INFERRING FUNCTIONAL CORTICAL NETWORKS FROM SPIKE TRAIN ENSEMBLES USING DYNAMIC BAYESIAN NETWORKS

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ABSTRACT

A fundamental goal in systems neuroscience is to infer the functional connectivity among neuronal elements coordinating information processing in the brain. In this work, we investigate the applicability of Dynamic Bayesian Networks (DBN) in inferring the structure of cortical networks from the observed spike trains. DBNs have unique features that make them capable of detecting causal relationships between spike trains such as modeling time-dependent relationships, detecting non-linear interactions and inferring connectivity between neurons from the observed ensemble activity. A probabilistic point process model was used to assess the performance under systematic variations of the model parameters. Results demonstrate the utility of DBN in inferring functional connectivity in cortical network models.

Index Terms—Functional connectivity, dynamic Bayesian network, spike trains

1. INTRODUCTION

An essential step towards understanding how the brain orchestrates information processing is to simultaneously observe the spiking activity of cortical neurons that mediate perception, learning, sensory and motor processing. Implantable high-density microelectrode arrays have enabled scrutinizing this activity at an unprecedented scale, and greatly accelerated our ability to monitor functional alterations of neural networks in awake, behaving animals [1][2]. Therefore, the need to develop machine learning and data mining techniques has emerged to enable analyzing the enormous amount of electrophysiological data being collected.

Dynamic Bayesian Network (DBN) is a graphical representation recently introduced to model dynamic systems in which temporal dependency governs the relationship between system elements [3]. This makes it capable of inferring functional connectivity between neurons given the temporal dependency between the interacting neurons that might arise as a result of synaptic delays.

Existing techniques for identifying neuronal connectivity such as cross-correlograms, partial correlation and partial spectral coherence [4] mainly rely on pairwise relationships. While these techniques may be feasible to implement for a small number of neurons, they become computationally prohibitive for large number of cells and inadequate to assess casual relationships in neuronal networks with polysynaptic connectivity. DBN, on the other hand, does not rely on pair-wise relationships. They rather take into account the activity of the entire population when searching for relationships between the examined variables. This enables DBN to identify only direct relationships which is of great importance when dealing with complex neuronal networks. In addition, DBN has a unique ability to detect non-linear relationships which suits neuronal interactions that are known to be non-linear, such as those in hippocampus formations.

In this paper, we investigate the applicability of applying DBN to reconstruct functional cortical networks from simultaneously observed spike trains. A probabilistic model is used to simulate neuronal firing patterns in which the firing probability of a given neuron depends on the history of the ensemble. We assess DBN success by examining networks of various characteristics with known connectivity.

2. THEORY

2.1. Bayesian Networks

A Bayesian Network (BN) is a graphical representation of probabilistic models widely used for statistical inference and machine learning [5]. A Bayesian Network is denoted as $B = \langle G, P \rangle$, where *G* is a directed acyclic graph (DAG) and *P* is a set of conditional probabilities. Each graph *G* consists of a set of nodes *V* and edges *E*, and is usually written as $G = \langle V, E \rangle$. Each node in *V*, denoted by v_i , corresponds to a random variable x_i (a neuron). Each directed edge in *E*, denoted by $v_i \rightarrow v_j$, indicates that node v_i is a parent (pre-synaptic neuron) of node v_j . We denote by $x_{\pi(i)}$ the set of random variables that are parents of x_i . The statistical dependence between x_i and its parent nodes $x_{\pi(i)}$ is captured by the conditional probabilities $P(x_i|x_{\pi(i)})$. Thus, the joint probability distribution of the random variables x_i can be expressed given the conditional dependence on the parents by

$$\Pr(x_1, x_2, ..., x_N) = \prod_{i=1}^{N} \Pr(x_i | \mathbf{x}_{\pi(i)})$$
(1)

A Dynamic Bayesian Network (DBN) is an extension of BN to handle time-series or sequential data [3]. In a DBN, the status of a node (variable) at time t_0 is conditionally dependent on its parents' status in the history. Specifically, given a random variable x_i at time T = t + 1, denoted by $x_i^{(t+1)}$, and its parents $x_{\pi(i)}$, the value of $x_i^{(t+1)}$ is decided by the values of its parents $x_{\pi(i)}$. Similar to Bayesian network, the statistical dependence between $x_i^{(t+1)}$ and $x_{\pi(i)}^{(1:t)}$ is captured by conditional probabilities $Pr(x_i^{(t+1)} | x_{\pi(i)}^{(1:t)})$, and the joint probability $Pr(x_1^{(t+1)}, \ldots, x_N^{(t+1)})$ is computed as

$$\Pr\left(x_{1}^{(t+1)}, x_{2}^{(t+1)}, \dots, x_{N}^{(t+1)}\right) = \prod_{i=1}^{N} \Pr\left(x_{i}^{(t+1)} \middle| x_{\pi(i)}^{(tx)}\right).$$
(2)

