Models of Synaptic Tagging

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Abstract

Synaptic tagging is a mechanism that allows late long-term potentiation (LTP) by protein synthesis initiated by repeated tetanic stimulation. This mechanism can be built by combinations of leaky integrator and attractor network. The model with modulated time constant shows decaying LTP despite hardly tweakable parameterization. On the other hand, simple linear combination of attractor and leaky integrator based model is easier to interpret but lacking of decaying mechanism.

1 Introduction

Synaptic tagging is a mechanism in which elevated synaptic strength and efficacy are induced by strong activity in a different set of synapses. These synapses are to produce a tag that other sets of synapses can use to exhibit late long-term potentiation. A study in rat hippocampus and Aplysia cell cultures has been showing evidence of synaptic tagging [3]. In the study, neurons that have experienced long-term and transcription-dependent plasticity can produce persistent synaptic strength.

The mechanism of synaptic tagging boils down to protein synthesis inside a neuron [2]. Ionotropic ion channels open upon upcoming action potentials releasing neurotransmitters at the pre-synaptic neuron. This allows the influx of positive sodium ions. The increase in potential opens voltage-gated calcium ion channels, which allows calcium ions inside. These ions bind to calcium-binding proteins that initiate a series of protein activation. These proteins enable the transcription of m-RNA inside the neuron so that the synthesis of new neurotransmitter receptors is possible. This then leads the neuron to be more receptive. However, the increase of efficacy in these dendrites should be verified by a generation of action potentials. When action potential happens in consequence of protein-induced synaptic increase, another set of proteins is generated at the soma and eventually binds to another m-RNA at the respective dendrites. This then allows tagging process. Additionally, soma-synthesized proteins can travel to other dendrites and initiate a similar synaptic strength elevation process which then allows cross-tagging [5].

The tagging process decribed above is initiated by a strong tetanization in a form of a train of high-frequency pulses [4]. The measure of successful tagging can be seen by the duration of long-term potentiation. Strong tetanization yields persistent long-term potentiation that can last for 8 hours. In contrast, weak tetanization can only produce 1.5 hours of long-term potentiation.

In this report, we present a comparison of synaptic tagging models which take the amount of tetanization. This amount of tetanization induces LTP as well as trigger the protein syntesis. The model will also accomodate the synthesis failure which leads to quick decay of LTP.

2 Building Blocks

The building blocks of synaptic tagging comprise leaky integrator and attractor network. In general, the integrator will model the decaying figure of LTP while the attractor network will devise the presence of proteins.

2.1 Leaky Integrator

Leaky integrator can be described by following equation:

$$\tau \dot{x} = -x + i \tag{1}$$

with solution in the form of exponential equation:

$$x(t) = k \exp -\frac{t}{\tau} + I \tag{2}$$

The parameter τ controls the rate of leak of the system. The decaying solution of leaky integrator can be utilize to model the decaying properties of the LTP both in the presence of protein or not.

2.2 Attractor Network

Atractor network is a system of connected nodes in which many stable fixed points exist [1]. These stable fixed points will act as an attraction in which the system would eventually settle on. The network is generally described by following equation:

$$\dot{x} = g(x) \tag{3}$$

The function $g(x)$ is a polynomial with fixed points. These fixed points would be considered stable when corresponding value of $g'(x)$ is negative.

3 Models

Models of synaptic tagging should be able to display elevated duration of LTP when protein synthesis is successful. Otherwise, the model should also be able exhibit a decaying trajectory.

3.1 Model 1

The first model is a linear combination of a leaky integrator and an attractor network which is shown in equation 4 . Both of these blocks take stimulation in order to perturb the system. The function $f(I)$ would translate the amount of stimulation to binary state of protein presence.

$$w = w_1 + w_2 \tag{4}$$
$$\tau \dot{w_1} = -w_1 + I \tag{5}$$
$$\dot{w_2} = -w_2(w_2 - \alpha)(w_2 - \beta) + f(I) \tag{6}$$

3.2 Model 2

The second model shown in equation 7 aims to modulated the time constant of the leaky integrator so that the decay would be prolonged when proteins are present. The modulator is an attractor network similar to the one in the model 1.

$$\frac{\dot{w}}{\gamma} = -w + I \tag{7}$$
$$\dot{\gamma} = -\gamma(\gamma - \alpha)(\gamma - \beta) + f(I) \tag{8}$$

4 Analysis and Simulation Results

4.1 Fixed Point Analysis of Attractor Network

Both of model 1 and model 2 incorporate attractor network as a tool to indicate the presence of proteins. The equation 9 has 3 fixed points which are $0, \alpha, \beta$. The second derivation shown in equation 10 of the attractor network indicates the stability of each fixed points in the equation 9.

$$\dot{x} = -x(x - \alpha)(x - \beta) \tag{9}$$
$$\ddot{x} = x(2\alpha + 2\beta - 3x) - \alpha\beta \tag{10}$$

Setting up the value of x to 0, α, and β give raise to the equation 11 :

$$\ddot{x} = \alpha(\alpha - \beta) \;\; for\, x = \alpha \tag{11}$$
$$\ddot{x} = \alpha(\beta - \alpha) \;\; for\, x = \beta \tag{12}$$
$$\ddot{x} = -\alpha\beta \;\; for\, x = 0 \tag{13}$$

These equation indicates that the network has at least 2 stable fixed points. One of them is at 0 and the other is either the bigger value of α or β. Therefore the smaller value will behave like a threshold which determine where the system will be attracted to.

