Robustness of Basket Cell Network Dynamics to Physiological Noise: Insights from Three-Cell Networks

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Abstract

Understanding how physiological noise affects network dynamics provides important information into the robustness of neuronal computations. In this paper, we construct a 3-cell network of basket neurons, which are connected by many dendritic gap junctions, to study the robustness of interneurons. We employ c`orrelation and weak coupling theory to unravel the intricate interplay between neurons and how they synchronize and communicate in the presence of noise, shedding light on the robustness and reliability of neuronal computations. Phase response curves are obtained in its crude form, but at its full potential they are used for predicting the network dynamics of basket cell networks that are linked at distant points.

Introduction and Motivation

Gap junctions play a crucial role in facilitating direct electrical communication among neurons within the central nervous system (CNS) [7], which span key brain regions like the hippocampus and neocortex. These dynamic conduits, comprised of clusters of 12 connexin proteins, are influenced by various factors such as age, pH levels, and phosphorylation, highlighting their importance in regulating neuronal network dynamics. Specifically, within inhibitory networks, gap junctions serve as vital components in coordinating population network rhythms, thus emphasizing their pivotal role in CNS function.

In the hippocampus, GABAergic interneurons display diverse cellular properties, with active dendrites being a notable feature. Specifically, parvalbumin-positive GABAergic neurons, known as basket cells, form connections via gap junctions located on their distal dendrites, thus playing a significant role in network synchronization [8]. Although traditionally recognized for their role in promoting synchrony, recent theoretical and modelling studies have unveiled that gap junctions can induce a spectrum of dynamic patterns, spanning from antiphase to bursting and phase-locked states.

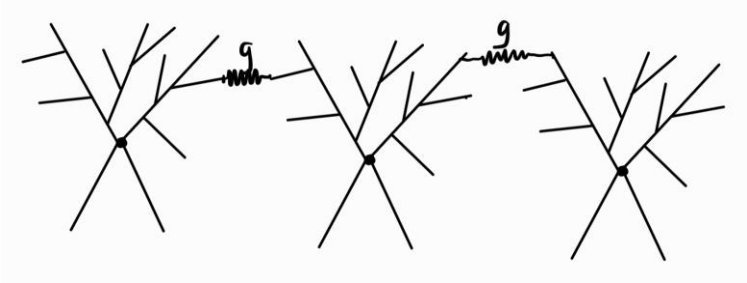
The emergence of distinct network patterns is intricately linked to cellular intrinsic properties, including intrinsic firing frequencies and the spatial arrangement of gap junctions. Despite considerable research on the interplay between gap junctions and network dynamics, a significant gap exists in our understanding of how these dynamics are influenced by noise within the nervous system. Neuronal activity is inherently susceptible to stochastic fluctuations stemming from various sources of noise, such as synaptic noise due to variability in neurotransmitter release, ion channel noise arising from stochastic gating processes, and environmental perturbations like temperature fluctuations. These diverse sources collectively contribute to neuronal noise, which can profoundly impact network dynamics. Closing this gap in understanding is crucial for elucidating the true complexity of how neuronal networks function in noisy biological environments.

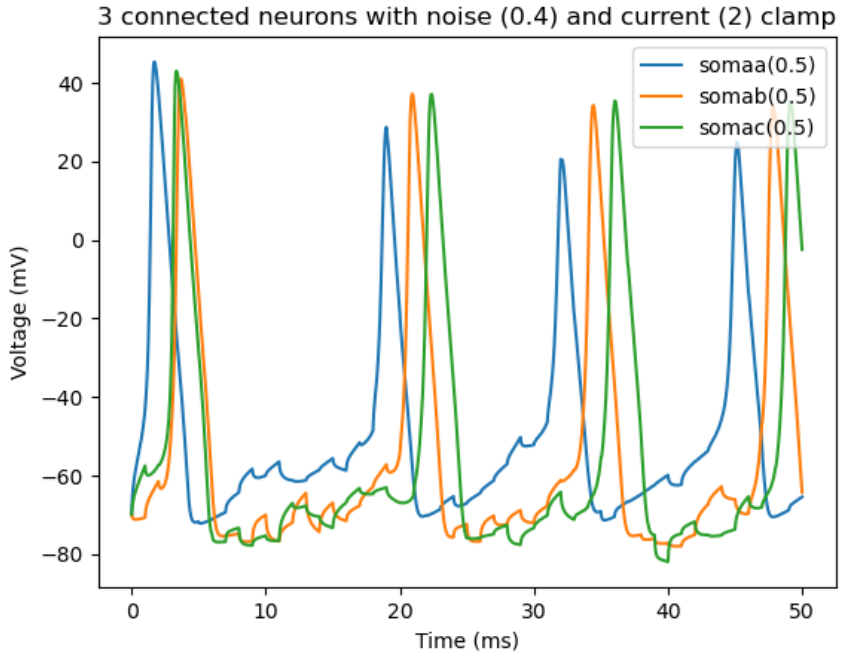
Exploring the impact of noise in the nervous system is crucial for several compelling reasons. For starters, neurons naturally behave in unpredictable ways, and grasping how this physiological noise influences network dynamics gives us critical insights into how reliable and resilient neuronal computations are. Additionally, noise is not just background interference; it helps shape the formation and stability of synchronized states in networks of interneurons, especially among those basket cells hanging out in the hippocampus. When we dive into what factors influence this synchronization, like the properties of cell junctions and the activity in dendrites, we start to uncover the intricate mechanisms behind how neural circuits sync up and process information.

