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On the problem of estimating connectivity from spike recordings in large neuron networks

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Abstract—Most of the existing methods to extract information about the interactions within a network of dynamical systems starting from measured data work well for networks with a limited number of interacting units, though they badly scale to networks containing hundreds of elements, the main limiting factor being the computational complexity. This paper deals with a method based on linear regression and particularly conceived for identifying networks of biological neurons. The method complexity scales linearly with the number of network elements. Some examples are proposed in order to validate the method and to evaluate to what extent the quality of the information about the interaction between two neurons is influenced by adding up to one hundred of nodes.

1. Introduction

Extracting information about the interactions within a network of dynamical systems starting from measured data is a key topic in many modern applied sciences. In particular, a major goal of neural data analysis is to characterize how neurons that are part of a network interact with each other. Various time series analysis techniques have been proposed for the description of interactions between dynamical processes and for the detection of causal influences in multivariate systems (e.g., see [1] and references therein). When more than two processes are analyzed, one has to face the problem that complex interaction structures between the processes may arise. For example, two processes in a multivariate system not necessarily interact directly. Therefore, bivariate analysis is often not sufficient to distinguish direct and indirect interactions.

The need for quick and efficient multivariate analysis methods has increased with the growing availability of multiple parallel measurements in modern experimental setups. Indeed, with the advent of the multi-electrode recording technology, it is now possible to record the activity of several hundred neurons simultaneously. Many techniques have been proposed for application to neuron networks. Among them, besides electron microscopy techniques [2], we can cite maximum likelihood approaches [3,4], probabilistic approaches [5], and graphical approaches [1]. The applicability of most of these methods to the analysis of spike trains of more than a few neurons has been limited due to their computational complexity.

In this paper, we use a very simple identification technique, based on a leaky integrate-and-fire (LIF) model and on the method proposed in [6]. The main goal is to find the "effective connectivity", i.e., the simplest model that takes into account any observable direct or indirect interaction between neurons and reproduces almost the same temporal relationships between neurons in a cell assembly as those observed experimentally [7]. The method is based on the time instants of spike occurrences (point events) and is applied to both networks of LIF neurons and Izhikevic neurons [8]. With respect to [6], the main difference is that the decay time scale is assumed to be known and equal for all neurons. This assumption is quite reasonable (the influence of the decay time scale on the network behavior is negligible) and allows us to identify the system parameters through *linear regression*, thus making the technique applicable to networks with hundreds of elements, since the method complexity scales linearly with the neuron number. Due to the choice of a LIF model, the method is quite reliable when each neuron belonging to the network to be identified spikes regularly, whereas the results are less accurate when the inter-spike intervals are not regular.

The proposed results concern a preliminary set of tests, conceived to validate the method and to evaluate to what extent the information about the interaction between two neurons of a network is influenced by adding up to one hundred of nodes.

2. The model

We consider a network of N interconnected neurons. For the j-th neuron during an inter-spike interval (ISI), we use the single-compartment LIF model [9]:

$$C\frac{dv^{(j)}}{dt} = -G(v^{(j)} - V_L) + I_0^{(j)} + I_{syn}^{(j)} \qquad (1)$$

When the voltage $v^{(j)}$ reaches a threshold (V_{TH}), the neuron output $y^{(j)}$ spikes (point event) and $v^{(j)}$ is re-

set to the resting membrane potential. The output of the j-th neuron, weighted by a synaptic coefficient, is input to all the other neurons of the network, excepted for the j-th neuron itself. The absence of self-feedback is a key assumption in order to have linear regressions.

We suppose that, over a fixed time window, the j-th neuron produces $N_{ISI}^{(j)}+1$ spikes, corresponding to $N_{ISI}^{(j)}$ ISI. By normalizing the state variables as follows

$$x^{(j)} = \frac{v^{(j)} - V_L}{V_{TH} - V_L} \tag{2}$$

we obtain the following set of normalized equations:

$$\frac{dx^{(j)}}{d\hat{t}} = -x^{(j)} + b^{(j)} + \sum_{i \neq j} w_{ij} y^{(i)} \tag{3}$$

where $\tau = \frac{C}{G}$, $\hat{t} = \frac{t}{\tau}$, $b^{(j)} = \frac{I_0^{(j)}}{G(V_{TH}-V_L)}$, and

$$\begin{array}{c} y^{(i)} = \left\{ \begin{array}{lll} 0 & \text{if} & x^{(i)} < 1 \\ 1 & \text{if} & x^{(i)} \geq 1 \end{array} \right. \\ \sum_{i \neq j} w_{ij} y^{(i)} = \frac{I_{syn}^{(j)}}{G(V_{TH}-V_L)} \end{array} \tag{4}$$

