Modeling a Simple Non-Associative Learning Mechanism in the Brain of Caenorhabditis elegans

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Abstract

The simplest type of non-associative learning exhibited by *Caenorhabditis elegans*, is habituation. It is defined as the decrease of the reflexive response of the worm, in presence of repetitive exposure to a particular kind of stimulus. Despite its simplicity, habituation involves several identified processes. In the present study, we computationally model and predict the biophysical kinetics that induce mechanosensory habituation, when the worm is exposed to periodic touch/tap stimuli. At the touch-sensory neuron, PLM, it was previously observed that repetitive mechanical stimulation leads to a sensible decrease in the concentration of the intracellular calcium. We model three mechanisms that can presumably be the mathematical origin of such dampened calcium response, during habituation: 1) Decrease of the potassium ion outflow as a result of auto-phosphorylation of a K^+ channel, modeled with a dynamic K^+ maximum conductance. 2) Modeling the EGL-19 calcium channel containing an inactivation gating mechanism. 3) Reduction of the inner calcium level, replicated by a sigmoid-like calcium pump conductivity variable. Moreover, at the signalling level, synaptic depression causes habituation. We mathematically address how synapses play a role in completion of habituation, dihabituation process and propagation of the neuronal habituation to the rest of a neural circuit.

1 Learning the Learning Mechanisms

In this study, we investigate biophysical mechanisms underlying non-associative learning in the nervous system of *Caenorhabditis elegans*. *C. elegans* is a 1mm-long, bodily transparent worm which dwells in soil and is considered the world's best understood organism [Ardiel and Rankin, 2010]. An adult's stereotypic nervous system comprises exactly 302 neurons connected through 8000 chemical and electrical synapses [White *et al.*, 1986]. The worm, at first, seemed to be a hardwired model organism that can simply crawl forward and backward. Later, it proved otherwise by illustrating fascinating behavioral plasticity. Evidence of expressing well-founded non-associative and associative learning behaviors has been observed in *C. elegans*. Examples include habituation (short-term and long-term memory) to mechanical stimulation [Wicks and Rankin, 1997; Kindt *et al.*, 2007; Cai *et al.*, 2009], in the context of non-associative learning, and decision making over various favorable environmental stimuli such as food, temperature and oxygen in the form of associative learning [Saeki *et al.*, 2001; Mohri *et al.*, 2005; Tsui and van der Kooy, 2008].

C. elegans is highly responsive to experience. This indicates that learning can be mediated from every sensory modality. For instance, mechanosensory habituation is a plasticity for the tap-withdrawal (TW) neural circuit (a circuit responsible for generating a reflexive response as a result of a mechanical tap on the petri dish in which the worm swims [Islam *et al.*, 2016]), where the amplitude and the speed of the reflex can be modified as a result of periodic tap stimulation [Wicks and Rankin, 1997]. Detailed studies on habituation in the TW circuit, reveal fundamental notes underlying learning principles in the *C. elegans*, such as:

- Sensory (input) neurons within the network are subjected to a mediation during the non-associative training process (repeated tap stimulation) [Kindt *et al.*, 2007].
- Intracellular calcium concentration in the sensory neuron is dampened gradually as a result of repetitive input stimuli [Suzuki *et al.*, 2003].
- Auto-Phosphorylation of a voltage-gated K^+ channel controls the habituation response [Cai *et al.*, 2009].
- A single gene's function during learning can interact with multiple postsynaptic connections. Such genes can potentially induce synaptic reconfiguration in several layers during memory consolidation [Stetak *et al.*, 2009].
- Effects of certain genes are local within a neuron; They do not influence the synaptic pathways distributed from that sensory neuron [Ohno *et al.*, 2014].
- During the learning process, change in the amount of neurotransmitter release is notable and indicates learning and memory [Jin *et al.*, 2016].
- Within a neural circuit, only a particular sets of interneurons are proposed to be the substrate of memory and habituation [Sugi *et al.*, 2014].

