MODELS FOR PROPAGATING FACILITATION IN INSECT VISUAL SYSTEM

Master's Thesis

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Outline

- Introduction
- Background
- What is Facilitation?
- Problem Statement
- Mechanism for Facilitation
- Models for Propagation
- Numerical Simulation
- Experiments
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- Conclusion

Introduction: Moving Target Detection & Tracking

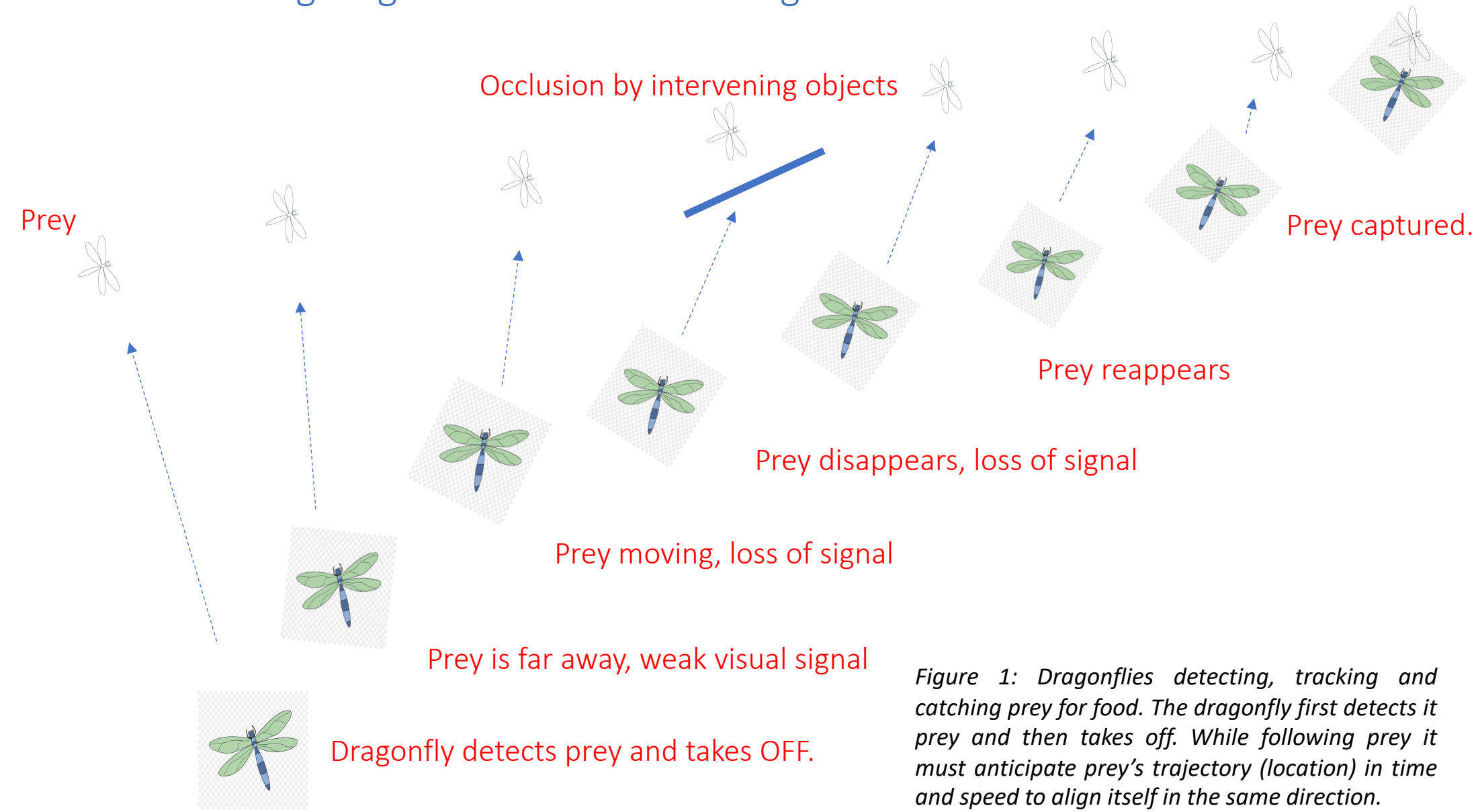


Figure 1: Dragonflies detecting, tracking and catching prey for food. The dragonfly first detects it prey and then takes off. While following prey it must anticipate prey's trajectory (location) in time and speed to align itself in the same direction.

Background

Detecting and tracking moving targets is a complex task.

1. Low Amplitude Signals - Poor Signal to Noise ratio
2. Loss of Signals - Cluttered environment/ background

Dragonflies capture prey with success rate of 97% even in the presences of distraction*.

- Evolved neural mechanism – STMD Neurons
- Evolved behavior – (tend to isolate the targets against the sky as compared to cluttered environment)

1. Small target motion-detector neurons (STMDs) display selectivity for small moving objects/ targets.
2. Two higher-order functions that (appear to) support this behavior:
   - *Selective Attention* : allows STMDs to respond to single target at a time.
   - *Facilitation* : enhances response of an STMD to a continuously-moving target.

** Robot eyes will benefit from insect vision. University of Adelaide. Phys.org*

What is Facilitation?

Facilitation is a mechanism that increase the excitability of a neuron to a continuously-moving target (stimulus)*.

Not a function of how long a neuron is excited by targets;

- Effect is pronounced when a targets moves along a continuous paths in the visual field

1. Mechanism to gain confidence in the target detection by exploiting the constraint of continuity of target motion.
2. Gives a significant boost to the reliability of detection.

** Wiederman, Fabian, Dunbier, O'Carroll, eLIFE 6:e26478, 2017*

Nature of Facilitation

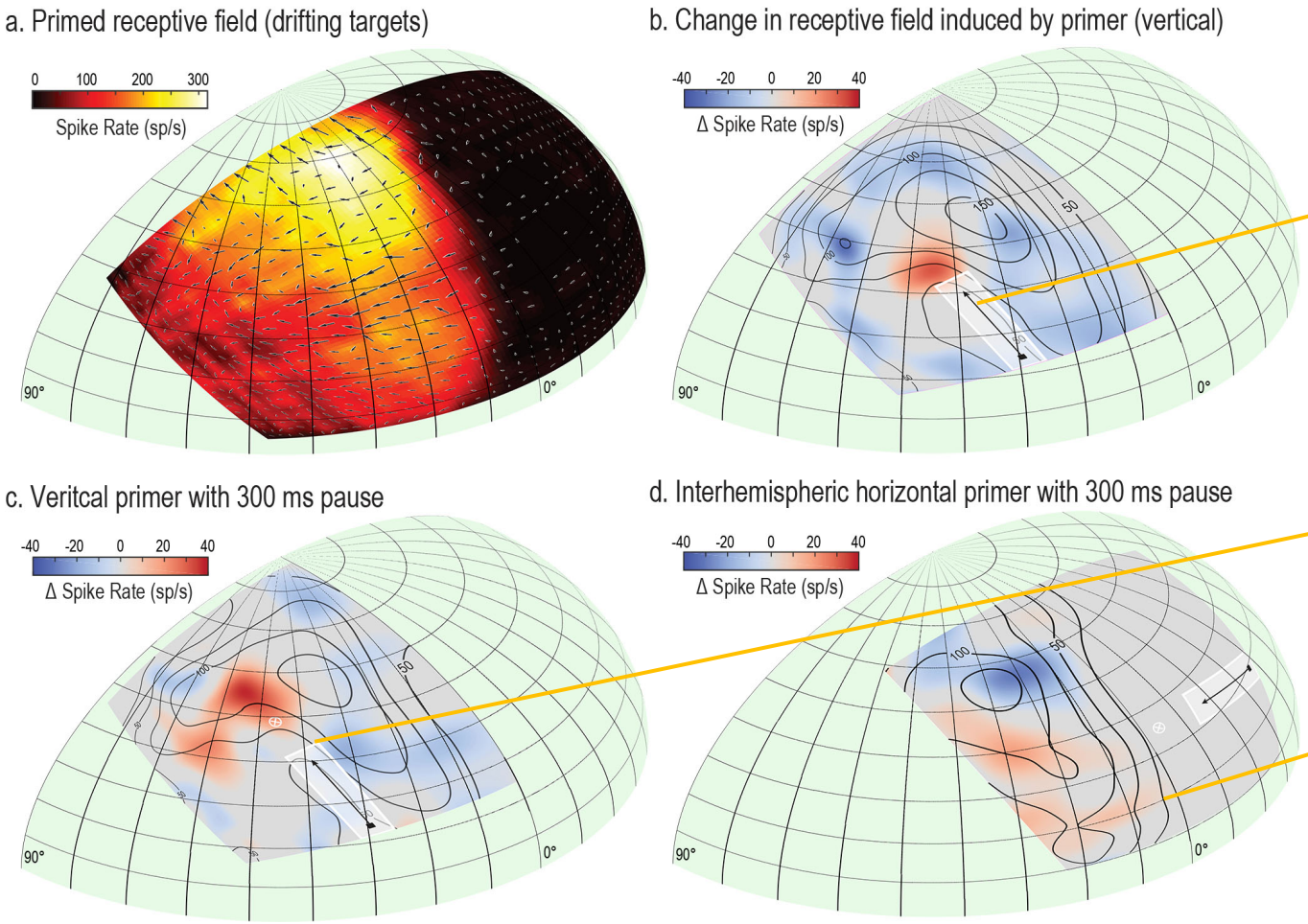


Figure 2: Panel 'A' depicts the baseline receptive field sensitivity of the neuron, and 'B' depicts the change in sensitivity induced by the primer, when the probe stimuli immediate follow it. In 'C' and 'D', there is a pause between the end of primer motion and the imposition of the probe stimuli.*

An increase in *excitability* with exposure to a moving target.

Facilitation is *spatially* local.

- appears near / in front of a target that has moved along a continuous path
- remainder of the receptive field: *depressed* responsiveness

Facilitation is *predicative* in nature.

- appears to propagate in retinotopic space after stimulus ends.

Inter-hemispherical *transfer* of facilitation.

- might be dedicated neuron that goes over the other side of the brain

Facilitation moves at a rate of 30-40 deg/sec in the visual field.

