Modeling the effects of Ephaptic coupling on Spike Timing Dependent Plasticity

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Brain, Dynamics, Computation-2025, IMSc, Chennai

Is it possible for neurons to communicate without any physical connection between them?

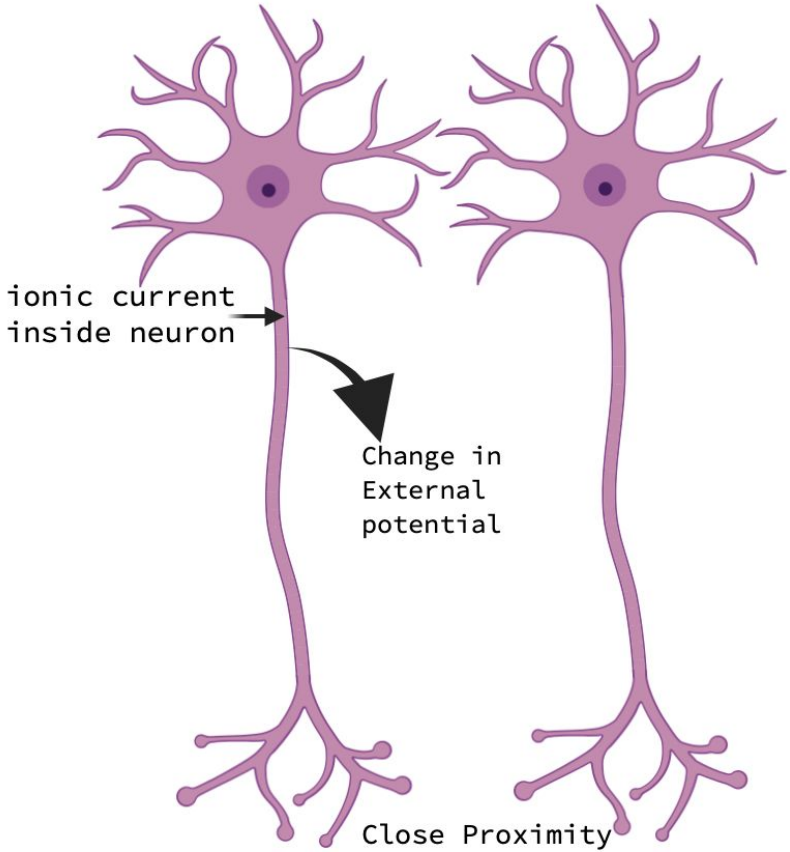
Is it possible for neurons to communicate without any physical connection between them?

Answer is actually yes, Ephaptic coupling is a phenomenon where neurons in close proximity can communicate without any physical contact

The most accepted explanation says change in Local Field Potentials(LFP), due to flow of ionic current in nearby active neuron.

This change in external potential actually alters the excitability of nearby neurons, because

$$V_m(x,t) = V_i(x,t) - V_e(x,t)$$


ionic current
inside neuron
Change in
External
potential
Close Proximity

Role of Ephaptic coupling

- Studies have demonstrated that its role in synchronizing oscillations of neurons in proximity receiving stimulus
- Propagation of seizures in certain areas of brain

CellPress

Neuron
Article

Ephaptic Coupling Promotes Synchronous Firing of Cerebellar Purkinje Cells

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Neurobiology of Disease

Propagation of Epileptiform Activity Can Be Independent of Synaptic Transmission, Gap Junctions, or Diffusion and Is Consistent with Electrical Field Transmission

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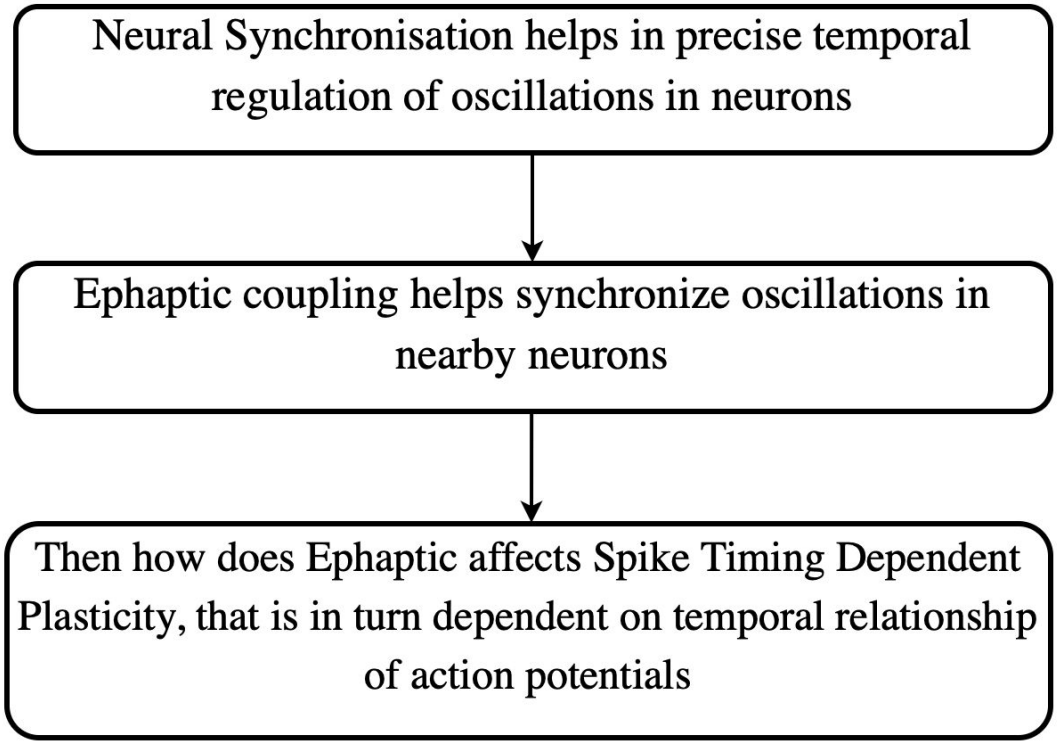
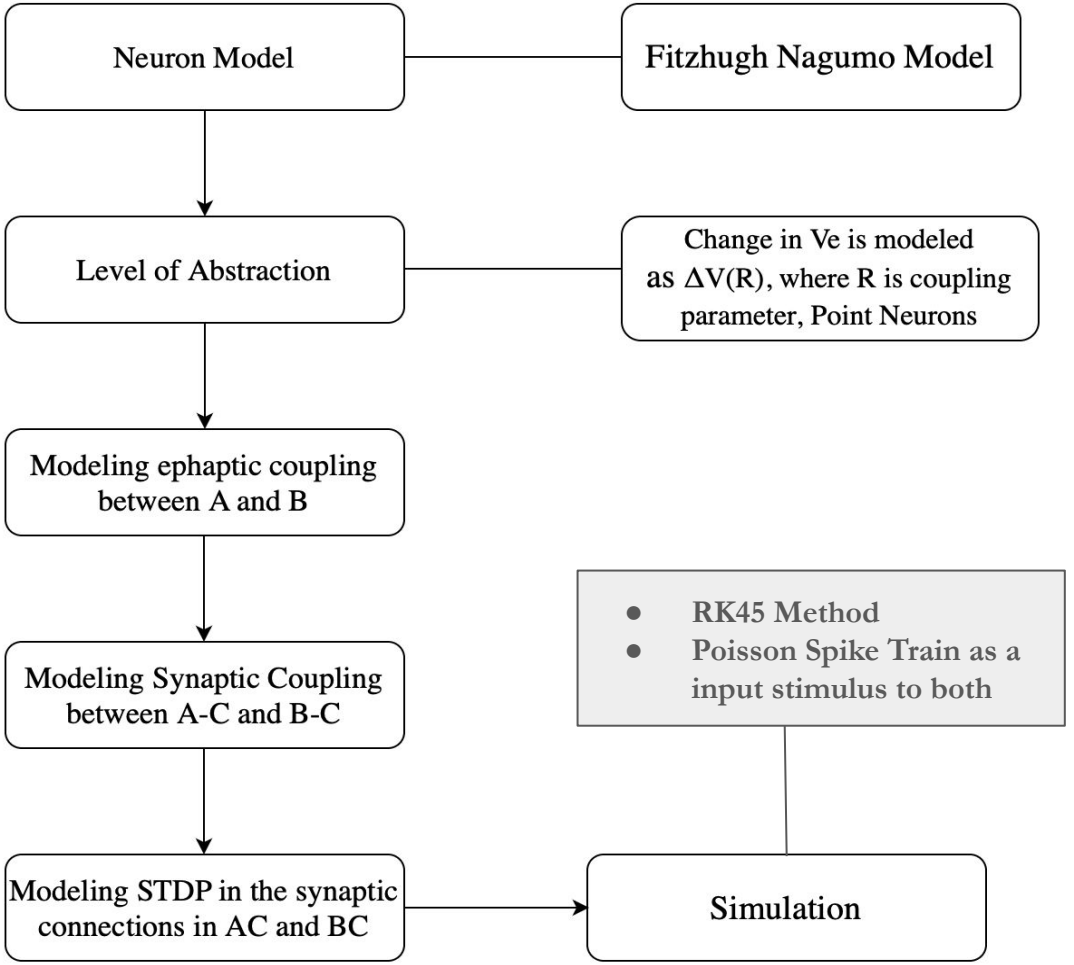
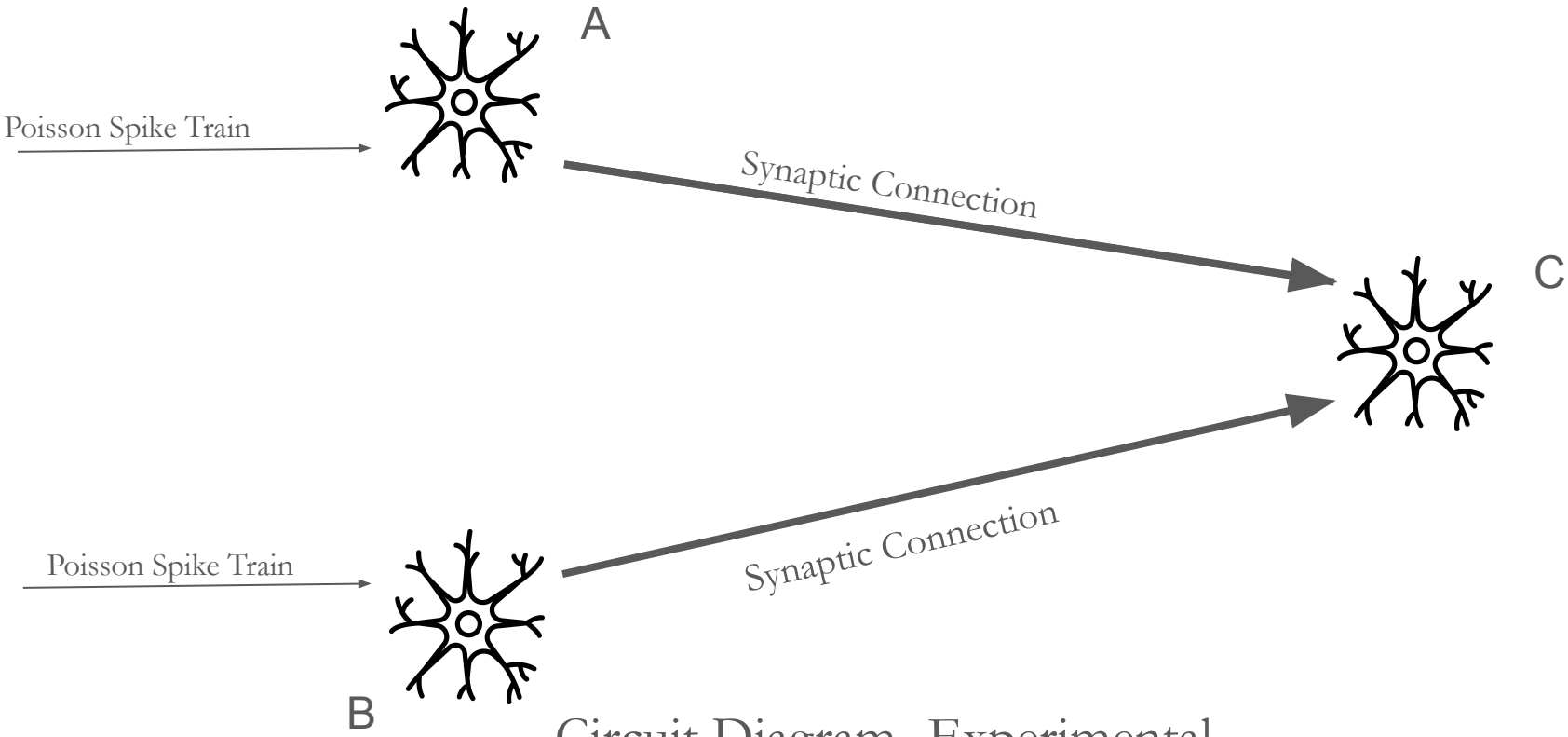
Question