Biological experiments on the principles of learning in *C. elegans*, from high-level behavioral features, to the dynamics of neural circuits, to the gene functional effects on the characteristic of ion channels in a neuron, have demonstrated the remarkable capability of *C. elegans* for learning and memory [Ardiel and Rankin, 2010].

We perform simulated physiological analysis on neurons and synapses, to explore non-associative learning principles originated from autonomous gene modifications, dynamics of ion channels, and variation of neurotransmitters concentrations. Accordingly, we hypothesize the computational origins of such class of learning within two paradigms of neuronal habituation and synaptic plasticity.

Within the neuronal habituation framework, we model and predict the neurophysiological elements that induce habituation. We simulate the effects of auto-phosphorylation of protein subunits, KHT-1-MPS-1, of a voltage-gated K^+ channel, on the gradual reduction of the calcium concentration, in the sensory neuron, during habituation. Correspondingly, we determine essential biophysical dynamics for imitating habituated response of a touch neuron and compare the modeled response to that of real sensory traces. Such short-term memory behavior is quantitatively expressed in the sensory neurons. By applying repetitive input stimulus, the state of an input neuron can be modified through some key mechanisms such as K^+ flux reduction, inactivation of Ca^{2+} channel and increase of the Ca^{2+} conductivity. This results in a local short-term memory (habituation).

Habituation is also controlled by changes in the neurophysiological properties of chemical synapses. Within the synaptic plasticity framework, we show that synaptic depression results in a habituated response for an interneuron. A dynamic synapse model can realize both short-term memory initiator (habituation), through control of the amount of available neurotransmitters at the presynaptic terminal, and also a forget gate (dishabituation), through synaptic release recovery.

2 Neuronal Habituation

It was shown that the auto-phosphorylation of a particular voltage-gated potassium channel inside a sensory neuron (PLM), can control habituation in *C. elegans* [Cai *et al.*, 2009]. A K^+ channel comprised of two protein subunits KHT-1 and MPS-1 was demonstrated to be essential for the exhibition of habituated behavior in presence of repetitive mechanical stimulations. Auto-phosphorylation of the KHT-1-MPS-1 causes a gradual reduction in the K^+ flux, slows down the repolarization of the sensory neuron (PLM), results in further inactivation of a Calcium channel (EGL-19) and consequently reduction in the level of excitability of PLM [Cai *et al.*, 2009].

We capture such consequences and include them in the dynamics of a Hodgkin-Huxley-based model of the sensory neuron, PLM.

In neurons, electrical signals are being generated and propagate as a result of transportation of ions through ion channels [Salkoff *et al.*, 2005]. Figure 3A graphically represents a simplified structure of a neuron of *C. elegans* in which we include voltage-gated calcium channel, calcium pump together with

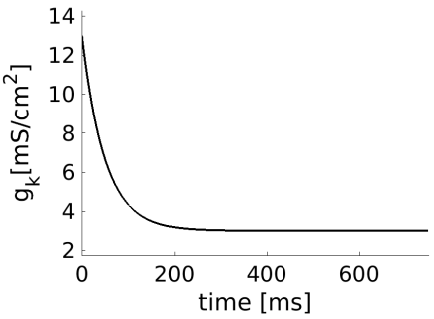

Figure 1: Potassium channel maximum-conductance as a dynamic variable in time

two different potassium channels and a leak channel. Neurons can get excited by external sensory stimulus, $I_{stimuli}$, or chemical and electrical synapses, I_{Syn}, from a presynaptic neuron. By considering the total membrane current, one can compose kinetics of the membrane potential and current as follows:

$$C_m \frac{dV}{dt} = -(I_{Ca} + I_K + I_{sk} + I_{Leak}) + \Sigma(I_{Syn} + I_{stimuli}), \tag{1}$$