** Image courtesy: David O'Carroll (Lund University) and Steven Wiederman (University of Adelaide)*

** Wiederman, Fabian, Dunbier, O'Carroll, eLIFE 6:e26478, 2017*

Anatomy and Physiology of STMD Systems:

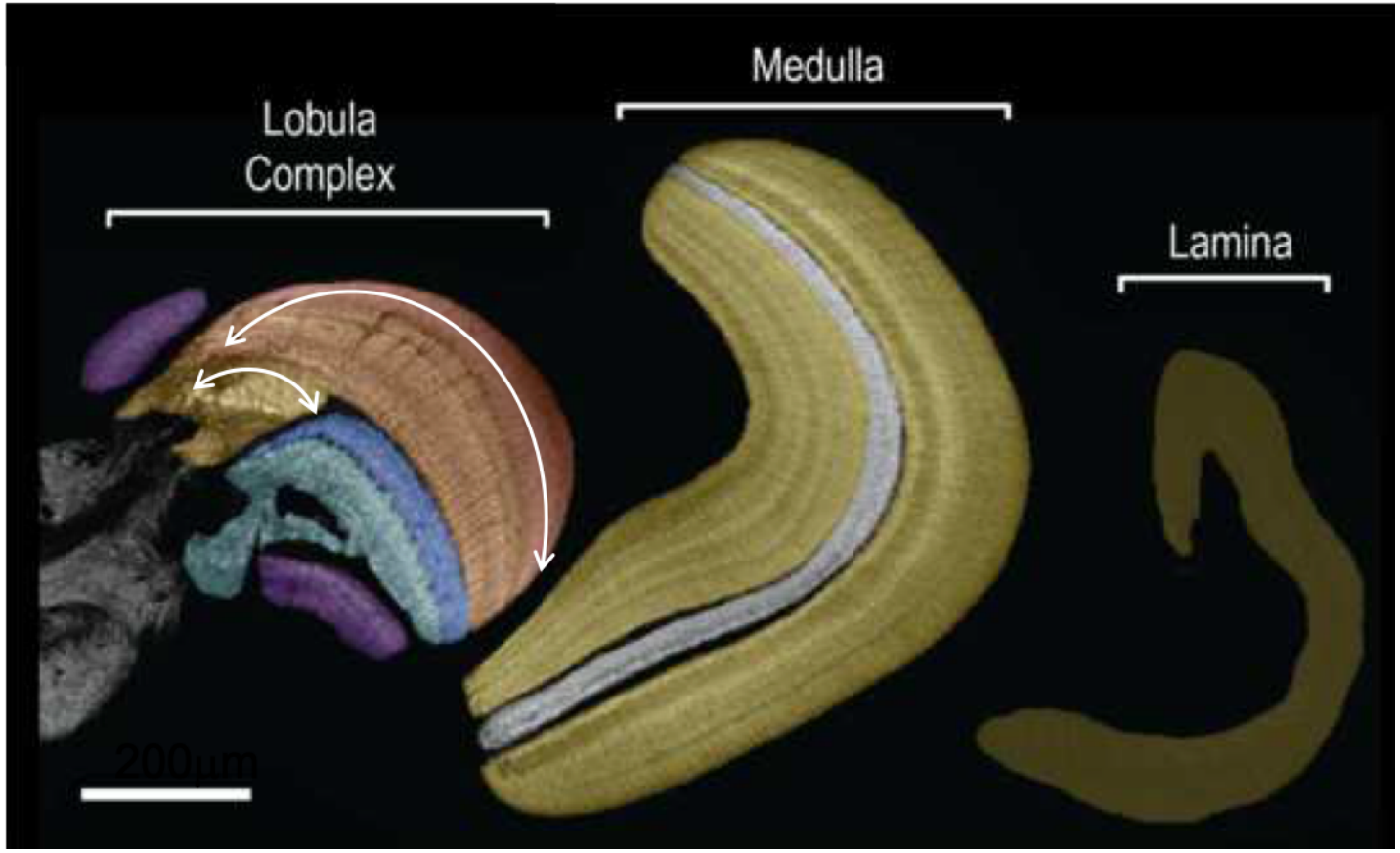


Figure 3: Horizontal section of the optic ganglia of the dragonfly Hemicordulia tau. This image is for the right eye and depicts 1) optic ganglion (lamina), 2) medulla, and 3) lobula complex, at left. The primary lobula, shown in pink, is where small-field STMDs receive their inputs, whereas wide-field STMDs arborize in the medial lobula, the smaller tan structure below the left part of the primary lobula.*

Dragonfly Optic Lobes

PRIMARY LOBULA (pink):

where *small-field* STMDs arborize / reside

- ~ 750 µm span ⇔ 135° subtense in visual space
- facilitatory signal here would have to propagate at ~ 170 to 220 µm/s

MEDIAL LOBULA (light tan):

where *wide-field* STMDs arborize

- ~ 180 µm span
- facilitatory signal here would have to propagate on the order of tens of µm/s

** Image courtesy of J. Fabian, B. el Jundi, S. Wiederman, and D. O'Carroll.*
** Release of this figure is embargoed pending publication by its authors.*

Problem Statement

Questions

1. Locus of facilitation is induced by moving target.
2. Location
3. Biological substrate
4. Speed range. Electrical signals in neurons are too fast.

Hypothesis

- Supported by traveling wave phenomena
- Retinotopically-organized regions of the visual system
- 2D networks of cells that interact with STMDs
- Calcium waves as a plausible candidate (slower wave propagation)

Mechanism for Facilitation

1. Network of Cells:
   - Facilitation can take place anywhere within the receptive field of many neurons
   - Might be supported by a network of cells
2. Regenerative Mechanism:
   - Active wave propagation requires a regenerative mechanism
   - Positive feedback
3. Propagation speed:
   - Signal needs to have a propagation speed less than a mm/s
   - Membrane potentials are far too fast (cm/s)

Glia Cells

- “Glia” is a Greek word, meaning “*glue*”.
- Glia was considered as glue of nervous system that holds neurons together.
- They are non-electrically excitable, unlike neurons.
- They display excitation consisting of variation of Ca^{2+} concentration in cytosol, also know was Ca waves.
- Propagate intra- and intercellular calcium waves in response to stimulation.
- Waves could be transmitted over tens of μm because of regenerative mechanism that is present in astrocytes.

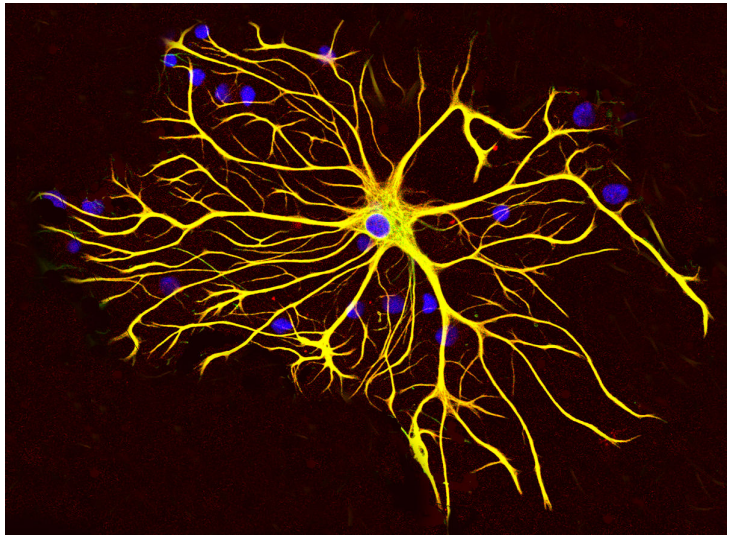


Figure: An astrocytic cell from rat brain.

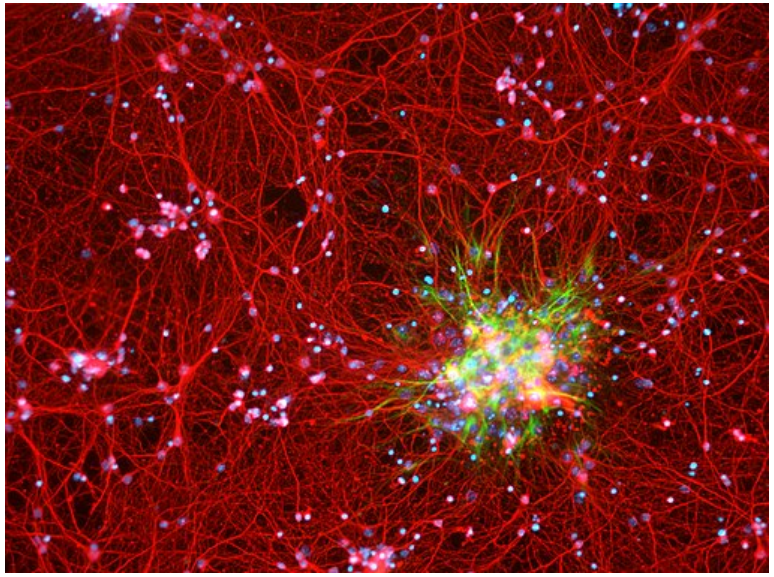


Figure: Astrocytes (green) in the context of neurons (red) in a mouse cortex.

Image Source: Wikipedia

Neurons

- A neuron, also known as a nerve cell, is an electrically excitable cell.
- Neurons communicates with other cells via specialized connections called synapse.
- Most neurons consist of three parts:
  1. Cell body
  2. Dendrites
  3. Axon
- Many interneurons are local and do not have clearly defined axons.
- Signaling process is partly electrical and partly chemical.
  - Membrane potential = Signal in cell
  - Chemical synapses = Signal between cells

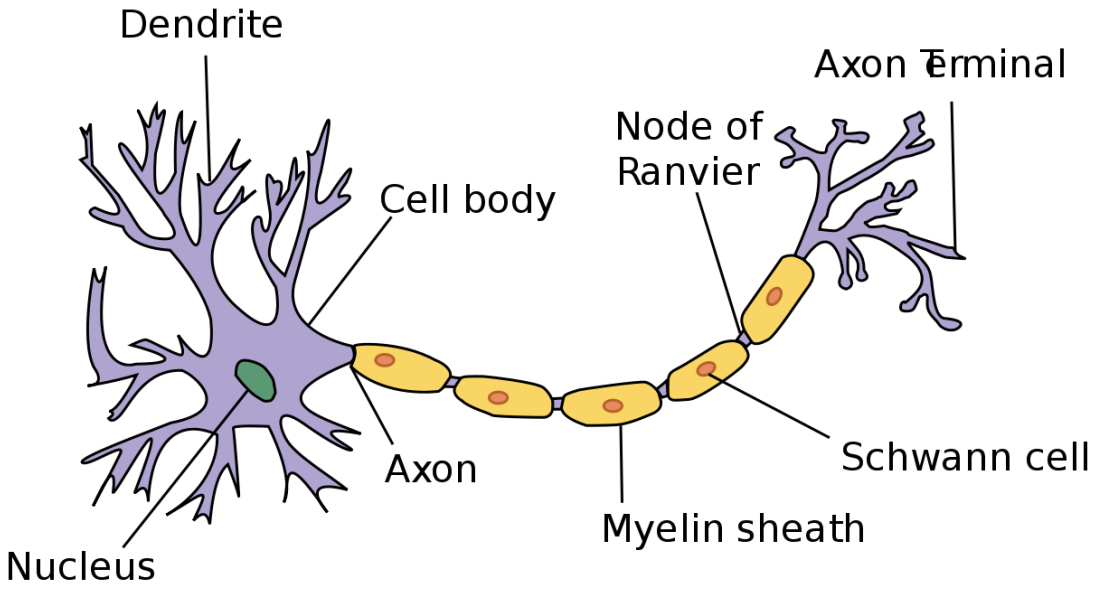


Figure: Diagram of neuron

Image Source: Wikipedia

Calcium Signaling

Calcium Wave: Moving and localized increase in cytosolic Ca^{2+} in a periodic wave-like fashion.

1. Intracellular - restricted to one cell.
2. Intercellular - transmitted to neighboring cells.

Triggering of Ca^{2+} waves:

1. Complex event, involve series of reactions.
2. Release of neurotransmitters onto the cells leads to chain of reactions, which activates receptor channels.
3. InP3 receptors responsible for Ca^{2+} release from the endoplasmic reticulum (ER).
4. Ryanodine receptors are responsible for releasing Ca^{2+} from internal stores.
5. Released Ca^{2+} then propagate throughout the cell by combination of diffusion and amplification mechanism.
6. Lateral Ca^{2+} transport is by governed diffusion equation.

