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Procedia Computer Science 218 (2023) 927–936

Procedia Computer Science

www.elsevier.com/locate/procedia

International Conference on Machine Learning and Data Engineering

Functional Connectivity Analysis of Neuronal Interactions

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Abstract

Advancements in Computational Neuroscience have resulted in the construction of physiologically realistic and computationally efficient neuronal networks. The developments of diverse neuronal models at various implementation scales have caused an affirmative leap in understanding the numerous causes of brain disorders and anomalies, yet the treatment of the brain is regarded as complicated. Observing the responses of a network of realistic neurons constructed using compartmental modelling makes it possible to overcome the shortcomings of descriptive models, such as their inability to highlight synaptic behaviour and their lack of biological realism in spiking behaviour, which in fact play a crucial role in understanding various cognitive mechanisms via the computational unit called neurons. Henceforth, the dynamics of a microscopic level of interacting neurons coupled hierarchically via feedback and feedforward connections are examined in this article. A tiny network of two and four coupled Hodgkin Huxley (HH) neurons integrated into Freeman KIII set topology have been built using the Spike Timing Dependent plasticity(STDP) algorithm. The entire network has been modelled in Neuron modelling environment using Python as the programming interface, and the functional connectivity between the layers has been analysed.

Keywords: Hodgkin and Huxley, STDP, Freeman KIII Topology and functional connectivity.

1. Introduction

The brain is an integral part of the nervous systems of both vertebrates and the majority of invertebrates. The complexity of the human brain is unparalleled as it is made up of 100 billion neurons with approximately 1000 trillion synaptic connections between them[1]. The neurons are responsible for receiving, processing, and transmitting

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1877-0509
10.1016/j.procs.2023.01.073

information across brain regions. These tasks are accomplished through neuronal firing, which is dependent on the dynamics of individual neurons and and the connectivity between each neuron in the neuronal mass.

To understand how the brain functions,we must examine neurons which are the building blocks.Synapses allow signals to be transmitted from one neuron to another by means of electrical stimulation or chemical messengers.To comprehend the communications between neurons, it is essential to discern the role of each neuronal component: the dendrite, which is a tree-like projection, the soma or cell body, and the axon, which regulates neuron firing [2]. The dendrite contributes to increasing the surface area of the cell body, and it receives information from neighbouring neurons via synapses and transmits it to the soma [3]. Synaptic connections between neurons can be dendro-dendritic, axo-axonic, or of other types. The soma, or cell body, is where all the impulses from the dendrites converge and are transmitted to the rest of the cell. The cell's nucleus and soma play no active part in the transmission of brain impulses, although these two components are essential for cell survival.

Axons are lengthy fibres that transport brain signals from the cell body to the terminal ends. The diameter of the object determines the rate of data transmission. Some axons include myelin, a fatty material with insulating properties, and they transmit information more slowly than neurons without myelin. If the intensity of the signal exceeds the threshold limit of the axon hillock, the axon hillock will send an action potential down the axon.

It is possible to represent brain functions using microscopic, mesoscopic, and macroscopic models. Depending on the requirement, each neuron at the microscopic level of modelling can be represented using the highly realistic Hodgkin and Huxley model (HH) or simpler models like the integrate and fire model, the FitzHugh-Nagumo model etc. This level of modelling describes the dynamics of gated channels and ion exchange across the semipermeable membrane and other subtle details. In mesoscopic modelling, population activity is emphasised but biological realism is compromised, as in the case of Freeman Kset [4] [5]. Macroscopic modelling, on the other hand, aims to reveal the global information flow across various brain regions, as opposed to what occurs at smaller scales. The type of model chosen depends on the application and time complexity requirements. In this work, the focus is to build a hierarchical network of HH neurons with multiple compartments and to analyse the functional connectivity between them.

The paper is organised as follows: The Literature Review is presented in Section 2, and the methods used to design the network using the STDP algorithm and the Transfer entropy technique for connectivity analysis are discussed in Section 3. In Section 4, we present several scenarios used to analyse the constructed network, like the effect of propagation delay and synaptic strength on the spiking behaviour of the interactive three sets of 2-coupled neurons and between the 2-coupled and 4-coupled neurons, as well as the analysis of the same in terms of Transfer entropy and correlation. In Section 5, we give our concluding thoughts and recommendations for future research.