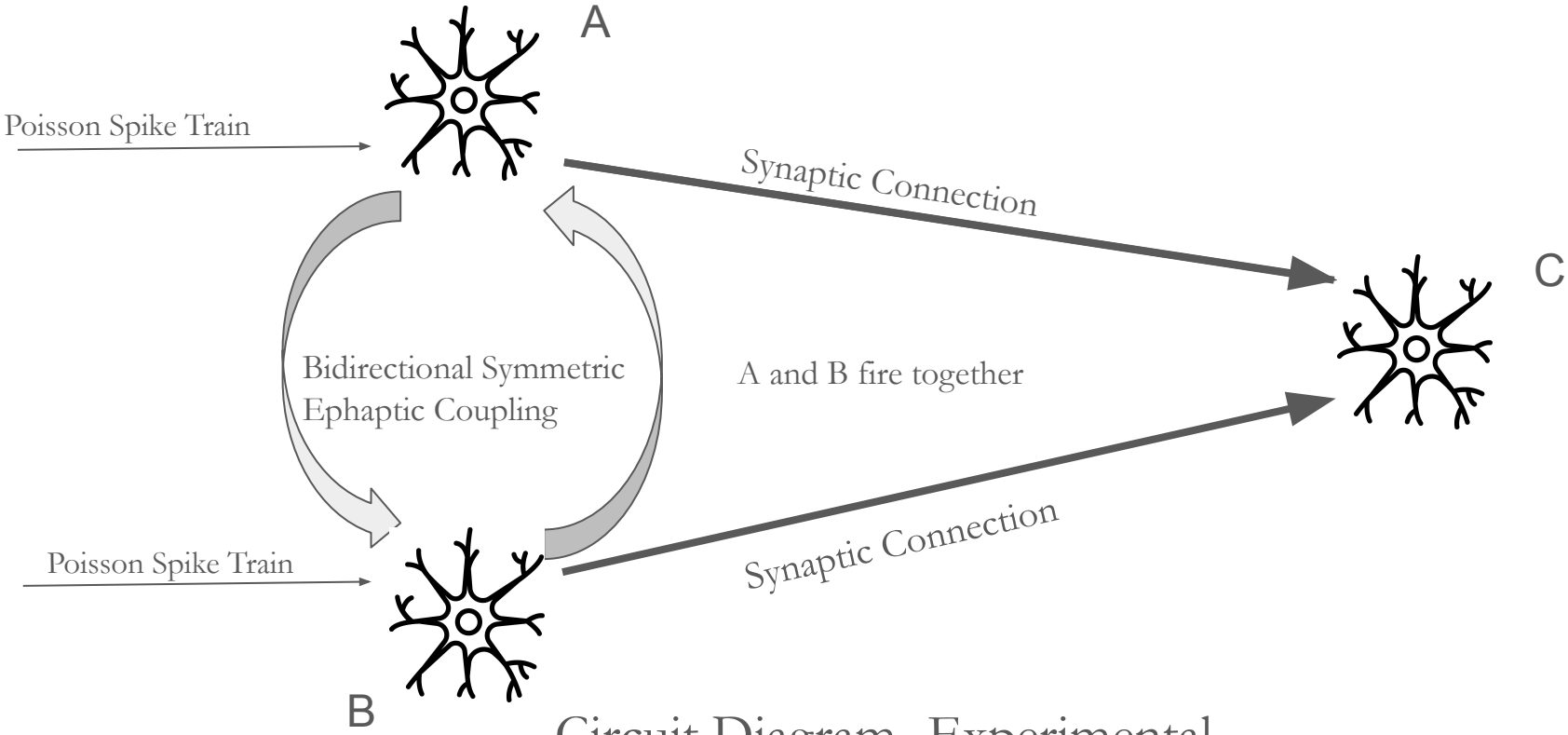

Neural Synchronisation helps in precise temporal regulation of oscillations in neurons
Ephaptic coupling helps synchronize oscillations in nearby neurons
Then how does Ephaptic affects Spike Timing Dependent Plasticity, that is in turn dependent on temporal relationship of action potentials

