Computational Science Research Center
San Diego State University

Master of Science

Thesis Proposal

Modeling Predictive aspect of Response Facilitation in Small-target-sensitive Visual Neurons

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Contents:

1. Abstract:

Flying insect species like dragonflies are capable of predicting the path or location of their target even if the target has occluded by some object for some period of time. This ability to predict the path is supported by a processing mechanism which is called response facilitation. We have been working on modeling this predictive aspect of response facilitation in small-target- sensitive visual neurons in dragonflies. This facilitation is known to increase sensitivity to small objects that move along continuous paths and is thought to increase reliability of small target detection. Because the locus of facilitation that is induced by a moving target propagates in visual space even after a small target stimulus ceases, we have proposed that it could be supported by traveling wave phenomena in retinotopically-organized regions of the visual system. Accordingly, we have proposed a biological substrate: a network of cells (quite possibly astrocyte-like glia) in which calcium waves are initiated by target stimuli and propagate via diffusion with the participation of regenerative mechanisms.

2. Introduction:

Detecting and tracking moving targets within a visual scene is a complex task, yet it is of great importance to animals that rely on catching/ chasing their targets for food and mating. Over millions of years many species of animal have evolved neural mechanisms for target analysis. Flying insect species like dragonflies show amazing ability to track the path or location of target that move against the visually cluttered background again and again. It has also been stated that dragonflies capture prey with success rate of 97% even in the presences of some distraction (Corbet, 1999).

Small target motion detector (STMD) neurons are likely to be involved in this behavior as they display an impressive selectivity for small moving objects (Nordstrom et al. 2009; Nordstrom and O'Carroll, 2009). As of now two relatively higher-order functions had been identified that appear to support this behavior: One is *selective attention* that allows STMDs to respond to single target at a time (Wiederman & O'Carroll, 2013); and second is a type of *facilitation* that enhances the response of an STMD to a continuously- moving target (Dunbier, Wiederman, Shoemaker, O'Carroll, 2012). Our project focuses on second mechanism. A number of experiment have been conducted to characterize the process of facilitation and it has been observed that facilitation is predictive in nature.

In this project we investigate the predictive aspect of response facilitation by assuming that it might be supported by the propagation of *calcium waves* in a network of astrocyte-like cells that interact with STMD neurons. We model such a network and then further analysis is done on propagation of calcium signals in this model in presence and absence of external stimulus that corresponds to moving target in real world. We also do comprehensive parametric study of our model outlining how and why it behaves with different values of parameters and thus characterizing the facilitation mechanism.

3. Background:

Historically, glial cells have been regarded as support cells in nervous system. They were considered to be gap fillers, whose sole purpose was support neurons mechanically and perhaps metabolically. But work in vertebrates over the last decade suggest that they may play significant role in the function of the nervous system.

3.1. Glial Cells:

Glial cells or simply glia were discovered in 1856 by the pathologist Rudolf Virchow in his search for a "connective tissue" in the brain. Glial cells, also called as Neuroglia, are non-neuronal cells that plays a very crucial role in central and peripheral nervous system. The term "Glia" comes from Greek name implies "glue" of the nervous system. They initially got this name, because they seem to fill spaces between neurons to hold them together.

There are different types of glial cells in the central nervous system. Glial cells include oligodendrocytes, astrocytes, ependymal cells and microglia, and in the peripheral nervous system glial cells include Schwann cells and satellite cells.

For over a century, it was believed that the glia did not play any role in neural signal processing. However, with improved techniques, researchers have found out that glia cells do have an important role to play in assisting/ supporting the neurons to form synaptic connections between each other or possibly between neurons and glia cells themselves.

Out of different types of glial cells, the most abundant type of cells in central nervous system are Astrocytes. They constitute up to 40% of all glia cells. Astrocytes are star shaped glia cells and are found in proximity to neurons.

Astrocytes are non-electrically excitable, unlike neurons. However, they do display a form of excitation that is based on variation of Ca^{2+} concentration in cytosol. Localized changes (increase or decrease) in concentration of Ca^{2+} can propagate in the form of a wave like pattern, which is called calcium wave. In last decade, studies and research in vertebrates has shown that astrocytes propagate intra- and intercellular calcium waves over tens of μm in response to stimulation.