2. Literature Survey

Modelling brain functions is considered to be very crucial because it allows us to better understand how it behaves in different situations [6]. Computational brain modelling aids in the identification of brain illnesses such as seizures, strokes, and other conditions that are difficult to anticipate using traditional biological diagnostics. It also aids in the development of more effective treatment options for neurological disorders and diseases, especially in the field of olfaction, which is largely overlooked, and in this article, an attempt has been made to build and understand the dynamics of it.

In the process of olfaction, the airborne odour molecules reach the receptor array which are G-protein coupled receptors. The signals produced are transmitted through the primary olfactory nerve to the olfactory bulb, which is made up of a group of neurons with synaptic connections. Finally, via the lateral olfactory tract, odour information is conveyed to Anterior olfactory nucleus (AON), Prepyriform cortex (PC), and Pyramidal cells for further processing, which results in olfaction [7]. The Freeman K-set is one of many mesoscopic models that tries to mimic the olfactory neural system behaviour using a KIII set that includes KO, KI, and KII sets.

Biological neuronal networks are networks with synaptic connections between axons and dendrites. In contrast, Artificial neural networks are models which are said to be inspired by biological neuronal networks. The simplest mathematical model with discrete state variables, coordinates, and time was discovered to be associated with the cellular automaton [8]. Several models have been created since 1907, when Lapicque created the Integrate-and-fire model, which is still in use. Some of the more prominent among them are the previously mentioned integrate-and-fire

neuron, the HH neuron, and the Izhikevich neuron. All of them are biological models which try to mimic the working of the human neural system when connected en masse.

One of the most successful differential equation based model is the HH model proposed by Hodgkin and Huxley in 1952 [9] [10]. It explained the ionic mechanisms involved in action potential propagation and initiation. HH neuronal networks have been utilised successfully to represent brain activity, and it has been discovered that they are effective in showcasing neuronal synchronisation, which are associated with cognitive tasks.

It has been shown that the experiential learning in any of the sensory systems occur through the strengthening of the links between nerve cells, and several adaptive algorithms have been employed to simulate this. Learning is mainly of two types: supervised, where the network gets labelled input and is commonly used to classify said labels, and unsupervised learning, where the input is unlabelled and is used to generate similar signals. Hebbian learning is an unsupervised learning method.

According to Hebbian theory, when an axon of cell A is close enough to excite a cell B and regularly or repeatedly participates in firing it, one or both cells undergo a growth process or metabolic change, enhancing A's efficiency as one of the cells firing B [11]. Hebb hypothesised that if pre-synaptic neuron input contributes to post-synaptic neuron firing, the synapse from pre-synaptic to post-synaptic neuron should be optimally reinforced, increasing the likelihood that they will fire as a pair. Long-term potentiation is achieved when pre-synaptic and post-synaptic neurons spike at the same time [12].

STDP (Spike-timing Dependent Plasticity) is an unsupervised learning process based on temporal correlations between pre- and post-synaptic spike timings that alters synaptic weights in real-time. This method accounts for the spiking behaviour of pre and post neurons in two adjacent layers in the past [13].

According to the STDP process, if the pre-synaptic spike occurs before the post-synaptic spike, the connection is strengthened, and if the pre-synaptic spike occurs immediately after the post-synaptic spike, the connection is weakened. Spike-timing-dependent plasticity gets its name from the fact that the weakening or strengthening of synapses is directly proportional to the timing of pre- and post-synaptic spikes. Because Hebbian learning lacks this feature, the STDP protocol outperforms Hebbian learning by making the weights weaker when presynaptic events occurs after post synaptic spikes. According to studies, synaptic strength degradation makes it easier for the STDP protocol to choose the shortest pathway over alternate longer paths [14]. In comparison to other learning algorithms, this method requires less rounds to reach the desired weight [14]. Henceforth, in this study we have used Hebbian learning with STDP implemented in the NEURON simulation environment.