Methodology





Circuit Diagram- Experimental



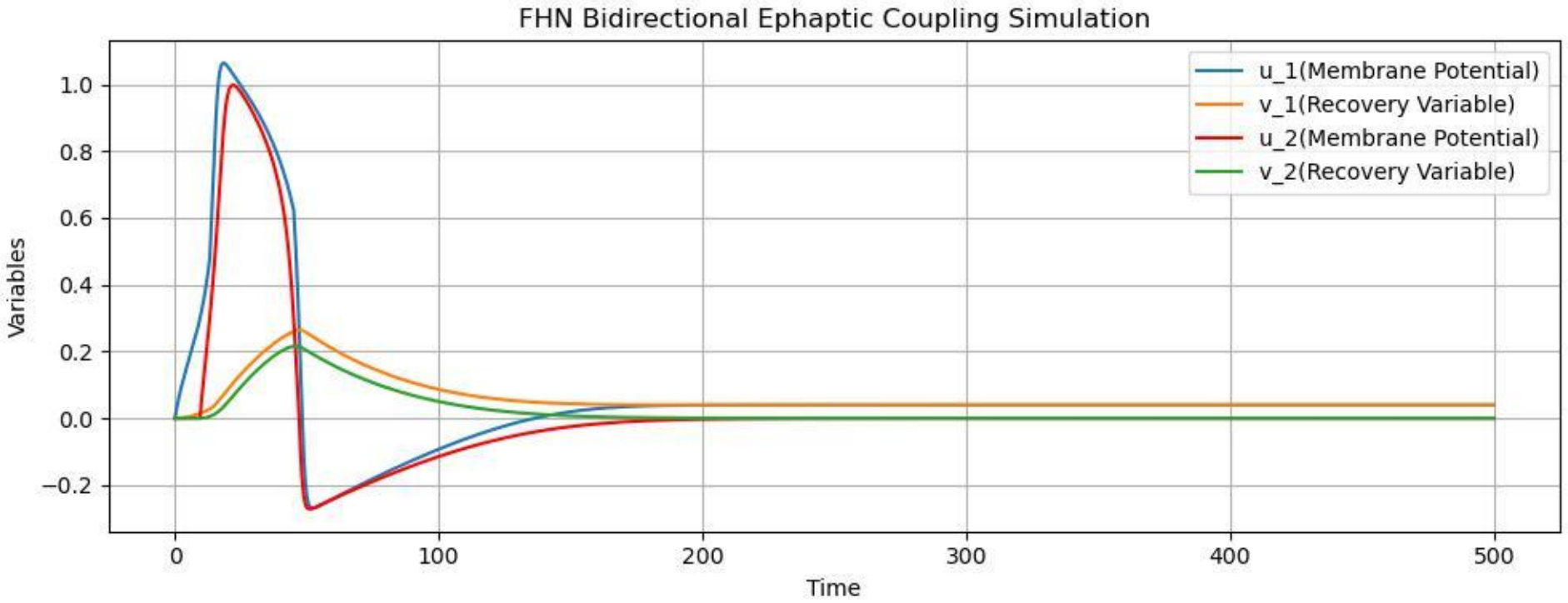
Circuit Diagram- Experimental

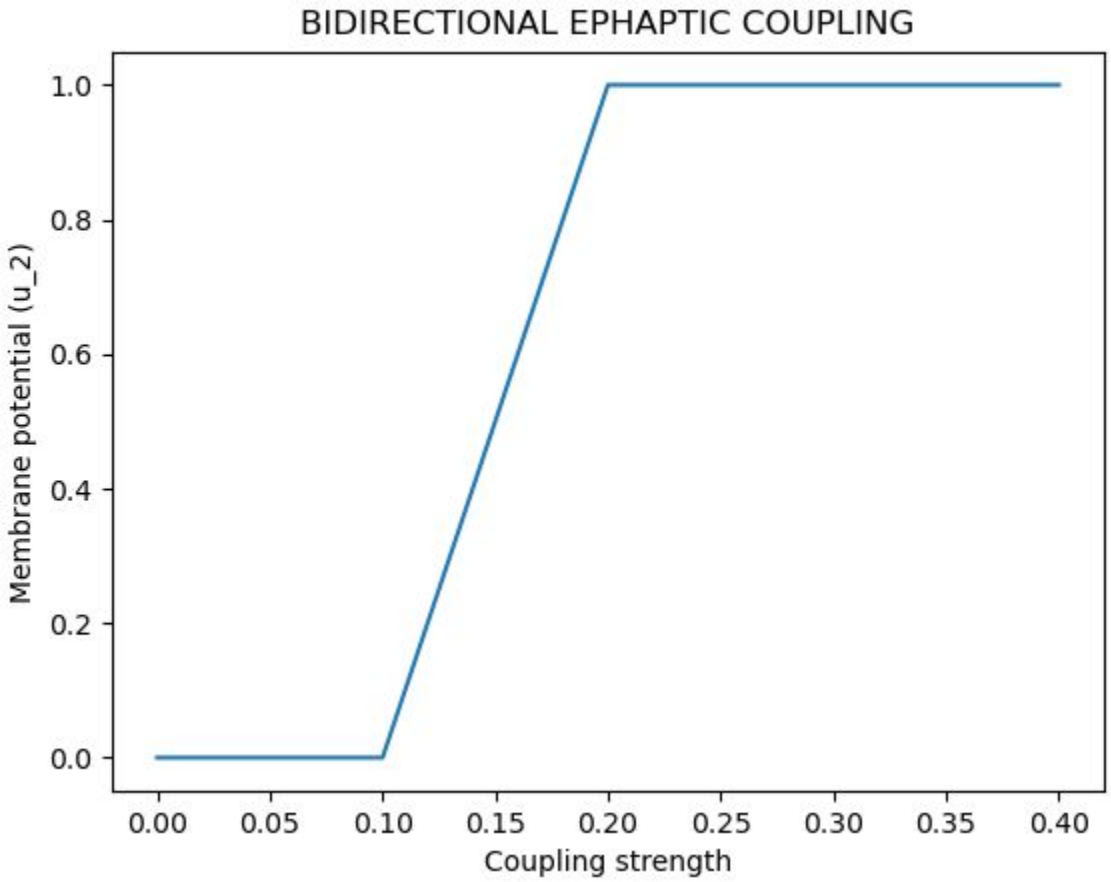
How Ephaptic coupling is modelled using FHN

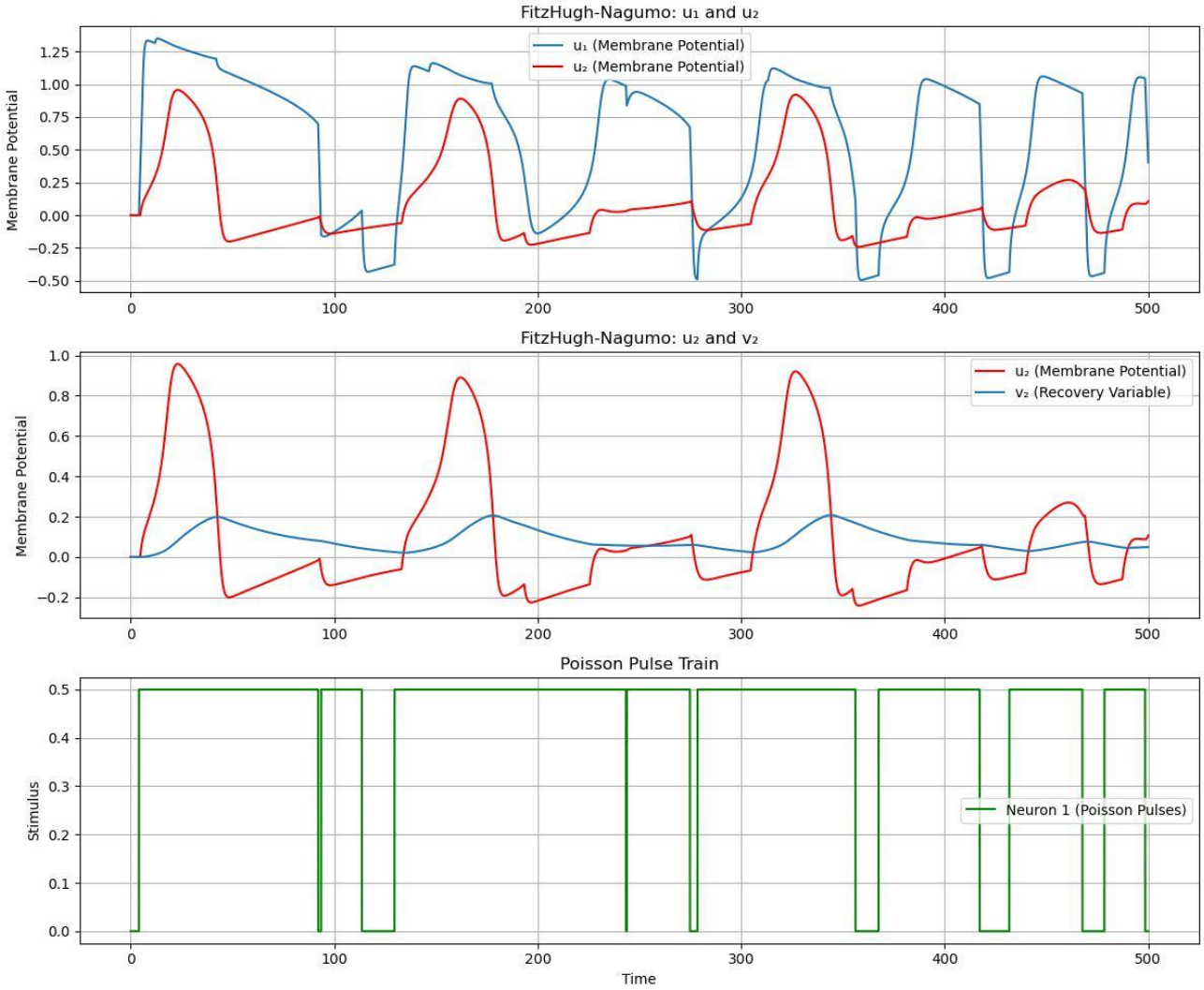
- To construct a simplified the coupling effect is introduced in the current
- The coupling is induced only when the Neuron A, shows an action potential
- If Neuron A crosses threshold it fires, inducing action potential in Neuron B

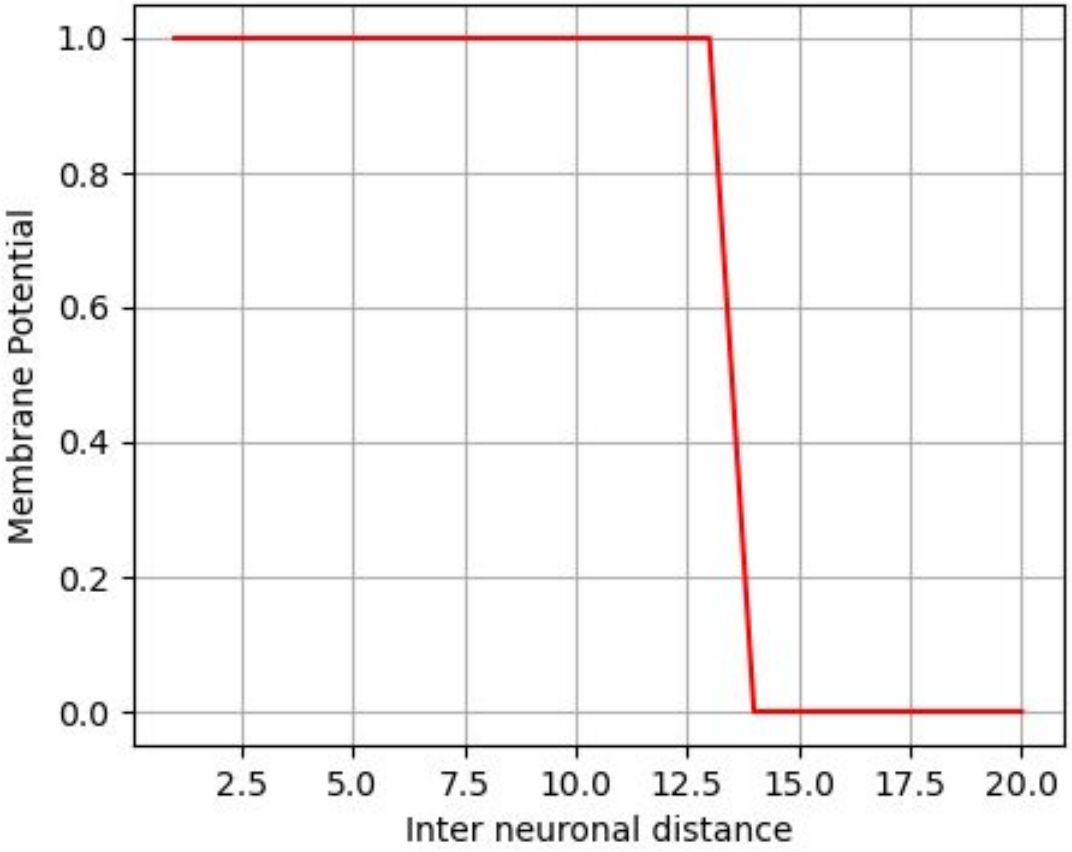
$$\frac{\mathrm{d}V}{\mathrm{d}t} = V(V-a)(1-V) - w + I$$
$$\frac{\mathrm{d}w}{\mathrm{d}t} = \epsilon(V - \gamma w),$$