3.2. Ca Signaling/ Wave:

A calcium wave is defined as a localized increase in cytosolic Ca^{2+} that is followed by a succession of similar events in a wave like fashion. These calcium waves can be restricted to one cell (intracellular) or transmitted to neighboring cells (intercellular). Calcium (Ca^{2+}) is an important ion with respect to function of almost all cell types. The dynamics of Ca^{2+} is very important in cellular physiology because Ca^{2+} regulates their activity and interactions. As we have noted, astrocytes are excitable cells with Ca^{2+} fluctuations being the waves by which they respond, integrate and convey signals. These waves are also called Ca signals.

3.3. Triggering and Transmission of Ca waves:

These calcium waves are triggered by activity of neurons with which glial cells come into contact. The recent results have shown that the neurotransmitter, in particular, glutamate can trigger actively propagating Ca^{2+} waves in the cytoplasm of astrocytes (Dani JW, 1992).

The law governing Ca^{2+} transport within a cell is provided by diffusion e.quation. Therefore, the extent to which these intercellular Ca^{2+} waves can travel are affected by the diffusion coefficient of Ca^{2+} ions in cytosol.

The transmission of Ca waves between cells takes place through two pathways. First is direct communication between cytosol of two adjoining cells through "gap junction" channels. Gap junctions are a specialized intercellular connection between two cells. They directly connect the cytoplasm of two cells, which allows various molecules and ions to directly pass through a regulated gate between cells.

Another type of pathway is via indirect communication, where there is no physical connection between the cytoplasm in two cells. This type of communication depends upon the release of gliotransmitters that activates membrane receptors on neighbor cells. Once membrane receptors are activated, these cells respond with increase in intercellular Ca^{2+} elevations. Gliotransmitter are chemicals released from glia cells that facilitates neuronal communication between neurons and other glia cells, and this communication may be triggered through calcium waves/ signals.

These waves propagating between different cells are called Intracellular calcium waves (ICWs). ICWs are spatially and temporally complex events involving the recruitment of elementary Ca^{2+} release sites, which then propagate through cell by amplification mechanism. This amplification mechanism involves four different types of components, two of which depend on positive feedback and other two depends on negative feedback.

4. Response Facilitation:

4.1. Facilitation:

Facilitation is an increase in excitability of an STMD neuron, and it is not strictly a function of how long an STMD neuron is excited by small targets; rather, its effect is most pronounced when a targets moves along *continuous paths* in the visual field (Dunbier, Wiederman, Shoemaker, O'Carroll, 2012). We can think of *facilitation* as a means to gain confidence in detecting small moving targets in the actual presence of a target. For the noisy and low-amplitude visual signals that are evoked by small targets, this may give a significant boost to the reliability of detection.

4.2. Predictive nature of Facilitation:

A variety of experiments have been conducted to characterize the process of facilitation. These experiments have been conducted with an immobilized insects viewing a screen on which moving small-target stimuli are presented. By analyzing the sensitivity of the STMDs to small target

contrast, Wiederman and O'Carroll and their labs have shown that facilitation corresponds to a modulation of contrast gain in the neural pathway leading to the STMDs.

In a critical subset of these experiments, the insects have been subjected to a priming target that moves part way through the receptive field of the STMD and then vanishes, followed by a probe stimulus consisting of a target moving briefly along a short path at some other location. By repeating this sequence for various probe locations, and recording the neural responses, a spatial map of the responsiveness of the STMD following the priming stimulus can be assembled. When this is compared to responsiveness map built without a primer, the degree of facilitation of the neuron due to the primer can be assessed as a function of position in the visual field. Comparing maps of the receptive field in facilitated and unfacilitated states, you can see that region of facilitation is limited in size and appears at and in front of the last position of the priming stimulus.

Moreover, when there is a delay between the end of the priming stimulus and the probe stimuli, it can be seen that the region of facilitation has actually propagated through space during the delay. These results clearly show that facilitation can be regarded as predictive in nature. Facilitation that doesn't propagate on its own could still move as a result of the fact that it is evoked by a moving stimulus, but in that case, the facilitation would not keep moving afterward.

