Simulating Facilitation in a Spiking Neural Network

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Abstract

Many insects are able to detect, isolate and track small targets that move quickly against a dynamic background. This ability is enabled by a group of neurons called small target motion detectors (STMD). These neurons, among other properties, have a type of short term memory called response facilitation. This type of facilitation is a phenomenon in which continued visual stimuli lead to an enhanced response, whereas single signals lead to little or no transmission of the signal. In previous studies on dragonflies, studies have shown that the facilitation waves have an intrinsic ability to travel throughout the neural networks even after the stimulus has stopped, which has not been simulated yet. The goal of this project was to examine which neuron and synapse models are currently available, then use those models to construct simulations of neural networks that could potentially support travelling facilitation waves in the ways that mimic the results of the *in vivo* studies. After a series of simulations the results show that even though NEST simulator currently has a number of synapse and neuron models that support facilitation, none of them could currently support a model with a travelling facilitation wave. The NEURON simulations were promising but overall proved to be inconclusive and required further experimentation.

Introduction

Being able to detect and track small targets is vital for many animal activities, like feeding and mating. Distinguishing quickly moving objects from the background is not a trivial task, especially for insects, who have compound eyes that consist of a hexagonal lattice of small eye sensors and generally lack resolution (Völker *et al*., 2003). Nevertheless, many of them, such as dragonflies and hoverflies have with time acquired tools that allow them to do just that - neurons that selectively respond to small object movements - STMDs (Nordström *et al*., 2006). These neurons, located primarily in the lobula complex, possess abilities such as small target motion selectivity, facilitation (which is a type of short term memory) and selective attention. Out of these abilities facilitation is, perhaps, the most interesting one, as it is widespread and present in many forms, but currently not completely understood (Wiederman *et al.*, 2017).

Synaptic facilitation is a type of short term plasticity that leads to the amplification of consecutive signals and enhanced synaptic transmission (Jackman & Regehr, 2017). It is a somewhat common phenomenon that plays important roles in information transfer and neural processing. Response facilitation produces its effect by increasing the probability of vesicle release (p) in a frequency-dependent manner (Jackman & Regehr, 2017). Synapses that support

facilitation tend to have very low initial *p,* which leads to single signals causing a very limited release of vesicles with the neurotransmitter and a little to no reaction in the postsynaptic cell.

This property may enable the synapses to function as high band passes, filtering out single, weaker signals. Interestingly, the concept of stronger activation upon repeated stimuli runs against the general property of synaptic transmission to weaken if activated repeatedly, called synaptic depression. Depression is generally a result of depletion of synaptic vesicles and subsequently lower rates of neurotransmitter release. The fact that facilitation occurs in spite of depression was initially thought to imply that synapses where facilitation takes place had some type of a special mechanism that allowed them to increase the rates of neurotransmitter release even when the intracellular pool should have been nearing depletion. However, in reality, due to low initial *p* values, the state of synaptic vesicle depletion was harder to reach than in neurons without facilitation (Jackman & Regehr, 2017).

The current understanding of the physical mechanism behind facilitation is that it is primarily a calcium-driven process. The exact molecular sensors responsible for facilitation were long a subject of intense research, until recently, when a work by Jackson *et al.* in 2016 demonstrated that proteins called Syt1 and Syt7 were the primary calcium sensor in humans and mice. Syt1 binds to both the plasma membrane and SNARE complex, which connects the neurotransmitter vesicles with the plasma membrane, thus creating a curvature in the plasma membrane (Kuzmin *et al.*, 2001). This lowers the energy barrier for the fusion of vesicles and the plasma membrane, which leads to more neurotransmitter being released into the synaptic cleft. Syt7 affects facilitation by working in tandem with Syt1. When Syt1 is present, Syt7 can greatly increase the vesicle release fusion rates, but, by itself, Syt7 can only cause very limited asynchronous release. The exact mechanism by which Syt7 amplifies the effect of Syt1 is currently unknown (Kuzmin *et al.*, 2001).