where C_m is the membrane capacitance and V represents the membrane potential. I_{Ca}, I_K, I_{sk} and I_{Leak} stand for the calcium current, potassium current, intercellular calcium-gated potassium channel current and leakage current respectively [Kuramochi and Iwasaki, 2010]. Each ion channel's dynamics is precisely modeled with an inspiration from Hodgkin-Huxley channel modeling technique where the current-voltage relationship is developed based on Ohm's law, $I_{ion} = G_{ion}(E_{ion} - V)$, while conductance of the ion channel, G_{ion} is considered to be the product of a constant maximum conductance with a dynamic parameter which is a function of the membrane potential [Hodgkin and Huxley, 1952]. We construct and simulate neurons in the SIM-CE Simulink platform [M. Hasani *et al.*, 2017].

As described, the effects of the auto-phosphorylation of KHT-1-MPS-1 are modeled as follows.

1) To imitate the progressive decrease in the K^+ current, we set the maximum conductance of the potassium channel to a dynamic variable in time. g_k is empirically parametrized and modeled as:

$$g_k = 10\, e^{-0.02\, t} + 3, \tag{2}$$

and it is shown in figure 1.

2) To model the cumulative inactivation of the EGL-19 calcium channel, we add a gating variable, h, to the model of the calcium current as:

$$\frac{dh}{dt} = \frac{h_\infty - h}{\tau_h}, \quad h_\infty = \frac{1}{1 + H\ \exp\frac{V - V_{1/2}}{k_h}}, \tag{3}$$

where h_∞ is the steady-state value of the inactivation gating variable, τ_h is the time constant of the dynamic activity. Note that parameters of the gating variable, h are summarized in Table 1.

Table 1: Parameters of the calcium inactivation gating variable, h

Parameter	Value	Unit
$V_{1/2}$	-45	mV
k_h	1	1/mV
$1/\tau_h$	0.5	1/s

3) It was previously observed that periodic mechanical stimulation of the PLM neuron drastically reduces the inflow of calcium [Suzuki *et al.*, 2003; Kindt *et al.*, 2007; Cai *et al.*, 2009] (See Figure 3B). Such behavior is captured by introducing sigmoid-like exponential dynamics to the calcium pump G_{pump} as follows.

$$G_{pump} = \frac{10}{1 + e^{-0.01(t+200)}} + 3.6 \tag{4}$$

The parameters are heuristically set such that the overall calcium response of the PLM neuron during habituation imitates the behavior of the real traces. Figure 2 simulates how the calcium pump's strength increases when repetitive tap-stimulus are induced.

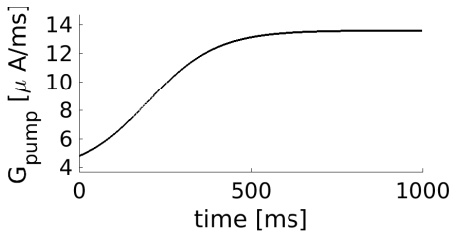

Figure 2: kinetics of the Calcium Pump's conductivity during habituation

In order to evaluate our assumption, we compare our result to the real sensory neuron habituation. With the right choice of parameters, the time-dependent increase of the potassium channel conductivity, the calcium inactivation mechanism included in the EGL-19 channel and the increase of G_{pump}, habituated sensory response of PLM is captured and shown Figure 3C. The dampened level of the intracellular calcium concentration happened when the PLM neuron is subjected to repetitive stimulation in both real experiments (Figure 3B) and the simulated experiment (Figure 3C).

Key finding 1: The state of the activation of a sensory (input) neuron can be modified by repeatedly induced stimulus, by means of an intrinsic parameter which is dynamically altered, as a function of time, input amplitude and its frequency.

3 Synaptic Plasticity

Fundamentally, many learning mechanisms originate from the alternation of the amount of neurotransmitters concentration. Decrease in neurotransmitter availability leads to presynaptic depression [Zucker and Regehr, 2002]. Presynaptic depression due to neurotransmitter depletion was identified as the mechanism of habituation the gill-withdrawal reflex in *Aplysia* [Castellucci and Kandel, 1974].