Once the connectivity is established between the nerve cells, the next step is to measure the effect of synaptic behaviour on the network dynamics. One of the measures used to assess the temporal coincidence of geographically distant neurological events and which aids in understanding the neuronal interaction dynamics is Functional Connectivity (FC) analysis [15]. If there is a statistical link between the recorded activity values, two distinct areas are said to have functional connectivity [16]. With this method of connectivity, regions are said to be connected or part of the same network if their functional performance has a regular correlation.Given that functional connectivity is based on a few priori assumptions, it backs up the intuitive notion that two events should be related if they happen at the same time. This approach also gives a a straightforward, observable assessment of functional linkages [16].

Another way of analysing the functional connectivity between different regions of brain is by estimating the Transfer Entropy (TE). It plays an important role in understanding how the connectivity varies during different cognitive tasks as well as during various pathological states [17]. TE can be used as an indicator of connectivity in the microscopic and mesoscopic levels which gives an idea about the transfer of information from one region of interest to another portraying the information flow in the network [17].

Various methods of measuring connectedness are cited in the literature [18] [19] [20] [21] [22]. Dynamic Causal Modelling (DCM) was determined to be the most preferred method for evaluating effective connection. DCM is found to depend extensively on apriori knowledge of the system's input and connectivity of the network [23]. To circumvent this constraint, Bayesian selection methods were frequently used. Though most FC approaches could provide useful information on casualties, but TE is found to be the most promising because it does not require prior information on input and connectivity.

One of the challenges involved while building a network of neurons with multicompartment models is assessment of the computational cost involved. Sergio Valadez-Godinez's paper offered three key criteria for determining the cost effectiveness of simulations, based on the idea of multi-objective optimization [24]. The cost effectiveness was

assessed using the Computational Cost Factor (CCF) based on CPU execution time, the Spike Coincidence Factor, that used the number of coincident spikes in a reference and testing simulation, and the Voltage Coincidence Factor, which assessed if a testing simulation's voltage is better than in a benchmark [24]. In our study, it is seen that the CCF increases as the number of cells under consideration increases as the implementation time for STDP is quite high.

3. Methodology

The entire network of neurons has been designed from scratch by using NEURON's Python bindings [25]. Libraries like Matplotlib and Bokeh were used to plot various graphs, Pandas was used for data preprocessing, and subsequent synchrony analysis, NumPy was used for various mathematical operations like finding the mean-field potential, and IDTxl (Information Dynamics Toolkit) [26] was used for calculations related to Transfer Entropy.

3.1. Modelling of neurons using multiple compartments

In order to decrease simulation time while maintaining complexity, compartmental modelling is used to define each neuron in the network. In the case of the 2-coupled network, each dendrite, axon, and soma are modelled as three compartments where voltage is made to vary only at the ends of the cylindrical compartment. The two fundamental abstractions used in each node of the network are called MCell and GCell. Because these two differ only in certain key areas, it should be sufficient to talk about one of them and then highlight the differences.

MCell is a Python class consisting of three NEURON sections and four exponential synapses. NEURON sections are unbranched, continuous cables that can be connected to form a single neuron. Sections can be connected to form any tree-like structure, but a structure with one dendrite, one soma, and one axon in that order is much simpler and faster to simulate. Both the axon and the dendrite have two exponential synapses defined using h.ExpSyn, that differ in their decay time constants and reversal potentials, and can therefore be considered either excitatory or inhibitory depending on the two. GCell is similarly defined, with the main difference being the length and diameter of each segment. The MCell's soma is defined as a cylinder of length and diameter of 18.8 microns. The dendrite has a length of 701.9 microns and a diameter of 3.18 microns. Similarly, the axon has a length of 152 microns and a diameter of 3.18 microns. The GCell's soma is defined to have a length and diameter of 30 microns, the dendrite has length of 100 microns and diameter of 3.18 microns, axon has length of 100 microns and a diameter of 2.18 microns. The MCell and GCell correspond to the KOe and KOi Freeman set, respectively. These neurons themselves need an ion channel definition in order to conduct voltage as expected, and HH channels are used for the same.

HH channels are simulated by using the insert keyword, which is an inbuilt function that makes the NEURON section use the default hh.mod file, which is an HH implementation included in NEURON [25]. It has a sodium channel and a potassium channel, which determines the voltage gradients in the section itself. The proposed model of two and four coupled neurons are as shown in Figure 1.