When it comes to the dragonfly STMDs, while some previous studies have tried to explain the actual process behind motion facilitation by using the NMDA synapses, the exact reasons for the travelling spotlight / wave of facilitation phenomenon remain unclear (Bekkouche *et al*., 2017). Some models have explained the spiking neural network's ability to encode occluded targets with using persistent spiking (Kaplan *et al*., 2013), however there is no evidence that such persistent spiking actually occurs in the STMD neurons during object occlusion (Wiederman *et al*., 2017). Another study attempted to explain the function of STMDs by using a biologically-inspired "Elementary STMD" model (Bagheri *et al.*, 2015). The ESTMD model successfully predicted several of the STMD neuron properties, such as spatio-temporal tuning, rejection of background motion and selectivity for dark targets. There have also been some attempts to model selective attention in STMD-like networks but none have implemented the ability to perform action potentials or try to explain the traveling facilitation wave observations (Shoemaker *et al.*, 2013).

The aim of this project was to determine whether it was possible to simulate a travelling facilitation wave in silico. NEST simulator is a Python package that is a widely used research tool in the field of neurobiology, and can be used to simulate spiking neural networks. The first part of the project involved finding out which of the synapse models that are currently available in NEST supported facilitation. Once the list of available synapses was determined, the next step was to apply them in various network models with different neuron types and connection profiles. There is a plethora of different subtypes of facilitation. In this case, as persistent spiking does not appear to occur in STMD neural networks, the models which would allow for travelling graded potentials were of particular interest. Graded synapses, however, were found to not be inherently supported within the NEST package, which is why NEURON simulator was used instead.

Methods

The simulations were conducted digitally on a personal computer using Microsoft Windows 10, version 1909. An Oracle VM VirtualBox version 6.0.18 virtualization software was installed onto the system and was used to run a Linux virtual machine with NEST simulator installed onto it. To further increase the usability of Python simulation, a development environment program called PyNEST was installed onto the virtual machine system.

The following models were built using NEST simulator in an attempt to create a travelling facilitation wave:

1) tsodyks2_synapse connection between two iaf_psc_exp (Leaky integrate-and-fire neuron model with exponential PSCs) neurons and a voltmeter connected to the second neuron.
2) static_synapse connection between two iaf_psc_exp neurons and a voltmeter connected to the second neuron.
3) Two tsodyks2_synapse connections between three iaf_psc_exp neurons and a voltmeter connected to second and third neurons.
4) Three hh_psc_alpha_gap neurons connected by gap junctions.
5) Three hh_psc_alpha_gap neurons simultaneously connected by gap junctions and tsodyks2_synapse connections.

The following connection parameters were used during the NEST simulations:

Tsodyks2 synapse - *"U" (Probability of release increment) = 0.1, "u" (Maximum probability of release) = 0.1, "x" (Current scaling factor of weight) = 1.0, "tau_rec" (Time constant for*

depression in ms) = 1000.0, "tau_fac" (Time constant for facilitation) = 100.0, "weight" (Connection strength) = 250.0.

Static synapse - *"weight" (Connection strength) = 55.0.*

Gap junctions - *"weight" (Connection strength) = 25.0, 'rule': 'one_to_one', "make_symmetric": True.*

Additional tests using another neuron model called ht_neuron were attempted, but we were unable to turn off the inherent depression mechanism that hindered the simulation. Since NEST simulator did not appear to be able to handle travelling facilitation wave simulations, another simulator was used. NEURON simulator is a more flexible and adaptable simulation environment that may be used for building computational models of neurons and networks of neurons. A Linux virtual machine with a pre-installed NEURON simulator was downloaded from https://neuron.yale.edu/neuron/ . Same as previously, to increase the usability PyNEST was installed onto the virtual machine.

The following models were built using NEURON simulator:

1) Two default neurons connected by a graded AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) synapse.
2) Two default neurons separately stimulated through embedded NMDA receptors.
3) Two default neurons connected by a graded AMPA synapse, stimulated through embedded NMDA receptors.

The following connection parameters were used during the NEURON simulations:

soma.Ra = 100; soma.cm = 1; soma.g_pas = 100e-6; soma_ena = 50; soma.ek = 85.

