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A sparse regression method to estimate neuronal structure from spike sequence

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Abstract: Recent imaging techniques enable us to observe activities of hundreds of neurons simultaneously as spike sequences. The objective of this study is to estimate the network structure based on such spike sequences. Our method is an extension of existing sparse regression technique, in which we have implemented the following three ideas: (1) Each spike time-series obeys a non-stationary Poisson process whose Poisson intensity is given by an auto-regression model. (2) Spike response functions are represented by a linear summation of smooth basis functions. (3) A group-LASSO regularization is applied to obtain a sparse regression solution. When applied to simulation datasets, our method showed a better estimation performance than that by an existing state-of-the-art method.

Keywords: Computational neuroscience, network estimation, sparse estimation, generalized linear model

1 INTRODUCTION

To estimate underlying structures of networks is one big challenge not only in the field of data mining but also in various biological fields. A typical application in the field of neuroscience is to estimate the network structure from neurons' spike sequences. Recently, a variety of high-throughput measurement systems of neural networks have been proposed; for example, multi-electrode array (MEA) [1] measures neurons' action potential by inserting an electrode array into a specific brain region. Another way is a high-throughput Calcium imaging, which is now available with as much as 1000 Hz. Not only these new technologies but also the development of sophisticated statistical methods have enabled us to estimate the network structure based on a rather limited data amount. Granger causal modeling (GCM) [2] and dynamic causal modeling (DCM) [3] are such innovative statistical methods. GCM estimates causal connections between neurons based on the predictability. According to DCM, on the other hand, we assume a dynamic equation between neurons, and the total dynamical system is identified by means of, say, Bayesian statistical method. In this study, we aim to present a robust network estimation method based on modification of existing generalized linear modeling (DCM). Since this is a simple sparse regression technique, it may work especially when the available data amount is rather small (Fig.1). Here, estimation of spike response functions has an important role.

The estimation of spike response functions has been done by hierarchical Bayesian modeling [4, 5], but it has some concerns on the stability of computation and appropriate setting of priors. In many applications of structure estimation methods, the target network is partially observable, i.e., there are some hidden structures which cannot be directly observed. In such cases, the structure estimation may be affected by indirect relationship between observable elements through unobservable structures. Even in such hard situations, there may be a way to separate observable elements into clusters based on their spike response functions. This is one advantage of network estimation via the estimation of spike response functions. Therefore, we put our focus on network estimation methods based on the estimation of spike response functions in this study.

2 GENERALIZED LINEAR MODEL

Our method is based on the generalized linear model (GLM) presented formerly by Stevenson et al. [4]. After briefly introducing GLM, we describe our extensions.

2.1 Poisson process with an auto-regression model

Let $N_i(t)$ be a random variable denoting a spike event; when $N_i(t) = 1$, the i-th neuron emits a spike once in the t-th frame, and when $N_i(t) = 0$, it does not emit a spike in the frame.

Following the formulation by Stevenson et al., each spike event of neuron i obeys a non-stationary Poisson process with the time-variant Poisson intensity $\lambda_i(t)$. Here, the continuous time axis is segmented into frames with a fixed interval $\Delta t > 0$, which is small enough to make each segmented time frame (with a center at t and a width of Δt) to include at most one spike event. With these notations, the binary random variable $N_i(t)$ obeys a Bernoulli distribution: $P(N_i(t) = 1|\lambda_i(t)) = 1 - \exp(-\lambda_i(t)\Delta t)$.

Stevenson et al. assumed the Poisson intensity is given by

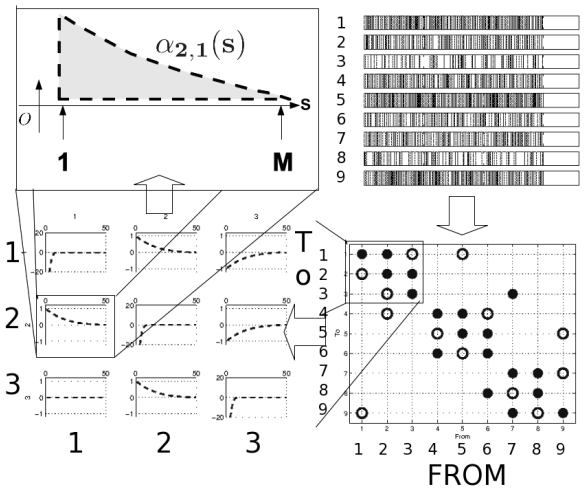

Fig. 1. Our objective is to estimate the network structure (right lower panel) from spike sequences over constituent neurons (right upper panel). In the right-lower matrix, a symbol ○ (●) denotes there is an excitatory (inhibitory) connection from neuron 'From' to neuron 'To'. No circle means no connection. The left lower panel shows the spike response functions of nine connections in the right lower panel (inset). The left upper panel shows a spike response function $\alpha_{2,1}(s)$, connectivity from neuron 1 to neuron 2.

