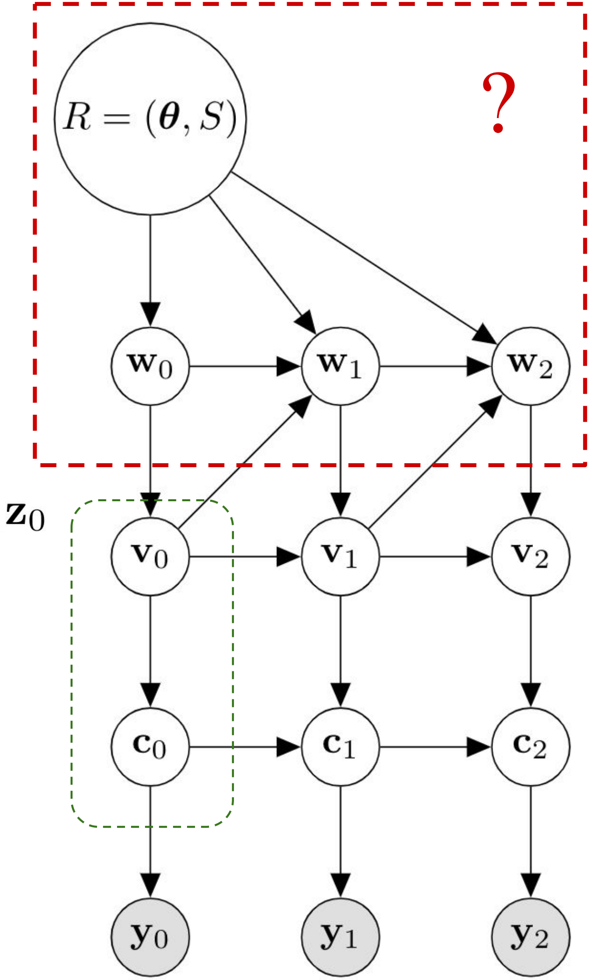
1) Samples $\{\mathbf{z}^{(i)}\}_{1\leq i\leq N} \sim p(\mathbf{z}|\mathbf{w}_0, \boldsymbol{\theta}_k, S_k)$

   - Sample with simulator, initialize $\mathbf{z}_0$ randomly

2) Emission density $p(\mathbf{y}_t|\mathbf{z}_t^{(i)})$

$$\mu_F = \kappa_F(\mathbf{c}_t^{(i)} \oslash (\mathbf{c}_t^{(i)} + K_d)) + d_F$$

$$p(\mathbf{y}_t|\mathbf{z}_t^{(i)}) = \frac{1}{\sigma_F\sqrt{2\pi}} \exp\left\{\frac{-1}{2}\left(\frac{\mathbf{y}_t - \mu_F}{\sigma_F}\right)^2\right\}$$



