EXPLORING THE MYSTERIES OF THE HUMAN BRAIN WITH PHYSICS

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The human brain is arguably the most important organ in the body. It regulates biological processes, and allows us to think and interpret the world around us. In spite of the importance of this remarkable organ, little is understood about how it functions due to its complexity. One of the principal questions regarding the brain is the relationship between its neural network structures and their function. With advances in technology, the spiking activity of individual neurons in networks can be recorded [1], creating data sets, which may contain information that can help improve the current understanding of this relationship. Many methods have been developed [1-4] to extract the causal connections and network architectures of neural networks from these data.

Each method, however, has limitations that reduce their practical utility, leaving the need for improved methods. Some of the common limitations include: computationally expensive calculations, which make an analysis unfeasible for large data sets; prior knowledge of the number of largely independent clusters in a network, which isn't always available; and difficulties with detecting and including the presence of inhibitory neural connections [1].

The ability to determine when a neural impulse causes the activity of other nerve cells, and through which path, is imperative to developing new diagnostic and treatment techniques for many brain disorders such as epilepsy. It is also a cornerstone in understanding complex neural functions such as the storage and recall of memory.

To accurately determine the causal connections between neurons, both inhibitory and excitatory connections must be identified and included; both are not only important in the function of the system but also the structure. Here, the Functional Clustering Algorithm (FCA) [5] was selected for its potential to resolve many of the limitations present in other methods and successfully detect both inhibitory and excitatory connections. The benefit of the FCA is that it was primarily designed for neural spike train data, collected as a neuron fires over time, and it requires no initial knowledge of the number of groups in a network [5]. Also, activity of each neuron need not be similar for analysis, one neuron could only have several spikes where as another could have hundreds. It was postulated that extreme dissimilarity could hint at the presence of inhibitory neurons.

SUMMARY

We develop an algorithm to determine connections between neurons to help better understand the relationship between structures and functions of neural networks in the brain.

The ability of the FCA to identify and group purely excitatory connections between neurons was evaluated with a method similar to the one described in [1]. Specifically, small simulated neural data sets with known architecture and causal connections were created such that the results of the algorithm could be directly compared with them, to determine its success. The ability of the FCA to detect inhibitory neural connections was then evaluated by studying an inhibitory connection of varying strength between two neurons. Finally, the FCA was tested on networks consisting of both excitatory and inhibitory connections to evaluate if the presence of inhibitory connections hindered the detection of excitatory connections, as documented for other methods in [1].

BACKGROUND

Basic Neural Properties

To create appropriate and biologically plausible simulated data, the key behaviours of neurons must be understood. Neurons are complicated biological systems, which can exhibit different behaviours depending on their environment and physiological makeup [6]. However, this level of complexity is not necessary to intuitively understand the basic behaviours of a neuron. A neuron can be viewed as a system that has both a rest state and a spiking state [7], with the ability to transition between the two depending on the applied stimuli. General properties of the neuron include the membrane potential, all-or-nothing threshold, refractory period and the ability to create either excitatory or inhibitory postsynaptic potentials in connected neurons. For more specific details on the biological structure and functions of neurons, in-depth discussions can be found in [6,8].

The membrane potential can be considered as a description of the current state of the neuron. For most

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neurons, the resting potential is approximately -65 mV [9]. At this potential the neuron is inactive and waiting for stimulation. If the connection (synapse) between two neurons is excitatory, then the presynaptic neuron increases the membrane potential of the postsynaptic neuron with an excitatory postsynaptic potential each time it fires. The postsynaptic neuron is now brought closer to its threshold. If this neuron is stimulated with excitatory postsynaptic potentials multiple times in quick succession, the sum of the excitations may raise the membrane potential passed its threshold (typically between -40 mV and -55 mV [10]). Once the membrane potential has been increased by any magnitude over its threshold value, the neuron fires a characteristic action potential spike that can be measured and related to signal transmission. This behaviour is known as the all-or-nothing response of the neuron.

Following an action potential spike, the neuron enters a refractory period during which the membrane potential is brought below its resting potential and the neuron is typically unable to immediately fire again. This ensures unidirectional travel of the signal from neuron to neuron [8]. With a similar mechanism, an inhibitory neuron creates an inhibitory postsynaptic potential that lowers the membrane potential of the connected postsynaptic neurons. This brings their state farther away from the threshold; additional stimulus of the postsynaptic neurons is now required for their membrane potentials to surpass the threshold and fire a potential spike.

Simulated Neuron Model

To encompass the basic neuronal behaviours discussed above and produce biologically relevant data for testing, the Izhikevich simple neuron model [1,9,10] was selected. It is a reduction of Hodgkin-Huxley-type neuronal models to a two-variable system [10]. This model is able to reproduce the spiking patterns and behaviours of many types of neurons [10], making it extremely versatile. The versatility of the model gives the capability to test different types of neurons in networks without having to use a different model for each. In addition to the versatility of the Izhikevich neuron model, one of its major benefits is that it is not computationally expensive, unlike most Hodgkin-Huxley-type models. A basic first order Euler's method of integration can be utilized to numerically solve the system. Stochastic stimuli can also be added to the model to simulate the intrinsic noise found in biological neurons. The intrinsic noise is necessary to increase the biological plausibility of the model because living neurons can often spontaneously fire without stimulation from other neurons [1,8,10]. Figure 1 shows an example of a small scale neural network that was created for testing, with both excitatory neurons (solid) and inhibitory neurons (dashed) present.