the following auto-regression model:

$$\begin{aligned}\lambda_i(t) &= \lambda_i(t;\boldsymbol{\alpha}_i) \\ &= \exp\left(\alpha_{i,0}+\sum_{c=1}^{C}\sum_{s=1}^{M}\alpha_{i,c}(s)N_c(t-s)\right), \quad (1)\end{aligned}$$

where $\boldsymbol{\alpha}_i \equiv \{\alpha_{i,0}, \alpha_{i,c}(s) | i = 1, \cdots, C, c = 1, \cdots, C, s = 1, \cdots, M\}$ are coefficients of the auto-regression model. Since the vector $\boldsymbol{\alpha}_{i,c} \equiv (\alpha_{i,c}(s))$ represents the connection from a pre-neuron c to a post-neuron i, it is called a spike response function.

2.2 Introduction of basis functions

According to the model (1), the spike response function for a neuron pair (i, c), $\boldsymbol{\alpha}_{i,c}$, may take an independent value for each time-delay s, i.e., M-dimensional. Since the spike response function is determined based on data, this large degree of freedom may be disadvantageous especially when the delay time is long (M is large). Moreover, since the spike response function is represented biophysically in reality, it should be smooth; that is, the difference between $\alpha_{i,c}(s)$ and $\alpha_{i,c}(s+1)$ is not very large. In order to reduce the effective dimensionality whereas allowing long time delay of the spike response function, we assume it to be represented by a linear summation of temporally smooth basis functions:

$$\begin{aligned}\lambda_i(t) &= \lambda_i(t;\boldsymbol{\alpha}_i) \quad (2)\\ &= \exp\left(w_{i,0}+\sum_{c=1}^{C}\sum_{s=1}^{M}\sum_{k=1}^{K}w_{i,c,k}b_k(s)N_c(t-s)\right),\end{aligned}$$

where $b_k(s), k = 1, \cdots, K$ are K pre-fixed basis functions, and $\boldsymbol{z}_i \equiv \{w_{i,0}, w_{i,c,k}, i = 1, \cdots, C, c = 1, \cdots, C, k = 1, \cdots, K\}$ are their linear coefficients (parameters). When $K \ll M$, the effective dimensionality of the spike response function is much reduced from the original M-dimensional one, thus the estimation variance from a fixed amount of data and computational cost are both reduced. Determining the parameters $\boldsymbol{z}_i$, we have the spike response function $\boldsymbol{\alpha}_i$, because $\alpha_{i,0} = w_{i,0}$ and $\alpha_{i,c}(s) = \sum_{k=1}^{K} w_{i,c,k}b_k(s)$. When $K = M$ and $b_k(s) = I(k = s)$, the model (2) becomes identical to the original GLM (1). Here, $I(A)$ is an indicator function, which takes 1 if the condition A is true and 0 otherwise. From this observation, the model with basis functions (2) is one extension of GLM.

We in particular used logarithmic cosine functions for the basis functions $b_k(s)(k = 1, 2, \cdots, K)$:

$$b_k(s) \equiv \begin{cases}\cos^2(D_1\log(1+(s-1)D_2)\pi/2-(k-2)\pi/4) \\ (\text{if } D_1\log(1+(s-1)D_2)\pi/2 \in \\ [-\pi/2+(k-2)\pi/4, \pi/2+(k-2)\pi/4]) \\ 0 \\ (\text{else})\end{cases}.$$

Here, D_1, D_2 denotes the scale parameter and is set arbitrarily. These basis functions have fine and coarse temporal resolutions when the corresponding delay times are short and long, respectively. This setting allows the resultant spike response function to represent well the rapid change of postsynaptic membrane potential after the spike input but to reduce the effective dimensionality simultaneously.