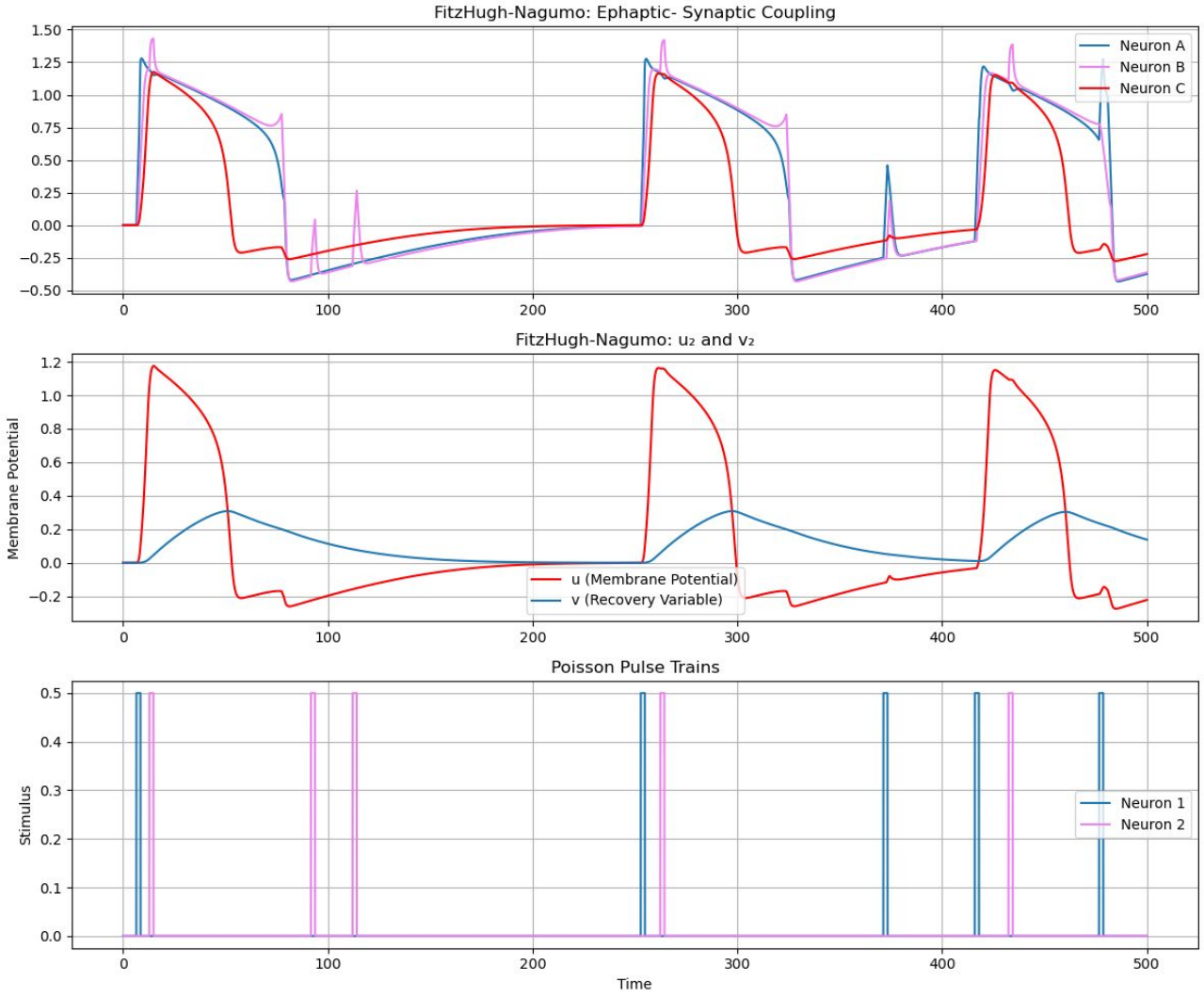
Results-Simulation




BIDIRECTIONAL EPHAPTIC COUPLING
Membrane potential (u_2)
1.0
0.8
0.6
0.4
0.2
0.0
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0.40
Coupling strength


FitzHugh-Nagumo: u₁ and u₂
u₁ (Membrane Potential)
u₂ (Membrane Potential)
Membrane Potential
1.25
1.00
0.75
0.50
0.25
0.00
−0.25
−0.50
0
100
200
300
400
500
FitzHugh-Nagumo: u₂ and v₂
u₂ (Membrane Potential)
v₂ (Recovery Variable)
Membrane Potential
1.0
0.8
0.6
0.4
0.2
0.0
−0.2
0
100
200
300
400
500
Poisson Pulse Train
Neuron 1 (Poisson Pulses)
Stimulus
0.5
0.4
0.3
0.2
0.1
0.0
0
100
200
300
400
500
Time

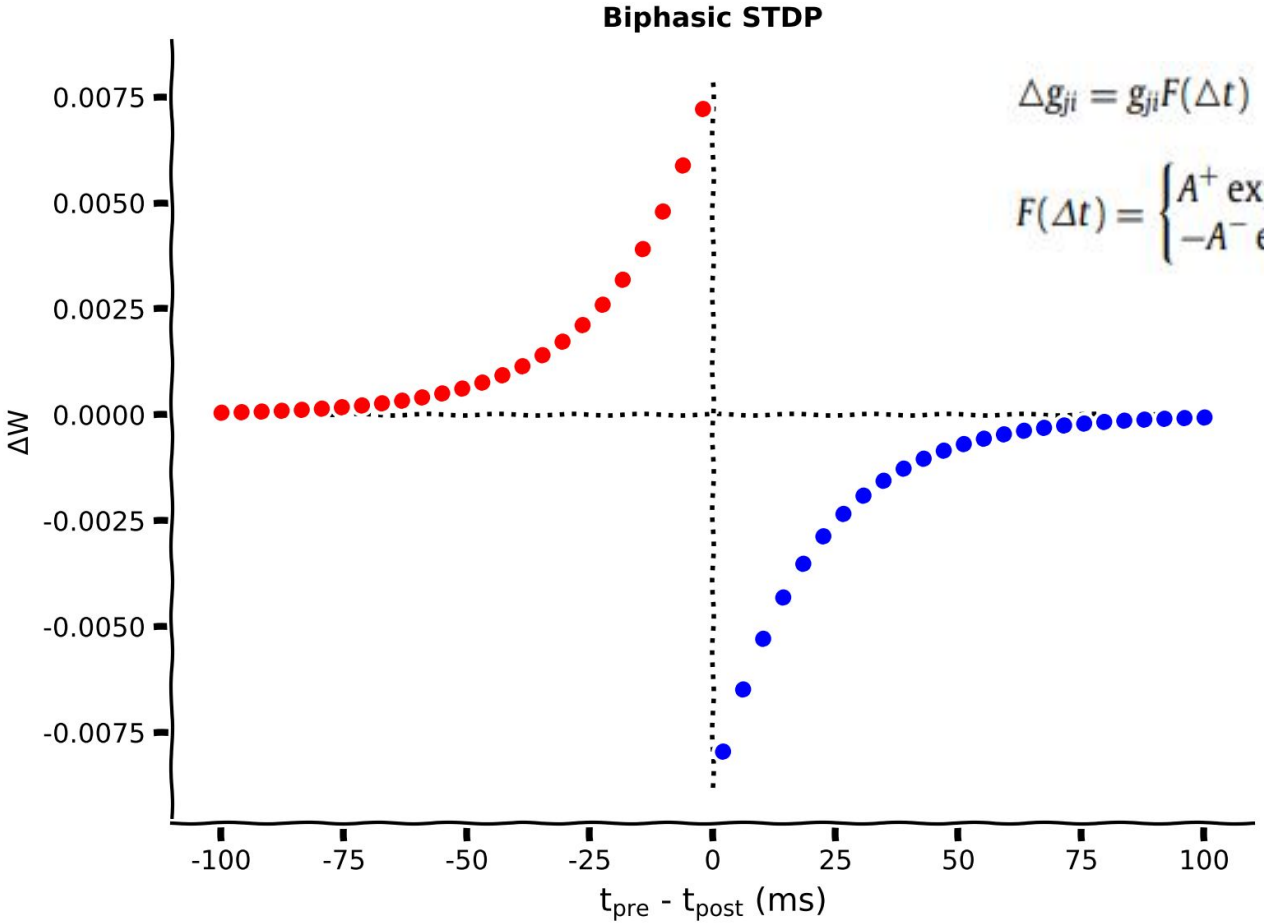

1.0
0.8
0.6
0.4
0.2
0.0
Membrane Potential
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
Inter neuronal distance


FitzHugh-Nagumo: Ephaptic- Synaptic Coupling
Neuron A
Neuron B
Neuron C
FitzHugh-Nagumo: u₂ and v₂
Membrane Potential
u (Membrane Potential)
v (Recovery Variable)
Poisson Pulse Trains
Stimulus
Neuron 1
Neuron 2
Time

What is Spike Timing Dependent Plasticity(STDP)?

- In Synaptic connections, the synapse is strengthened or weakened based on the timing difference.
- This is displayed by the change in the synaptic conductance

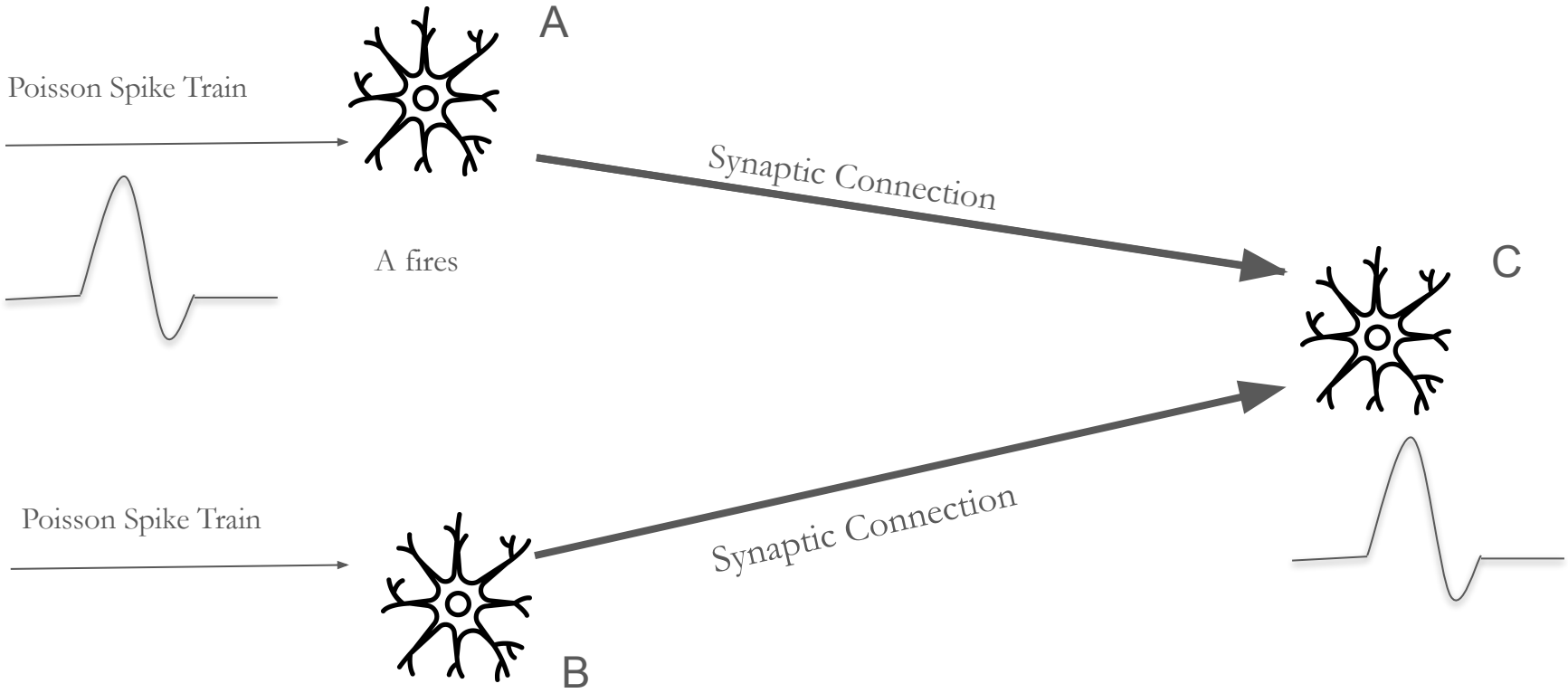
$$I_i^{syn} = g_{syn} \sum_{j=1}^{N} A_{ij} \ (V_i - E_{syn}) \ s_{ji},$$