At this level of abstraction, the KI set, which is two KOe sets coupled with each other, corresponds to two MCells connected to each other's excitatory synapse with the help of NEURON's NetCon, which is a library function that provides network-level connections and handles all events of spiking to and from either of the cells [4]. NetCon is a function that takes a voltage reference (or None) as a source, and sends all spiking events to a target, which is usually another NEURON section [25]. There is also a required positional argument called sec, which corresponds to the source of the NetCon. This function records events created by the source and transfers weight and time information to the target.

The KII set can also be incorporated in the same class as two MCells and two GCells coupled with each other by using NetCons, incorporating the inhibitory and excitatory nature of the connections by connecting the appropriate exponential synapses. The final network, the KIII set, requires multiple such KI and KII sets to be coupled to each other in a specific manner, which is made simpler by the fact that each such KI and KII set can be defined as a single Python class that is made to interact with other classes using NetCons. As such, the network relies heavily on NetCons to carry events. NEURON's inbuilt events and simulation capabilities are key to simulate various voltages along the entire network.

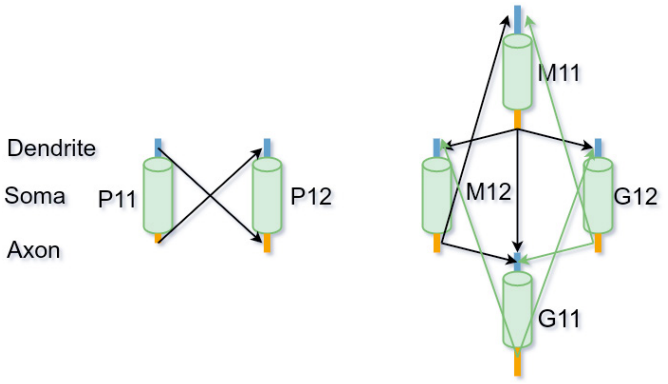


Figure 1. Proposed Compartmental model of two and four-coupled neurons

3.2. Establishing the connection between the cells using STDP

Adaptive learning algorithms play an important role in developing the synaptic connections between the neurons. In our network, the network is made to learn, or in specific terms, made to change the weights of its various networks using Hebbian learning in general and the STDP algorithm in particular. Hebbian learning suggests a potential causal link between the pre-synaptic neuron and post-synaptic neuron, which would mean that the pre-synaptic neuron would fire before the post-synaptic neuron. STDP makes these connections' weights change as a function of the relative timing of pre- and postsynaptic action potentials, which is called the STDP function or learning window and it depends on the synapse used. In STDP, a function F(Δt) governs the amount of synaptic modification derived from a single pair of pre- and postsynaptic spikes with the time difference given by $\Delta t = t_{pre} - t_{post}$.

The weight change, defined as Δw_j, is defined as in equation 1.

$$\Delta w_j = \sum_{m=1}^{N} \sum_{n=1}^{N} F(t_i^n - t_j^m) \tag{1}$$

The learning window F(Δt) is given in equation 2.

$$F(\Delta t) = \begin{cases} A_+ exp(\dfrac{-\Delta t}{\tau_+}), & \text{for } \Delta t < 0 \\ -A_- exp(\dfrac{\Delta t}{\tau_-}), & \text{for } \Delta t \geq 0 \end{cases} \tag{2}$$

Here Δt is the difference in the spike times of pre and post-synaptic neurons i.e. $t_{pre} - t_{post}$ [27], A_+ and A_- are positive and negative weight coefficients which determine the maximum change in weight value, and their values are chosen as 0.01 and 0.011 respectively. τ_+ and τ_- are time constants whose values are both taken as 30ms.

The mean field potential of the network is calculated at certain instances, because it is a better metric than individual voltages.