2.3 Optimization problem

We estimate the linear coefficients of the basis functions, $\boldsymbol{z}_i$, such to minimize the following loss function with a regularization term:

$$\boldsymbol{z}_i^* = \text{argmin}_{\boldsymbol{z}_i}\mathcal{L}_i(\boldsymbol{z}_i) + \Lambda\mathcal{G}(\boldsymbol{z}_i), \quad (3)$$

where $\mathcal{L}_i(\boldsymbol{z}_i)$ is the loss function for the i-th neuron, and $\mathcal{G}(\boldsymbol{z}_i)$ is the regularization term that is explained in the section 2.4. $\Lambda > 0$ is a balancing factor between the loss function and the regularization term, whose value is determined by a cross-validation method such to show a good generalization performance.

Since we assume that the random variable $N_i(t) \in \{0, 1\},\ i = 1, \cdots, C,\ t = 1, \cdots, T$ obeys an independent

Bernoulli process, the log likelihood is given by

$$\sum_{t=1}^{T} \log P(N_i(t)|\lambda_i(t)). \tag{4}$$

Since the Poisson intensity $\lambda_i(t)$ is determined by the parameter vector $\boldsymbol{z}_i$ (equation (2)), the log likelihood is a function of the parameter vector. Then, the maximum likelihood estimation of the parameter vector is equivalent to the minimization of the following loss function with the auto-regression model (2) in terms of the parameter vector $\boldsymbol{z}_i$:

$$\mathcal{L}(\boldsymbol{z}_i) \quad = \quad -\sum_{t=1}^{T} \left(N_i(t) \log \lambda_i(t) - \lambda_i(t)\right), \tag{5}$$

where we have used the likelihood of the Bernoulli process.

2.4 Group-LASSO regularization

The regularization term in equation (3) is given by

$$\mathcal{G}_i(\boldsymbol{z}_i) = \sum_{c=1}^{C} \sqrt{\sum_{k=1}^{K} w_{i,c,k}^2} \quad , \tag{6}$$

which is a kind of group-LASSO regularizer. A linear regression method employing an L^1 regularizer $\mathcal{G}_i^{(\mathrm{L}^1)} = \sum_{c=1}^{C}\sum_{k=1}^{K} |w_{i,c,k}|$ is called LASSO and tends to produce a sparse solution whose linear coefficient is likely to be zero. A group-LASSO is an extension such that the sparseness works in each group of linear coefficients. According to the regularization term (6), $\{w_{i,c,k}|k = 1, \cdots, K\}$ constitutes a group, and the variables in a single group are often estimated as zero simultaneously. In our particular application, $w_{i,c,k}, k = 1, \cdots, K$, should be simultaneously zero if a neuron pair (i, c) has no connection. When applying to estimation of neuronal network structure, therefore, a group-LASSO-based regularization method would work well.

3 SIMULATION

The proposed method was applied to simulation spike datasets.

3.1 Simulation setting

Simulation 1 Kim et al. [2] prepared a network model consisting of nine neurons (Fig. 2), and produced a spike dataset by introducing specific spike response functions to the connected neuron pairs. Although the spike response functions are not presented, the simulated spike sequence is open for public[1]. The spike sequence with a frame rate of 1,000 Hz is for 100,000 frames (100 seconds).

[1] http://www.neurostat.mit.edu/gcpp

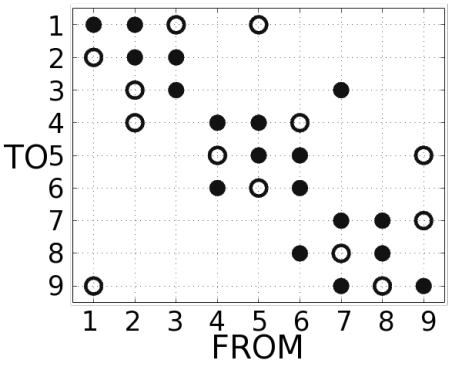

Fig. 2. The connection matrix showing the true network structure in simulation 1

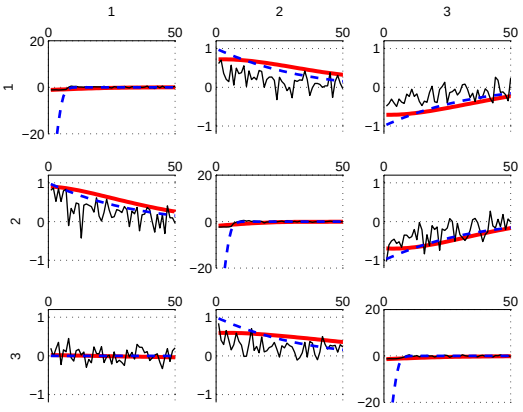

Fig. 3. The true spike response function and its estimation in simulation 2. The figure shows spike response functions between three neurons out of nine neurons. A dotted line is the true one. A thick solid line and a thin solid line show the estimated response functions with and without the logarithmic cosine basis functions, respectively.