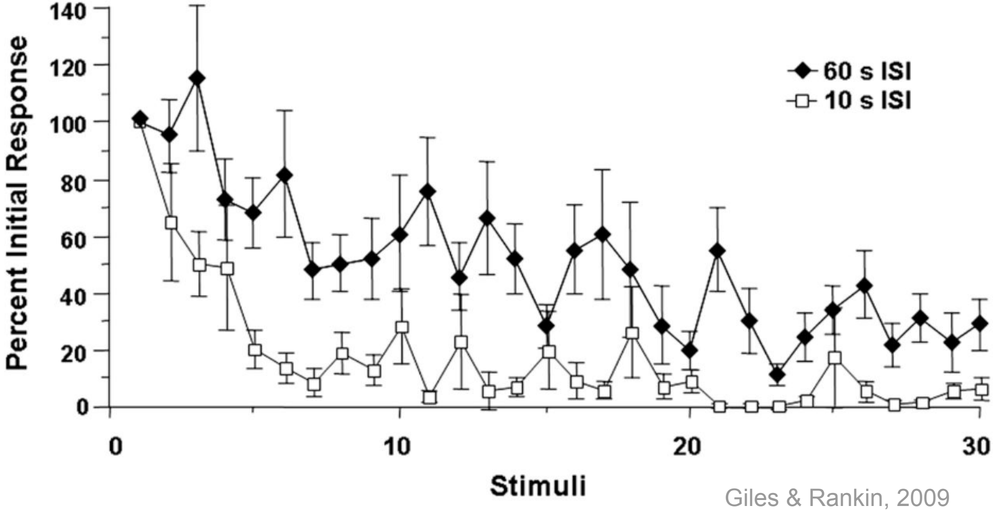
Synaptic Update Rule Finder

Algorithm 1 Synaptic Update Rule Finder

procedure SURF$(d, k, n, N \in \mathbb{Z}^+)$
  $\mathcal{L} \leftarrow \mathbf{0}_{k\times 1}$
  for $i \leftarrow 1$ **to** k **do**
    $(\boldsymbol{\theta}_i, S_i) \leftarrow G(d)$ ▷ Randomly initialize rule structure and parameters
    $\mathbf{w}_{0,i} \sim p(\mathbf{w}_0 | \boldsymbol{\theta}_i, S_i)$ ▷ Randomly initialize initial weights
    for $t \leftarrow 1$ **to** n **do** ▷ Descend gradient n times, with variable step size η
      for $j \leftarrow 1$ **to** N **do** ▷ Generate N samples for MC integration
        $\mathbf{z}^{(j)} \sim p(\mathbf{z} | \mathbf{w}_{0,i}, \boldsymbol{\theta}_i, S_i)$
      end for
      $\mathcal{L}_i \leftarrow -\log\left(\frac{1}{N}\sum_{j=1}^{N}\prod_{t=1}^{T} p(\mathbf{y}_t | \mathbf{z}_t^{(j)})\right) - \log(p(\mathbf{w}_{0,i} | \boldsymbol{\theta}_i, S_i)) - \log(p(\boldsymbol{\theta}_i | S_i))$
      $[\mathbf{w}_{0,i}, \boldsymbol{\theta}_i] \leftarrow [\mathbf{w}_{0,i}, \boldsymbol{\theta}_i] - (\eta)^t \nabla_{\mathbf{w}_{i,0}, \boldsymbol{\theta}_i}(\mathcal{L})$
    end for
  end for
  $j \leftarrow \operatorname{argmin}_{1 \le i \le k} \mathcal{L}_i$
  return $(\mathbf{w}_{0,j}, \boldsymbol{\theta}_j, S_j)$
end procedure

Experiment

Plastic behaviour of interest: Tap-withdrawal response habituation in *C. elegans* (roundworm)

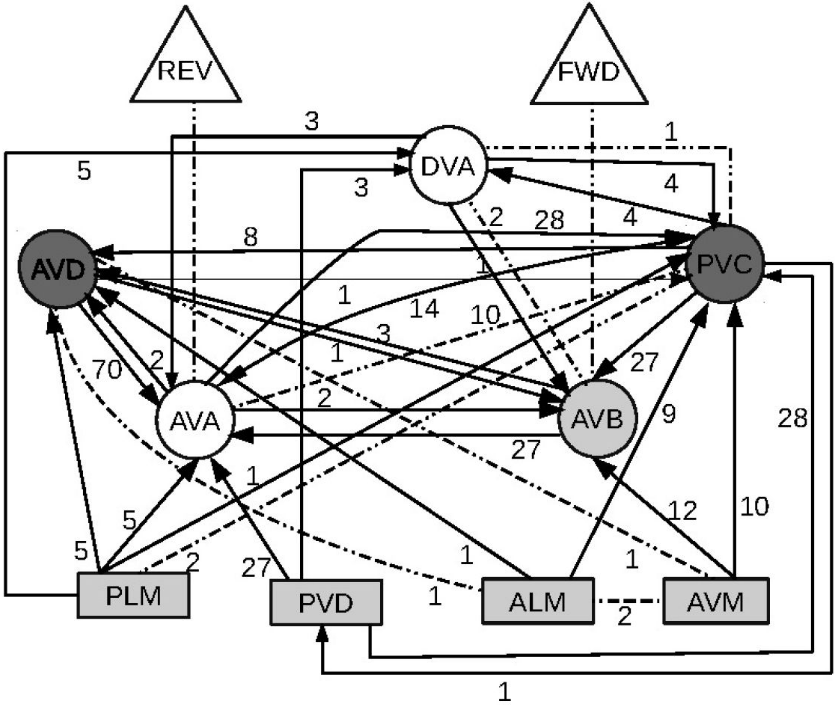


Giles & Rankin, 2009

Experiment

Tap-withdrawal circuit has been identified

- Mechanosensory neuron-interneuron synapses thought to be site of plasticity
- Simulator = circuit + ODEs