Results

It was first determined that there are currently four synapse models that include short term plasticity. Tsodyks_synapse_hom is a synapse model that uses homogenous parameters for all synapses. Tsodyks_synapse is a basic synapse type with short term plasticity. Tsodyks2_synapse is a variant of Tsodyks_synapse that produces lower amplitude levels under similar conditions, but is otherwise functionally identical. Quantal_stp_synapse is a probabilistic synapse model that implements short-term depression and facilitation according to the model described by Fuhrmann et al. in 2002.

Due to irregularities with the quantal_stp_synapse status dictionary parameters, tsodyks2 synapse was chosen as the primary synapse model. During the first experiment, the first of the neurons was stimulated with 400 pA for 200 ms twice with a 50s delay between the stimuli, where the first stimulus was the "prime" signal and second was the "probe" signal. The voltmeter connected to the second iaf_psc_exp neuron detected the difference in amplitude between the two signals that is typical for the facilitation phenomenon (Fig. 1A). This result was then compared to the result of this pair of neurons being only stimulated once with the "probe" signal,

which showed a signal signature that lacked the increased amplitude from the first initial simulation (Fig. 1B). Additionally, it was deemed appropriate to also test if the synapse type was indeed what created the facilitation effect. To achieve that, another neuron pair model was created, but this time they were connected by a static synapse model, which should have theoretically not supported any kind of plasticity. Application of two 400 pA stimuli have produced no increase of amplitude upon the probe signal (Fig. 1C).