Models for Propagation

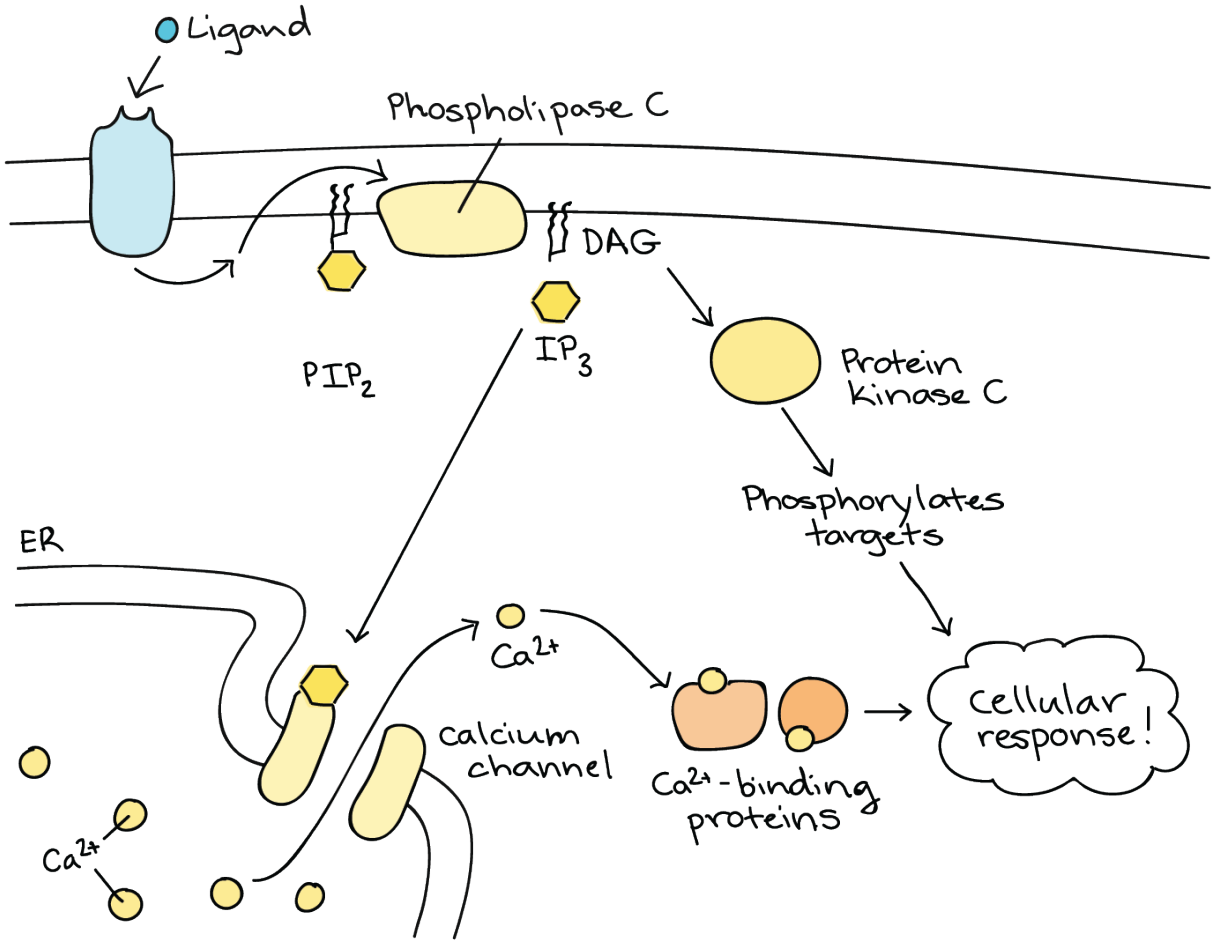
1. Modeling diffusion in 1D
   - Cellular process are thin-long 1D tubes
   - Diffusion in axial direction
2. Lateral calcium transport by diffusion in a dendrite.

$$\frac{\partial}{\partial t}[Ca^{2+}] = D_{Ca}\frac{\partial}{\partial x^2}[Ca^{2+}] + j_{ca}$$

where,

- $[Ca^{2+}]$ - concentration of calcium ions
- $\frac{\partial}{\partial t}[Ca^{2+}]$ - local time rate of change in calcium ion concentration
- D_{Ca} - Ca diffusion coefficient
- j_{ca} - influx of calcium ions in every compartment (from pumps and receptor channels)

Calcium Signaling Pathway



- Signaling molecule binds to GPCR, G protein activation.
- GPCR activates PLC β.
- PLC cleave PIP2 into IP3 and DAG.
- IP3 diffuses over to ER and binds with calcium ion channel
- Ca^{2+} flow from inside of the ER to the cytosol.
- DAG activate PKC, influence the cellular response.
- Calcium buffers (binding proteins) reduce free Ca.

1. GPCR = G protein-coupled receptor
2. PLC = Phospholipase C
3. PIP2 = Phosphatidylinositol 4, 5 bisphosphate
4. IP3 = 1, 4, 5-inositol trisphosphate
5. DAG = Diacylglycerol
6. ER = Endoplasmic Reticulum
7. PKC = Protein Kinase C

Image Source: Khan Academy

Trans-membrane Calcium transport model for Astrocytes

Neural input (glutamate) causes 2nd messenger release.

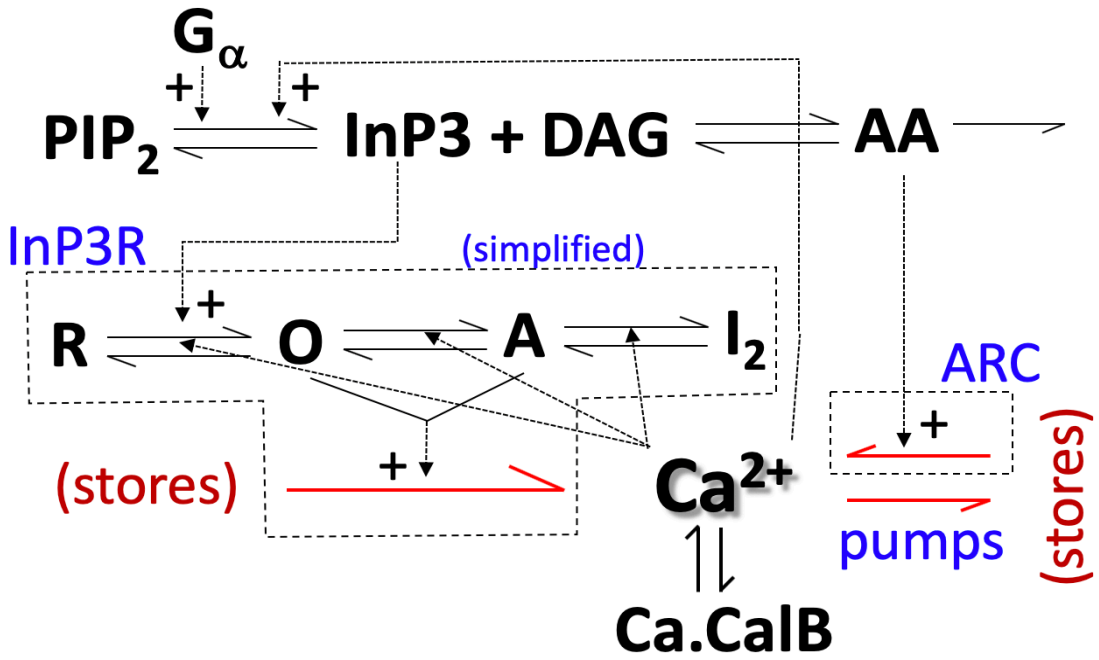
2nd messenger catalyzes the production of InP3 and DAG

DAG promotes the production of AA, which open ARC channels (local to input)

InP3 & Ca (from ARC channels) activates InP3 receptors, Influx of more Calcium.

Reduction of open probability of the InP3 receptor (loop gain less than unity)

Positive-feedback loop is terminated



ARC channels = source of initial calcium entry
Pumps = removing calcium from the cytosol.
Ca.CalB = Ca^{2+} buffers

Figure: ⇌ (in black color) represents reversible reactions and ⇌ (in red color) represents flow of calcium in and out of Ca^{2+} stores. Dotted lines and arrows represents influence of a given molecule/chemical on a reaction; and a + sign represents a positive influence on that reaction. InP3R indicates the InP3 receptor, and R, O, A and I_2 are different states for this receptor's calcium channels; ARC represent Arachidonate-regulated calcium channels.

InP3 Receptor Kinetics

1. Complex and Non-linear System
2. Calcium influx through InP3 receptor channels:

$$j_{InP3} = k_{Ca} * Open_{InP3}$$

$$Open_{InP3} = (f_O * O + f_A * A)^4$$

where,

- k_{Ca} - calcium influx rate constant for open InP3 channels
- $Open_{InP3}$ - probability of open states in InP3 channels.
- f_O - relative dependence of open probability on O state.
- f_A - relative dependence of open probability on A state.
- Φ - are state dependent rates

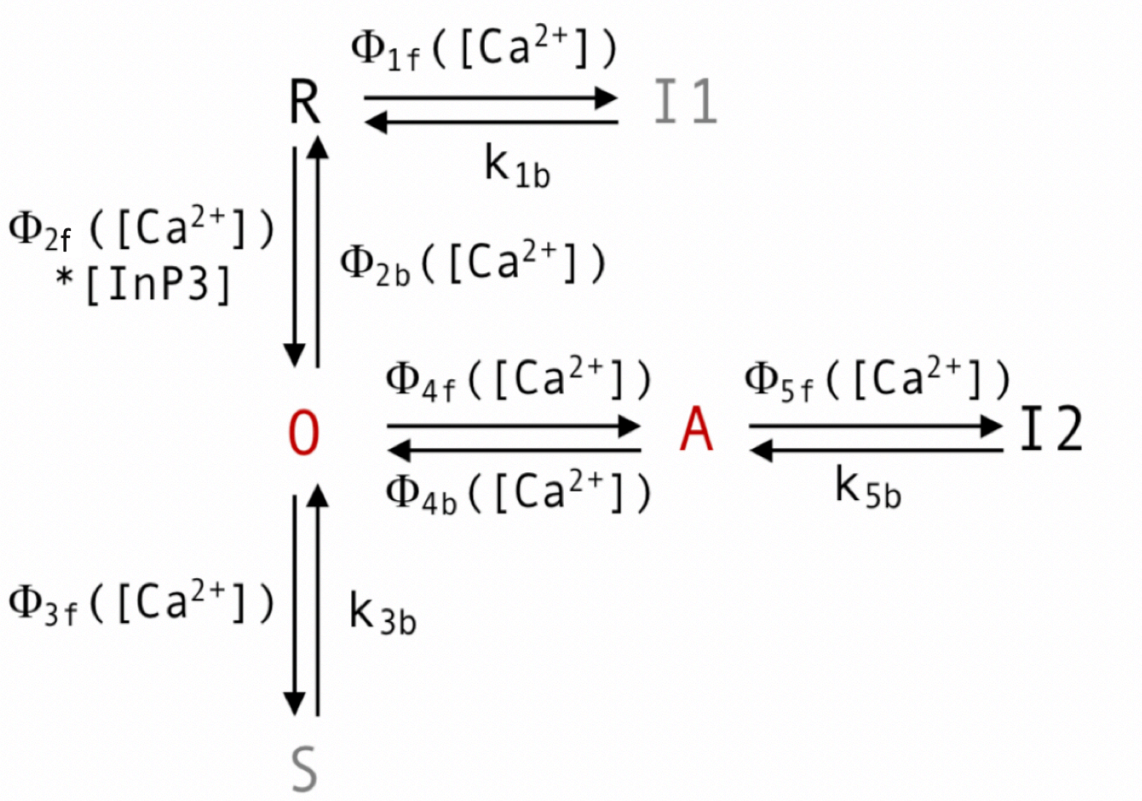


Figure: Sneyd-Dufour model for InP3 receptor kinetics. The states in gray, I1 and S were found to have little participation in receptor function under the conditions we simulated and are not included in our models.

Sneyd and Dufour, 2002

Model of Calcium Pumps in Astrocytes

- Mechanism for Calcium transport through the membrane.
- Efflux of Calcium is given by combination of plasma membrane & SERCA pumps.
    1. Plasma Membrane Pump : first order Hill's equation
    2. SERCA Pump : second order Hill's equation

$$j_{pumps} = k_{1p} * \left(\frac{C_s}{(k_{1pc} + C_s)} \right) + k_{2p} * \left(\frac{C_s^2}{(k_{pc} + C_s^2)} \right)$$

where,

- $k_{1p}, k_{2p,}\ k_{1pc}, k_{2pc}$ = calcium 1st and 2nd-order pump constants
- C_s = cytosolic calcium concentration
- j_{pumps} = calcium efflux due to pumps.