By sampling the system with a step $\hat{h} = \frac{h}{\tau}$, we obtain the following discrete-time system ($j = 1, \ldots, N$)

$$x_{k+1}^{(j)} = \tilde{A} x_k^{(j)} + \tilde{B} \left[b^{(j)} + \sum_{i \neq j} w_{ij} y^{(i)}(k\hat{h}) \right] \tag{5}$$

where $\tilde{A} = e^{-\hat{h}}$ and $\tilde{B} = \left(1 - e^{-\hat{h}}\right)$, whose explicit solution (valid within each ISI of the j-th neuron) is

$$x_k^{(j)} = \tilde{A}^k x_0^{(j)} + \sum_{p=0}^{k-1} \tilde{A}^{k-p-1} \tilde{B} \left[b^{(j)} + \sum_{i \neq j} w_{ij} y^{(i)}(p\hat{h}) \right]$$

3. The identification method

At the beginning of the r-th ISI (for $k = 0$), we have $x_0^{(j)} = 0$, since the j-th neuron has been reset after a spike. At the end of the considered ISI (for $k = \bar{k}_r^{(j)}$), the j-th neuron reaches the threshold $x_{\bar{k}}^{(j)} = 1$, thus spiking. The same condition can be imposed for any ISI of the j-th neuron ($r = 1, \ldots, N_{ISI}^{(j)}$):

$$1 = \tilde{B} \sum_{p=0}^{\bar{k}_r^{(j)}-1} \tilde{A}^{\bar{k}_r^{(j)}-p-1} \left(b^{(j)} + \boldsymbol{w}^{(j)} \boldsymbol{y}^{(j,r)} \right) \tag{6}$$

where the vector $\boldsymbol{w}^{(j)}$ is the j-th column of the connectivity matrix W, excepted for the w_{jj} element, which is always set to 0. Since $\sum_{p=0}^{\bar{k}_r^{(j)}-1} \tilde{A}^{\bar{k}_r^{(j)}-p-1} = \frac{\tilde{A}^{\bar{k}_r^{(j)}}-1}{\tilde{A}-1}$, Eq. (6) can be expressed as follows:

$$1 = b^{(j)} \left(\tilde{A}^{\bar{k}_r^{(j)}} - 1 \right) + \tilde{B} \boldsymbol{w}^{(j)} \boldsymbol{z}^{(j,r)} \tag{7}$$

where $\boldsymbol{z}^{(j,r)} = \sum_{p=0}^{\bar{k}_r^{(j)}-1} \tilde{A}^{\bar{k}_r^{(j)}-p-1} \boldsymbol{y}^{(j,r)}$. Then, the system to be solved in least squares sense is

$$\left[\begin{array}{c|c} \tilde{B}\boldsymbol{z}^{(j,1)} & 1 - \tilde{A}^{\bar{k}_1^{(j)}} \\ \vdots & \vdots \\ \tilde{B}\boldsymbol{z}^{(j,N_{ISI}^{(j)})} & 1 - \tilde{A}^{\bar{k}_{N_{ISI}^{(j)}}^{(j)}} \end{array} \right] \left[\begin{array}{c} \boldsymbol{w}^{(j)} \\ -- \\ b^{(j)} \end{array} \right] = \left[\begin{array}{c} 1 \\ \vdots \\ 1 \end{array} \right]$$

We remark that the parameter τ (decay time scale in the linear model (1)) acts as a scaling factor for the time axis, but also influences the regression matrix, through the terms $\tilde{A}$ and $\tilde{B}$. Then, we can choose τ, within a physically reasonable range, in order to have a regression matrix with good condition number.

4. Validation of the method

In this section, the proposed identification technique is applied to a simple LIF neuron network. The regression set is generated by simulating a network of LIF neuron models (3) with bi-directional synaptic connections, both excitatory and inhibitory, as sketched in Fig. 1. All the simulations have been performed by using forward Euler integration algorithm, with 50000 steps of length 10^{-3} and with initial condition 0.5 for each neuron. The network can be made up of either the two black neurons only or all the eight black and grey neurons. In the latter case, the non-zero elements of the weight matrix W^8 are shown in Fig. 1. The element w_{rs}^8 represents the influence of the s-th neuron on the r-th one. The bias vector is $b^8 = [5.5 \quad 5.0 \quad 4.5 \quad 4.0 \quad 3.5 \quad 3.0 \quad 2.5 \quad 2.0]$. For the two-neuron network, the weight matrix W^2 is the upper-left 2×2 block in W^8 and the bias vector b^2 is made up of the first two elements of b^8.