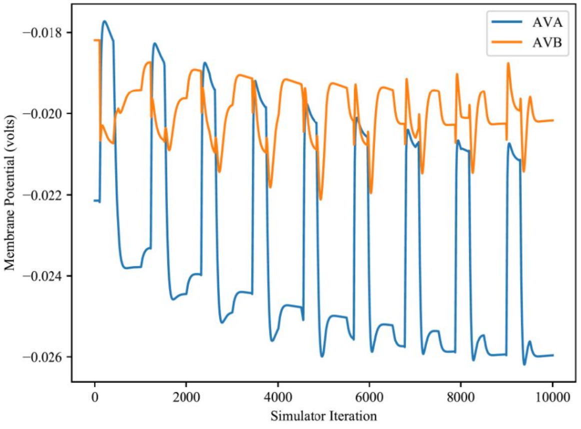


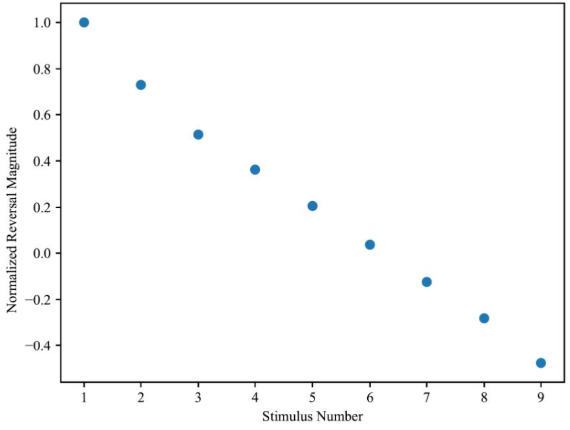
Experiment

Problem: No available observations from tap-withdrawal circuit during habituation

Solution: Build synthetic observations using Hebb's rule, which results in habituation-ish simulator dynamics

1) Initialize $\mathbf{v}_o$ and $\mathbf{c}_o$ independently with samples from Gaussian
2) Initialize $\mathbf{w}_o^{(c)}$ and $\mathbf{w}_0^{(e)}$ with experimentally determined naive synaptic weights
3) Set $\mathrm{R}^{(c)}$ and $\mathrm{R}^{(e)}$ to Hebb's rule, $\tau_w^{(c)} = \tau_w^{(e)} = 0.001$
4) Simulate forward with habituation-inducing currents injected into mechanosensory neurons
5) Sample calcium fluorescence observations with $\kappa_F(\mathbf{c}_t \oslash (\mathbf{c}_t + K_d)) + d_F + \mathcal{N}(0, \sigma_F)$





$$\int_{t_{start}}^{t_{end}} V_{AVA} - V_{AVB}\, \mathrm{d}t$$

Results: Generated Candidate Rules

Observation-generating rule pair:

$$\mathbf{w}^{(c)} \leftarrow \mathbf{w}^{(c)} + 0.001(\mathbf{v}\mathbf{v}^T \odot C^{(c)})$$

$$\mathbf{w}^{(e)} \leftarrow \mathbf{w}^{(e)} + 0.001(\mathbf{v}\mathbf{v}^T \odot C^{(e)})$$

Observation-generating rules:

Sampled with recursive random rule generator G(d)

Candidate rule pair A

$$\mathbf{w}^{(c)} \leftarrow \mathbf{w}^{(c)} + C^{(c)} \odot e^{\boldsymbol{\theta}_1^{(c)}} \mathbf{w}^{(c)} \mathbf{v}$$

$$\mathbf{w}^{(e)} \leftarrow \mathbf{w}^{(e)} + C^{(e)} \odot \left(e^{\boldsymbol{\theta}_1^{(e)}} \mathbf{v} + \boldsymbol{\theta}_2^{(e)} \right)$$