Breit and Queisser, 2018

Calcium Buffering

1. Uptake & release of free calcium in cytosol by Calcium binding proteins.
2. Simplified buffering model:
   - Modeled (multiple possible) buffering reactions as a single reversible reaction.
   - Control reaction rate as a parameter

$$Ca^{2+} + CalB \leftrightharpoons Ca.CalB$$

$$j_{s_{fb}} = k_{c_{bf}} * C_s * (CalB0 - [Ca.CalB])$$

$$j_{s_{bf}} = k_{c_{bb}} * [Ca.CalB]$$

$$\frac{dC_s}{dt} = j_{s_{bf}} - j_{s_{fb}}$$

$$\frac{d[Ca.CalB]}{dt} = j_{s_{fb}} - j_{s_{bf}}$$

where,

$k_{c_{bf}}, k_{c_{bb}}$ buffering rates and CalB0 = 40 µM

$C_s, [Ca.CalB]$ is cytosolic and bound calcium concentration.

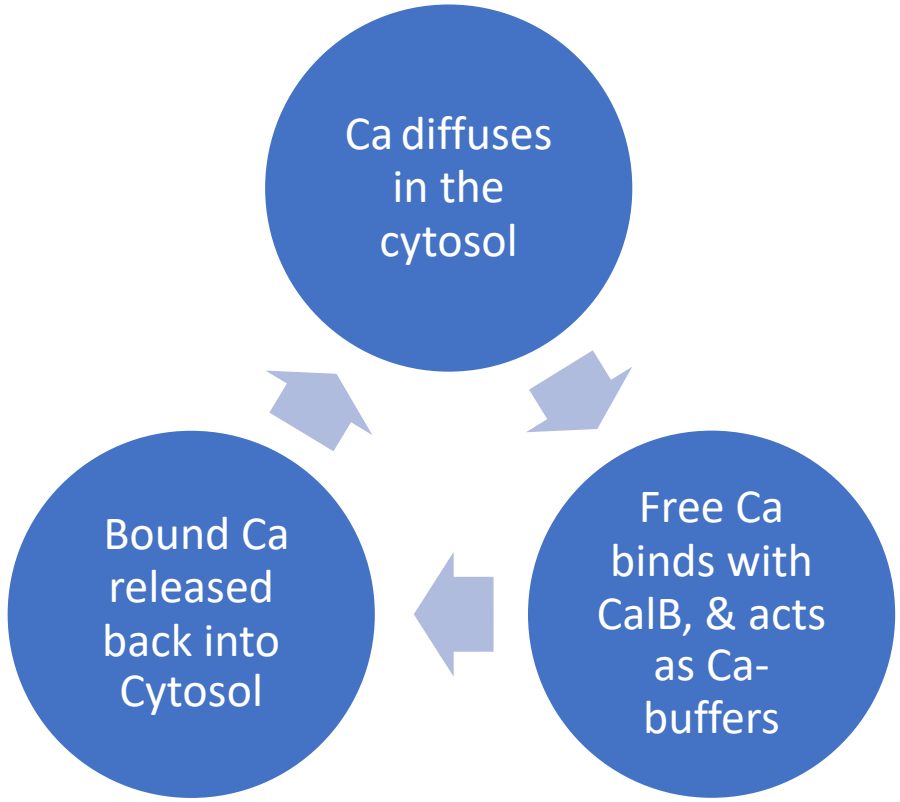


Figure: Flow chart for Calcium buffering. CalB (Calbindin) is the calcium binding protein.

ARC Channels

1. Arachidonate-regulated Ca^{2+} (ARC) channels depend on the receptor-mediated generation of low levels of intracellular arachidonic acid.
2. Only responsible for initial local influx of calcium.
3. Local to where cell receives glutamatergic input.

$$j_{ARC} = k_{aa} * AA$$

where,

- k_{aa} = calcium influx rate for open ARC channels
- AA = concentration of arachidonic acid.

Leakage

1. Influx of calcium per unit area of plasma membrane.
2. Assumed to be constant, because the difference in calcium concentration between cytosolic and external calcium is nearly constant.

$$j_{leakage} = k_{lk}$$

where,

- k_{lk} = calcium leakage rate

Gap Junctions

1. Intercellular connection between cells.
2. Allows molecules, ions to directly pass through a regulated gate between cells.
3. We model exchange of InP3 through gap junctions.
4. Evidence for exchange of Calcium ions through gap junctions is very weak*.
   - Gap junctions have very low permeability to Calcium ions.

$$j_{Gap} = rinp3 * ([InP3_{c1}] - [InP3_{c2}])$$

where,

$rinp3$ = rate constant for inp3 flow between cells

j_{Gap} = influx or efflux of InP3

** In personal communication with Dr. James Sneyd, University of Auckland*

Models for Calcium dynamics in Neurons

Trans-membrane calcium transport model for neurons

Neural input induces calcium influx (NMDAR's)*

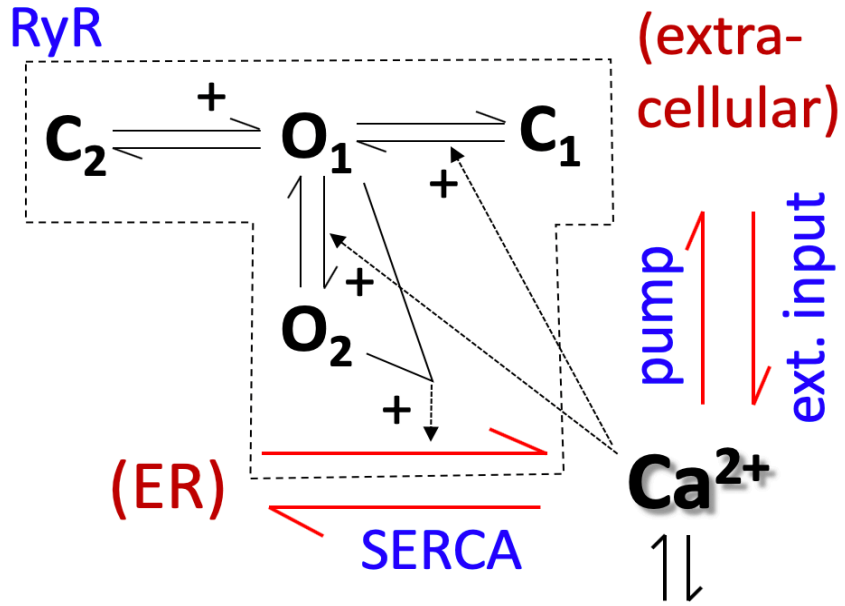
Influx of calcium opens RyR channels.

RyR channels leads to influx of more Ca from ER stores.

More calcium opens more RyR Channels

Positive-feedback loop is terminated by nonlinear calcium pumps.

** NMDARs are also glutamatergic receptors.*



Pumps = removing calcium from cytosol.
Ca.CalB = Ca^{2+} buffers

Figure: ⇌ (in black color) represents reversible reactions and ⇌ (in red color) represents flow of calcium in and out of cell (and ER) by external input and pumps (SERCA and plasma membrane pumps). '+' sign represents positive influence on the reaction, dotted arrow represents influence of a given molecule/chemical on the reaction. C_2, O_1, C_1 and O_2 are different states for RyR receptor's calcium channels.

Model for Calcium Pumps in Neurons

Model for SERCA pumps is a 2nd order Hill equation (with ER calcium conc. in the denominator*)

$$j_{serca} = k_{p2} * \left(\frac{C_s^2}{(k_{pc2} + C_s) * C_e} \right)$$

Model for Plasma membrane pump is a 1st order Hill's equation.

$$j_{plasma} = k_p * \left(\frac{C_s}{(k_{pc1} + C_s)} \right)$$

where,

1. kp2 and kpc2 = calcium 2nd-order pump constants
2. kp1 and kpc1 = calcium 1st-order pump constants
3. Cs = Cytosolic calcium concentration
4. Ce = local ER calcium concentration
5. j_{serca} = Calcium efflux due to SERCA pumps

** Breit and Queisser, 2018*

Model for Ryanodine receptor (RyRs)

Assumption: We are assuming there can be depletion of the ER calcium conc., So the driving force is reduced.

The calcium flux density through RyR channels in the ER membrane is given by:

$$j_R = r_{Ca} * Open_{RyR} * (C_e - C_s)$$

where,

r_{Ca} = calcium influx density for open RyR channels

C_e = Calcium conc. in ER

C_s = Cytosolic calcium conc.

$Open_{RyR}$ = open probability for open RyR channels.

Ca buffering and Leakage:

Model for Ca buffering and leakage is identical to what was introduced in astrocytes section.

Breit and Queisser, 2018

Cells and Networks

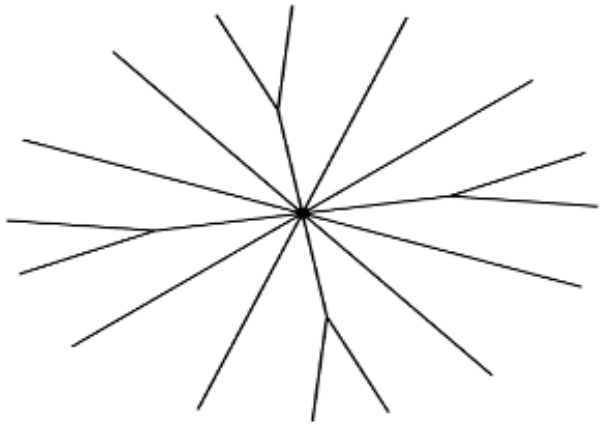


Fig: Single cell in our model

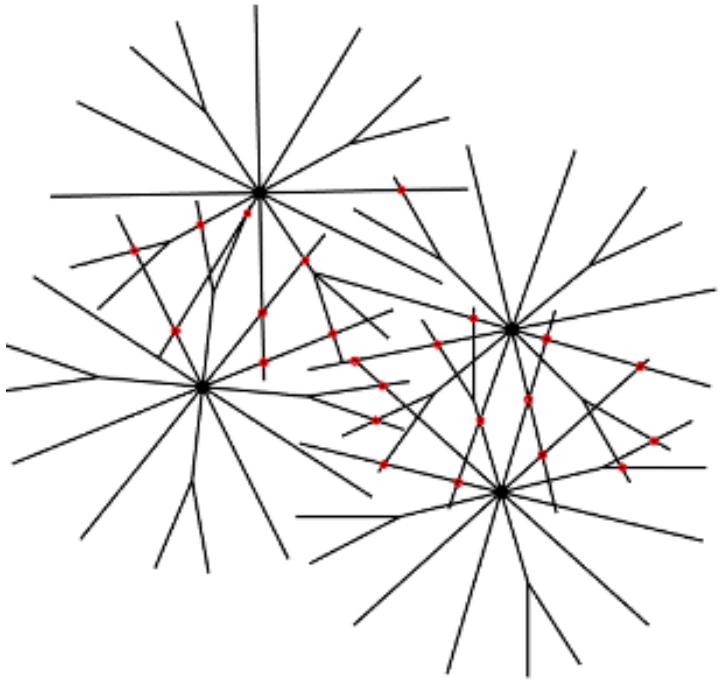


Fig: Four interconnected cell in our model

Morphological Structure

Our model cells are made up of 3 morphological subunits:

1. cell body (single compartment)
2. straight dendrites (10 compartment)
3. branched dendrite (3 segments, 5 compartment each)

These subunits are composed of compartments, which can be regarded as defining discrete finite elements or a *grid* for our signal propagation model.

