VOL. 12, NO. 2, JANUARY 2017 ISSN 1819-6608
ARPN Journal of Engineering and Applied Sciences

www.arpnjournals.com

INFERRING AN OPTIMAL ALGORITHM FOR DETECTING BRAIN NEURON NETWORK CONNECTIVITY IN RESPONSE TO EXTERNAL STIMULI

Rahul Mani[1] and Vinod Dubey[2]
[1]McLean High School, McLean, Virginia, United States of America
[2]Department of Computer Science, George Mason University, Fairfax, Virginia, United States of America

ABSTRACT

The focus of neuroscience research over the years has been to understand how neurons respond to a variety of stimuli and communicate with each other and to construct models that attempt to predict responses to similar stimuli. Findings have been used for establishing better treatments for human diseases like, epilepsy, stroke and Alzheimer's. This in turn has also been helpful in designing appropriate prosthetic devices. The recent advances in multiple-electrode recording and computational capacity have made it possible to study the simultaneous spiking activity of multiple neurons. A systematic analysis and understanding of simultaneous spike recording of multiple neurons using computational algorithms offers new promise for investigating some of the fundamental questions concerning how the brain works. This research contributes to this growing literature through using new datasets and computational techniques. In this paper, we develop a computational algorithm to estimate the neural connections of a simulated neuronal network data of 10 cultured neurons obtained from the MLBio+ Lab at George Mason University. The inferred brain network derived from the algorithm was then compared using statistical techniques such as RMSE and MAE with observed truth data which mimic actual functioning of the brain. The results suggest that average error between truth and simulated network decreases as the number of time steps increases. This means, longer it takes between the stimuli and firing of neuronal responses, the closer we get to the optimal network. This type of research is very relevant as it can help neuroscientists design complex experiments and as a consequence, answer some of the key on the functioning of the brain.

Keywords: neural networks, bioinformatics, computational algorithm, spike train analysis.

INTRODUCTION

The focus of neuroscience research over the years has been to understand how neurons respond to a variety of stimuli and communicate with each other and to construct models that attempt to predict responses to similar stimuli. A central question that neuroscientists have been grappling with over the years relates to how the neurons send messages to each other: is it the rate of spiking or the timing of firing that defines the messages being carried? Another question of interest is whether we can infer anything about the input stimuli by observing and analyzing the network output.

To understand all this better, the best approach is to potentially administer a stimulus and simultaneously record neural activity from a brain region believed to respond to that stimulus. The recent advances in multiple-electrode recording have made it possible to study the simultaneous spiking activity of many neurons (in fact more than 20). This allows us to understand how neurons act in concert to define the function of a given brain region. Brown and others (2004) suggest that “simultaneous recording of multiple neurons offers new promise for investigating some of the fundamental questions concerning how the brain works.” The research question can thus be addressed by characterizing the relation between the stimulus and the neural responses and/or by studying the relation among the spiking activity of the neurons within the group.

There has also been much interest in the neuroscience community to understand better the structure and functioning of these “neural networks.” Of particular interest is the connectivity structure of these networks. It has been observed in general that the connectivity changes as a function of network development or in response to an applied stimuli. Hamilton et al. (2013) suggest that, “tracking these changes is essential for understanding the underlying dynamical evolution of the network, and serves as a valuable tool for experimental interventions.” Findings from such research could potentially be used for establishing better treatments for diseases that are likely to lead to brain degeneration, for example, epilepsy, stroke and Alzheimer's (Kosik, 2013; Duch, 2007). This in turn can also help to design appropriate prosthetic devices.

HYPOTHESIS

In this paper, we develop a computational algorithm to estimate the neural connections using the relation between the stimulus and the ensemble neural responses in the brain. Specifically, an algorithm is developed to correlate the spiking activity of the brain neurons across time in a network of cultured neurons recently sampled by a microelectrode array. The inferred brain network derived from the spike signals are then compared using statistical techniques with observed truth data that mimics actual functioning of the brain network. Optimization of the inference procedure like this can then lead to reconstruction of the optimal structure that best reproduces the connections within the brain. The two main objectives are:

- To detect the presence of spike coincidences in simultaneously recorded multiple spike trains across time; (or, the transmission time among different neurons in response to the stimulus)

- To identify the connectivity structure from the simulated data that best corresponds to the observed data.