5. Mechanism for Facilitation:

5.1. Network of Cells:

Although it is spatially local, facilitation is a mechanism that can take place anywhere within the receptive field of the many wide-field neurons, and thus many neurons might be involved in the computation of facilitation over a broad region. Thus we assume that it is supported by a network of cells that forms a heavily-interconnected web with many randomly-oriented processes and interconnections between these cells, through which signal propagates.

5.2. *Signaling*:

Signal that propagates in such a network needs to have a propagation speed less than a mm/s. Membrane potentials in cable-like cellular structures are far too fast for our purpose as they have propagation speed on the order of cm/s or more. Chemical signals (esp. Calcium signals) with slower diffusion speeds are a possible alternative. Calcium waves have been observed in astrocytes and neurons. Also, there is evidence that such waves can propagate intercellularly, so we will consider them as means for propagation of facilitation.

5.3. Regenerative Mechanism:

The active wave propagation, whether chemical or electrical, requires a regenerative mechanism in order to take place. In astrocytes, this regenerative mechanism is associated with voltage-dependent calcium channels as they have appropriate dynamics (speed).

5.4. Location for facilitation:

It is not entirely certain at present where the facilitation phenomenon takes place: there is evidence that small-field STMDs, which arborize in the primary lobula, may be subject to

facilitation (Wiederman *et al*., 2017) – and the locus of the facilitatory 'hot spot' is (perhaps not coincidentally) roughly the same size as the receptive fields of small-field STMDs. However, it cannot be ruled out that the moving facilitation takes place in the medial lobula, where dendritic arborizations of wide-field STMDs occur. For example, it is plausible that a facilitatory network residing in this structure is stimulated by the small-field inputs that converge on the wide-field STMDs, but then exerts its action on the dendrites of the wide-field neurons themselves.

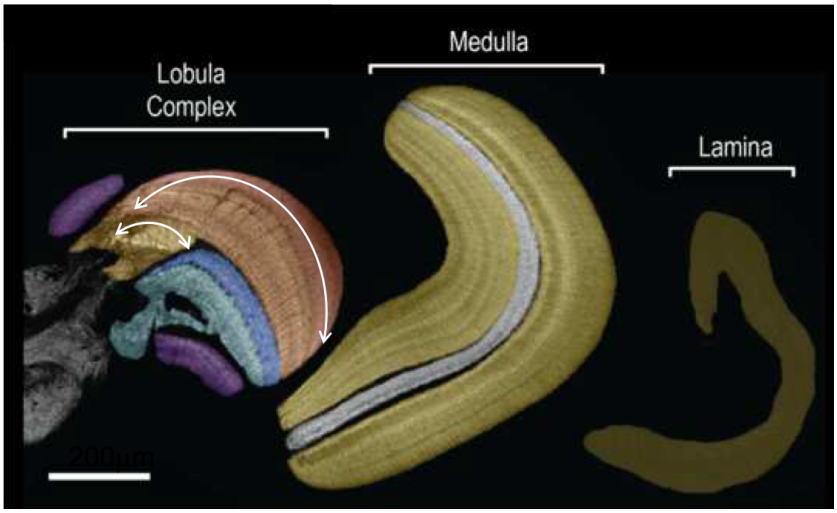

Figure 1: Horizontal section of the optic ganglia of the dragonfly Hemicordulia tau, showing the lobula complex at left. The primary lobula, shown in pink, is where small-field STMDs receive their inputs, whereas wide-field STMDs arborize in the medial lobula, the smaller tan structure below the left part of the primary lobula. Image courtesy of J. Fabian, B. el Jundi, S. Wiederman, and D. O'Carroll.

5.5. Propagation speed:

The outer layers of the primary lobula as seen in the Figure 1 span about 750µm in horizontal section, corresponding to roughly 135° subtense in visual space; this implies that a moving facilitatory signal in this neuropil would have to propagate at ~170µm/s to 220µm/s. The medial lobula, conversely, is around 1/4 to 1/5 of this size; although it is not certain how this structure or the dendrites within it scale relative to the visual space they service, it is clear that required propagation speeds would be smaller, on the order of tens of µm/s, if propagating facilitation takes place there.