Candidate rule pair B

$$\mathbf{w}^{(c)} \leftarrow \mathbf{w}^{(c)} + C^{(c)} \odot \exp\{\boldsymbol{\theta}_1^{(c)} + \mathbf{v}^T \mathbf{v}\}$$

$$\mathbf{w}^{(e)} \leftarrow \mathbf{w}^{(e)} + C^{(e)} \odot (\boldsymbol{\theta}_1^{(e)} \mathbf{v}\mathbf{v}^T + e^{\boldsymbol{\theta}_2^{(e)}})$$

Same structure as "true" rules

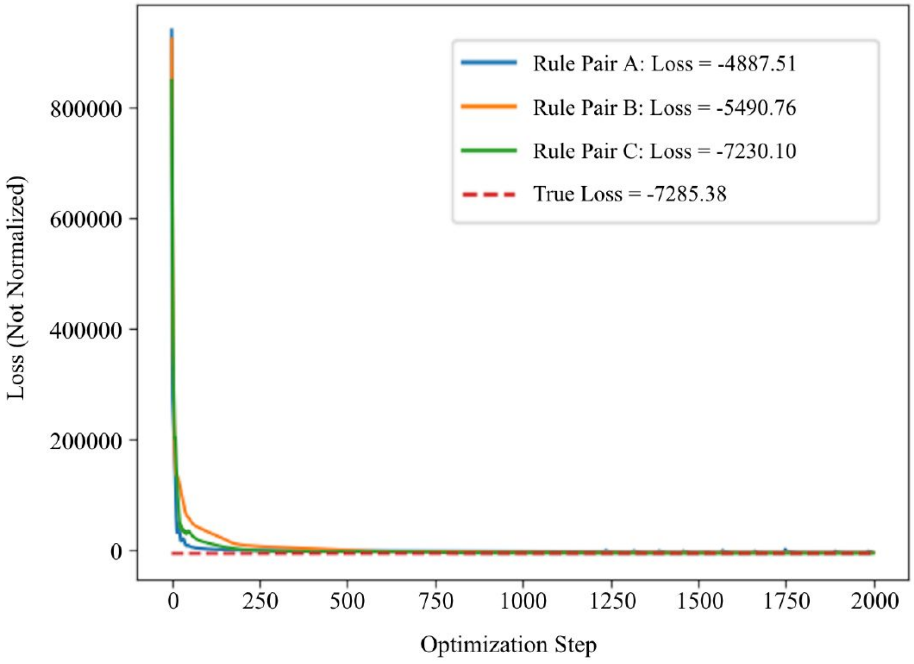
Candidate rule pair C

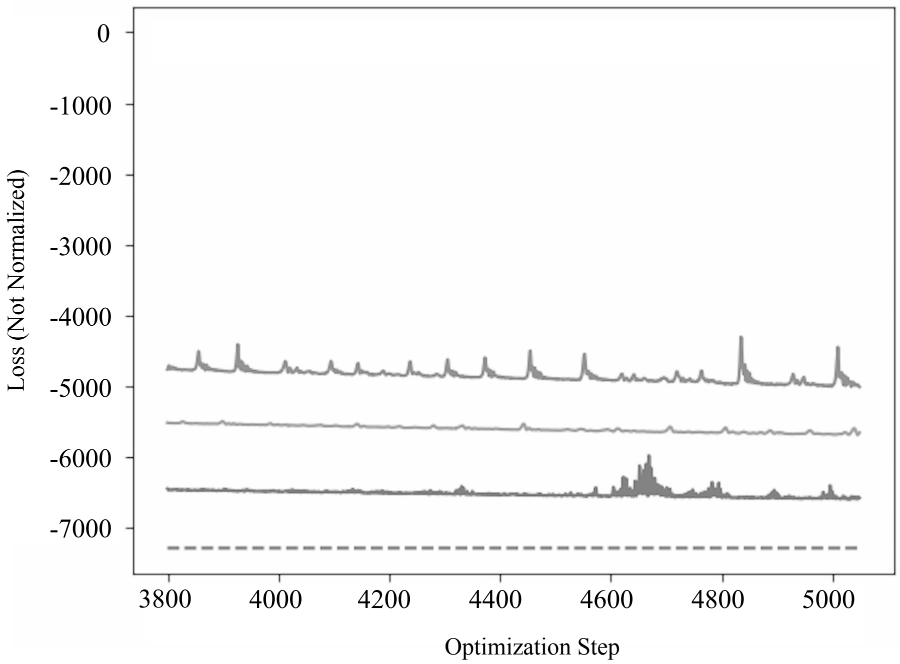
$$\mathbf{w}^{(c)} \leftarrow \mathbf{w}^{(c)} + C^{(c)} \odot \boldsymbol{\theta}_1^{(c)} \mathbf{v}\mathbf{v}^T$$