In many cases, it is often assumed that $x_i^{(t+1)}$ is only dependent on the value of its parents observed at time T = t, which simplifies the conditional probabilities to $\Pr\left(x_i^{(t+1)}|x_{\pi(i)}^{(t)}\right)$. This is

called the Markov assumption with *Markov lag* equal to 1 which can be extended to include multiple Markov lags. For instance, a DBN with maximum Markov lag of 3 implies that $x_i^{(t+1)}$ is decided by the value of its parents observed at time T = t, t - 1, t - 2.

2.2. Learning Bayesian Network Structure

Learning a Bayesian network from data involves two tasks: learning the structure of the network and learning the parameters of the conditional probability distributions. Structure learning of Bayesian networks is much more difficult compared to parameter learning because once the structure is known; it is easy to learn the parameters of the conditional probability distributions using existing algorithms like Maximum Likelihood Estimation (MLE).

Score-based approaches are typically used to learn Bayesian networks structure [5] in which a criterion is first defined by which a given Bayesian network structure can be evaluated on a given dataset, then a search is carried out through the space of all possible structures to find the graph with the highest score. Scorebased approaches are typically based on well established statistical principles such as Minimum Description Length (MDL) [6] or Bayesian score like BDe score [5] and Bayesian Information Criterion (BIC) [7].

3. PROBABILISTIC SPIKING MODEL

In this model, the spike train S_i of neuron *i* is modeled using an inhomogeneous Poisson point process with a conditional mean intensity function $\lambda_i(t|H_i(t))$, where $H_i(t)$ denotes the firing history of all the processes that affect the firing probability of neuron *i* up to time *t*. In this paper, we focus on two main components contributing to $\lambda_i(t|H_i(t))$: a) the neuron's background level of activity and b) the spiking history of both the neuron itself and that of other neurons connected to it. Thus, the firing probability of neuron *i* at time *t* can be modeled as [8]

$$\lambda_{i}(t|H_{i}(t))\Delta = \left(\exp\left(\beta_{i} + \sum_{j=1}^{N}\sum_{m=0}^{M_{ij}}\alpha_{ij}(m\Delta)S_{j}(t - (m + l_{ij})\Delta)\right)\right)\Delta, \quad (3)$$

where Δ is the bin width, β_i is the log of the background rate of neuron *i*, *N* is the total number of neurons in the population, M_{ij} is the number of history bins that relate the firing probability of neuron *i* to activity from neuron *j*, α_{ij} models the connection between neuron *i* and neuron *j* (which may be excitatory or inhibitory), l_{ij} is the synaptic latency in bins associated with the connection between neurons *i* and *j*, and $S_j(t - (m+l_{ij})\Delta)$ is the number of spikes fired by neuron *j* in bin $m+l_{ij}$ (which is either 0 or 1). The spiking history interval of the interaction between neurons *i* and *j* is thus $M_{ij} \ge \Delta$.

In order to mimic the influence of excitatory post-synaptic potential (EPSP) and inhibitory post-synaptic potential (IPSP) on the post-synaptic neuron firing, we utilized the following decaying exponential functions to model synaptic coupling

$$\alpha_{ij}^{\pm}(t) = \pm A_{ij} \exp\left(-3000t/M_{ij}\right), \tag{4}$$

where t is the time in seconds, +/- indicate excitatory/inhibitory



Fig. 1. Performance vs. (a) Number of pre-synaptic connections per neuron, (b) Ratio of inhibitory and excitatory synaptic strength.

connections, and A_{ii} models the strength of the connection.

4. RESULTS

We tested the algorithm on networks simulated using the point process model given in (3). For each parameter setting in the results that will follow in this section, we generated 100 networks of different structures each containing 10 randomly connected neurons, where the indices of pre-synaptic neurons were drawn from a uniform distribution. In addition to the random connections, each neuron had a self-inhibitory connection. The duration of the generated spike trains was set to 1 minute with a bin width of 3ms.