Additionally, evaluating how well network dynamics hold up against physiological noise is an interesting question in neuroscience. It delves into whether the synchronization patterns we see in networks of basket cells remain intact when real-world conditions, complete with all their noisy nuances, come into play. Getting a handle on how resilient network dynamics are to this noise gives us valuable insights into just how stable and trustworthy neuronal communication is in the brain. This, in turn, helps us unravel the intricate mechanisms that drive cognitive processes and underlie neurological disorders. Thus, digging into how noise interacts with network dynamics will improve our understanding of both how the brain functions and what goes awry when it doesn't.

Methods

Model





To model basket neurons, we employed a properly implemented 372-compartment model, comprising a soma and dendrites, constructed within the NEURON environment by [2] and [3]. This morphological

representation, though simplified, accurately mirrors the intricacies of basket cells found in the hippocampus.

In our simulations, we utilized three basket neuron cells: A, B, and C; where A and B, as well as B and C, were connected via gap junctions. This setup mimics the intercellular communication observed in neural networks.

The core of our model lies in the cable equation, spatially discretized to capture the spatial decay of voltage for high-frequency signals, as depicted by the equation:

$$C\frac{dV}{dt} = \gamma(V_2 - V_1) - I_{ionic}$$

Here, γ is the coupling conductance, axial resistance is set to $134/\Omega cm$, and capacitance is $1\ \mu F/cm^2$, providing the foundation for electrical signal propagation within the neuron.

All neuronal components are equipped with fast sodium and delayed rectifier potassium channels, whose dynamics are governed by Hodgkin-Huxley (HH) equations [4]. Specifically, the kinetics of the channels are described by equations as follows:

For Delayed Potassium, we have

$$\frac{dn}{dt} = (1-n)\alpha_n(V) - n\beta_n(V)$$

Where α and β are numerically given as:

$$\alpha_n(V) = -0.01\frac{V + 55 +}{exp\left(-\frac{V+55}{10} - 1\right)}$$

$$\beta_n(V) = 0.125\, exp\left(-\frac{V+65}{80}\right)$$

And for Na channel we have, opening and closing rates for both m and h as follows:

$$\alpha_m^{Na} = 0.32\frac{(13 - V_2)}{\left[exp\left(\frac{13-V_2}{4}\right)\right]}$$

$$\beta_m^{Na} = \frac{0.28(V_2 - 40)}{\left[exp\left(\frac{V_2-40}{5}\right)\right]}$$

$$\alpha_h^{Na} = 0.128\, exp\left(\frac{17 - V_2}{18}\right)$$

$$\beta_h^{Na} = \frac{4}{1 + exp\left(\frac{40-V_2}{5}\right)}$$

Gap junctions, crucial for intercellular communication, are modelled using a defined formula

$$i_{gap} = g_{gap}(V_2 - V_1)$$

with conductance values dictating the strength of coupling between neurons. The values of conductance are around 10-100 pS.

To stimulate neuronal firing, a current of 2nA is injected into the neuron, ensuring its activation. We varied this input to achieve signal-to-noise ratios ranging from 5 to 10, demonstrating the robustness of the system against varying levels of noise.

Our analysis delves deep into network dynamics, employing correlation and weak coupling theory [5] to unravel the intricate interplay between neurons and how they synchronize and communicate in the presence of noise, shedding light on the robustness and reliability of neuronal networks.