Black Dot – Cell Body
Black Outline – Dendrites
Red Dot - Interconnections

Astrocyte Network Model

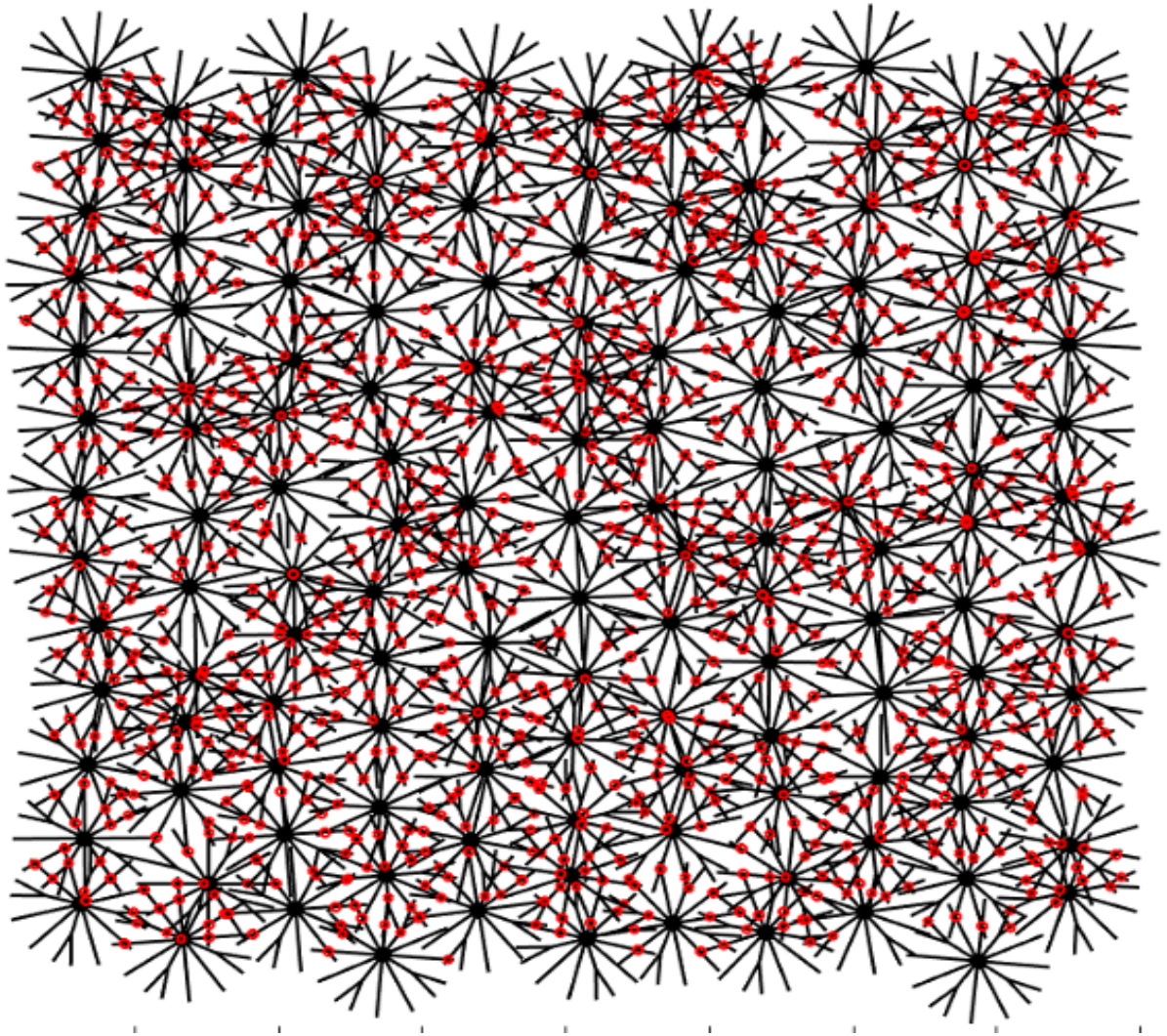


Fig: Network of 143 astrocytes interconnected together.

- Gap junction-mediated interconnection
- Each cell is multi-compartment model

- Randomness in:
  - Placement of cells
  - Orientation of cells
  - Position of cells

Network Modeling

- We only model *astrocytes* arranged in a 2D network and in individual dendrites.
- No network models of neurons.
- Our work on neurons is limited to dendritic propagation only.

Uncertainties in modeling Neural Networks:

1. Neural model is complicated by the fact that calcium entry typically causes depolarization as well.
2. How to best model intracellular transmission (neuron to neuron)?
   - Either by synapses or gap junctions?

Numerical Simulation

- Our model (dendrites and cell body) is discretized into compartments.
- Solved our model numerically using Mimetic Discretization Methods*.
- MOLE (*Mimetic Operators Library Enhanced*) library*.
    1. Implements high-order mimetic operators to solve partial difference equations.
    2. Provides discrete analogs of vector calculus operators: *Gradient*, *Divergence*, *Laplacian* and *Curl.*
    3. Act on staggered grids (uniform and non-uniform).
    4. Satisfy local and global conservation laws.

- MOLE library for spatial integration and simple quadrature for temporal integration.
- Robin boundary condition in MOLE:
    1. Dirichlet Coefficient (a) = 0
    2. Neumann Coefficient (b) = 1
- Dendrites are sealed at one end (flux = 0) and the flux out at the other end is set to match the flux into the cell body/ dendrite.

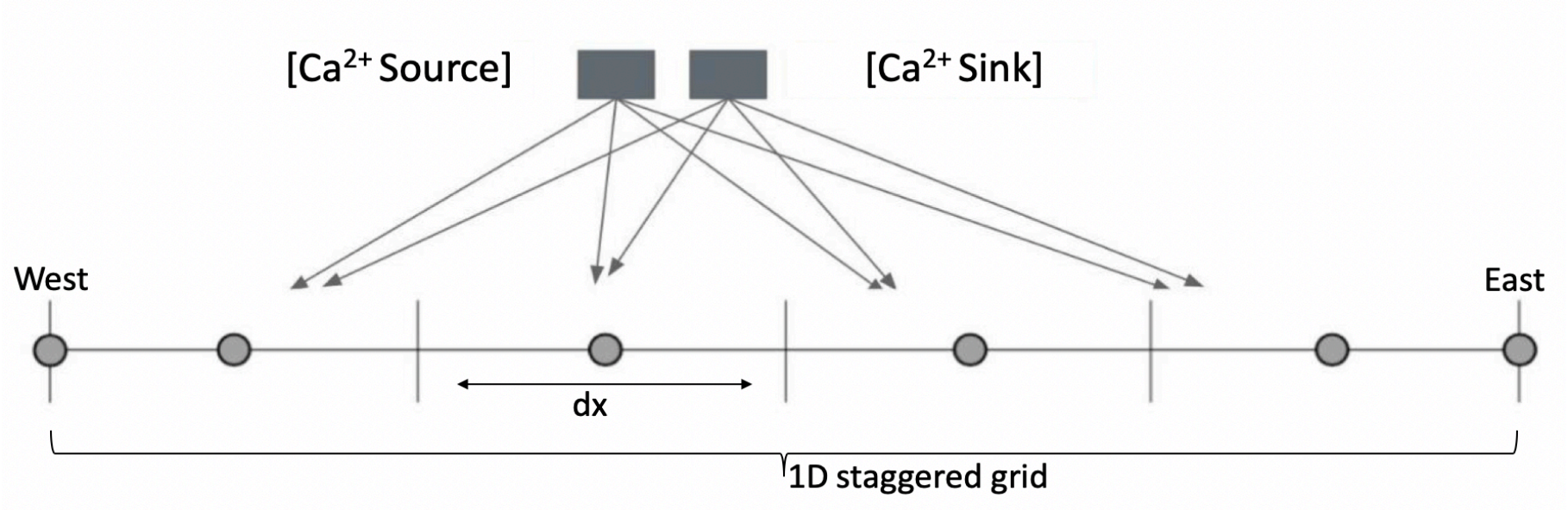
** Johnny Corbino and Jose E.Castillo (2020)*

Numerical Simulation

$$\frac{\partial}{\partial t}[Ca^{2+}] = D_{Ca}\frac{\partial}{\partial x^2}[Ca^{2+}] + j_{S_{rc}} - j_{S_{nk}}$$

$$U^{n+1} = L * U^n + (S_{rc} + S_{nk})$$

where, L is our mimetic Laplacian operator (matrix) and S_{rc} and S_{nk} are vectors that represent flux from source and sink components in our model.



Experiments

Different types of test beds:

1. Single dendrite
2. Two dendrites connected through cell body
3. Two cells connected end-to-end through two dendrites
4. Network of complete cells interconnected to each other randomly

Characteristics Examined:

1. Wave Regimes
2. Wave speed
3. Wave amplitude
4. Region of influence

Important Parameters & Physical Intuition

Parameters	Definition	Baseline Value
kd1f	[Ca]-dependent production of InP3	5 $\mu m.s^{-1}$
kaa	Calcium influx rate for open ARC channels	6 $\mu m^2.s^{-1}$
fCa	Fraction to reduce DCa due to intracellular crowding	0.3
fInP3	Fraction to reduce DInP3 due to intracellular crowding	0.7
kCa	Calcium infux rate constant for open InP3R channels	600 $\mu m.s^{-1}$
kcbf	Rates for calcium buffering	0.7 $\mu m^{-1}.s^{-1}$
kcbb	Rates for calcium buffering	10 s^{-1}
ki2	Rate for inhibition of InP3 production by PKC	0.0943 μm^{-1}

Results : Qualitative Analysis

Parameters	Regeneration	Damping	Wave Speed	Wave Amplitude	Effect
kd1f	Strong Positive	Strong Negative	Strong Positive	Strong Positive	Global
kaa	Positive Indirect	NO EFFECT	Positive	NO EFFECT	Global
fCa	Strong Negative	Strong Positive	Strong Negative	Strong Negative	Global
fInP3	Strong Negative	Strong Positive	Strong Positive	Strong Positive	Global
kCa	Positive	Strong Negative	Strong Positive	Strong Positive	Global
kGl	NO EFFECT	NO EFFECT	Positive	Small Positive	Local
rInP3	Small Positive	NO EFFECT	Small Positive	NO EFFECT	Local
kcbf	Strong Negative	Strong Positive	Strong Negative	Strong Negative	Global
kcbb	Strong Positive	Strong Negative	Positive	Strong Positive	Global
Ki2	Strong Negative	Strong Positive	Strong Negative	Strong Negative	Global

Table: Chart for model parameters and its effects on the Ca wave dynamics. Strong Positive means that the quantity (like speed) becomes larger or the phenomenon becomes more pronounced when the parameter increase. Strong Negative means that the quantity (like speed) becomes smaller or the phenomenon diminishes as the parameter increase. NO EFFECT means that change in parameter value have no effect on the wave. Small positive and Small negative means that increase in parameter value will have small (less-strong) impact on the wave. Local and Global means whether the change in parameter value locally will impact locally or globally.

Chart for model parameters and its effects on the Ca Wave Dynamics.