$$\Delta g_{ji} = g_{ji} F(\Delta t)$$

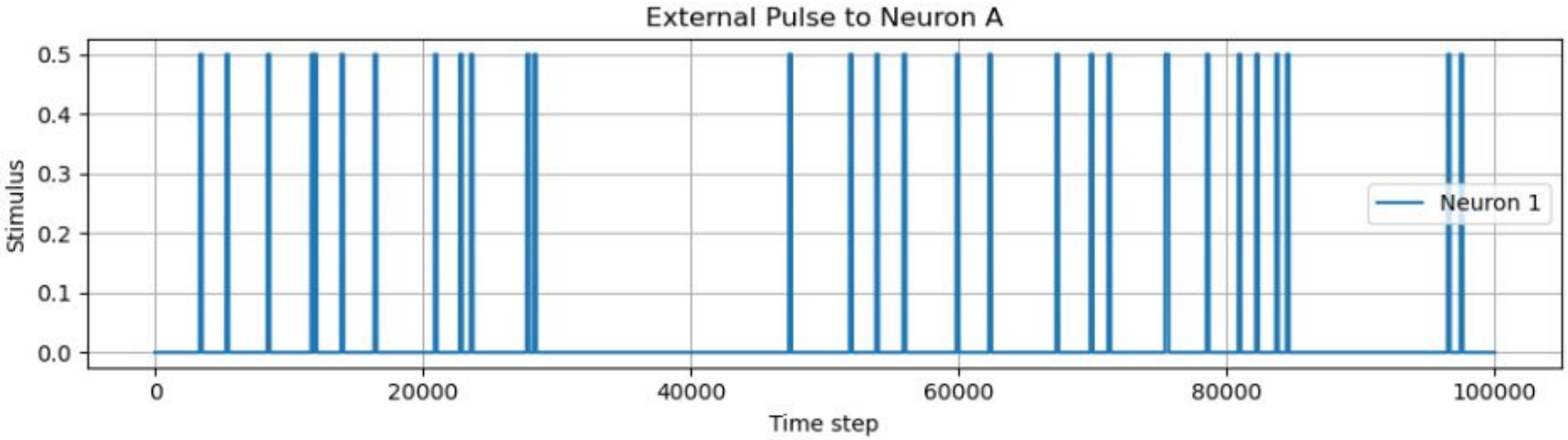
$$F(\Delta t) = \begin{cases} A^+ \exp(-\Delta t/\tau^+) & \text{if } \Delta t > 0 \\ -A^- \exp(\Delta t/\tau^-) & \text{if } \Delta t \leq 0 \end{cases}$$

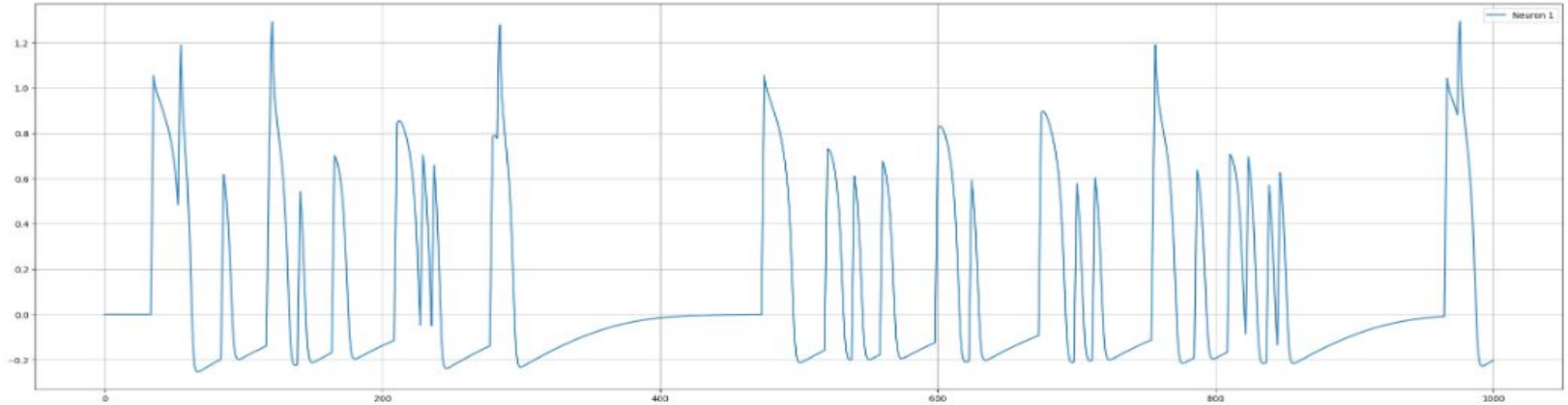
Credits: Neuromatch Academy

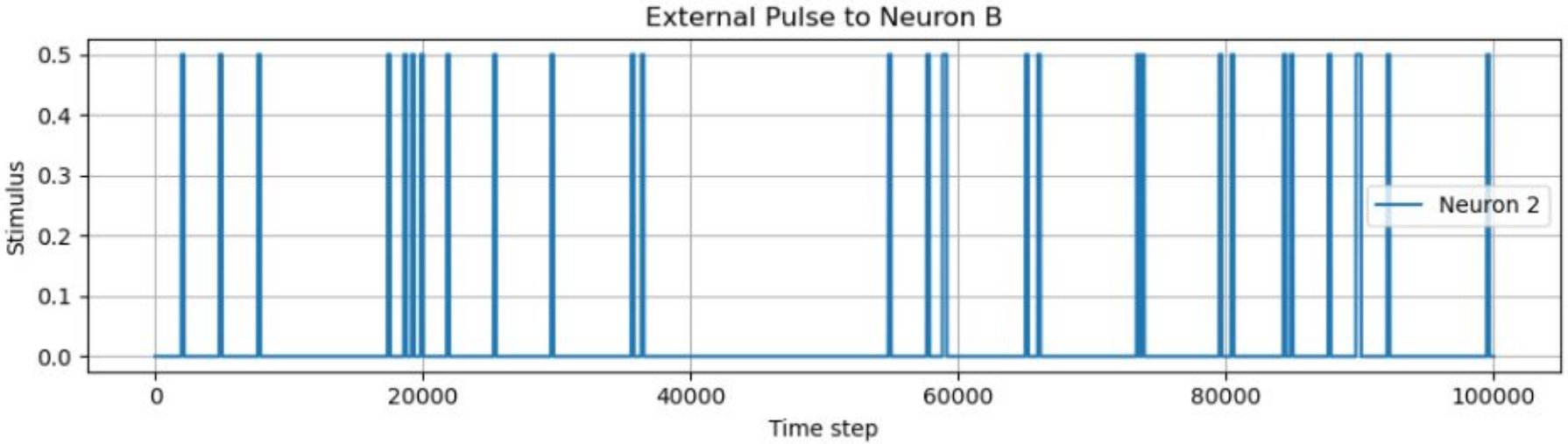


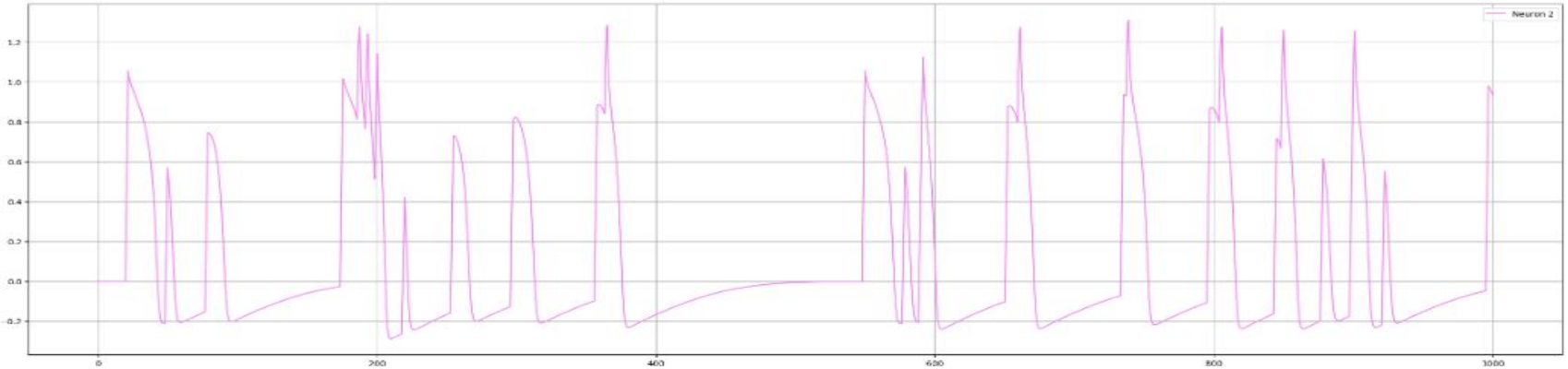
Circuit diagram-experimental

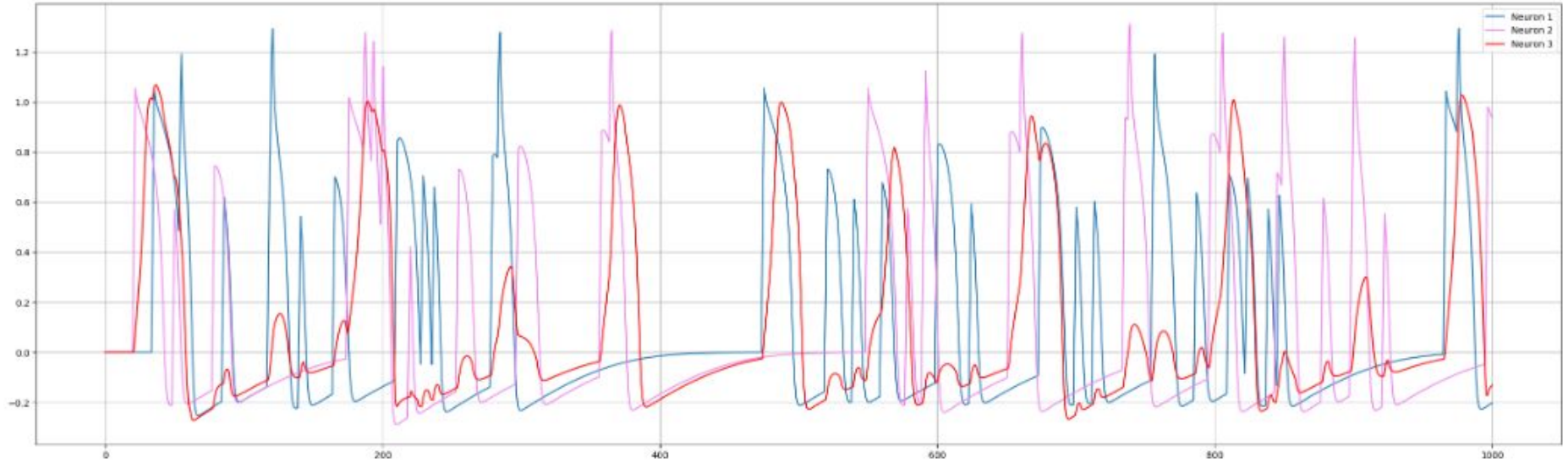
Synaptic connection between A and C, B and C