We setup a case where two neurons are communicating through chemical excitatory synapses. The presynaptic neuron is subjected to repetitive stimulations and synapses into the postsynaptic neuron. we investigate the calcium response of the postsynaptic neuron in order to demonstrate synaptic mechanisms inducing habituation. Information propagates from a presynaptic neuron to a postsynaptic neuron through synapses. The information transportation process depends on several circumstances; the state of the activation of the presynaptic cell which causes the neurotransmitter secretion tone $m(t)$, the amount of available neurotransmitters, $n(t)$ at the presynaptic end, number of available receptors at the postsynaptic neuron and the probability of the neurotransmitters binding to the postsynaptic receptors, $S(t)$. A detailed model of a chemical synapse's current therefore can be derived as follows [Schutter, 2009].

$$I_{chem} = G_{max}\, m(t)\, S(t)\, n(t)\, (E_{chem} - V_{post}) \tag{5}$$

$$\frac{dm}{dt} = (m_\infty - m) \cdot \frac{1}{\tau_m} \tag{6}$$

$$m_\infty = \frac{1}{\exp(\frac{V_{shift} - V_{pre}}{V_{range}}) + 1} \tag{7}$$

$$\frac{dS}{dt} = -\frac{S}{\tau_F} + h \tag{8}$$

$$\frac{dh}{dt} = -\frac{h}{\tau_R} - h_0 \cdot \delta(t - t_0) \tag{9}$$

$$\frac{dn}{dt} = k_n(n_\infty - n) \; - k_r\, n \; - n\, m \tag{10}$$

In Equation 6, G_{max} is the maximum conductance of the synapse and E_{Syn} represents the reversal potential of a synapse [Schutter, 2009]. Table 2 contains the parameter values for the synapse model.

Table 2: Parameters of the synapse model

Parameter	Value	Unit
τ_m	5	ms
V_{range}	4	mV
V_{shift}	-30	mV
τ_r	2.5	ms
τ_f	5	ms
h_0	10	
t_0	when V_{pre} >-59 mV	
n_∞	10000	
k_r	0.01	1/ms
k_n	0.08	1/ms

$m(t)$ is the voltage-dependent conductivity, which varies with a change in the presynaptic membrane potential with time-constant, τ_m. $S(t)$ describes the dynamics of neurotransmitter transport over the synaptic cleft and neurotransmitter binding to the receptors. $S(t)$i rises with τ_R and decays with τ_F. $n(t)$ describes the availability of neurotransmitter-filled vesicles. Based on Equation 11, the amount of neurotransmitter, n, decreases at the activation of the neuron, and it is refilled again until it reaches a maximum amount n_∞. This is similar to the vesicle state-model described in [Sterratt *et al.*, 2011] and the more complex model introduced in