6. Models for Propagation:

Initially, we identified two candidates for biophysically-plausible substrates that might support propagating facilitation: 1) a network of cell in which the signal is carried by diffusing calcium ions, and waves are propagated with a regenerative positive feedback mechanism; and 2) A network of small neurons in which propagating electrical signals are delayed frequently by the presence of excitatory synapses with slow kinetics. This project/ report is focused on the first model: a network of astrocytes. In the meantime, continued reading of the literature has shown

that calcium waves have been observed in some vertebrate central nervous system neurons (AC Charles, 1996; Ross WN, 2012), and that they travel faster than calcium waves in astrocytes. Therefore, these cells will be considered under the study as well.

6.1. Propagation of Ca waves:

Lateral calcium transport occurs in astrocytes by diffusion, but a purely dissipative process cannot support wave propagation. A regenerative mechanism that can give rise to wave must be present in a form of positive feedback. In this case, a second messenger, whose release is initiated by the presence of calcium in the cytosol, activates receptors that allow additional calcium to flow into the cell. The chemical is called inositol trisphosphate (InP3), and it is cleaved from a precursor called diacylglycerol (DAG) in a cascade that is triggered by intracellular calcium. The diffusion of InP3 in the cytosol is inhibited, and thus it remains a signal with relatively local spatial effect.

6.2. *Model for InP3 receptor kinetics:*

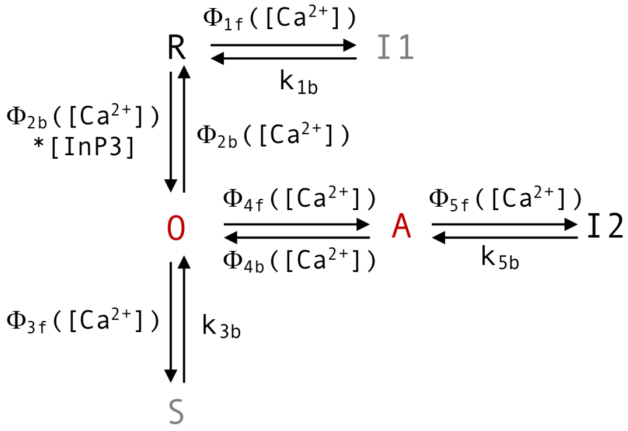

Fig 2.: The Sneyd-Dufour model for InP3 receptor kinetics.

The figure shown above is the Sneyd-Dufour model for InP3 receptor kinetics. Opening of the receptor's calcium channel is associated with states O and A. The functions denoted by ϕ are calcium-dependent rate functions. Transition from the native state R to O involves binding of the ligand InP3, reflected by its presence as a factor in the rate for that transition. The states rendered in gray, I1 and S, were found to have little participation in receptor function under the conditions we simulated, and are not included in our models. This kinetic structure is associated with each of four subunits of the complete receptor.

In terms of channel open probability, the state O corresponds to 'weakly open' and A to 'strongly open'. The kinetics in Figure 1 apply to each of four subunits that make up the complete receptor; the total open probability is thus $(0.1 * O + 0.9 * A)^4$. When InP3 concentration is stepped, the time-course of the distribution of the subunits among the states leads to a brief period of high open probability followed by much lower open probability. This feature is essential to the formation of calcium waves in cells incorporating the InP3 receptor.

With the InP3 receptor model so defined, the positive feedback loop for calcium entry into the cytosol can be described as follows: Neural input (presumably glutamate release) opens calcium channels; the influx of calcium triggers the cleaving of InP3 from DAG; InP3 activates InP3 receptors, leading to the influx of more calcium; the positive-feedback episode is terminated by reduction of open probability of the InP3 receptor, which reduces the loop gain to less than unity, and calcium pumps and other sequestration mechanisms remove calcium from the cytosol.