Simulation details:

The simulations were conducted using a combination of Python programming language and the NEURON simulation [2] and [3] environment, renowned for its robustness in modelling neuronal dynamics. A default integration time of 25 µs was used to ensure accurate temporal resolution.

At the onset of each simulation run, the membrane voltage of the neurons was initialized to -70 mV, a physiological starting point reflective of resting membrane potentials.

To introduce realistic neuronal variability, Gaussian noise with a $\mu = 0$ and a σ of 0.4 nA was added to the simulations. This noise model captures the stochastic nature of biological systems, enabling the exploration of neuronal responses under realistic conditions. Simulations were conducted over a duration of 500ms to observe sustained behaviour and allow for the emergence of phase-locked states.

The analysis of phase differences between neurons was approached with careful consideration. Rather than utilizing the traditional 0 to 2π phase representation, percentages ranging from 0 to 100 were employed. This choice was motivated by the desire to simplify the analysis, particularly for spiking neurons exhibiting periodic but asymmetrical oscillations. Phase difference distributions were visualized using histograms, providing insight into the synchronization dynamics of the network.

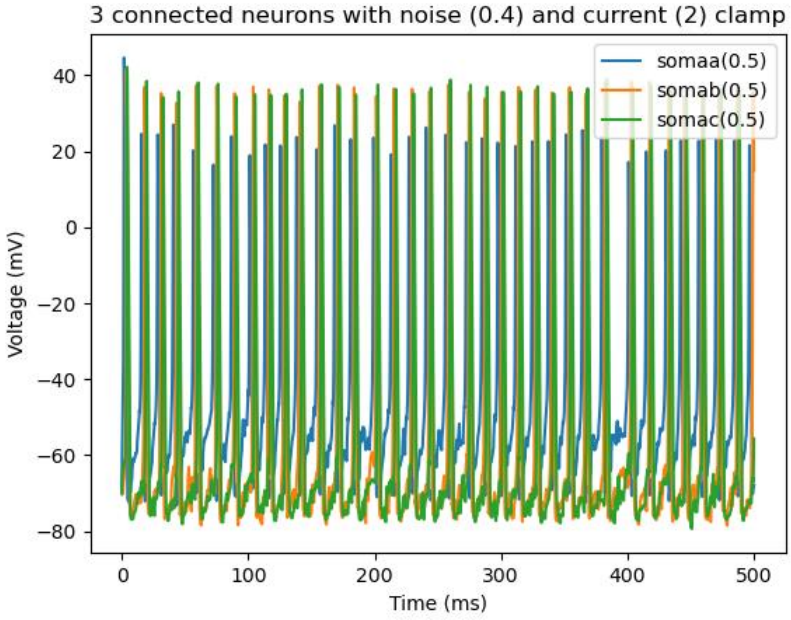
Robust estimation techniques were employed to ensure the reliability of data analysis. Median calculation was utilized as a robust measure to handle noisy data, effectively mitigating the influence of outliers. Additionally, standard deviation analysis was conducted to assess the consistency and reliability of the data.

To investigate the impact of gap junction conductance variability on network dynamics, conductance values were systematically varied. The standard deviations of Gaussian noise in the conductance values were set to 0.4 and 0.1 nA, allowing for the exploration of how different levels of noise affect network behaviour.

Cross-correlation analysis was performed to examine the relationship between voltage traces of neuron pairs. This analysis provided valuable insights into how neuronal activity synchronizes and desynchronizes in response to varying levels of noise, offering a comprehensive understanding of network dynamics under perturbed conditions.

Precise response curves (PRCs) are employed to quantify how perturbations affect a system's oscillation timing. They are produced by introducing stimuli into a particular cell site at a given amplitude and duration, then observing the phase shift that results. PRCs are utilized to analyse the nonmonotonic relationship between intrinsic frequency and percentage active in a system with active dendrites. They can indicate both advances and delays in perturbation phases near the somatic peak.