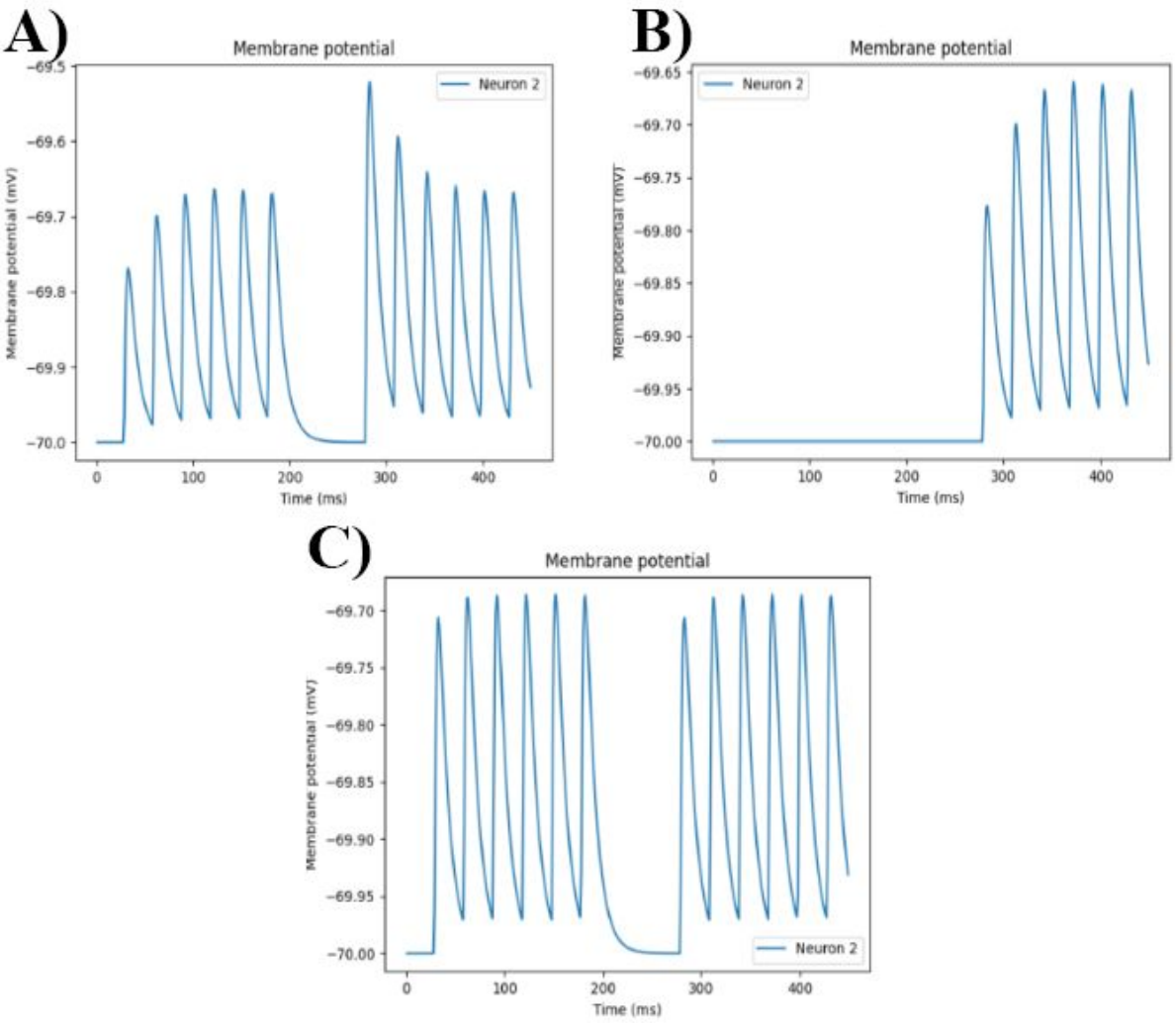

Figure 1. A) Stimulation of two iaf_psc_exp neurons connected through a tsodyks2 synapse with two 400 pA signals applied to the first neuron. B) Single 400 pA stimulation of the same system. C) Stimulation of two iaf_psc_exp neurons connected through a static_synapse with two 400 pA signals.

Gap junctions alone are unable to produce the facilitation effect upon repeated signalling and tsodyks2 synapses alone could not spread the signal, then it was decided to investigate whether their combination would produce the desired effect. Three hh_psc_alpha_gap neurons were connected as a chain, with both gap junctions and tsodyks2 synapses between them. The simulation results have failed to demonstrate any facilitation upon tandem 400 pA stimulations.

Further investigation of just two hh_psc_alpha_gap neurons connected through a tsodyks2 synapse have failed to produce any facilitation either. This can be the result of two factors - either the hh_psc_alpha_gap neuron model has high intrinsic "p" value, high synaptic depression constant or it does not support facilitation whatsoever.

Further simulations were done with the NEURON simulator as it presented a more robust simulation environment due to more opportunity to fine tune the parameters of the created cell models. First and foremost, it was important to test whether or not it was possible to simulate a transduction of a graded potential from neuron to the other. For that purpose, two neuron bodies (somas) were created and connected via a graded AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) synapse (Fig. 2).

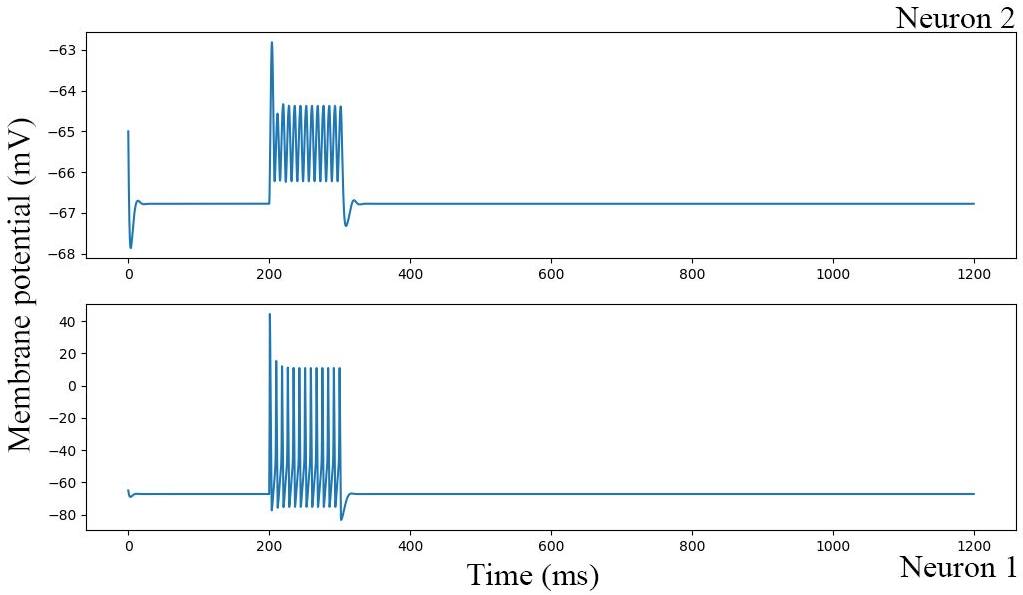

Figure 2. Stimulation of two neuron somas connected through an AMPA synapse in NEURON.