The hypothesis is that the mean absolute square error between the simulated brain connectivity matrix and the observed matrix is minimized as the number of time steps between stimulus administration and response time of the brain neurons increases.

Independent Variable: Number of time steps between stimulus administration and response time of the brain neurons

Dependent Variable: Correlation between predicted matrix and truth connectivity matrix (computed through Mean Absolute Error as well as Root Mean Square Error).

REVIEW OF RELATED LITERATURE

Simultaneous recording of multiple spike trains from several neurons offers a window into how neurons work together to generate specific brain functions. There is a growing literature that has delved on this issue. An attempt is made here to contribute to this literature by using most recent data and computational techniques.

A most comprehensive review of the literature can be found in Brown et al. (2004). They provide a nice overview of statistical methods for the analysis of multiple neural spike-train data and discuss future challenges for methodology research in that field. The authors argue that, “without substantial methodology research in the future, our ability to understand these brain functions will be significantly hampered.” They further suggest that, “computational algorithms to detect precise patterns of spike timing are important tools that offer a lot of promise for measuring associations among neural spike trains.” Brown et al. (2004) also suggest that, “any extension of this research will have immediate, significant implications for improving the design and implementation of neural prosthetic devices and brain–computer interfaces.”

A most recent research similar to ours can be found in Hamilton et al. (2013). They also develop a statistical algorithm to determine and track effective connections between ensembles of cultured spinal cord neurons measured with multi-electrode arrays. In particular, they study the connectivity structure of a neuronal networks in order to understand how the connectivity changes in response to an applied stimuli. The authors show in simulation and with measured data from neural cultures that such a method can work successfully. This research is quite useful as it too uses data from cultured neurons from multi-electrodes.

In a similar research, Brooks (2007) attempt to understand better the structure of the network from time series of neural outputs and also examine how nature of the connections between the neurons relate to the network’s structural complexity. The two main objectives of the paper in the words of the author are to: “(i) to analyze the time series output of a simulated neural network and make inferences about the underlying synaptic structure that produced it, and (ii) to show a correspondence between a complexity measure on the time series output and a complexity measure on the network’s structure.” The paper also contains a nice overview of the literature on neural network connectivity analysis.

Analysis of huge time series data from a neuronal network can be quite challenging at times especially if it involves more than two neurons. Kass et al. (2005) provide a nice overview of various statistical tools that are available. In their review article, they describe the various well established statistical principles, statistical tools and algorithms that can be effectively utilized to estimate the firing rate and time-varying correlation which in turn can provide improvements in experimental sensitivity equivalent to large increases in the number of neurons examined.

Analyzing neural networks involved dealing with vast amounts of data and manipulating those using modern computational techniques. Li et al. (2015) present examples on state-of-the-art studies and techniques in algorithms, analytics, and applications of Big Data.

Finally, there is evolving literature on how this type of research can be utilized for dealing with real-world situations. According to Kosik (2013), “several lines of evidence suggest that networks of neurons in the brain operate as local processing units, with few long-range connections between them. I believe that tools to analyze how neuron networks operate in the human brain will be crucial to probing the changes to brain circuitry underlying cognitive impairment in Alzheimer's disease.”