Results

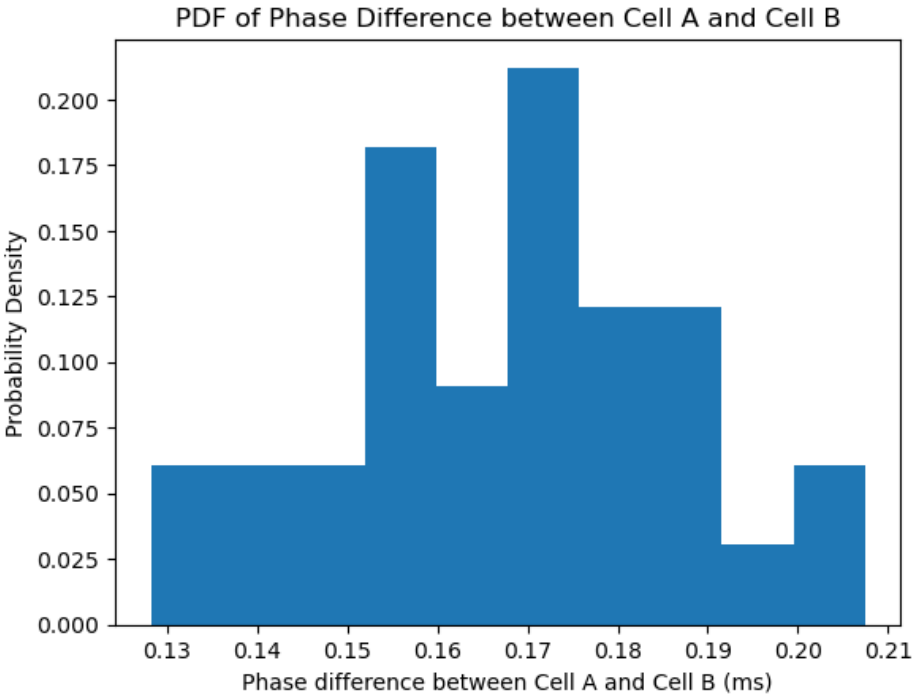


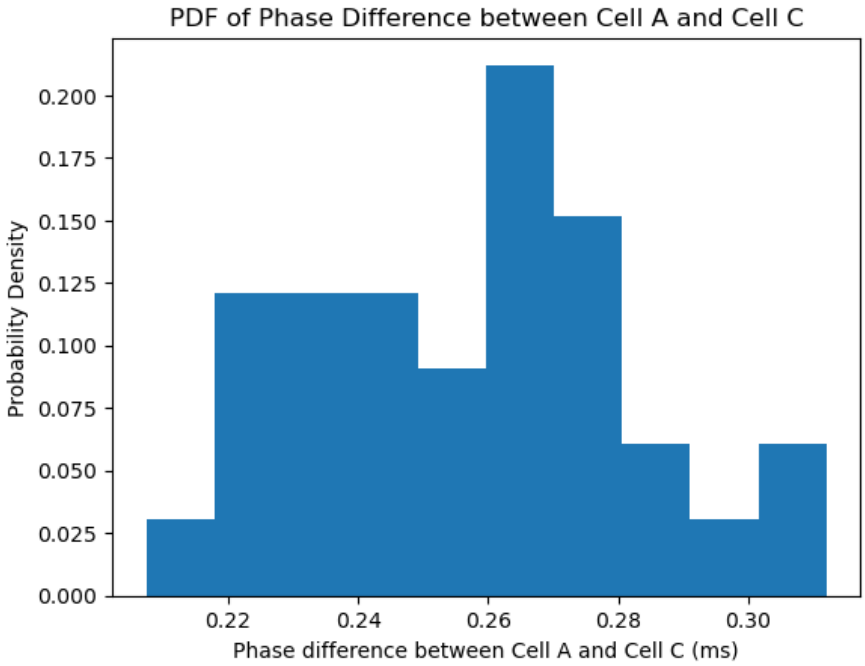
We obtain median and standard deviation of phase differences as follows,