Another component of the proposed model for facilitation is the additional signal input through an NMDA receptor. Two neuron somas were created, each with an NMDA receptor embedded. 300 pA stimulatory signals were applied to the neurons through the NMDA receptors for varying lengths of time and the spike frequencies were compared to confirm the consistency of spiking strengths (Fig. 3).

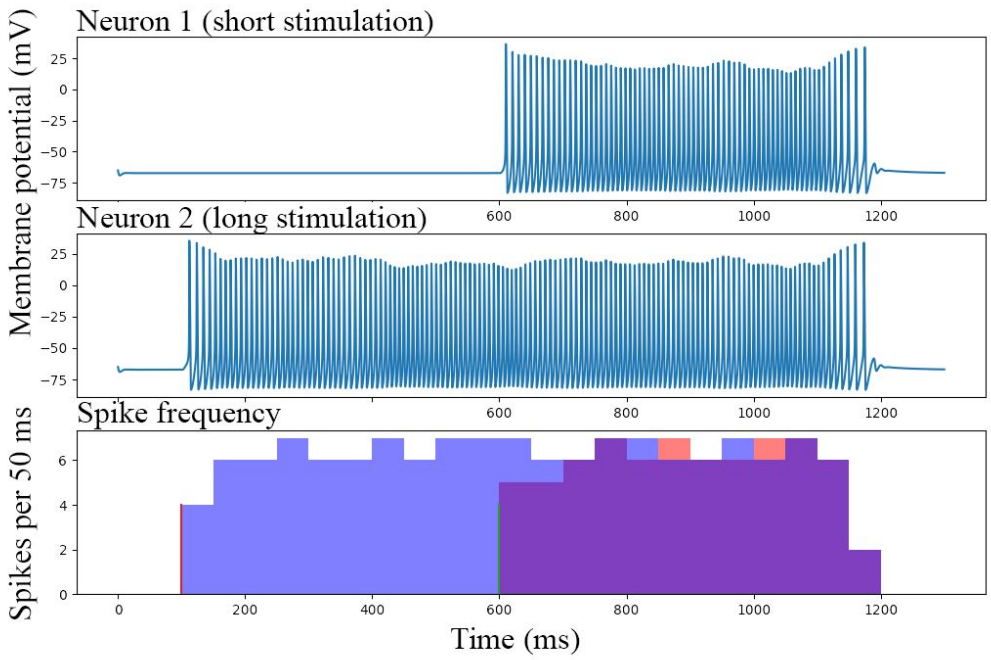

Figure 3. Two neurons stimulated for varying amounts of time and their spiking frequency compared.

The last experiment combined the previous two setups. Two neurons were connected through an AMPA synapse and NMDA connections were established to both neurons separately. The first neuron received a priming spiking stimulus that was 500 ms long (Fig. 4A). After the priming signal on the first neuron has subsided, the second neuron was also stimulated with a 500 ms long "probe" spiking signal (Fig. 4B). A third separate neuron received only the "probe" signal (Fig. 4C), and then the probe spiking frequencies from the second and third neurons were compared (Fig. 4D). Initial simulations showed little to no difference between the two neurons, but lowering the passive membrane potential to -110 mV and adjusting the membrane leak channel parameters led to what appeared to be a facilitation-like effect.