External Pulse to Neuron B
Stimulus
0.5
0.4
0.3
0.2
0.1
0.0
0
20000
40000
60000
80000
100000
Time step
Neuron 2



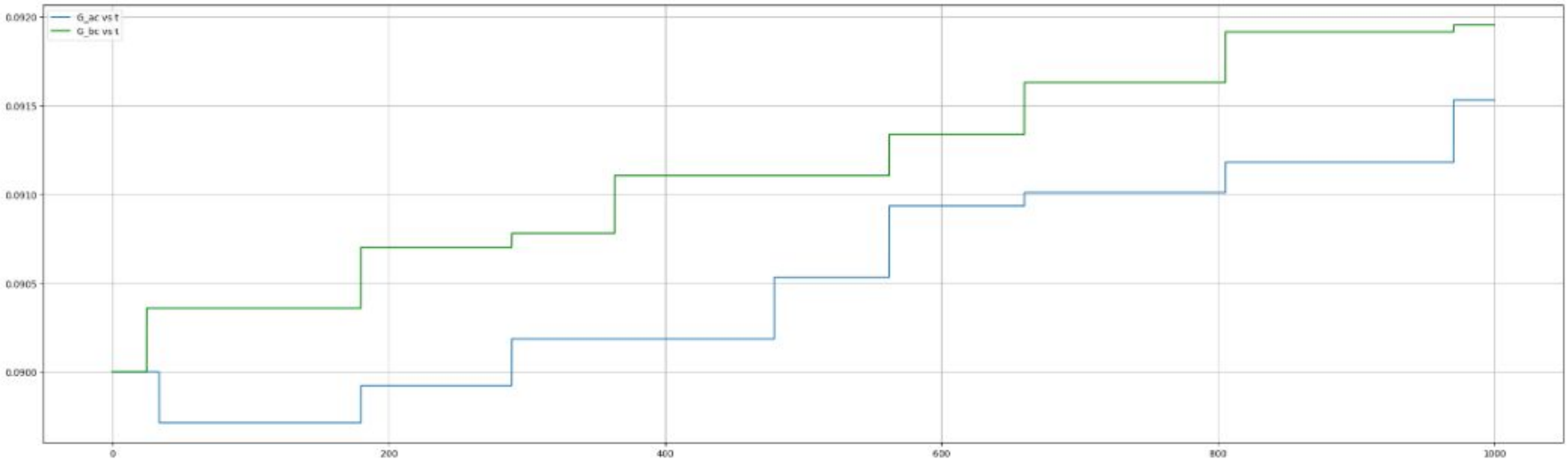


Plot of time vs membrane potential

- The Spiking of C influences the Synaptic conductances

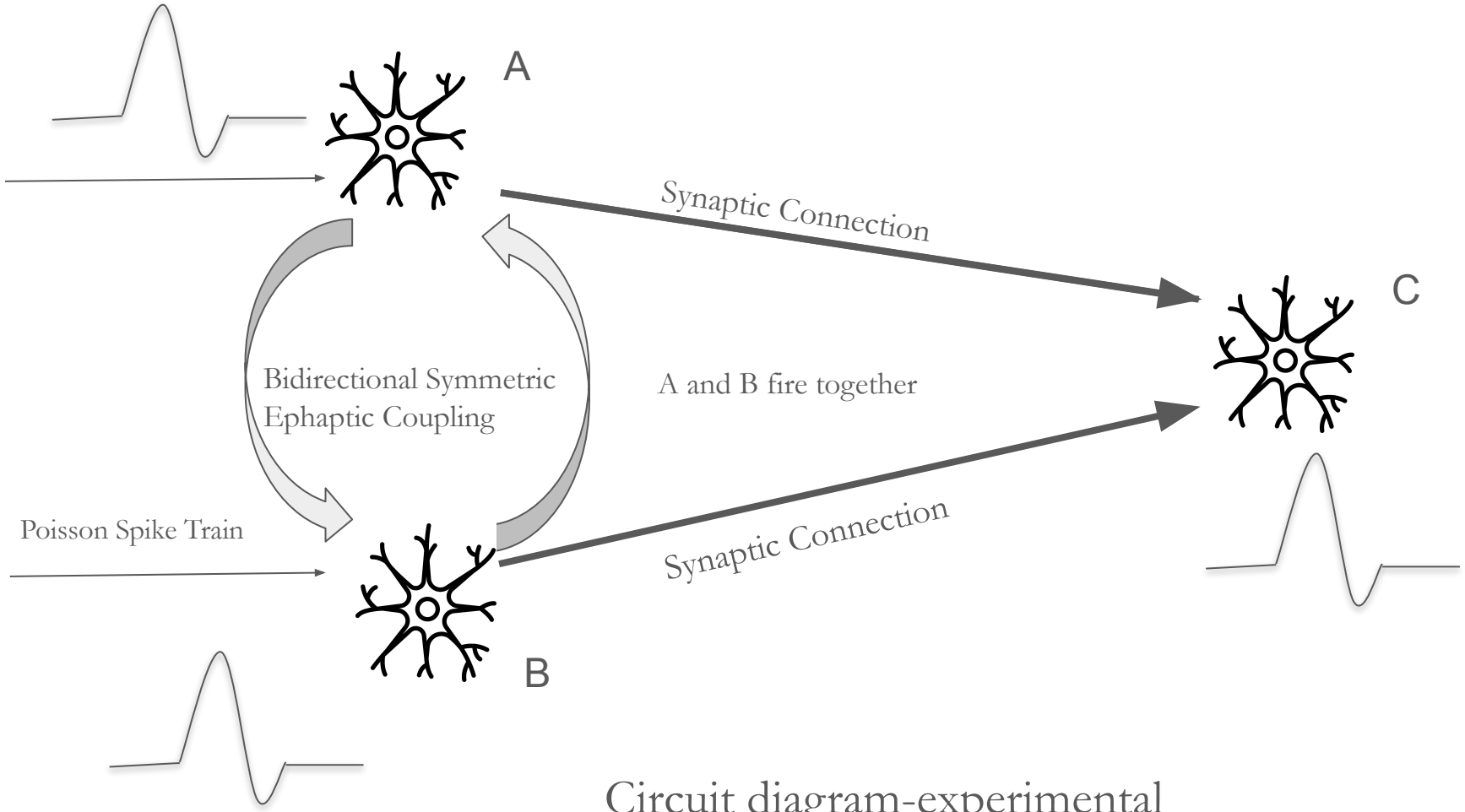
- For the randomised input pulses,
  "How much would the conductance change?"

Results from Synaptic coupling:

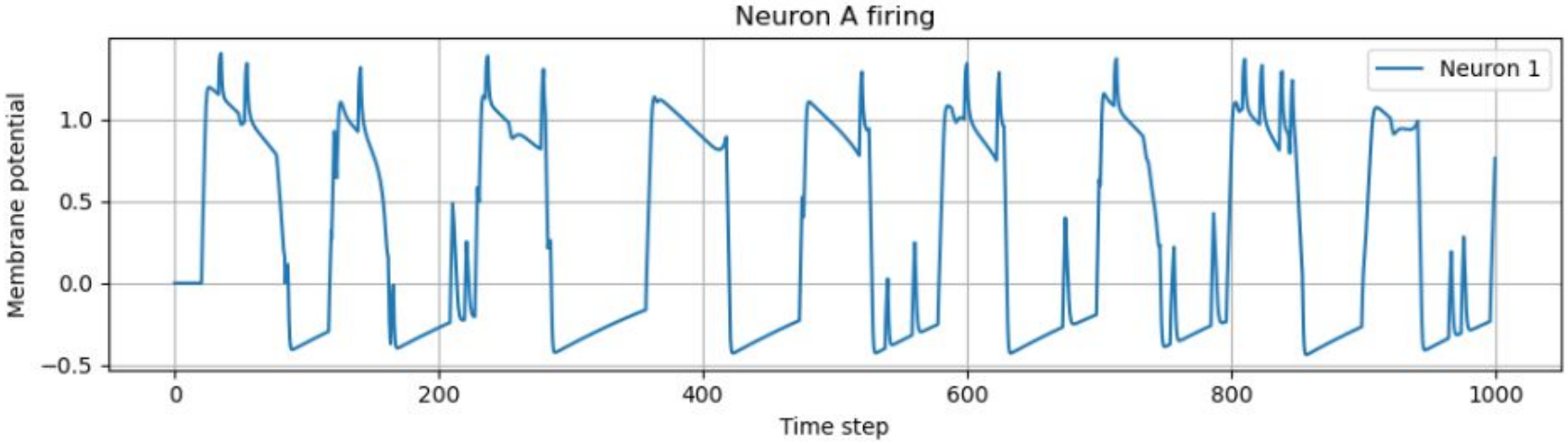


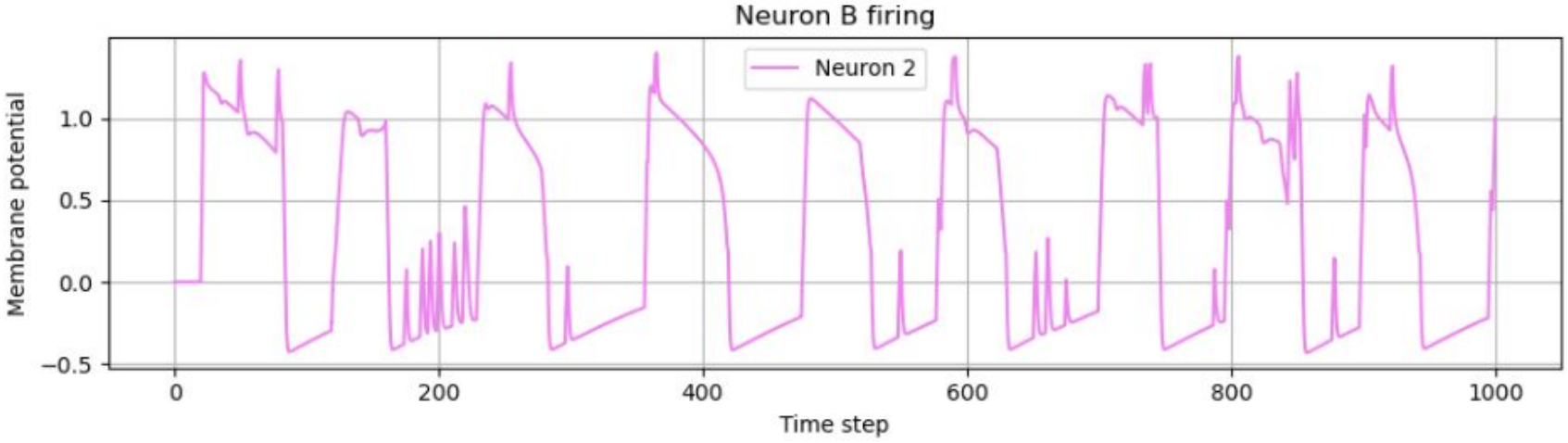

```
The value of g_ac is 0.09153
The value of g_bc is 0.09195
```

Initially both the synapses were given 0.09 as conductance

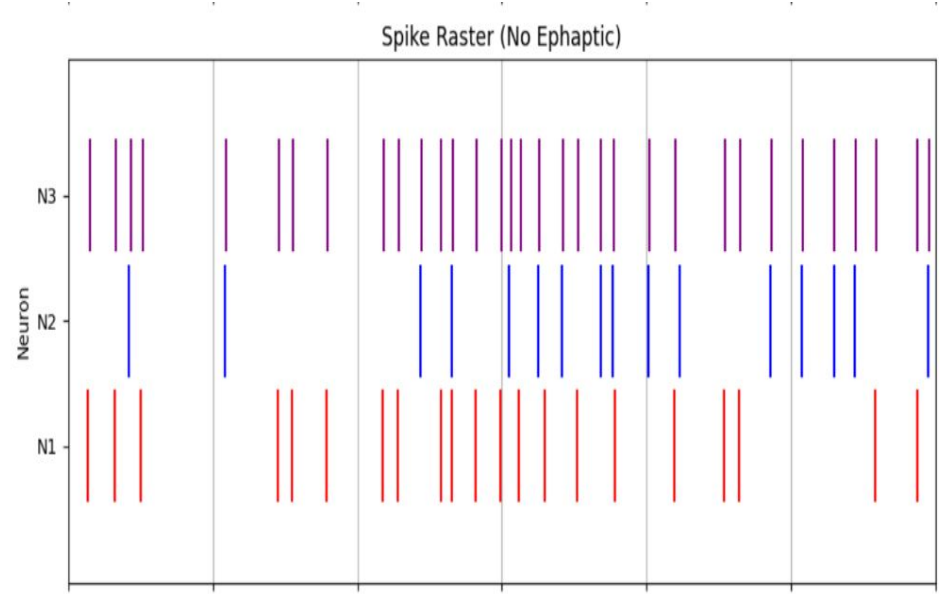


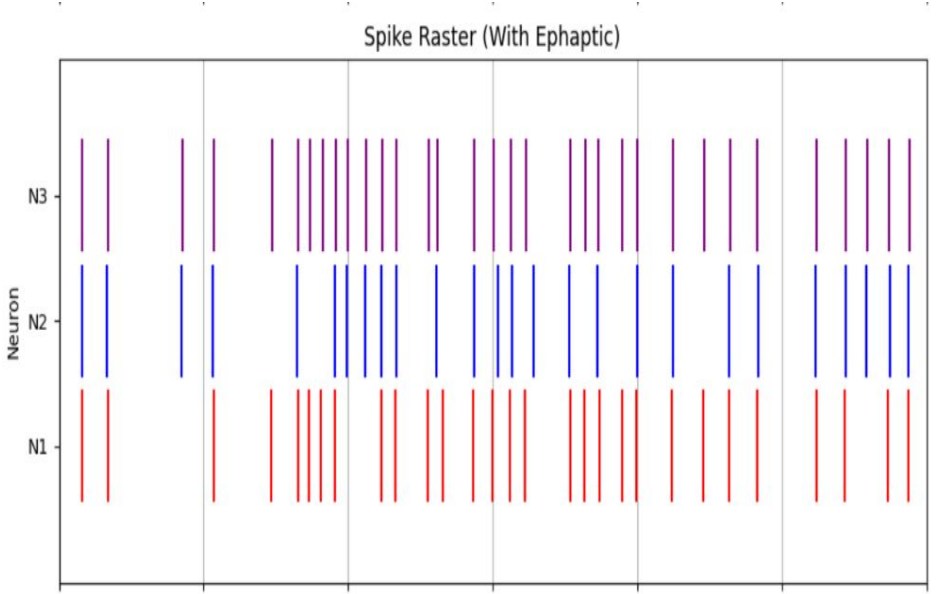
Circuit diagram-experimental


Neuron A firing
Neuron 1
Membrane potential
1.0
0.5
0.0
−0.5
0
200
400
600
800
1000
Time step

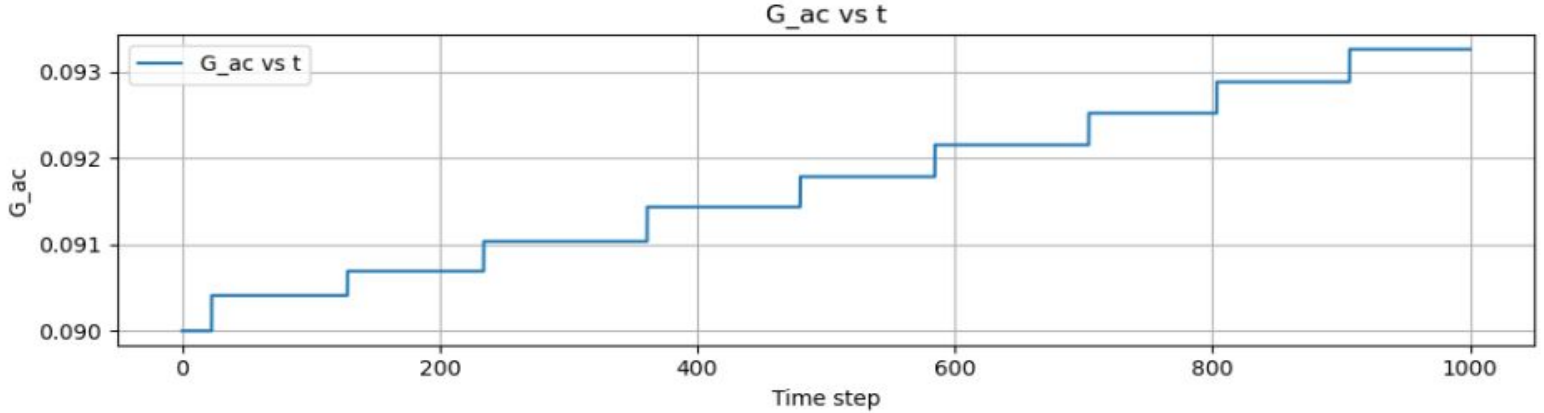

Neuron B firing
Neuron 2
Membrane potential
1.0
0.5
0.0
−0.5
0
200
400
600
800
1000
Time step

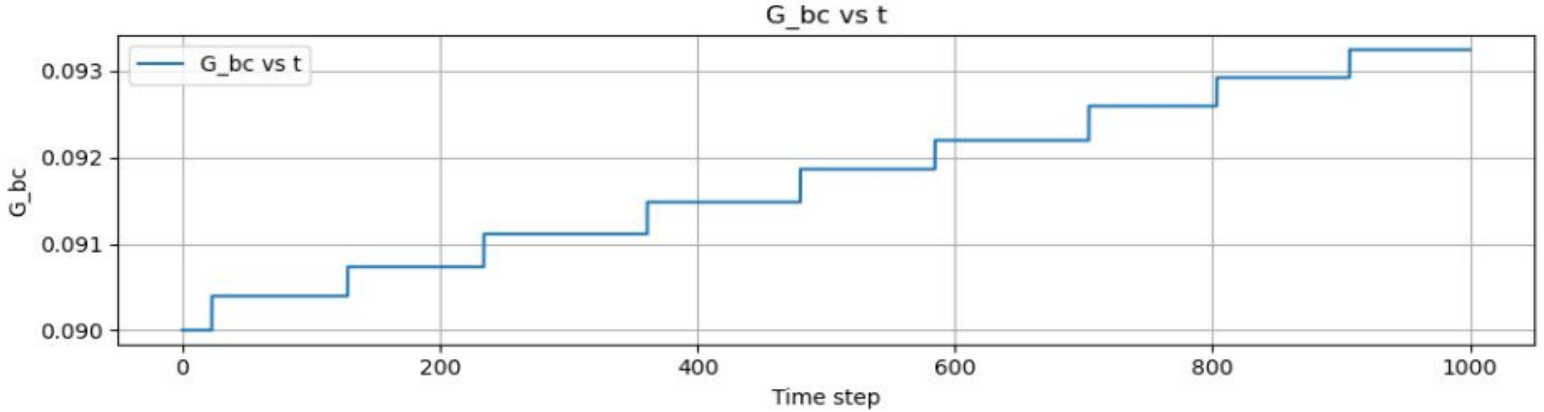
Synchrony exhibited in case of ephaptic coupling