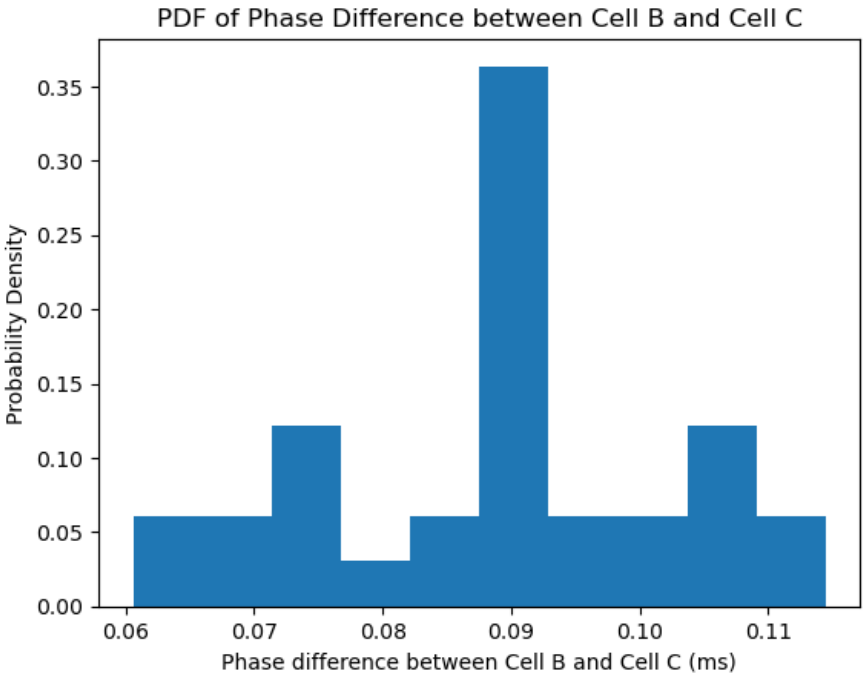
AB: 17%, 1.82%

AC: 25.8%, 2.55 %

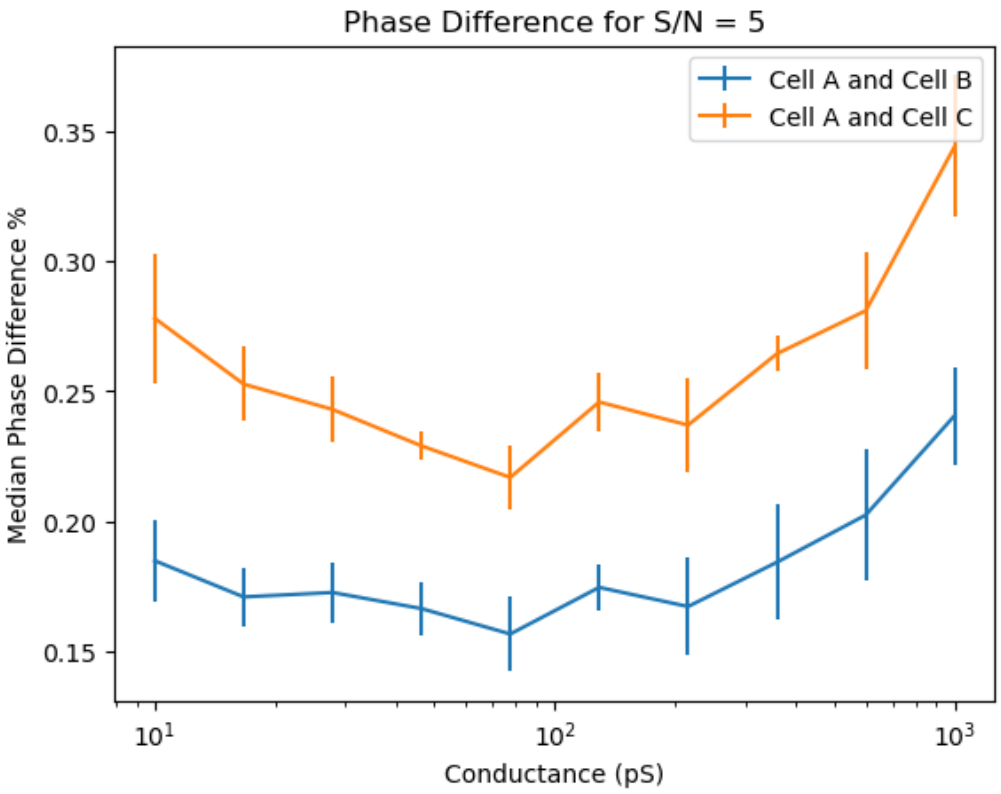
BC: 8.9%, 1.34%

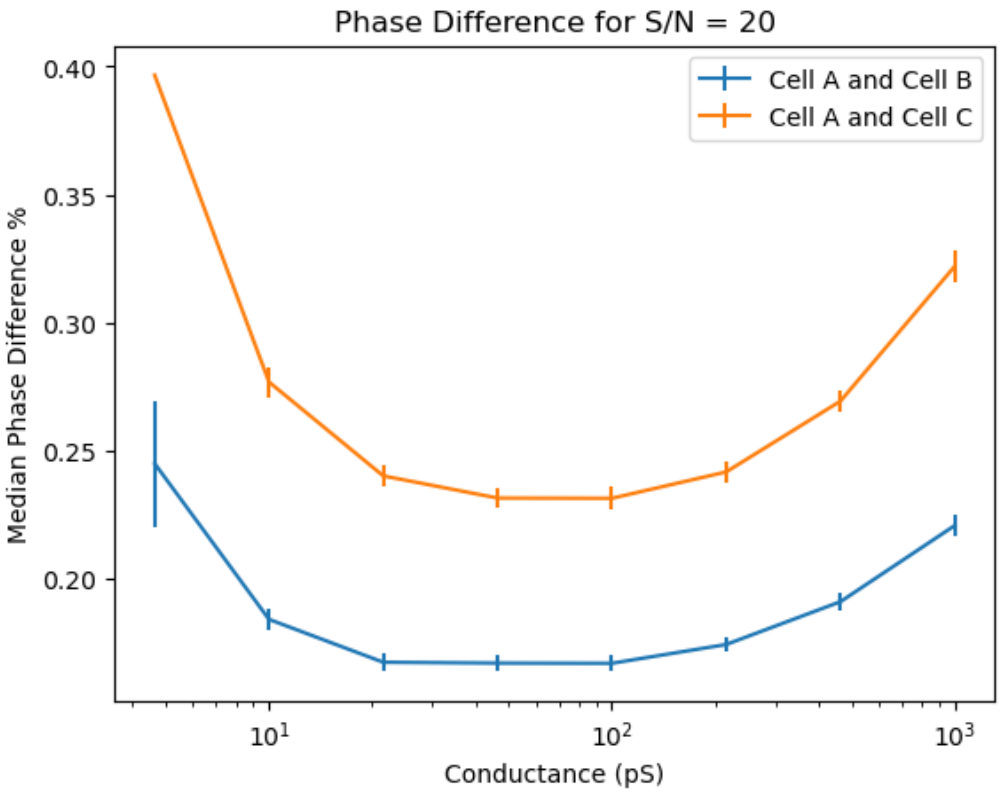