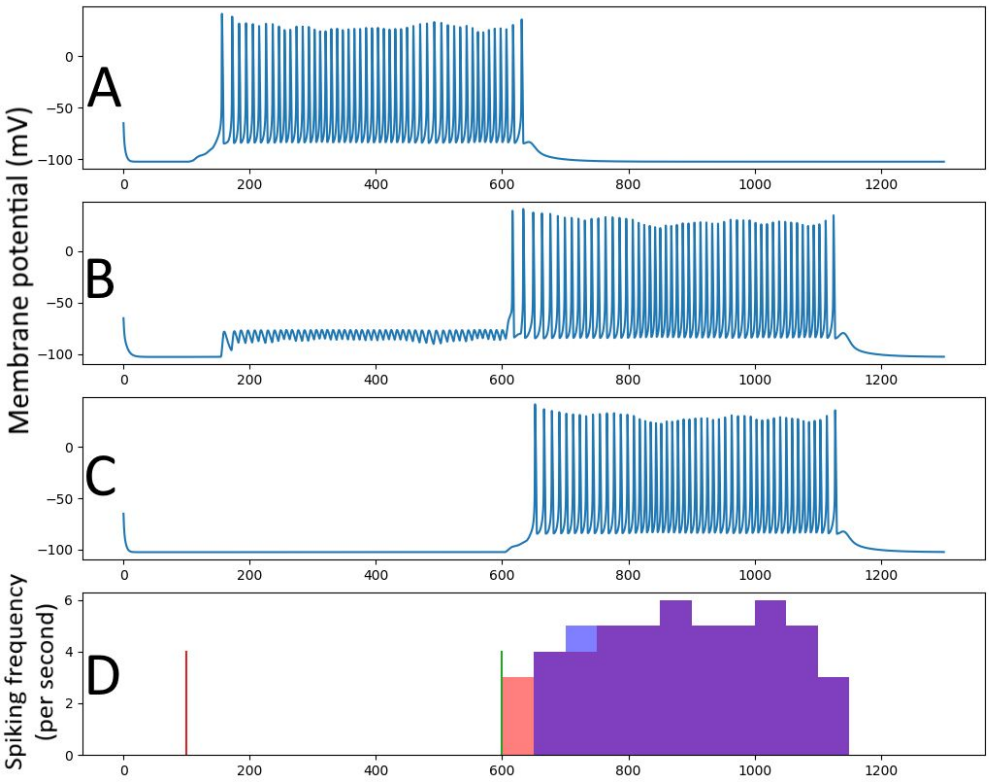

Figure 4. A) First neuron is stimulated with a spiking priming signal for 500 ms. B) Second neuron, besides receiving a graded potential from the first neuron, also receives a probe spiking signal at t = 600 ms, for 500 ms. C) Third independent neuron that also received a probe spiking signal at t = 600 ms, for 500 ms. D) Comparison of spiking frequencies between neurons two and three.

Discussion

The results indicate that while there are a few NEST simulator neuron and synapse models that support facilitation, none of them are advanced enough to create a fully-fledged facilitation wave as seen in live experiments. The combination of a iaf_psc_exp neuron model and a tsodyks2 synapse model has been able to induce a facilitation-resembling voltage pattern in the postsynaptic neuron. That transmission, however, was only able to occur if the presynaptic neuron spiked, which goes against the pattern seen en vivo, where graded potentials were able to spread throughout the neural networks without spiking. Tsodyks2 synapse model was unable to transmit graded potentials even when the connection weight was exceedingly high.

While connections with gap junctions did manage to successfully transfer graded potential signals throughout the neuron chain, they were unable to modulate the signal and create anything resembling facilitation. Additionally, iaf_psc_exp neurons do not support connections through gap junctions, which led to another neuron model, hh_psc_alpha_gap, being used instead. It was later discovered that this older neuron does not seem to support facilitation, which makes any

attempts at combining synapses and gap junction difficult. Hypothetically, a double connection using both a synapse and a gap junction may provide both the required signal modulation and a pathway for postsynaptic graded potentials to spread further throughout the network, but currently there are no neuron models that support both facilitation and gap junctions. Additionally, since all the gap junction connections in NEST are bi-directional, there may be some issues with feedback signals interfering with the simulations.

After the simulations with the NEST simulator have led to limited success, a different simulator was adopted for the remaining body of work. NEURON simulator allows for creation and separate adjustment of parameters for various parts of the nerve cells. While a facilitation-like effect appeared to happen in the time interval between 600-650 ms. in the primed neuron (Fig. 4D), more experimentation needs to be done in the future studies. Some of the possible directions may be replacing the graded AMPA synapse between neurons one and two with a graded NMDA synapse or adjusting various Hodgkin-Huxley parameters such as the spiking threshold.

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