Results of STDP from ephaptic coupling



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In the presence of ephaptic coupling
The value of g_ac is 0.09326
The value of g_bc is 0.09325
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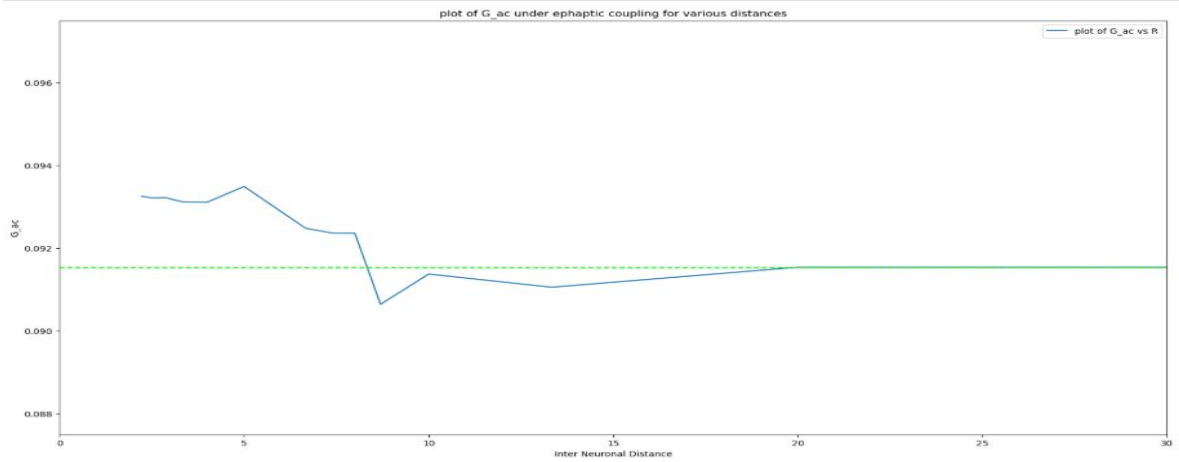
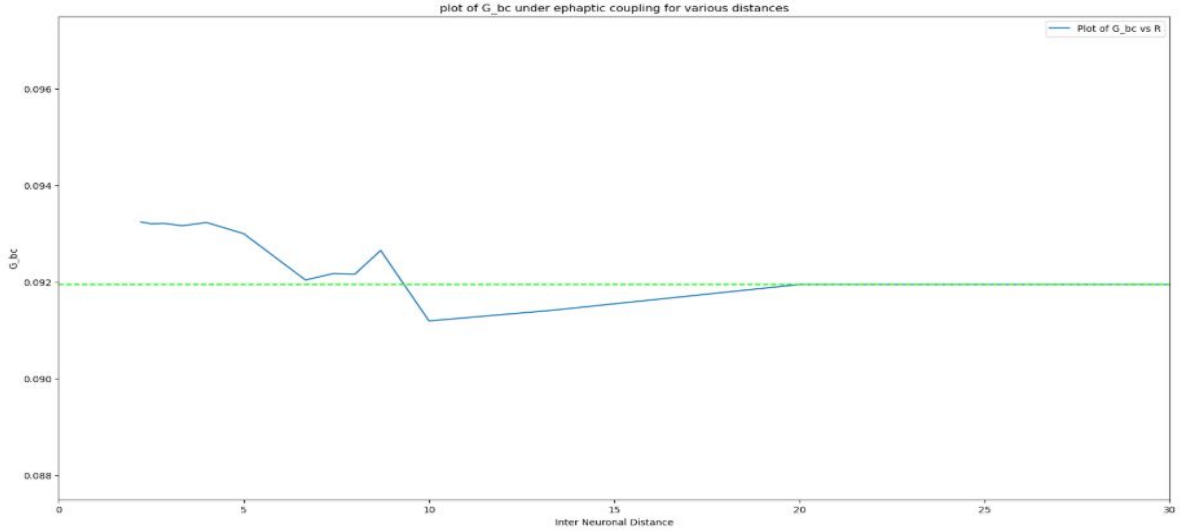

plot of G_ac under ephaptic coupling for various distances
plot of G_ac vs R
G_ac
0.096
0.094
0.092
0.090
0.088
0
5
10
15
20
25
30
Inter Neuronal Distance


plot of G_bc under ephaptic coupling for various distances
Plot of G_bc vs R
G_bc
0.096
0.094
0.092
0.090
0.088
0
5
10
15
20
25
30
Inter Neuronal Distance

Synaptic weight change in the presence and absence of Ephaptic coupling

Average % increase in synaptic weights in absence of ephaptic coupling:

- A-C Synaptic connection: 26.3%
- B-C Synaptic connection: 27.1%

Average % increase in synaptic weights in presence of ephaptic coupling:

- A-C Synaptic connection: 41.7%
- B-C Synaptic connection: 41.5%

(Note:The above computation is for a time period of 10000ms or 10s)

Potential developments in future:

- Understand the phenomenon of Ephaptic coupling in a network of neurons
- Effect of Ephaptic coupling in enhancing memory via LTP
- Use of cable models to include the axonal length

References and Resources

1. https://compneuro.neuromatch.io/tutorials/W2D3_BiologicalNeuronModels/student/W2D3_Tutorial4.html
2. https://compneuro.neuromatch.io/tutorials/W2D3_BiologicalNeuronModels/student/W2D3_Tutorial3.html
3. Han, Kyung-Seok, et al. "Ephaptic coupling promotes synchronous firing of cerebellar Purkinje cells." *Neuron* 100.3 (2018): 564-578.
4. Zhang, Mingming, et al. "Propagation of epileptiform activity can be independent of synaptic transmission, gap junctions, or diffusion and is consistent with electrical field transmission." *Journal of Neuroscience* 34.4 (2014): 1409-1419.
5. Anastassiou, Costas A., and Christof Koch. "Ephaptic coupling to endogenous electric field activity: why bother?." *Current opinion in neurobiology* 31 (2015): 95-103.
6. Janaki R, Vytheeswaran AS. The interplay of inhibitory and electrical synapses results in complex persistent activity. arXiv preprint arXiv:2104.02794. 2021 Apr 6.
7. Li X, Wang W, Xue F, Song Y. Computational modeling of spiking neural network with learning rules from STDP and intrinsic plasticity. Physica A: Statistical Mechanics and its Applications. 2018 Feb 1;491:716-28.
8. de Sousa MP, Cunha GM, Corso G, dos Santos Lima GZ. Thermal effects and ephaptic entrainment in Hodgkin–Huxley model. Scientific Reports. 2024 Aug 29;14(1):20075.

Thank You

Supplementary references:

Efficient Rapid Ephaptic PC→PC Signaling

Several factors make ephaptic coupling between PCs effective at promoting synchrony. First, they contain a large number of Na channels in their initial segments that produce large extracellular signals (Lorincz and Nusser, 2008). Second, the cell bodies of PCs are located in a single layer in close proximity to each other. Consequently, many of their AISs are close enough to each other to promote ephaptic signaling. Third, PCs are spontaneously active and spend a large fraction of time at potentials where small, sudden depolarizations can promote the opening of Na channels (Carter et al., 2012; Raman and Bean, 1997).

The excitatory ephaptic coupling we describe for PCs is well suited for promoting short-latency synchronous firing. The speed of signaling begins with the opening of the Na channels in the AIS during the upstroke of the action potential. This signal is maximal prior to the peak of the action potential. In addition, the potential of extracellular space changes immediately for ephaptic signaling and PC ion channels are influenced without delay. In contrast, electrical and chemical synapses require changing the intracellular potential, which is limited by the membrane time constant of the cell. As a result, ephaptic coupling

It seemed likely that PC pairs with correlated firing must excite one another, and we therefore determined the spike-triggered average (STA) to provide insight into the mechanism responsible for correlations. We measured spontaneous spiking of a PC pair with on-cell recordings to determine the extent of correlated firing, as in Figure 4A for a PC pair with strongly correlated firing. Then we obtained whole-cell recordings from both cells. Under current clamp, one PC was allowed to fire spontaneously while the other was voltage clamped to determine the STA at different holding potentials (Figure 4B). The STA was also determined in the other direction. For this example PC pair, bidirectional inward currents of 28 pA were observed at −50 mV. The responses were evoked with a latency of 0.1 ms and were strongly attenuated at holding potentials of −60 mV and −70 mV (Figure 4B). STA responses were not strongly influenced by PC firing rates (Figures S3E and S3F). For neighboring PCs with uncorrelated firing (Figure 4C), STAs were extremely small (Figure 4D). There was a linear relationship between the magnitudes of STA currents measured at −50 mV and the degree of correlated activity (Figure 4G). These experiments suggest that PC correlations arise from a bidirectional communication between PCs in which the spontaneous action potentials of one PC directly triggered an inward current in neighboring PCs.

Supplementary references:

The excitatory ephaptic coupling we describe for PCs is well suited for promoting short-latency synchronous firing. The speed of signaling begins with the opening of the Na channels in the AIS during the upstroke of the action potential. This signal is maximal prior to the peak of the action potential. In addition, the potential of extracellular space changes immediately for ephaptic signaling and PC ion channels are influenced without delay. In contrast, electrical and chemical synapses require changing the intracellular potential, which is limited by the membrane time constant of the cell. As a result, ephaptic coupling between PCs promotes synchrony on a more rapid timescale than can be readily achieved by electrical coupling or chemical synapses (Figure S5) (Dugué et al., 2009; Mann-Metzer and Yarom, 1999; Vervaeke et al., 2010).

Propagation can be explained by electrical field effects

The observation that the 4-AP-induced propagation cannot be explained by synaptic transmission, gap junction, or diffusion suggests that electrical field transmission could be responsible because it is the only other known way for neurons to communicate. To test this possibility, we use the low osmolarity 4-AP aCSF to decrease the extracellular space volume, thereby increasing the effect of the electrical field. Experiments were carried out in the longitudinal slice because the field effect is strongest in that direction. Experiments have shown that the time delay between the signals measured from two glass pipettes located along the CA3 layer significantly ($p < 0.001$) decreased from 13.98 ± 4.08 ms ($n = 86$ spike-pair from 3 slices) to 9.06 ± 5.18 ms ($n = 144$ spike-pair from 3 slices in low osmolarity over 10 min) in the 4-AP aCSF with a decrease of the osmolarity by 15%. This decrease corresponds to a speed increase by 35% in lower osmolarity solutions. This result is consistent with the effect of low osmolarity on speed of propagation previously reported (Shahar et al., 2009). Furthermore, a NEURON computational model was developed to simulate a hippocampal CA1 pyramidal neuronal network in a Ca^{2+}-free medium, synaptic transmission independent, and with electrical field coupling as the sole means of communication. The model was based on low-calcium neuron simulation developed earlier (Avoli et al., 2013); the parameters of the model were slightly modified but remained within the physiological ranges (Warman et al., 1994; Migliore et al., 1999). The network

$$\Phi = \frac{I}{4\pi\sigma}\frac{1}{r}$$