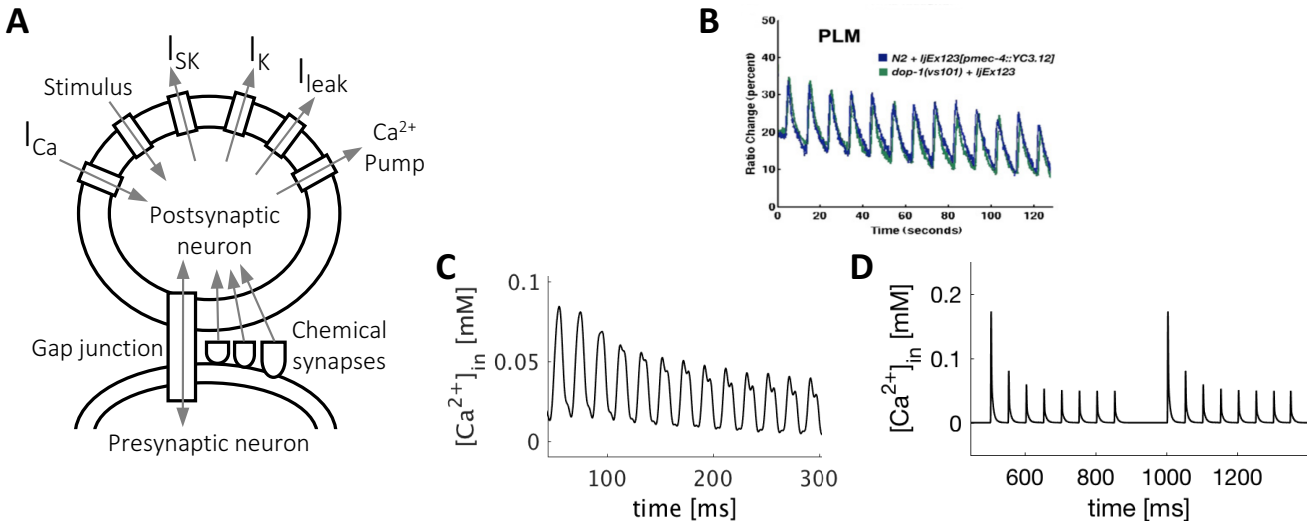

Figure 3: Learning the learning representation. A) Structure of a neuron B) Habituation of a real sensory neuron (reprinted with permission from [Kindt *et al.*, 2007]) C) Model of a neuronal habitation D) Response of an interneuron habituated and dishabituated with synaptic plasticities.

[Gingrich and Byrne, 1985]. When a neuron fires, according to Equation 11, $n \times m$ vesicles at the synaptic terminal are removed. Vesicles are refilled from a reserve pool with a rate k_n and move to the reserve-pool with a rate k_r, [Sterratt *et al.*, 2011].

This leads to a decrease in the calcium concentration of the postynaptic neuron after a series of periodic input stimulation shown in Figure 3D, the first train of habituated calcium responses in the time-interval 500 to $900ms$. Rankin and Wicks in [Rankin and Wicks, 2000] showed that the glutamate concentration considerably modifies the habituation responses in touch sensory neurons. Such behavior is captured as a property of a synapse where simultaneous dynamics of the variables $n(t)$ and $S(t)$ results in the similar tap-withdrawal response.

Without exposure of the neuron to stimulus, the calcium concentration level recovers over time and the interneuron dishabituates. This is shown in Figure 3D, at the start of the second train of habituated response in the time interval 1000 to $1400ms$, where the amount of calcium concentration is restored to its maximum value.

Key finding 2: Synapses with an internal state can autonomously modify the behavior of the system. Synapses can presumably be involved in completion of a habituation process, dishabituation process (See Figure 3D the second calcium spike train) and propagation of a neuronal habituation to the rest of the neural circuit.

4 Discussions

Learning is an essential attribute for survival. *C. elegans* expressed optimal adaptive behavior to numerous environmental circumstances, for survival. Learning how the animal learns and adapts not only is a notable step forward towards decoding the brain's working principles but can also lead us to the development of better learning algorithms.

We reported mathematical dependencies of a simple learning mechanism, habituation, to the biophysical parameters of neurons and synapses. We quantitatively recapitulated such short-term memory behavior in the sensory neurons and chemical synapses. We found that by applying repetitive input stimulus, the state of an input neuron can be modified through several mechanisms (K^+ flux reduction, inactivation of Ca^{2+} channel and increase of the Ca^{2+} conductivity), result in a local short-term memory (habituation). We also showed how to control the habituation to stimulus, through synapses. A dynamic synapse model can realize both a short-term memory initiator (habituation) and also a forget gate (dishabituation).

For the future work, we aim to construct bio-inspired learning algorithms for simple behavior such as habituation, based on our key findings discussed here.

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