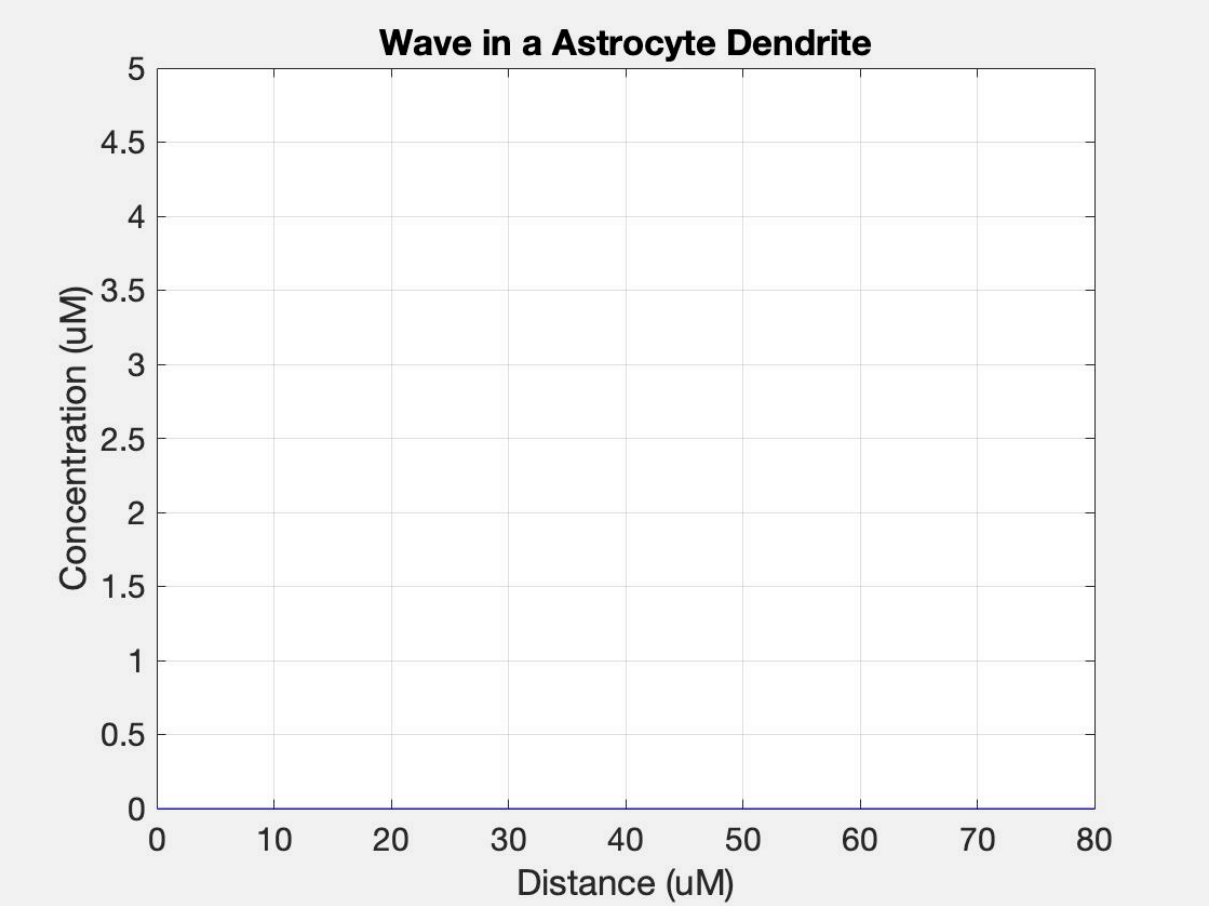
Different Regimes for Calcium waves

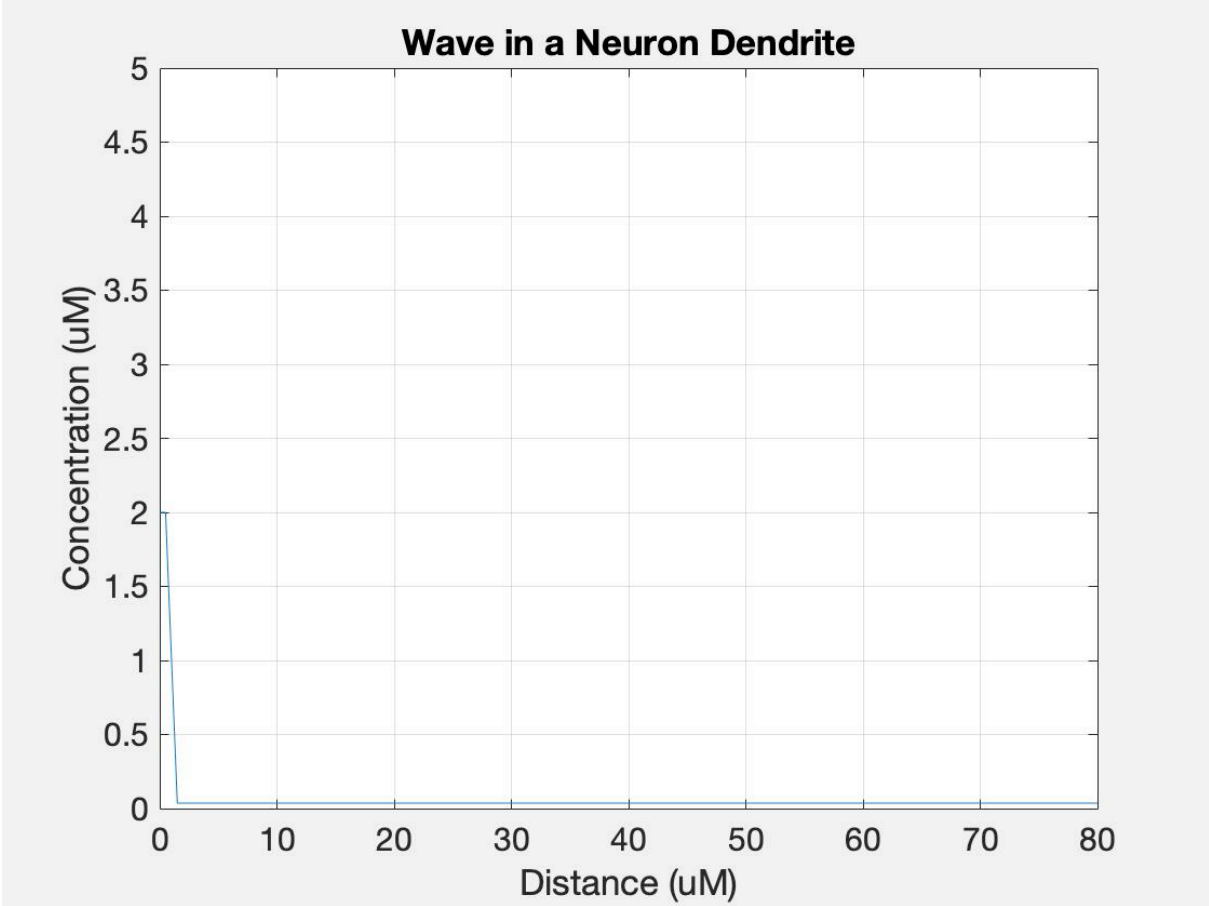
Regenerative : Travel across network of cells by regenerating itself.
Damping : Damped as it propagates and tends to die out with distance.
Abortive : Not able to generate waves.

Parameters	Regenerative Regime	Damping Regime	Abortive regime	Baseline value
kd1f	>= 5	4 < kd1f < 3	< 3	5
kaa	> 4	4 < kaa < 2	< 2	6
fCa	< = 0.3	0.3 < fCa < 0.5	> 0.5	0.3
fInP3	> 0.7	0.7 < finp3 > 0.5	< 0.5	0.7
kCa	> 500	500 < kCa< 400	< 400	600
kcbf	< 1	1 < kcbf < 4	> 4	0.7
kcbb	> 5	5 < kcbb < 3	< 3	10
ki2	< 1	1 < ki2 < 5	> 5	0.0943

Table for range of parameter values for different wave behavior. Every parameter is varied separately while keeping other parameters at their baseline value. All experiments were performed on a test bed of two cells with two dendrites each.

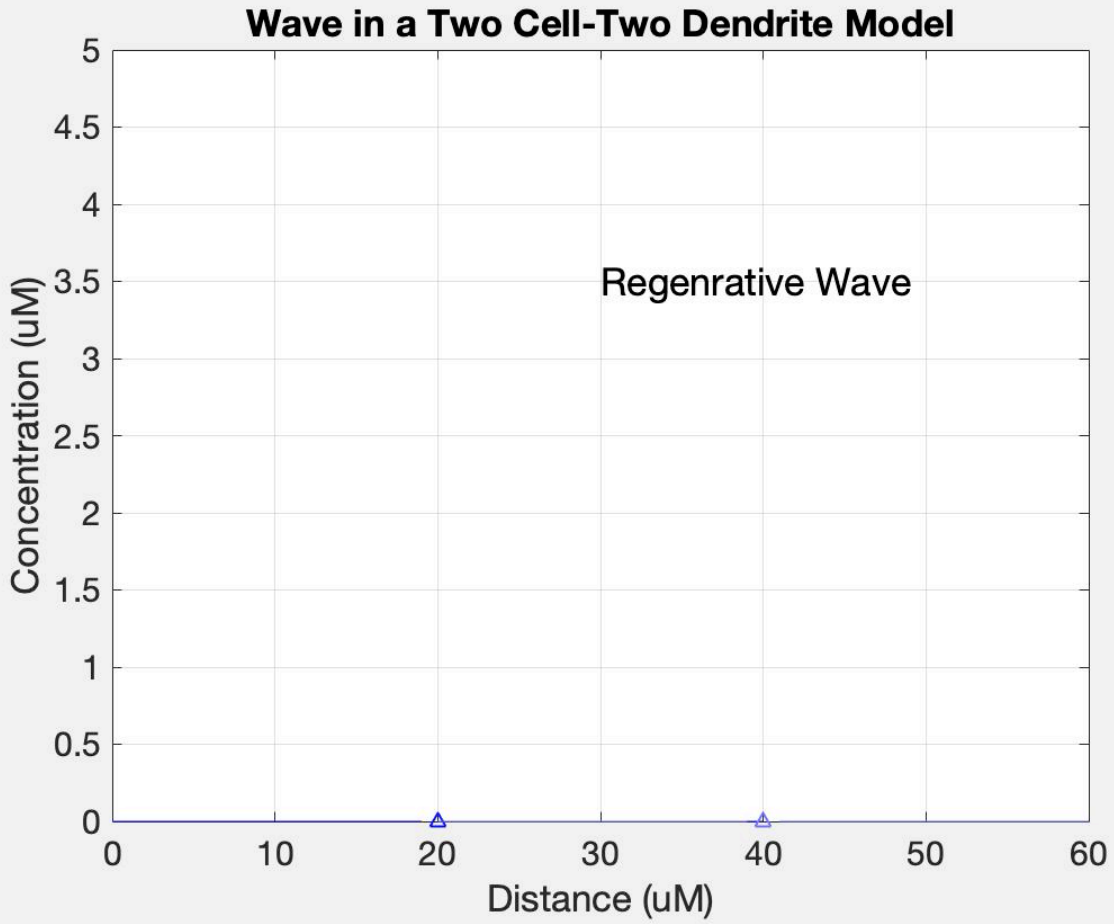
Calcium Wave in a Single Astrocyte & Neuron Dendrite