$$\mathbf{w}^{(e)} \leftarrow \mathbf{w}^{(e)} + C^{(e)} \odot \boldsymbol{\theta}_1^{(e)} \mathbf{v}\mathbf{v}^T$$

Results

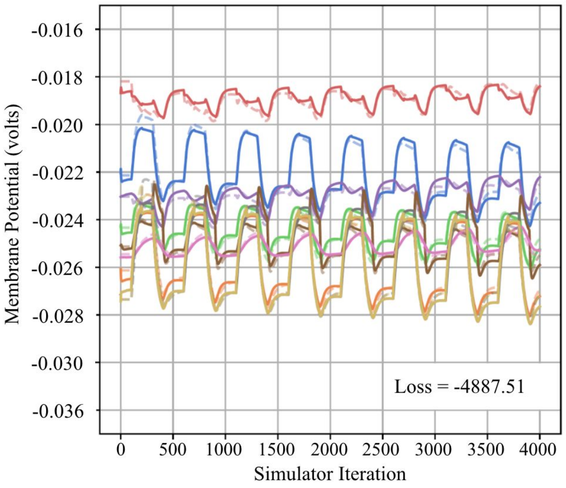
Candidate pair with “true” structure achieved lowest loss



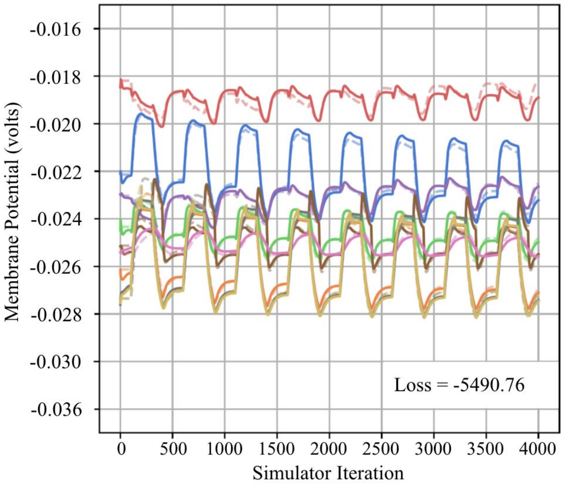


Results

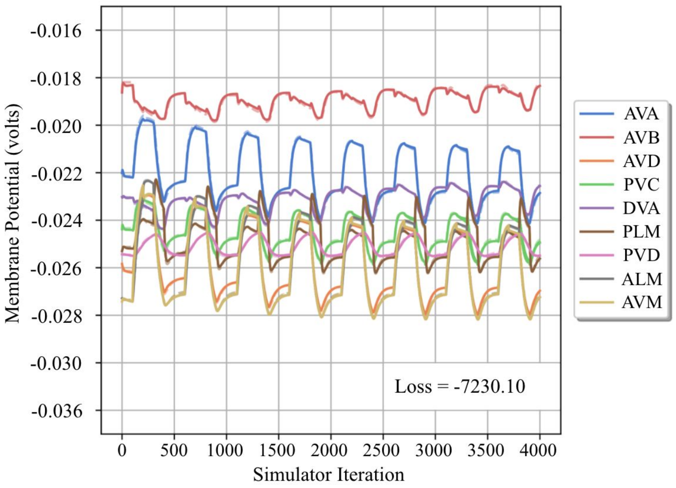
Candidate pair with “true” structure produced best qualitative reconstruction of latent dynamics during habituation after optimization