PROCEDURE USED

1. Organize the data in JAVA readable form (.txt file)
2. Begin with a time series matrix ensemble of cultured neuron spike train that represents response of neurons to a certain stimuli. To start with, examine interaction between 10 neurons (neurons n1 to n10) across T (approx. 713,000) time steps.
3. If neuron i connects into neuron j, then d[i][j] = 1, otherwise d[i][j] = 0. For example, d[1][4] = 1 implies that neuron 1 sends signals to neuron 4 and d[4][1] implies that neuron 4 sends signals to neuron 1. A connection is established if both happen simultaneously.
4. Neurons are assumed not to connect into themselves, so d[j][j] = 0 for all j.
5. Objective: to find out the number of time steps its takes for both neurons fire simultaneously.
6. Develop an algorithm using JAVA Programming that will calculate the 10x10 matrix of simultaneous connectivity from the ensemble matrix for the various different time steps.
7. Here are possible experimental steps:

8. Download truth data in 10X10 matrix form

VOL. 12, NO. 2, JANUARY 2017 ISSN 1819-6608
ARPN Journal of Engineering and Applied Sciences

www.arpnjournals.com

Table-1. Procedure to evaluate how neuron networks operate in human brain

Baseline Approach:	Assumption
Same time step	Neurons i and j both fire and connect within the same time step.
Approach #2 (Delay)	
2 Timesteps	Neurons i fires in time T but j fires a delay of two time steps (T+2).
4 Timesteps	Neurons i fires in time T but j fires a delay of four time steps (T+4).
10 Timesteps	Neurons i fires in time T but j fires a delay of ten time steps (T+10).
50 Timesteps	Neurons i fires in time T but j fires a delay of 50 time steps (T+50).
100 Timesteps	Neurons i fires in time T but j fires a delay of hundred time steps (T+100).

9. Calculate Mean Absolute Error and Root Mean Square Error will be calculated for each of these derived 10x10 matrix in comparison to the observed truth matrix to see to what extent the recorded and predicted numbers of spikes agree.
10. Formula for MAE = [Truth (i)(j) – Pred (i) (j)]; for i = 1 to 10, j = 1 to 10
11. Formula for RMSE = √ [Truth (i)(j) – Pred (i) (j)]2; for i = 1 to 10, j = 1 to 10.

DATA AND METHODOLOGY

We use the data of cultured neurons (Binary Connectivity/Transpose) and truth data collected by the Machine Learning in Biomedcal Informatics (MLBio+) Laboratory of the George Mason University. The truth data as shown in Figure-1, is the observed simultaneous recording of spiking activity across 10 neurons.

The binary connectivity matrix represents the response of each neuron to the stimulus. This is raw data and the responses were re-coded using multi-electrodes. It depicts the interactions between 10 neurons (neurons n1 to n10) across T time steps (approximately 713,000).

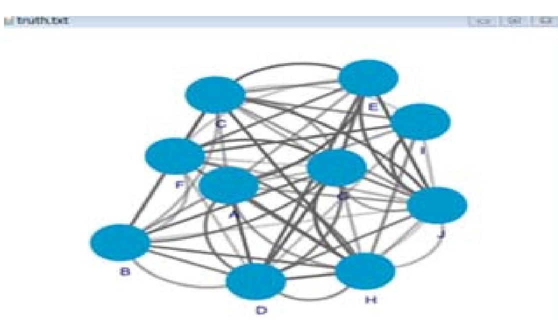


Figure-1. Connectivity structure in truth matrix.

Whenever one neuron fires, the spike it produces will affect all the neurons connected to it. These neurons in turn may fire spikes of their own. The structure of a neural network is defined by how the neurons connect to one another. A spike train is nothing but a time series graph of the output of a neuron or a set of neurons. In general a simulated neural network comprises of inputs and outputs of N individual neurons over T discrete time steps.

One objective of this research is to analyze the spike train of a simulated neural network and make inferences about the underlying structure. In other words, to analyze the transmission time among different neurons in response to a stimulus. The other objective is to identify the optimal connectivity structure that corresponds closest to the observed truth data.

For example, if neuron i connects into neuron j, then dij = 1, otherwise dij = 0. For example, d14 = 1 implies that neuron 1 connects to neuron 4. Neurons are assumed not to connect into themselves, so djj = 0 for all j. A designated neuron receives an artificial external stimulus every time step to drive the system. We develop an algorithm that will calculate the 10x10 connectivity matrix from the ensemble matrix for the following Step 7 of the procedure, based on the theory that neural interconnectivity is directly related to the delay at which neurons fire.