3.3. Transfer Entropy

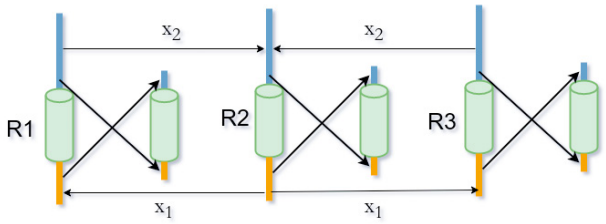
The transfer entropy, which is one of the connectivity measures is defined as the difference between the conditional entropies, as shown in equation 3, and IDTxl in Python is used to calculate transfer entropy in this article [26].

$$TE(X \rightarrow Y|Z) = H(Y^F|Y^P, Z^P) - H(Y^F|X^P, Y^P, Z^P) \tag{3}$$

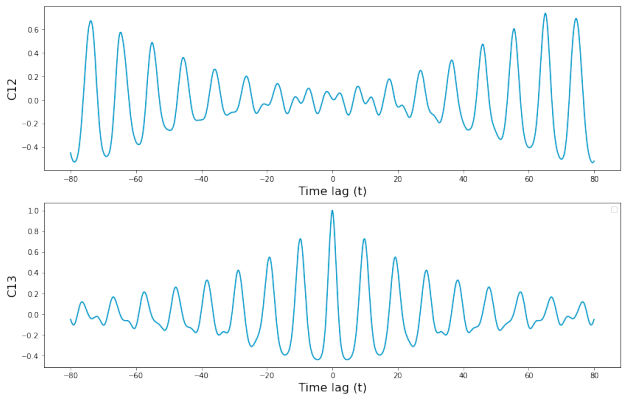
In comparison to the previous time-series X^P,Y^P, and Z^P, Y^F is a time-advanced version of Y at lag Δt. Within this framework we say that X does not G-cause Y relative to side information Z if and only if $H(Y^F|Y^P, Z^P) = H(Y^F|X^P, Y^P, Z^P)$, i.e., when $TE(X \rightarrow Y, Z^P) = 0$ [28].

4. Results and Analysis

It has been found that the information encoding in the brain happens through spike coincidence of neurons and that time delays play an important role in establishing synchrony. In this study, an attempt has been made to mimic the scenario of having three hemispheres of brain interacting with each other by looking into the synchronisation of three 2-coupled MCells connected end to end, as shown in figure 2(a) with x_1 and x_2 being the lateral connection weights from R3 to R2 and from R1 to R2 respectively [29]. The currents i_1 and i_2 represent the stimuli given to the inner and outer region respectively. A propagation delay of 65ms is also applied.



(a)



(b)

Figure 2. (a) The network used for correlation analysis. (b) Correlation plots between three 2-coupled neuronal sets. Parameters used are lateral delay: 65 ms, x_1: 4, x_2: 2, i_1: 0.8 nA, $i2$: 2 nA

The analysis has been done by taking the correlation between the mean field potentials generated by different regions for all possible time lags [29]. By computing the correlation, the similarity between signals can be found. From the figure 2(b), it can be seen that the correlation between R1 and R2, i.e., C12, is highest around 65-80 ms,

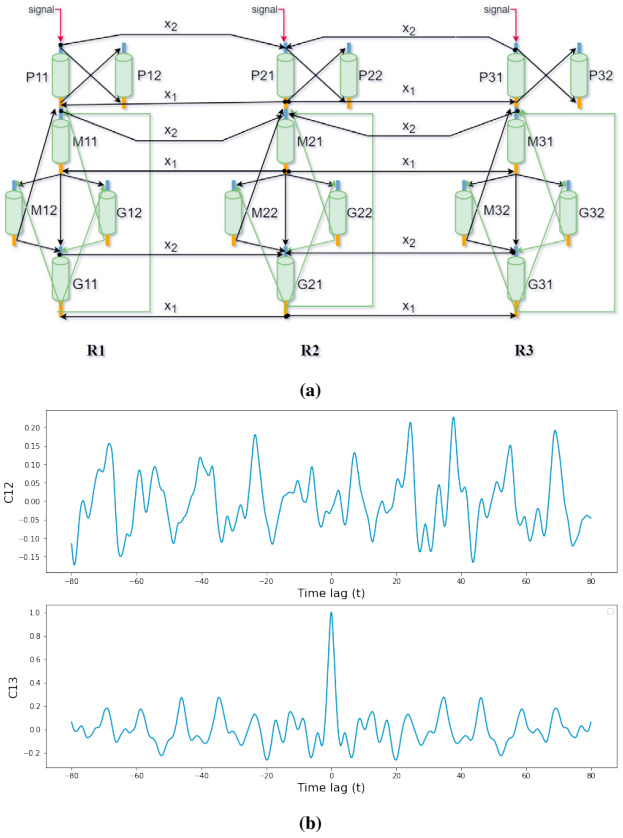


Figure 3. (a) Another network used for correlation analysis. (b) Correlation plots between the 2-coupled and 4-coupled parts of this network. Parameters used are lateral delay: 65 ms, x_1: 6, x_2: 2, i_1: 0.8 nA, $i2$: 2 nA