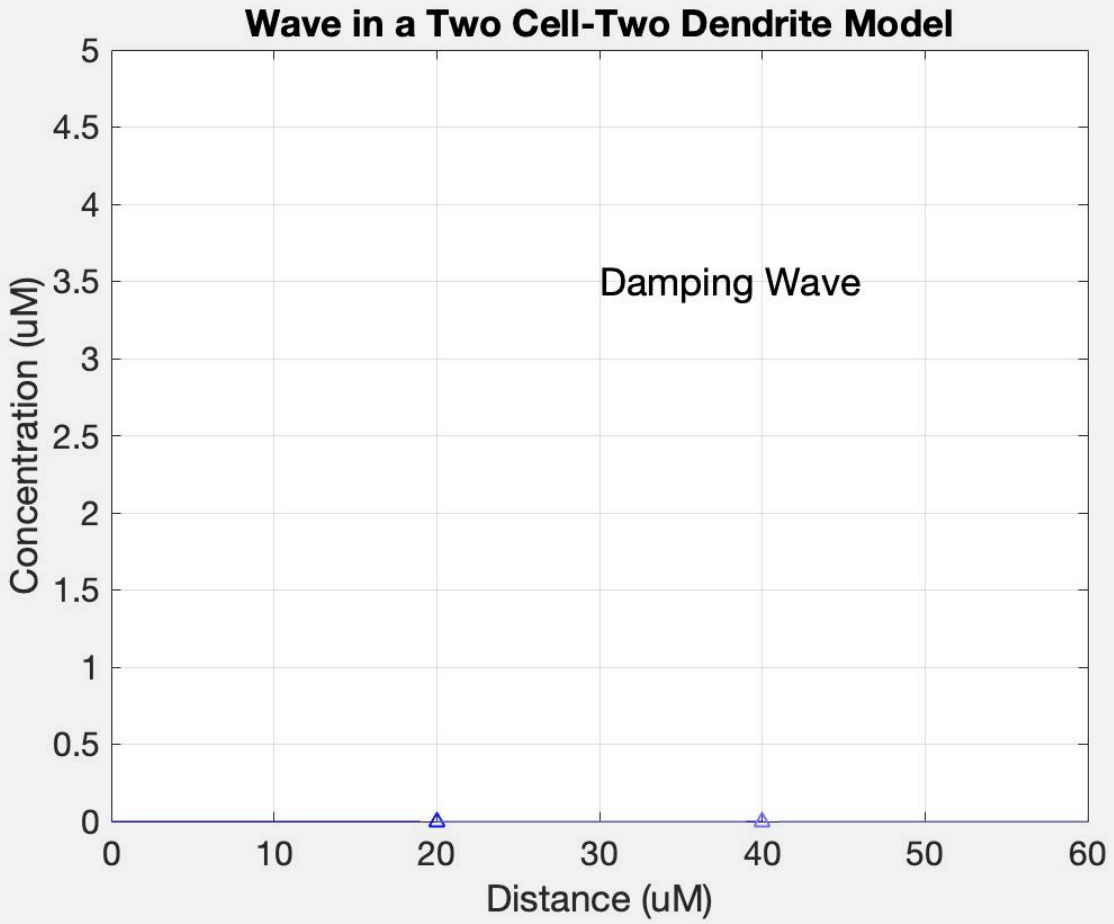


Different Ca wave Regimes

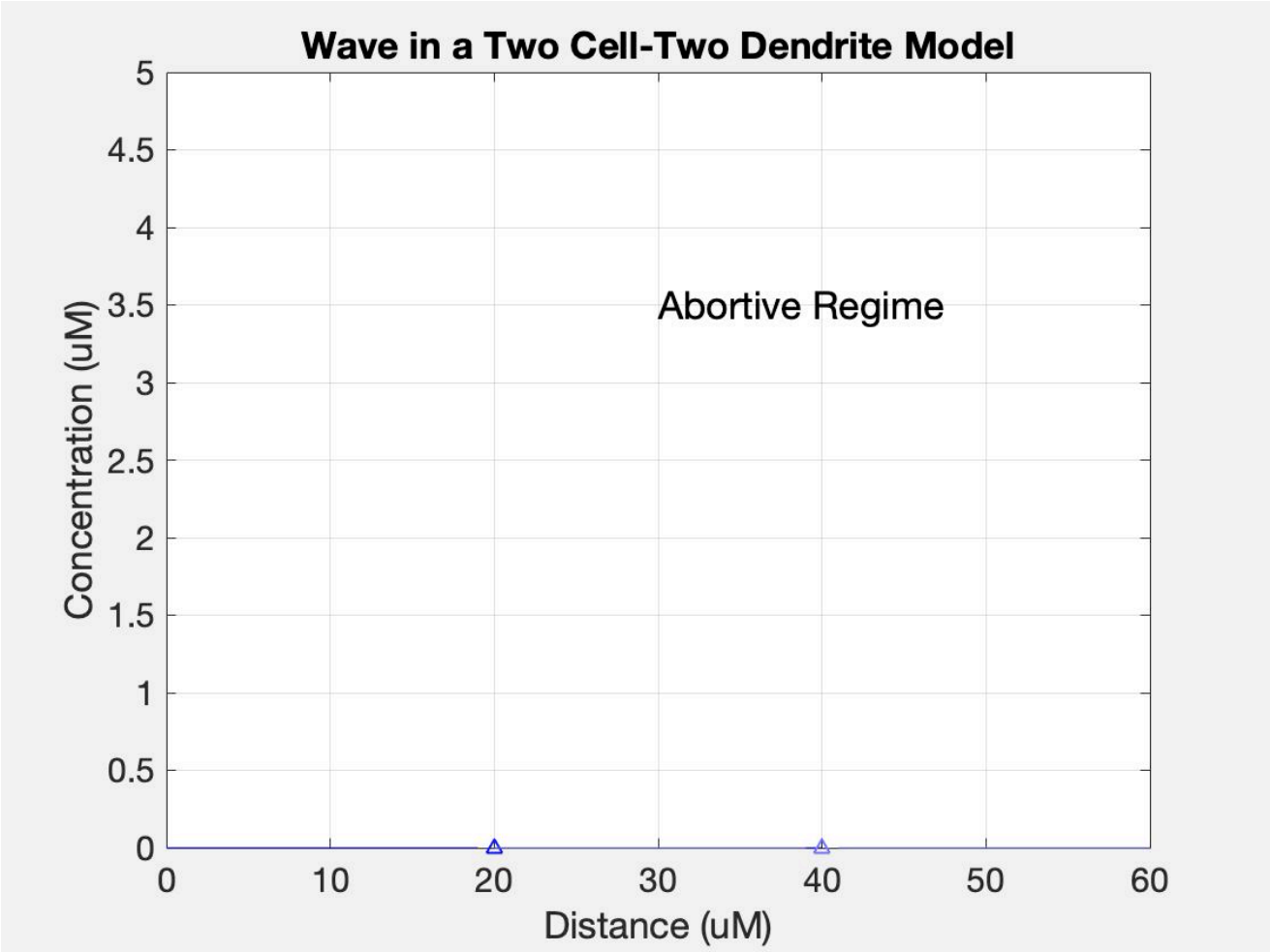
Regenerative Regime



Damping Regime



Abortive Regime



Quantitative Analysis: Astrocyte Model (Dendrites)

kd1f	V	kaa	V	fCa	V	fInP3	V	kCa	V	kGI	V	Ki2	V	kcbf	V	kcbb	V
8	37.7	9	33.8	1	29.8	1	38.4	1500	105.2	120	38.4	5	20.0	5	0	14	34.4
7	35.7	8	33.3	0.8	30.7	0.8	34.4	1200	95.2	100	37.7	3	24.6	3	15.8	10	33.3
6	33.3	6	33.3	0.6	31.7	0.7	33.3	900	83.3	80	37.0	1	29.8	1	2	6	30.7
4	21.2	4	32.2	0.3	33.3	0.5	28.1	600	33.3	45	33.3	0.5	32.2	0.7	33.3	3	27.0
2	0	2	31.2	0.2	32.7	0.3	19.2	400	-	20	22.4	.09	33.3	0.3	38.4	1	19.4
0	-	0	-	0	29.8	0	-	0	-	10	-	0	0	0	-	0	19.4

kd1f	A	kaa	A	fCa	A	fInP3	A	kCa	A	kGI	A	Ki2	A	kcbf	A	kcbb	A
8	4	10	2.6	1	1	1	3.1	1500	15.4	120	3	5	0.9	5	0	14	2.9
7	3.2	8	2.6	0.8	1	0.8	2.6	1200	12.7	100	2.9	3	1.2	3	1	10	2.3
6	2.3	6	2.3	0.6	1.4	0.7	2.3	900	9.7	80	2.8	1	1.8	1	2	6	1.8
4	1	4	2.3	0.3	2.3	0.5	1.8	600	6.1	45	2.3	0.5	2	0.7	2.3	3	1.4
2	0	2	2.2	0.2	3.7	0.3	1.1	400	3.9	20	1.4	0.09	2.3	0.3	3.2	1	0.8
0	-	0	-	0	5.8	0	-	0	-	10	0	-	2.5	0	-	0	0.7

Red – Baseline
Yellow – Max
Blue - Min

Table for Wave speed (V) and Wave Amplitude (A) with change in parameter value. All experiments are done on a single dendrite, where every parameter was varied once (while others were kept constant at their baseline value). Values in red color in every column are the baseline value for that parameter. "-" represents no wave for those set of parameter value. Units for A is uM and V is um/s .

Neuron Model (Dendrites)

Wave Speed

fCa	V	rCa	V	kcbf	V	kcbb	V
1	416.66	100	$1.2e^{+03}$	10	-	100	454.54
0.8	384.61	50	1000	5	156.25	50	454.54
0.6	333.33	20	714.28	1	384.61	35	416.66
0.4	263.15	10	555.55	0.7	416.66	20	416.66
0.2	178.57	5	416.66	0.3	454.54	10	416.66
0	-	0	-	0	500	0	416.66

Wave Amplitude

fCa	A	rCa	A	kcbf	A	kcbb	A
1	3	100	5.2	10	-	100	3.2
0.8	3	50	4.8	5	1	50	3.2
0.6	3	20	4.2	1	2.8	35	3
0.4	3	10	3.8	0.7	3	20	3
0.2	3	5	3	0.3	3.5	10	3
0	-	0	-	0	3.9	0	3

Red – Baseline
Yellow – Max
Blue - Min

Table for Wave speed (V) and Wave amplitude (A) with change in parameter value . All experiments are done on a single dendrite, where every parameter was varied once (while others were kept constant at their baseline value). Values in red color in every column are the baseline value for that parameter. "-" represents no wave for those set of parameter value. Units for A is uM and V is um/s .

Calcium Wave in Network

Wavefront in a network involves:

1. Delays because of cell body
2. Delay because of gap junction
3. Mis-alignment between dendrites and overall direction of propagation.

These factors will lead to:

1. Rich spatial structure
2. Significantly reduced wave speed.

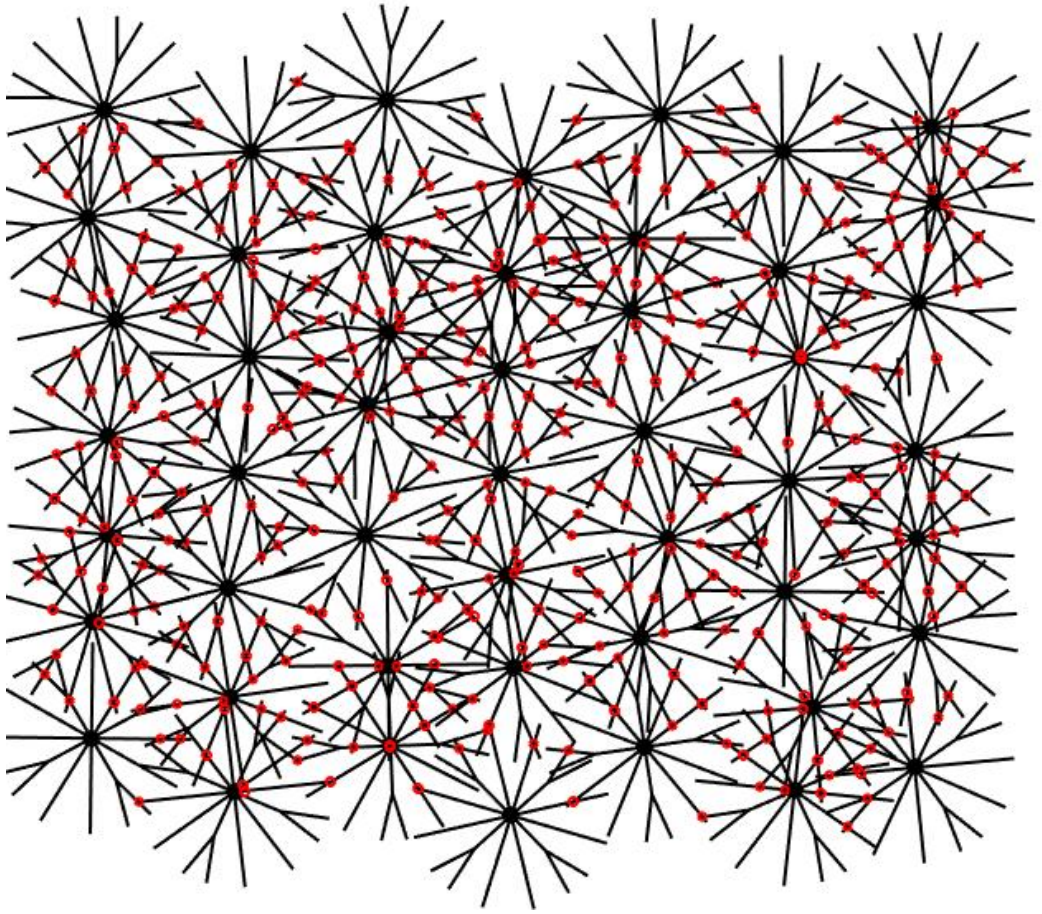


Figure: 7 by 7 Network of cells

Approximation for initial analysis of wave speed:

1. Only Considering waves in dendrites in a network.
2. Effects of cell bodies and gap junctions are being neglected.

Theoretical computation of Wavefront Speed

- Effects of cell bodies and gap junctions are being neglected.