We then computed the 10x10 matrix for the simulated network along the assumptions described above by summing across i's and j's. Mean Absolute Error and Root Mean Square Error are calculated for each of these derived 10x10 matrix in comparison to the observed truth matrix to see to what extent the recorded and predicted numbers of spikes agree.

Formula for MAE = [Truth (i)(j) – Pred (i) (j)]; for i = 1 to 10, j = 1 to 10

Formula for RMSE = √ [Truth (i)(j) – Pred (i) (j)]2; for i = 1 to 10, j = 1 to 10.

*i's and j's represent respective indices for the data. i represents the row number, and j represents the column number.

RESULTS

As described above, we develop a computational algorithm to estimate the neural connections using the relation between the stimulus and the ensemble neural responses in the brain. Specifically, an algorithm was developed to correlate the spiking activity of 10 brain neurons across time in a network of cultured neurons sampled by a microelectrode array. The inferred brain network thus derived from the spike signals was compared using statistical techniques with observed truth data which mimic actual functioning of the brain network.

The results are presented in Table-1. Both MAE and RMSE are reported for each of the model specification comparing simulated data with truth data. A visual illustration is also presented in Figure-2 which compares truth data with the connectivity structure derived from multiple time steps. The results suggest that both MAE and RMSE decrease as the number of time steps

ARPN Journal of Engineering and Applied Sciences

www.arpnjournals.com

increases suggesting that larger the number of time steps closer we get to the optimal network structure (Figure-3). The best results are achieved for 100 time steps.

This analysis can be extended in the future in a number of ways. For example, using the simultaneity of occurrences of neuron firing (seeing whether a neuron firing will lead to a sustained reception by another) we can develop a similar algorithm. We can also look at series' of neuron firing (i.e from a to b to c) rather than just a direct one to one approach. Finally, we can look to see rather than a concrete time step delay, whether there may simply be a range of time steps between which neural connectivity takes place. This list is definitely not the end-all and be-all, but still offers a perspective on where research may first be taken in the near future.

CONCLUSIONS

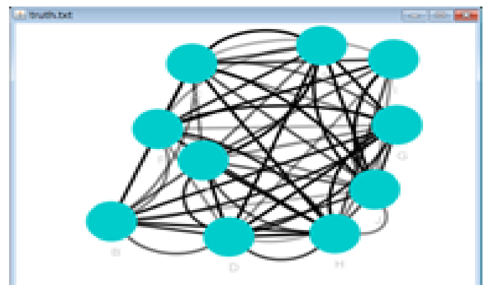
While this is not the first in this type of analysis of time-varying interactions among multiple neurons, it contributes to a growing literature that is offering new insights into the workings of particular aspects of a brain. This research just explored one possible theory/dimension in determining and figuring out how brain networks work. Obviously, neural impulses and connectivity will depend on much more than just the delay between firings in certain neurons. Neural networks are extremely complicated, and much work is still being done to determine how they function today. In actuality, these networks probably depend on a combination of attributes to work, such as delays between firings, linking of neurons, and so on.

However, this research is useful in that as the number of neurons whose interactions can be accurately measured increases, neuroscientists will be able to increase the complexity of their experiments and as a consequence, the questions they investigate.

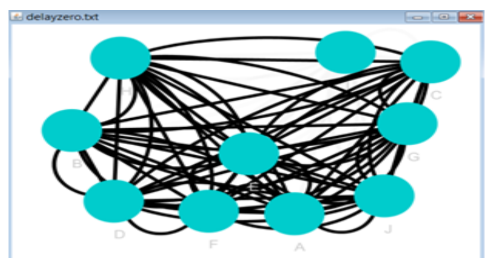
Table-2. Computation of MAE and RMSE between predicted and truth data.