which is almost the propagation delay provided between the two regions, whereas C13, between R1 and R3, is highest at 0 ms, showing that it is highly correlated. The same result can be well appreciated if we look into the phase space trajectories as shown in figure 4, in which V1 and V3 have a linear relationship as in figure 4(a), whereas V2 and V1 show strange attractor behaviour with randomness as in figure 4(b).

A different scenario on the connectivity aspect has been discussed, wherein the two coupled and four coupled layer interactions are shown in the figure 3(a). As in the previous case, both the layers have been provided with a delay of 65 ms and the effect of time delay can be seen in the C13 plotted in figure 3(b).

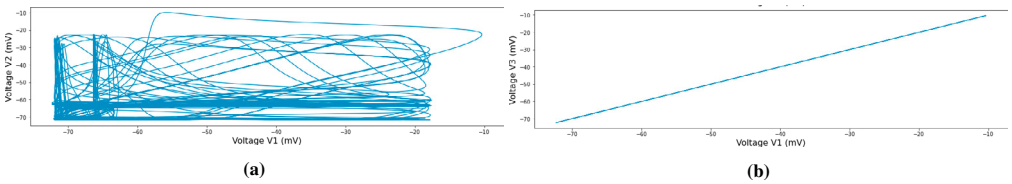


Figure 4. (a) Phase plot between V1 and V2. Since they are not in synchrony the plot looks chaotic. (b) Phase plot between V1 and V3.

The effect of coupling strength on the oscillatory behaviour of the network has been demonstrated by varying the strength of connections between 2-coupled neurons in figure 2(a). Because of the high disparity in input currents, we could observe a nearly 1:2 voltage spike oscillation in figure 5(a) with weak coupling, where each 2-coupled region was coupled with a weight 0.01. It could also oscillate as shown in figure 5(b) with nearly 1:1 phase locking when

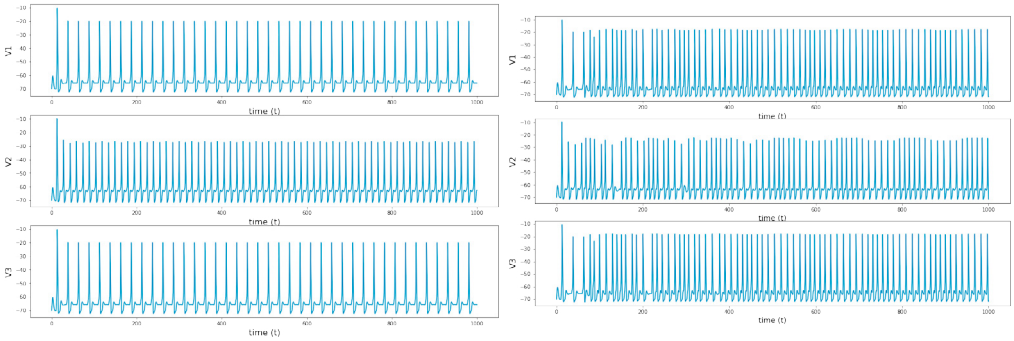


Figure 5. (a) Weak coupling: x_1: 4, x_2: 2, i_1: 2 nA, i_2: 4 nA. (b) Strong Coupling: x_1: 4, x_2: 2, i_1: 2 nA, i_2: 4 nA.

coupled strongly with each 2-coupled region coupled using a weight 0.06. This reveals the sensitivity of the network to minute changes in connection weights.

The necessity and influence of temporal delays in a network to maintain synchronisation across regions can now be fully understood, however unmanageable synchronised oscillations may result in pathological states like epilepsy [29].

The entire network is graphed using NEURON and Matplotlib as shown in figure 6. Each MCell is shown with a long teal line, and each GCell is shown with a short teal line. This is to show that they are of different dimensions, and operate differently. Connections between cells are also graphed.