6.3. Calcium dynamics model for astrocytes:

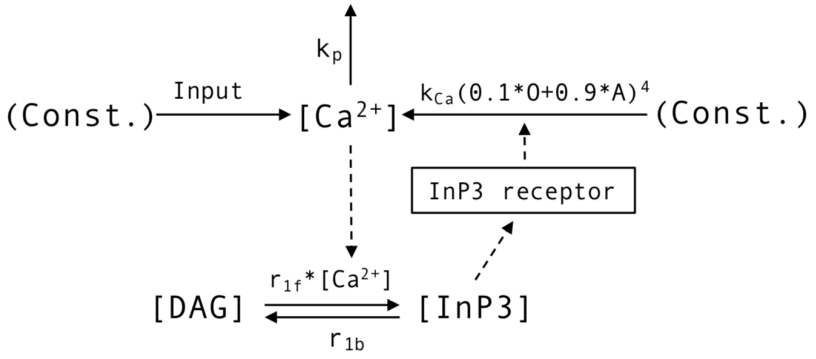

Fig 3: Calcium dynamics model for astrocytes in our model

The figure above shows the complete intracellular calcium dynamics model for astrocytes in our model, in quasi-kinetic form. All processes for removal of free calcium -- efflux, sequestration, or buffering -- are characterized by a single rate constant k_p that is proportional. k_{Ca} is a constant proportional to InP3 receptor density and open-state calcium diffusivity; r_{1f} is a second-order rate constant for InP3 production, and r_{1d} a first-order rate constant for uptake of InP3, which is modeled as simple conversion back to DAG. The effect of InP3 receptor binding on the total concentration of InP3 is neglected (Sneyd and Dufour, 2002). Not depicted is the flow of calcium that can occur at locations where cells are interconnected together by gap junctions.

6.4. Modeling Propagation of Calcium in a dendrite:

The lateral transport of calcium during the propagation of calcium waves in one-dimensional cellular processes (dendrites) is expressed by diffusion equation and it is solved numerically using MOLE library.

MOLE is a library that implements high-order mimetic methods to solve 1D, 2D, and 3D partial differential equations (Corbino and Castillo, 2017). It provides discrete analogs of the most common vector calculus operators: Gradient, Divergence, Laplacian and Curl. These operators (matrices) act on staggered grids (uniform and nonuniform) and they satisfy local and global conservation laws (Castillo and Grone, 2003).

7. Structure of Astrocytes/ Cell:

As noted, astrocytes are star-shaped cells that have radiating cellular processes that we will refer to as ‘dendrites’ for simplicity (even though ‘dendrite’ is usually used to refer to a form of neural process). Every cell in our model has a stereotyped morphology and is made of 3 parts: cell body (or more precisely, the region at which the dendrites meet), straight dendrites and branched dendrite. And, these parts are made of compartments, which you can think of as building blocks for our model. Cell body is itself a single compartment, straight dendrites are made of 10 compartments each and every cell have 8 straight dendrites. Branched dendrites are made of 3 segments and these segments are made of 5 compartments each, we have 12 branched dendrites in our model. Below you can see a diagram of a cell, having one cell body, eight straight dendrites, and four branched dendrites with a total of 12 branched segments.

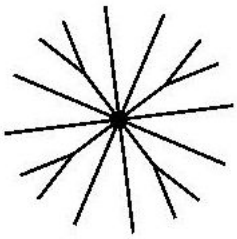

Fig 4.: Single cell in our model.

Figure 5 is an image of 2 cells interconnected together through some randomly-placed interconnections (red dots). In a typical network, we will have hundreds of such cells interconnected together.

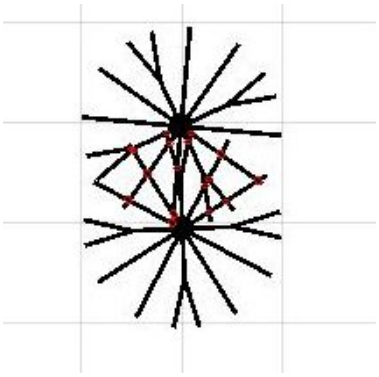

Fig 5.: Two interconnected cell in our model

8. Simulations:

We simulate the propagation of calcium wave in a model of astrocytes arranged in a network like fashion. These network simulations are carried out using Matlab scripts. One script generate networks consist of astrocytes with a stereotypical architecture, but with randomness introduced in their placement and orientation. Cells are placed on a hexagonal grid for symmetry, but random offsets in the x and y directions are added to the cell positions, and they are rotated randomly at placement. Below you can see an skeletonized diagram of a network of 25 astrocytes interconnected to each other.