Baseline Approach:	MAE	RMSE
Same Timestep	2342.9728	2850.767567
Approach #2 (Delay)	MAE	RMSE
2 Timesteps	2596.6328	3104.596037
4 Timesteps	2308.5228	2782.377157
10 Timesteps	2175.1128	2591.52021
50 Timesteps	170.7116	228.5012602
100 Timesteps	111.9726	151.4488769

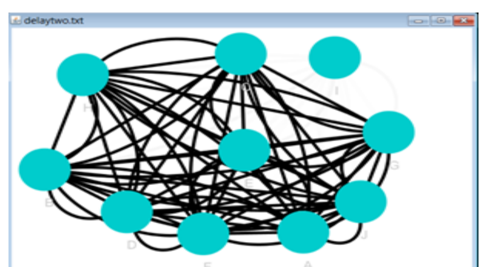
Figure-2. Average error between predicted and truth data decreases as number of timesteps increases.



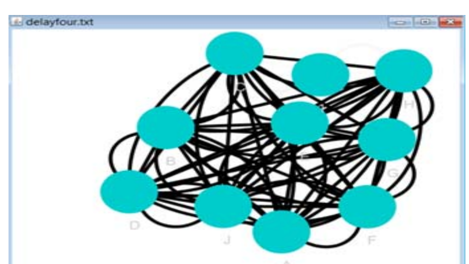
Truth data



Delay zero (Same timestep)



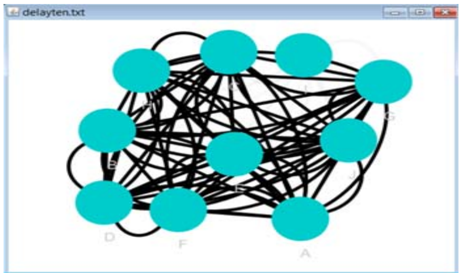
Delay two timesteps



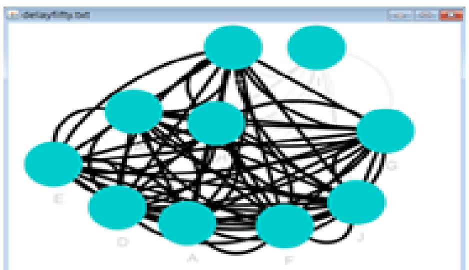
Delay four timesteps

ARPN Journal of Engineering and Applied Sciences

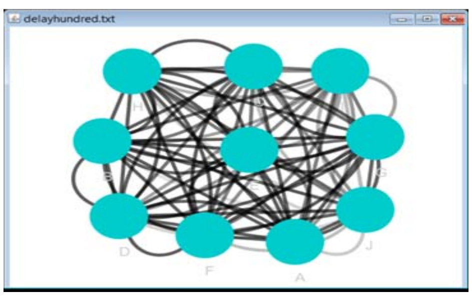
www.arpnjournals.com



Delay ten timesteps



Delay fifty timesteps



Delay hundred timesteps

Figure-3. Comparing connectivity structure of truth data with simulated data using different timesteps

REFERENCES

[1] Brook, E. (2007). Determining Properties of Synaptic Structure in a Neural Network through Spike Train Analysis, Master's Thesis: University of North Texas.

[2] Brown, E.N., Kass, R.E. and Mitra, P.R. (2004). Multiple neural spike train data analysis: state-of-the-art and future challenges. Nature Neuroscience 7, 456 – 461.

[3] Duch W. (2007). Computational models of dementia and neurological problems. Methods in Molecular Biology 401, 305–336.10 1007/978-1-59745-520-6_17

[4] Hamilton, F., T. Berry, N. Peixoto, and T. Sauer (2013). Real-time tracking of neuronal network structure using data assimilation, Physical Review E 88, 052715 (2013).

[5] Kass, R.E., Ventura, V. and Brown, E.N. (2005). Statistical issues in the analysis of neuronal data, Journal of Neurophysiology, 94: 8-25.

[6] Kosik, K.S. (2113). Study Neuron Networks to Tackle Alzheimer's, Nature, 7 November 2013, Vol. 503.

[7] Li, K., Jiang, H., Yang, L.T., and Cuzzocrea, A. (2015). Big Data: Algorithms, Analytics, and Applications. New York: Chapman and Hall/CRC Press.