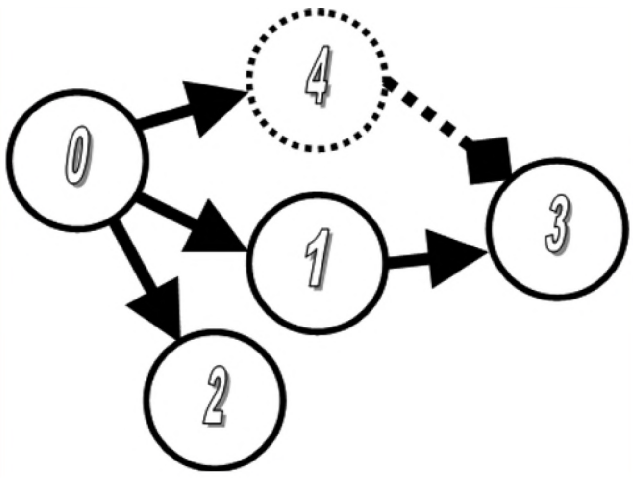

Fig. 1 Example of a small scale neural network that was created for testing, with both excitatory neurons (solid) and inhibitory neurons (dashed) present. The ratio of excitatory neurons to inhibitory neurons of 4:1 matches that found in a typical mammalian cortex [10] to increase the biologically plausibility of the simulations. The excitatory connections between neurons were successfully detected, even in the presence of the inhibitory neuron.

METHODS

The Functional Clustering Algorithm (FCA)

The FCA was first implemented according to the specifications presented in [5]. It was designed to analyze neural spike data; however, it is generic enough to be applied to any type of discrete multivariate event data [5], which makes it of interest for other applications as well [11]. First, the algorithm calculates the similarity in pairs between the activities of each neuron with all other neurons in the network according to a similarity metric. These values are used to form a matrix of similarity values. Next, spike train data from the pair of neurons with the largest similarity are removed from the rest of these data and joined (clustered) into a new data set. This allows for continued comparison between them and the other remaining (unclustered) neurons. This process is repeated until there are no significant matches left, or all the neurons have been joined into a single spike train. Figure 2 illustrates the joining process for sample data from a network of three neurons.

To establish the significance of the similarity between two neurons, the distance in time from each spike in one train to the closest in the other, and vice versa, is summed into a distance value; the smaller this distance value is the more likely the connection is significant. The significance of this value is then determined by comparing it to a large distribution of distance values generated from random surrogate data pairs created from the original data.

RESULTS, CONCLUSION AND OUTLOOKS

Through working with the FCA in various testing scenarios a new algorithm was also developed, the First Pass Clustering Algorithm (FPCA), which matched the functionality of the FCA at a reduced computational expense. This new algorithm also has the potential to provide additional network connectivity information that the FCA cannot provide.

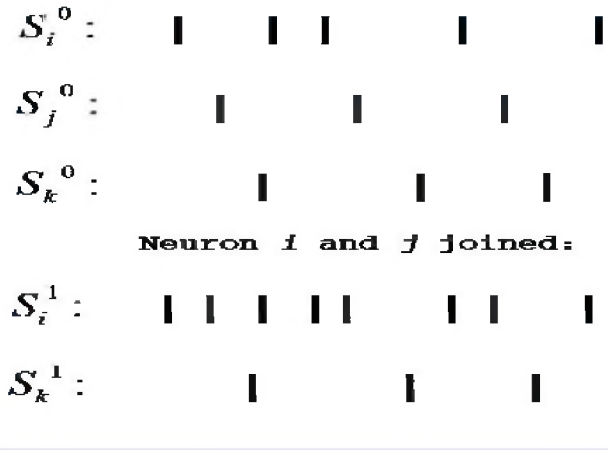

Fig. 2 A graphical representation of three data trains from neurons *i*, *j*, and, *k* before the first iteration of the FCA. Each vertical line represents a spike in the membrane potential of that neuron. In the first iteration the algorithm has determined that neuron-*i* and neuron-*j* are connected, so their spike trains are joined. The process is repeated until there are no more significant matches, or all of the neurons have been joined.

The FCA and its derivative, the FPCA, were found to be insensitive to the presence of inhibitory connections between neurons. The algorithms with the current similarity metric provide no way of distinguishing an inhibitory connection between neurons and no connection at all. In their present state the FCA and the FPCA are, hence, unable to resolve the limitation of other algorithms in detecting inhibitory connections.

In terms of excitatory connections, the FCA and FPCA were successful in identifying causally connected clusters of neurons in all of the networks tested. In networks consisting of both excitatory and inhibitory connections, both algorithms were also able to successfully identify the excitatory causally connected clusters. The presence of the inhibitory connections in the small scale tests did not interfere with the algorithms' ability to group the excitatory connections, which is a limitation present in other methods [1].

The FPCA was also able to determine the specific excitatory connections between neurons within a cluster in a large number of test networks. There were a few networks, however, where the FPCA was unable to successfully determine the specific excitatory network connections within a cluster of neurons in that network, while still successfully identifying the cluster itself. There is potential that, with further refinement, the FPCA will be able to overcome this and reliably detect the specific excitatory network connectivity between neurons in all networks. If this is possible, the FPCA will provide a new tool to help study the relationships between neural network structures and their functions in the brain. This will ultimately aid in working towards a better understanding of one of the fundamental questions regarding the human brain; what is the relationship between its neural network structures and their function?

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