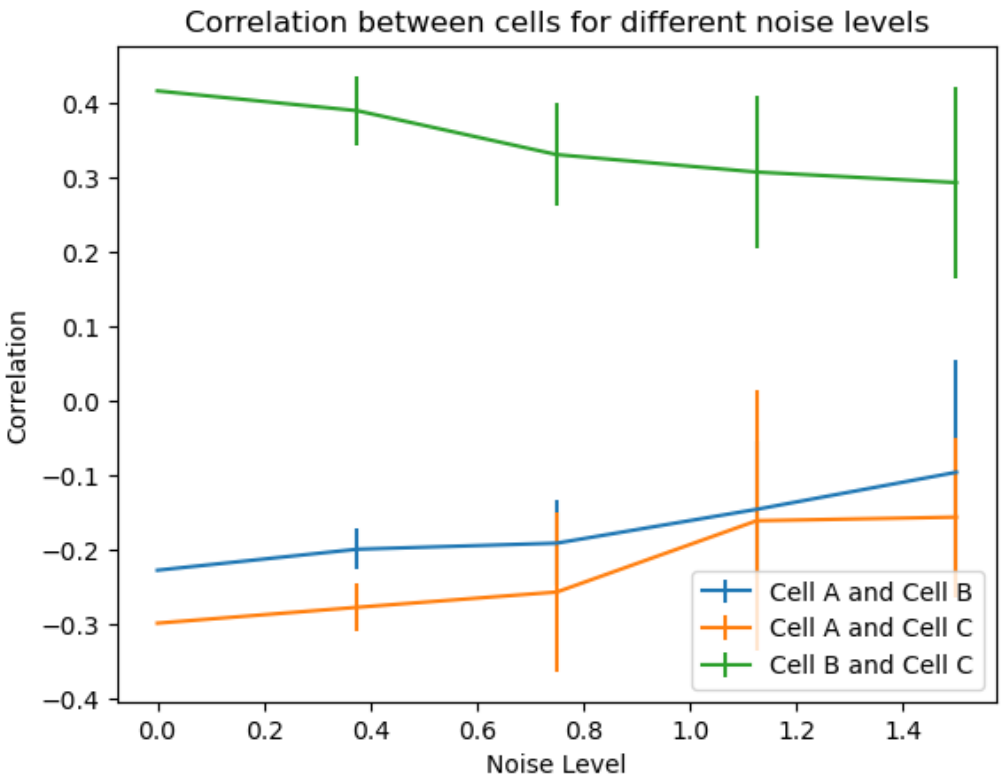


The standard deviation in all these probability density functions is very less compared to the median values and it heavily peaks at its median.