In our experiments, we used the Bayesian Network Inference with Java Objects (BANJO) toolbox [9]. We utilized the simulated annealing search algorithm with 1 minute of maximum search time in all the analyses. We used the *F*-measure typically used for quantifying information retrieval to quantify the inference accuracy. This measure is the harmonic mean of two quantities: the recall *R* and the precision *P*, defined by [10]

$$R = \frac{C}{C+M}, P = \frac{C}{C+W}$$
$$F = \frac{2RP}{R+P} = \frac{2C}{2C+M+W},$$
(5)

where C is the number of correctly inferred connections, M is the number of missed connections and W is the number of erroneously inferred connections. Thus, F will equal 0 if and only if none of the true connections are inferred and will equal 1 if and only if all of the true connections are inferred.

4.1. Networks with Fixed Synaptic Latency

We investigated the performance of DBN in inferring connectivity by varying the parameters of the model in (3) while keeping the synaptic latency l_{ij} for all neurons fixed at 1 bin (3ms). We initially examined networks of excitatory connections as the number of pre-synaptic neurons connected to each neuron was varied between 1 and 6 while fixing all other parameters. The history interval was set to 180 ms. We decreased the weights A_{ij} in (4) as the number of pre-synaptic connections increased in order to keep the mean firing rate around 25 spikes/sec while the background rate was set to 10 spikes/sec.

Fig. 1a demonstrates that the mean accuracy is greater than 85% even when all the neurons in the population have 6 presynaptic connections per neurons. This represents a high degree of connectivity given that the maximum number of connections per neuron in a network of 10 neurons is 9.

Fig. 1b illustrates the performance in the presence of inhibitory connections as their weights were varied relative to the



Fig. 2. Performance vs. Markov lag for variable history intervals.

excitatory connections. The number of pre-synaptic connections per neuron was set to 2, with one excitatory and one inhibitory. All other parameters were set as previously described. For an Inhibitory/Excitatory (I/E) ratio below 1, a low inference accuracy was observed. The drop in the performance was caused by the DBN failure to infer weak inhibitory connections. This can be attributed to the fact that at low background rates, a neuron tends to be silent most of the time. Thus, a weak inhibitory input will not change its firing characteristics significantly. As the I/E ratio increases above 1, the accuracy gets closer to unity and does not deteriorate even when the inhibitory connections are 4 times stronger than the excitatory connections indicating that strong inhibitory connections.

We further investigated the performance when there is a mismatch between the DBN Markov lag and the synaptic latency as shown in Fig. 2. Each neuron had two pre-synaptic connections, one excitatory and one inhibitory of the same strength. The synaptic latency was fixed for all neurons at 4 bins (12 ms). As can be seen, when the Markov lag is set to a value smaller than the true synaptic latency, almost none of the connections was inferred. This is expected since when the synaptic latency is set to l_{ij} , the firing of any post-synaptic neuron at time bin *t* is only affected by the firing of the pre-synaptic neurons in the range $[t-M, t-l_{ij}]$, where *M* is the number of history interval bins.

When the Markov lag matched the synaptic latency, DBN attained accuracy close to unity. The inference accuracy deteriorated slightly when the Markov lag was set larger than the synaptic latency, particularly at relatively large M. This can be explained given the EPSP and IPSP characteristics used in our model. For a small M, the influence of a pre-synaptic spike on the post-synaptic neuron firing decays rapidly. Thus, DBN was not able to identify connectivity at Markov lags much larger than the synaptic latency. On the other hand, for large M, the effect of a pre-synaptic spike on the post- synaptic neuron firing lasts relatively longer, thereby enabling the DBN to infer those connections despite that the Markov lag is larger than the synaptic latency.

4.2. Networks with Variable Synaptic Latencies

In reality a cortical network may not always have a fixed synaptic latency. Delays in chemical synapses can reach a few milliseconds in addition to the limited sample size that precludes the ability to record all directly connected neurons in a given population. We investigated the performance when multiple synaptic latencies exist. Fig. 3 demonstrates the accuracy for cortical networks having different synaptic latencies. We first define the heterogeneity index as the number of different synaptic latencies in the population. A heterogeneity index of 1 on the x-axis implies



Fig. 3. Performance vs. the heterogeneity index using a range of Markov lags for analysis (Blue) and a combination of the networks inferred at distinct Markov lags (Red).