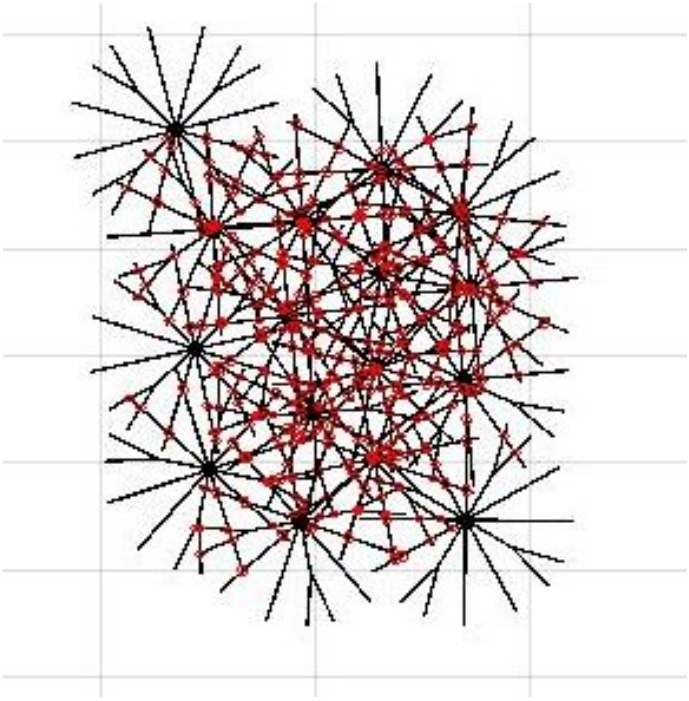

Fig 6.: Network of 25 astrocytes interconnected together .

Our script discretize the straight dendrites into 10-element grid and each segment of a branched dendrites into 5-elements grid for numerical solution while maintaining the second-order accuracy. And for each grid (compartment) a storage structures has been defined that maintains the value of required states (which include, $[Ca^{2+}]$, [DAG], [InP3], and R, O, A, and I2 for the local receptor populations). These are updated incrementally in time-domain simulations, according to the governing dynamical/rate equations.

These scripts also define interconnections between dendrites of different cells through which the wave may pass. In vertebrate astrocytes, evidence suggests that there is both direct exchange of calcium through gap junction-like interconnections, and release of transmitters that can induce the opening of calcium channels in neighboring cells, but for simplicity, we are initially modeling only direct flow of calcium.

9. Experimentation:

At this time, we have finished simulating a 5 by 5 array of cells (25 cells) with initial conditions applied at one of the end/tip of a dendrite in a cell and a wave propagating (in all direction) across all the cells can be observed.

We are in the process of debugging a model where external stimulus is applied only for a short period of time in a particular direction which leads to propagating wave just like previous case. And, when this external stimulus is ceased we can still see a wave propagating for some time. Although, this needs to be explored more by running more experiments, we believe this nature of wave (or wave front) propagating even after stimulus is ceased corresponds to predictive nature of facilitation.

10. Results:

10.1. Propagation Speed:

We have observed variations in the propagation speed of the wave within individual dendrites as we vary feedback strength and receptor rate constants. In some cases we have observed propagation speed which is in accord with the speed of calcium waves observed in vertebrate astrocytes (Bazargani and Atwell, 2016; Jaffe and Creton, 1998). However, the net speed of the wave propagation would be somewhat slower in an interconnected network, since dendrites may be at oblique angles with respect to the overall direction of propagation. Thus, speed is definitely slower than necessary to support propagating facilitation in the primary lobula of dragonflies, and possibly too slow even for the medial lobula.

10.2. Varying different parameters:

However, in an nonlinear system where many factors affect the dynamics of propagation, diffusion coefficient alone cannot govern the propagation speed, factors like feedback gain and other rate constants could also play a significant role.