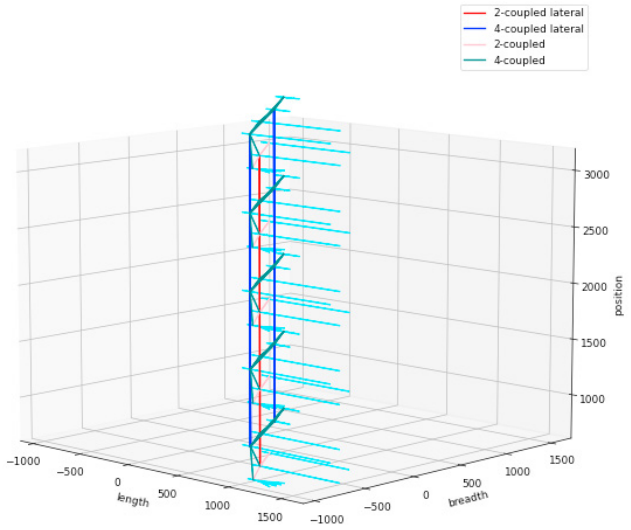


Figure 6. The simulated network, graphed with NEURON and Matplotlib

Transfer Entropy is also an important measure of Functional Connectivity. Transfer Entropy was calculated using a library called IDTxl, which uses a Multivariate Transfer Entropy (mTE) algorithm [26] [30]. The benefit of using Multivariate Transfer Entropy is that multiple sources are considered for information transfer to the target, as opposed to a single source in bivariate Transfer Entropy. The results of using their algorithm on our network of 15 sets of 2- and 4- coupled neurons while taking 2-coupled neurons as source and 4-coupled neurons as the target is as follows:

Compared to the respective values on Table 1(b), Table 1(a) has higher values. This shows that 2-coupled to 4-coupled connections bring more transfer of information, since higher values of mTE correspond to a higher transfer of information.

Table 1: (a) Omnibus mTE while taking 4-coupled cells as target and 2-coupled cells as source. (b) Omnibus mTE while taking 2-coupled cells as both source and target.

Target Set (4-coupled)	Omnibus mTE	Target Set (2-coupled)	Omnibus mTE
1	0.1161	1	0.0358
2	0.1159	2	0.0420
3	0.1082	3	0.0444
4	0.1101	4	0.0444
5	0.1075	5	0.0441
6	0.1140	6	0.0442
7	0.1103	7	0.0444
8	0.1173	8	0.0443
9	0.1103	9	0.0443
10	0.1141	10	0.0443
11	0.1074	11	0.0443
12	0.1102	12	0.0445
13	0.1082	13	0.0443
14	0.1161	14	0.0419
15	0.1162	15	0.0358

For the time complexity analysis given in Table 2, CPU execution time was chosen as the metric. Time complexity is seen as increasing linearly as the network increases in number of sets (without learning). In this study, scaling up of the network remained challenging due to the computational complexity of STDP algorithm discussed and would need extended GPU support .

Table 2: Time complexity analysis

Total Sets		Time Taken (s)
5 sets	Without learning	17.63
	With learning	64.94
30 sets	Without learning	39.92
	With learning	163.14
250 sets	Without learning	13.07
	With learning	1122.58
500 sets	Without learning	32.35
	With learning	2824.35

5. Conclusion

The information encoding in the brain can only be comprehended if one understands how nerve cells connect and disconnect from each other and how this facilitates the transmission of information. The modelling of the interaction of a tiny set of coupled Hodgkin-Huxley neurons connected hierarchically has been detailed in the paper which would give an insight into the connectivity mechanism as well as the transfer of information that is incomprehensible using mesoscopic and macroscopic models. The application of multivariate transfer entropy has also been demonstrated in understanding the amount of information transfer as well as the direction of information transfer among the neuronal populations in the network. The relevance of propagation delay in maintaining synchronous spiking in a network of neurons has also been established using correlation plots between mean-field potentials of different levels of the network. This research could pave the way for a better understanding and differentiating the information flow in various pathological states like epilepsy as well as in other cognitive states when scaled. The work could also be useful in understanding brain signals generated by various odourant stimuli.

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