Simulation 2 Since the true spike response functions are unknown in the Kim et al.'s dataset, we did a simulation by applying our own spike response functions (therefore, we know the truth) to the same network structure as that used by Kim et al.

3.2 Estimation of spike response functions

Fig. 3 shows the spike response functions obtained by applying the proposed method to the dataset in simulation 2. In particular, this figure shows the performance of the logarithmic cosine bases, which can be seen by comparing the group-LASSO regression with (thick solid line) and without (thin solid line) logarithmic cosine basis functions. In both cases, the regularization coefficient Λ was set at 10. We can see that the smoothness constraints due to the logarithmic cosine functions worked well to obtain smooth and hence biologically natural response functions.

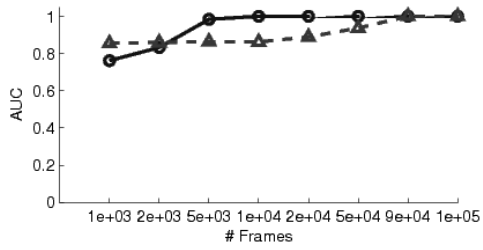

Fig. 4. Network estimation when applied to the dataset of simulation 1. A dotted line and a solid line show the AUC values by Kim et al. and our method, respectively.

3.3 Estimation of network structure

Based on the estimated spike response functions, we can estimate the network structure.

We say there is an excitatory (inhibitory) connection from a pre-neuron c to a post-neuron i if the auto-regression coefficient $\alpha_{i,c}(s)$ is consistently positive (negative) for all delay times $s = 1, \cdots, M$. We also say there is no connection from c to i if $\alpha_{i,c}(s)$ is consistently zero. However, it may be the case of estimation that $\alpha_{i,c}(s)$ is positive with some delay times but negative with other delay times. Such an estimation result may be obtained due to the estimation variation and/or to the mixture of direct effects and indirect (i.e., multi-synaptic) effects. In order to extract a reasonable structure from such ambiguous spike response functions, we needed a heuristic criterion; by defining the connectivity strength: $Q_{i,c} = \sqrt{\sum_{s=1}^{M} \alpha_{i,c}^2(s)}$ and the connectivity polarity: $R_{i,c} = \mathrm{sign}(\sum_{s=1}^{\tilde{M}} \alpha_{i,c}(s)), \tilde{M} < M$ we determined as follows, either excitatory, inhibitory or no connection from pre-neuron c to post-neuron i.

- If $Q_{i,c} > h$ and $R_{i,c} = 1$, an excitatory connection.
- If $Q_{i,c} > h$ and $R_{i,c} = -1$, an inhibitory connection.
- If $Q_{i,c} < h$, there is no connection.

In the above criterion, h is a positive threshold to be pretuned. Although we tuned it heuristically in this experiment, it should be determined by controlling the false positive rate in more realistic applications [2].

In our method, we obtained spike response functions from the given spike dataset, and then the network structure was determined by applying the above criterion to the estimated spike response functions. We also applied the network estimation method by Kim et al. to the same dataset. Here, we examined the estimation performance by varying the number of frames (i.e., sequence length).

From Fig. 4, we can say that the proposed method shows a good performance for network estimation over a wide range of available number of frames. Here, AUC (area under the receiver-operator curve) shows the general accuracy by integrating both of the false positive rate and false negative rate; the larger it is, the better the classifier is.

4 CONCLUSION AND DISCUSSION

In this study, we presented a GLM-based network estimation method employing smooth basis functions such to reduce the effective dimensionality whereas maintaining the representation capability of the model. In addition, the group-LASSO-type regularization introduced an effective and biophysically natural sparseness into the estimation, and hence was effective for stabilizing the estimation.

There are some remaining issues in our network estimation method. First, performance of network estimation will be deteriorated when the target network receives structured inputs from external networks. One possible solution is to incorporate location information of each network element into our model. Second, we have not established a good criterion to extract the network structure from the estimated spike response functions. We have applied a cross-validation technique to determine the threshold value in the criterion, but also found its result behaves unstably especially when the data amount is not sufficient. There are some remaining issues like above, and we will cope with them in our future study.

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