Also, Sneyd-Dufour model applies to the type-2 vertebrate InP3 receptor; it is entirely plausible that receptor comprised of different subunits and in different species, might have similar kinetic structure but different rates. Thus, we have examined how propagation speed varies as the feedback strength (k_{ca}) is varied and the InP3 rates constants are scaled.

We observed increasing propagation speed as k_{ca} or other rate constants are increased with less than linear relationship between these parameters and speed of the wave. We will be working more on such analysis and a more comprehensive study will be done in the remaining part of the project.

11. Conclusions to date:

Based on our study so far we have tentatively concluded that a calcium signal could possibly support a propagating facilitation phenomenon in the medial lobula, but likely not in the larger

primary lobula. The dendritic calcium waves that we have observed so far appear to be fully regenerative with no decay as the wave propagate. Our experiments have shown that if there is a range of parameter values for which waves propagate while decaying in amplitude, it would seem to be very narrow.

12. Future Work:

We have broadly divided the future workflow of this project into the following parts with each part addressing the different aspect of the project.

12.1. Parallelizing the model:

By now it's very clear to us that this is a resource intensive problem (CPU intensive + memory intensive). Simulating a single cell can easily take more than 3 minutes and if we increase the network size by adding more cells with some random interconnections it can go for few hours. For example: Running a network of 25 cells takes more than 3 hours to run on the following system:

System Configuration:

a) MacBook Pro (13 inch)
b) Processor 2.3 GHz Intel Core i5
c) Memory 8 GB RAM

On the basis of the above result, we estimate running a network of a few hundred cells (say, 100, 200) will easily take over a day to run, if not a few days. Also, going further, running these simulations on local system is no more possible because of the amount of resources it requires.

In order to tackle this computational problem, we have come up with a twofold plan: Firstly, we will use CSRC clusters to run our simulations, as this will give us more compute power and time to run simulations for bigger models. Secondly, we will use MPI to parallelize our model and then run it over different nodes on the CSRC cluster. This will give us significant speedup in simulation time.

12.2. Investigating nature of facilitation:

According to experimental results, facilitation is seen to follow a pattern that looks like a 'blob'. This blob-like structure appears in front of where the target (stimulus) was last seen. Also, facilitation is considered to be predictive in nature. We will investigate the nature and characteristics of the facilitation mechanism by addressing the following questions:

a) How big (shape, size) is facilitation blob for various size of stimulus?
b) How fast facilitation move with the varying speed of stimulus, as key parameters are varied?
c) How much longer does facilitation blob continue to exist even if the stimulus is ceased?

12.3. Parametric variation/ study:

In the next 2-3 months, we will do a comprehensive parametric study of our model, investigating how different parameters affect the propagating wave. We already did some work on this during the last few months but more time will be spent on this part as we have a bigger and more complex network up and running.

We are considering to follow two strategies for this study: Firstly, *Grid Search*, where a grid of parameters values (kca and other InP3 rate constants) will be defined and every combination of these values will be tested. Secondly, *Random Search*, where random combinations of different parameter values will be tested. We have already done some work using random search in our past experiments. We might look into *Randomized-Grid Search*, where random combinations of different parameter values defined in grid will be tested.

The goal of this study is twofold:

a) First, to characterize the range of parameter values that can support propagating facilitation.
b) Second, to study dynamics of calcium wave in a network of cells.

12.4. Characterizing the propagating wave:

Since we have assumed that the predictive nature of response facilitation might be supported by the propagation of calcium waves in a network of astrocyte-like cells, it is important to characterize the propagation of calcium wave.

We would like answer following questions:

a) How does wave behave for different speed of stimulus?
b) How does wave behave for after cessation of stimulus?
c) How does a wavefront vary with variation of parameters assumed for the stimulus (e.g., size and overlap of the projection)?
d) What parameters govern propagation speed of the wave, and how?
e) Is there a parameter range for which the wave transitions from decaying to completely regenerative?
f) How is wave propagation affected by the strength of the inter-cellular connections?

12.5. Alternative Models:

We will also explore a second model for propagating facilitation: calcium waves in a neural network, rather than in astrocytes. We expect that the infrastructure we have built for modeling astrocyte networks should be fairly straightforward to modify in order to simulate neural calcium waves.

Acknowledgements:

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