Candidate rule pair A



Candidate rule pair B



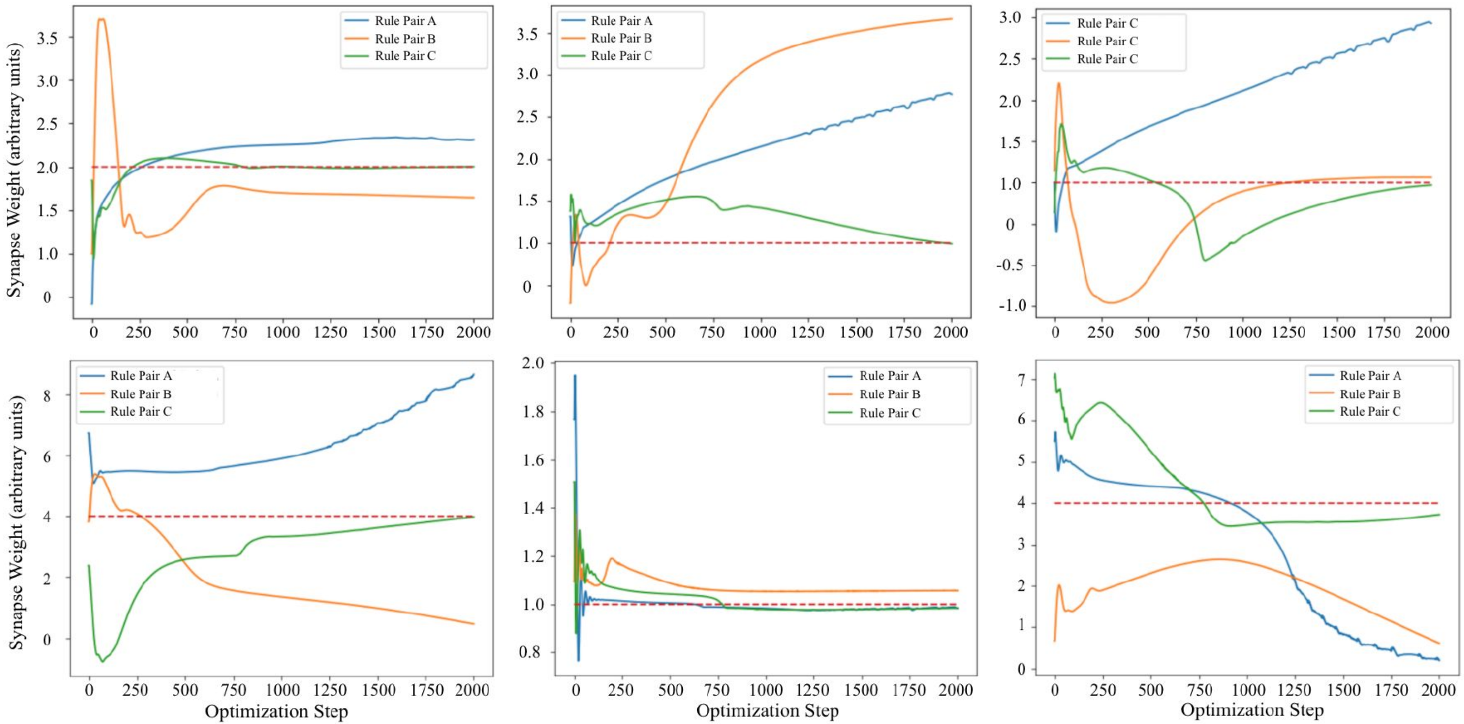
Candidate rule pair C

Results

Candidate pair with “true” structure achieved correct initial synaptic weights $\mathbf{w}_0^{(c)}$ and $\mathbf{w}_0^{(e)}$.

Electrical Synapses

Chemical Synapses



Future Directions

Develop strategy for searching over infinite, discrete space of rule structures

- This thesis showed that given enough samples, SURF finds the correct rule and initial weights
- Frame as infinitely many-armed bandit with finite gradient descent budget during structure exploration

Test SURF using observations (1) which capture more of habituation’s characteristic features, and (2) from real organisms undergoing habituation

- Infer intracellular [Ca2+] in tap-withdrawal neurons from videos of worms undergoing habituation, and convert this inferred value to fluorescence
- Use feature-based optimization to estimate rule and initial weights from behavioural data (e.g. reversal magnitude) gathered during habituation

Perform bayesian inference instead of maximum a posteriori estimation

- Use stochastic simulator
- Perform inference with sequential Monte Carlo or Metropolis-Hastings estimation.

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