Fig. 4. Performance vs. no. of neurons in the examined population.

that all neurons had the same synaptic latency while 5 implies that every two neurons out of the 10 had distinct synaptic latency. Each neuron received 1 excitatory and 1 inhibitory connection of 180 ms history interval. [1]

In order to capture connections at different synaptic latencies, we applied DBN with a range of Markov lags where the maximum Markov lag matched the maximum synaptic latency in the population while the minimum Markov lag was set to 1. The blue curve in Fig. 3 shows that as the synaptic latencies become more heterogeneous, the inference accuracy decreases reaching an accuracy of 78% at the most heterogeneous network we studied.

To improve the accuracy, we applied DBN to the same population with individual Markov lags instead of a range of Markov lags. For example, in the case of a heterogeneity index of 5, we applied DBN 5 times with Markov lags 1, 2, 3, 4 and 5. We then combined the networks inferred by adding them together. The red curve in Fig. 3 shows the improvement attained in this case.

4.3. Identifying Connectivity in Large Populations

All the analyses shown so far were carried out on populations of 10 neurons each. These populations might be considered small given that multi-electrode arrays can theoretically record up to a few hundreds of neurons. We investigated the scalability of the approach as a function of the number of neurons per population by simulating 10 different populations, 120 neurons each. Each population consisted of 12 *clusters* of neurons, 10 neurons each, in which each neuron received 3 excitatory pre-synaptic connections from neurons belonging only to its own cluster. The history interval was set to 180 ms and the synaptic latency to 1 bin (3ms).

Fig. 4 shows a poor inference accuracy of 0.15 when DBN was applied to the spike trains of the entire 120-neuron populations. However, the performance improved when DBN was applied to each of smaller subpopulations. For example, by dividing each of the 120 neuron populations into 2 subpopulations, 60 neurons each, the accuracy increased compared to the 120 neurons case. This can be a result of the reduction in the search space compared to the 120 neurons case. Fig. 4 illustrates the performance of applying DBN to subsequent divisions of the 120



Fig. 5. Mean IS vs. Markov lag for variable history intervals.

neuron populations into 3, 4, 6 and 12 subpopulations, with 40, 30, 20, and 10 neurons each, respectively. An inference accuracy of 1 was achieved on populations of sizes 10 and 20 neurons each. This suggests that breaking large populations into smaller subpopulations facilitates identifying neuronal connectivity using DBN, which we were able to achieve by applying a multiscale clustering algorithm prior to using the DBN [11].

4.4. Estimating the Markov Lag of Maximum Accuracy

We have demonstrated how the DBN performance is highly dependent on the selection of the Markov lag and that the accuracy is maximized when the Markov lag is equal to or slightly greater than the population true synaptic latency. When dealing with real data, prior knowledge of this synaptic latency is not available, and thus some measure is needed to estimate the best Markov lag. For that purpose, we computed the mean influence score which is the mean of the absolute value of the influence score (*IS*) computed for each inferred connection as [12]

$$IS(i, j) = \frac{1}{4} \sum_{h=0}^{1} \sum_{g=0}^{1} \left(C_{i_h j_h k_g} - C_{i_h j_{\bar{k}} k_g} \right), \tag{6}$$

where IS(i, j) measures the influence of neuron *j* on neuron *i* firing that is independent of the output of other parents of neuron *i* (*k* in this case), \overline{h} denotes the logical complement of *h*, and

$$C_{i_k j_k k_g} = \sum_{q=0}^{n} \Pr(i = q | j = h, k = g),$$
(7)

is the cumulative distribution function of the conditional probability that neuron i output is less than or equal h given that neuron j and k outputs are h and g, respectively. The conditional probabilities used in (7) are the same ones used in inferring the network. *IS* can be either positive or negative depending on whether the connection is excitatory or inhibitory, respectively.

Fig. 5 shows the mean IS at different Markov lags for the data sets investigated in Fig. 2. Comparing Fig. 5 with the accuracy shown in Fig. 2, it can be seen that for each choice of history interval bins M, the mean IS is maximized at the same Markov lag where the accuracy peaks. Thus, the mean IS can be used to quantify the confidence in the inferred network.

5. CONCLUSION

We demonstrated the use of DBN in identifying the structures of neural networks from observed spike trains. DBN can identify direct synaptic connections between distinct neuronal elements. It can also identify the direction of those connections. We have applied the method to probabilistic neuronal circuit models that mimics the stochastic variability experimentally observed in the discharge pattern of cortical neurons. The results demonstrate the capability of DBN to identify direct connections in multiple networks of various characteristics. The proposed approach can be useful in quantifying synaptic plasticity that involves variation in synaptic interactions typically associated with learning. Another application is considering the obtained networks as different states of the population that can be used in neural decoding.

6. REFERENCES

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