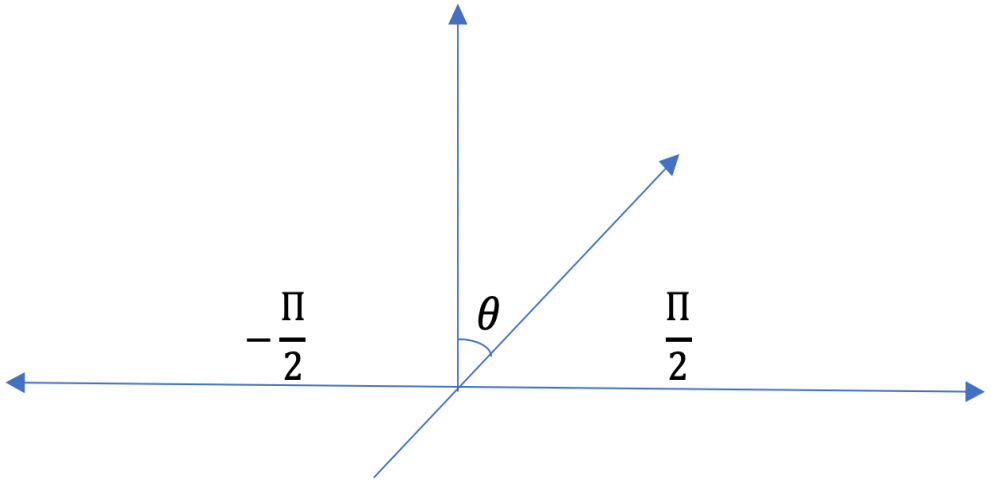


Figure: Plane wave approximation. θ is the angle between direction of wave front and perpendicular to plane wave. Dendrites are uniformly distributed with respect to θ and can be anywhere from -90º to 90º.

$$v_{astrocyte} = \frac{2*33.33}{\pi} \cong 21\,\frac{um}{s}$$

$$v_{neuron} = \frac{2 * 416.66}{\pi} \cong 265\,\frac{um}{s}$$

$$\int_{-\frac{\pi}{2}}^{\frac{\pi}{2}} f(\theta)d\theta = 1$$

$$\int_{-\frac{\pi}{2}}^{\frac{\pi}{2}} c * d\theta = 1$$

$$c * \pi = 1 \Rightarrow c = \frac{1}{\pi}$$

$$v_{avg} = c * \int_{-\frac{\pi}{2}}^{\frac{\pi}{2}} v_{den}\cos(\theta)\,d\theta$$

$$v_{avg} = c * v_{den} * \int_{-\frac{\pi}{2}}^{\frac{\pi}{2}} \cos(\theta)\,d\theta$$

$$v_{avg} = c * v_{den} * \left[sin\left(\frac{\pi}{2}\right) - sin\left(-\frac{\pi}{2}\right)\right]$$

$$v_{avg} = c * v_{den} * 2$$

$$v_{avg} = \frac{2 * v_{den}}{\pi}$$

Empirical Calculation of Wavefront Speed

1. Wavefront in terms of (single) farthest compartment in each cell that experience a calcium wave peak.
2. Effects of gap junctions and cell bodies are included.

Network Size (m by n)	Wavefront Speed (um/s)
3 by 4	16.66
5 by 5	17.34
7 by 7	14.94
10 by 9	14.78
11 by 13	14.67
13 by 15	14.12

*Table for wavefront speed measurement in different networks of astrocytes. Network of size m by n, have m*n cells, arranged on a grid of m by n. All the parameters were set to their baseline values.*

Algorithm for Wave-front Speed:

Give stimulus to network
Origin = Location at which network gets stimulus

For Cell → Network:
  For Comp* → Cell:
    if Comp → Wave peak:
      Store distance from origin;
      Store time taken by wave;
    end

  Choose Comp farthest from origin;
  Dist = distance b/w origin & farthest comp;
  Time = time taken to reach farthest comp;
  Speed = Dist/ Time;

end

Avg Speed = Sum Speeds / Total number of cells

* Comp = compartment in cell

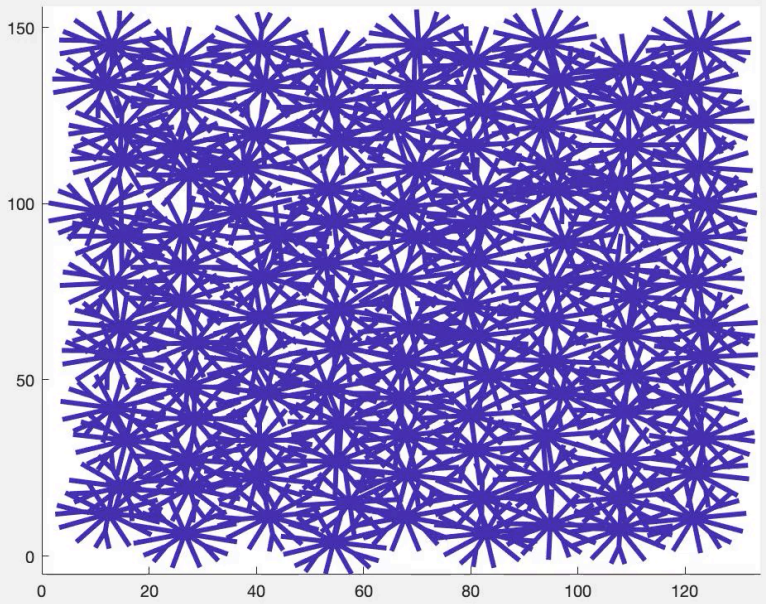
What does wave propagation look like in a network?

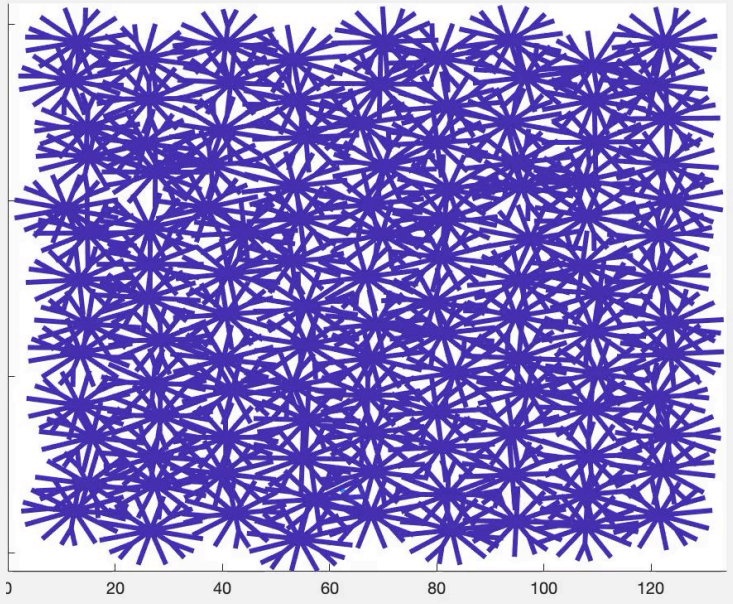
- When stimulus is active or stopped
- For different stimulus speed

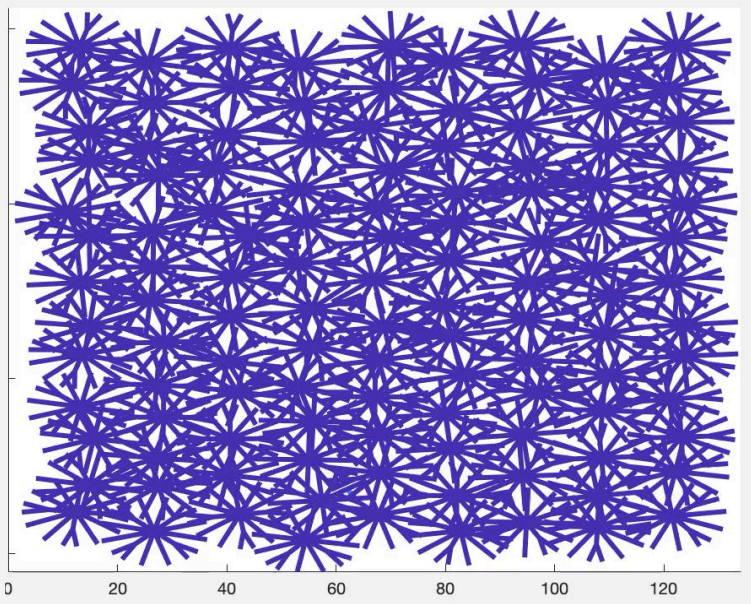
Experiment:

- Stimulus is active for t seconds (where t << total simulation time)
- Stimulus acts on X-axis.
- Stimulus moving upward with some speed.

Astrocyte 2D (13 x 9 cells) Network Simulation







Stimulus Speed: 8 um/s 16 um/s 32 um/s

Conclusion

Astrocytes:

- Wave Speed in dendrites: 20 – 100 μm/s [1] ✓ Slow but consistent (in lower range) with physiological results in vertebrates.
- Waves Amplitude: 1.2 – 12 μm ✓ Consistent with physiological results in vertebrates
- Wavefront Speed in network: 14 – 16* μm/s ✗ Too Slow for facilitation, delay because of gap junctions

* for standard parameters

Astrocytes calcium waves might be sufficient to support facilitation in smaller structures like the medial lobula (but would require higher receptor densities).

Neurons:

- Wave Speed in dendrites: 150 – 500 μm/s ✓ Fast and consistent with physiological results in vertebrates
- Wave Amplitude: 1 – 4 μm ✓ Consistent with physiological results in vertebrates

Neuronal calcium waves may indeed be sufficient to support facilitation at the level of primary lobula.

1. NOTE: Higher wave speeds could only be achieved with extremely high receptor densities (possibly unrealistic).

Computational Conclusion

- Modeled 1D dendritic model (neuron & astrocyte)
- Modeled cellular (astrocyte network) models
- Large Scale simulation on clusters.
- Designed complex data structures to hold and process gigabytes of data.
- Exhaustive experimentation and Comprehensive analysis of wave behavior.

Major References

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Thanks.