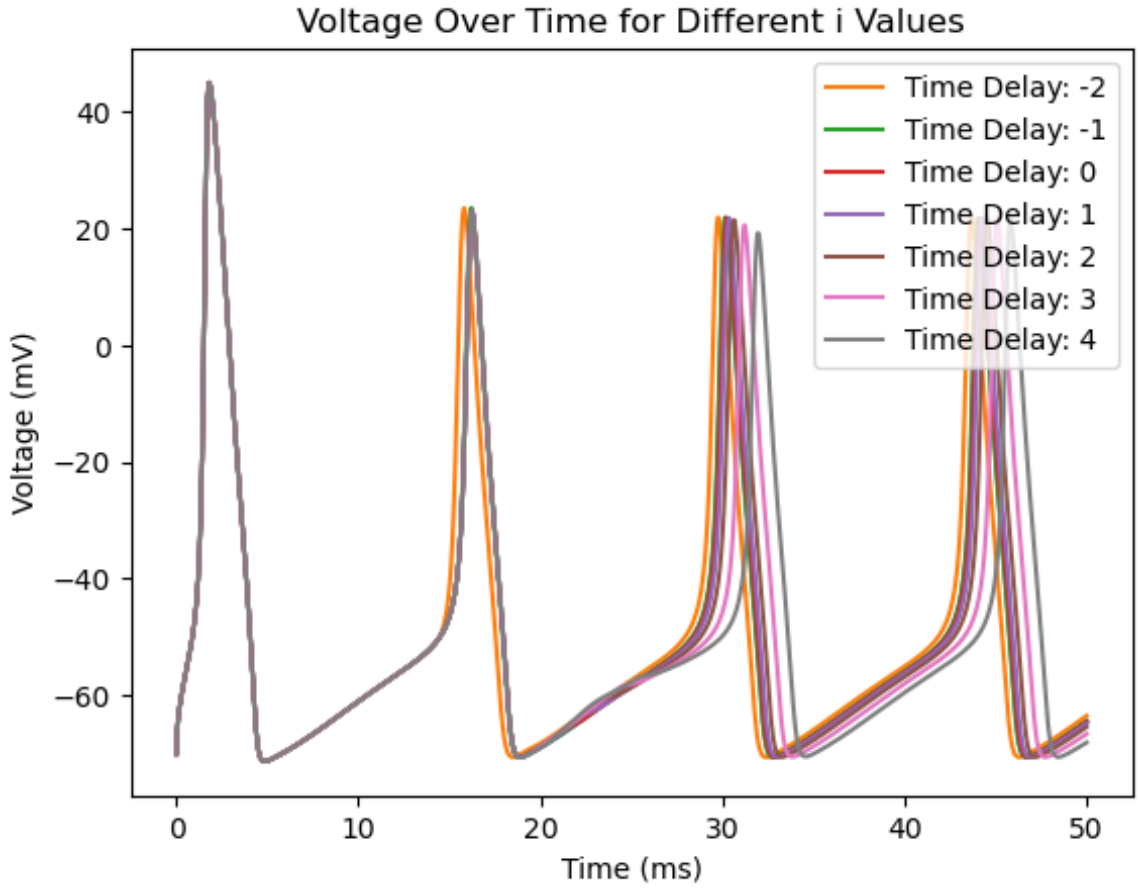


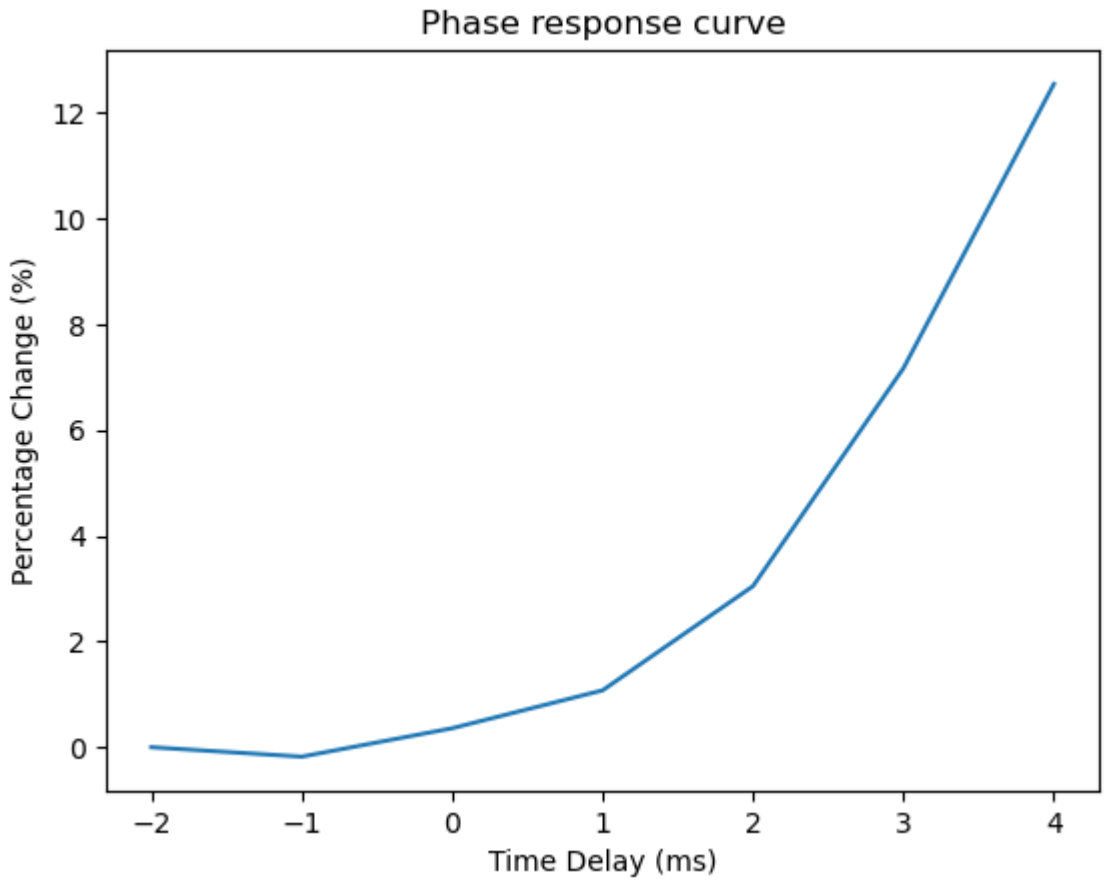


Here we observe decrease in mean phase difference for smaller values of conductance. But for larger values, we observe constant increase across. We observe a fall and then monotonic rise of phase difference as we increase the conductance.



In the cross correlation amongst cells, we observe negative correlation between AB and BC, while a positive correlation between AC neuronal voltages.





We observe a constant increase in percentage change of the phase as we increase the delay of stimulus with respect to the peak at the soma.

Discussion

In this study, we successfully constructed a 3-cell network of Basket neurons which were connected by gap junctions. We were able to show the phase locked behaviour at varying level of noise.

From the results we observed that probability of deviating from the mean of phase difference distribution is very low. Thus, we can say the phase locking in the model is robust to noise even of the S/R ratio of 5. We also observe the phase difference between BC to be lowest and AC to be highest, this could be explained by the fact that gap junctions are placed at the distal ends of both neurons, thus the distance signal has to travel from A to C is very high.

The phase difference wrt conductance curves are similar to as specified in [1]. The U-shaped relationship graph results from the effects of electrical coupling on the electrotonic properties of cells, notably in the outward direction from the soma. This relationship is determined by the cell's intrinsic frequencies and gap junction conductance levels. As the gap junction conductance increases, the network shifts from pure synchrony to pure asynchrony, then back to synchronous mode. The changing gap junction conductance impacts the electrotonic distance and signal attenuation in the outward direction, resulting in the U-shaped connection shown in the graph.

The correlation is high when spikes lined up and cells fire with synchrony, and it is negative when cells fire out of phase leading to anti synchrony. As explained above, we have phase difference between BC

very low, the nearly fire in synchrony. Thus, leading to high correlation. Meanwhile AC and AB has high phase difference, leading to anticorrelation between the voltages of these pair of cells.

Phase response curves, in this paper are obtained in its very crude form, but at its full potential they are used for predicting the network dynamics of basket cell networks that are linked at distant points. To predict synchronous or asynchronous network dynamics, phase response curves are quantified in terms of skewness. When the entire compartmental models were coupled at basal or apical dendrites, the researchers discovered that the predictions from quantified phase response curves held up quite well. Furthermore, the quantification of phase response curves can be utilized to forecast the output of networks that are connected with gap junctions at multiple locations. This shows that phase response curves can help predict the network dynamics of basket cell networks connected by many dendritic gap junctions.

References

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