4.2 Bifurcation Analysis of Attractor Network

The fixed points can be diminished when a proper input I is applied to the system. The amount of input can be determined by finding the maxima/minima of the derivative of attractor network shown in equation 10. Thus this raise to two extreme points:

$$x_1, x_2 = \frac{1}{3}(\alpha + \beta \pm \sqrt{\alpha^2 + \beta^2 - \alpha\beta}) \tag{14}$$

Thus assuming that x_1 is bigger than x_2 and α is bigger than β, the system would settle at value bigger than α when input I is bigger than x_1. The same pattern happens when the input value is less than x_2 in which the system settles at value less than 0.

4.3 Simulations

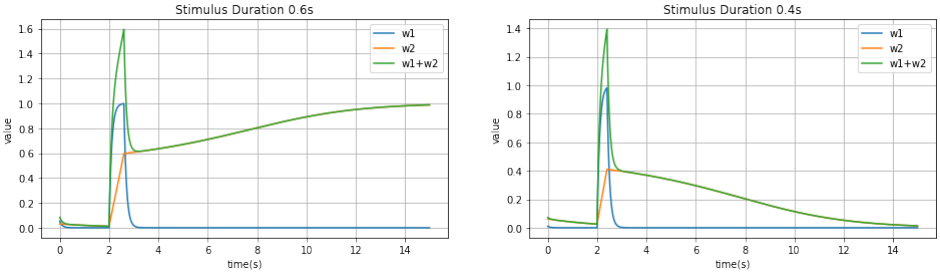

Figure 1: Different stimulation duration on model 1. Here, time constant of 0.1s, and parameter α and β of 0.5 and 1 respectively are implemented.

Different durations of stimulus have a significant effect to the dynamics of the model as shown in figure 1. When stimulation is long enough, the attractor network can finally goes and settle at the higher stable fixed point. Thus the model can mimic the same behavior of protein synthesis triggered by high frequency tetanic pulse assuming that it has been low pass filtered.

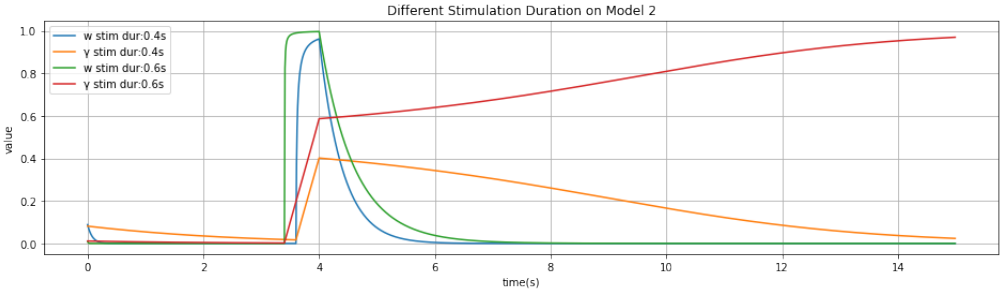

Figure 2: Different stimulation duration on model 1. Here, time constant of 0.1s, and parameter α and β of 0.5 and 1 respectively are implemented.

In model 2, the durations also have noticable effect on the model as shown in 2. The decaying figure is modulated by the attractor network in which prolonged by the attractor network. However the difference is not significant.

5 Discussion

Both of model 1 and model 2 can produce the same result that signify the presence of proteins. However there are several properties on both model that should be carefully taken into account.

In model 1, elevated synaptic strength can be easily achieved by driving the attractor network toward its higher stable fixed point. However, one must also be mindful of possible overshot caused by the leaky integrator due to longer stimulus duration. The choice of parameter is crucial when fitting this model to a real dataset. Adding additional leaky integrator can also help to flattened out the overshot albeit more computation and delays.

Furthermore, one of the major drawbacks of the model is that it does not really capture the slow-decaying synaptic strength observed in reality. When finally reaching to the higher stable fixed point, the system becomes stationary. Thus one might argue that the model is not biologically plausible.

On the other hand, model 2 aims to address major pitfall that is observed in model 1. However simulation shows that higher modulation value is necessary to obtained sustained synaptic strength. In addition, the trajectory of the attractor network strongly depends on the duration of the stimulus. Although certain duration is enough to push the attractor network beyond its unstable fixed point, the whole system will not pick up the modulation instantly since more time is required for the attractor network to arrive at its stable fixed point. Therefore, more parameter tuning would be necessary.

Finally, codes and report can be accessed at this repository: `https://github.com/bramantyois/synaptic_tagging`

References

[1] C. Eliasmith. Attractor network. *Scholarpedia*, 2(10):1380, 2007. revision #91016.

[2] Uwe Frey and Richard G. M. Morris. Synaptic tagging and long-term potentiation. *Nature*, 385(6616):533–536, Feb 1997.

[3] Kelsey C. Martin and Kenneth S. Kosik. Synaptic tagging — who's it? *Nature Reviews Neuroscience*, 3(10):813–820, Oct 2002.

[4] Roger L. Redondo and Richard G. M. Morris. Making memories last: the synaptic tagging and capture hypothesis. *Nature Reviews Neuroscience*, 12(1):17–30, Jan 2011.

[5] Sreedharan Sajikumar and Julietta U. Frey. Late-associativity, synaptic tagging, and the role of dopamine during ltp and ltd. *Neurobiology of Learning and Memory*, 82(1):12–25, 2004.