4.1. Parameters identification

We choose $\tau = 1$ to have a well-scaled regression matrix and to obtain parameters which are directly comparable with the original ones.

As a first test, we identified the model parameters for the two-neurons subnetwork and then for the complete network. As pointed out in Fig. 1, the two black neurons are influenced only by each other, so the identification should provide almost the same results as for the complete network. By applying the identification

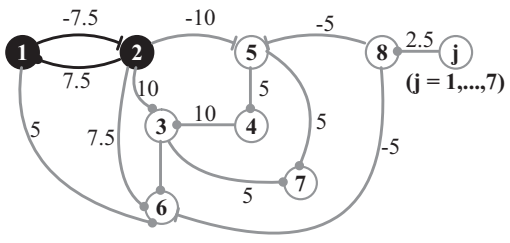

Figure 1: Simulated network.

method to the time series generated by the network with two neurons, we obtain the following parameters (with two decimal digits precision): $w_{1,2} = 5.65$, $w_{2,1} = -8.66$, $b_1 = 5.49$, $b_2 = 5.00$. The condition numbers of the two regression matrices are about 610 (first neuron) and 710 (second neuron), corresponding to singular values [2.8603 0.0047] and [2.9982 0.0042], respectively.

If we apply the method to the network with eight neurons, we obtain (with two decimal digits precision):

$$W = \begin{pmatrix} 0 & 5.64 & 0.12 & 0.06 & 0.02 & 0.13 & -0.05 & -0.03 \\ -8.66 & 0 & -0.01 & -0.08 & 0.05 & -0.10 & -0.02 & -0.08 \\ -0.08 & 9.38 & 0 & 8.89 & 0.11 & -0.14 & -0.20 & -0.15 \\ 0.06 & -0.08 & -2.64 & 0 & 1.37 & -0.02 & 0.04 & 0.04 \\ -0.12 & -10.26 & 0.01 & 0.04 & 0 & 0.22 & -0.05 & -5.35 \\ 5.37 & 7.15 & 4.54 & 0.49 & 0.00 & 0 & -0.04 & -5.25 \\ 0.10 & 0.07 & 4.92 & 0.21 & 4.82 & -0.09 & 0 & 0.04 \\ 2.37 & 2.30 & 2.60 & 2.50 & 2.79 & 2.18 & 2.79 & 0 \end{pmatrix}$$

and $b = [5.49 \;\; 5.00 \;\; 4.50 \;\; 4.01 \;\; 3.50 \;\; 3.00 \;\; 2.50 \;\; 2.00]$. Then, as expected, the identification of the two target weights and biases is almost the same as before.

For the chosen value of τ, the condition number of the regression matrices is again in the order of 10^3, and the largest singular value of the matrix is about three order of magnitude larger than the other ones. Since the biases are determined with higher accuracy, we can guess that the largest singular value of each regression matrix is strictly related to the bias.

In order to check the robustness of the identification method, we perform a sensitivity test. By slightly perturbing one parameter (weight or bias) of the original network, we expect that (i) the estimated parameters do not change dramatically and (ii) the larger changes concern the identification of the perturbed parameter. In all cases, we performed 100 simulations and the initial condition for each neuron was fixed to 0.5.

4.2. Sensitivity to parameter variations

As a first test, we fix the biases and perturb the element $w_{1,2}$ of the weight matrix W (that is either W^2 or W^8) in the k-th simulation ($k = 1, \ldots, 100$), by replacing it with $w_{1,2}(1 + \varepsilon)$, where ε is a random number uniformly distributed in the range $[-0.1, 0.1]$.

For the network with two neurons, the mean identified weights are $w_{1,2} = 5.69$ and $w_{2,1} = -8.73$, with standard deviations 1.59 and 0.05, respectively. The mean identified biases are $b_1 = 5.49$ and $b_2 = 5.00$, with standard deviations 2 10^{-3} and 3 10^{-4}, respectively. For the network with eight neurons, the mean values (standard deviations) of $w_{1,2}$ and $w_{2,1}$ are 5.49 (1.73) and -8.75 (0.05), respectively. Among the other weights, the one with the largest variance (1.03) is $w_{4,3}$. The mean values of b_1 and b_2 are 5.49 and 5.00, with standard deviations 2 10^{-3} and 3 10^{-4}, respectively (similar accuracies hold for the other biases).

If we perturb b_1, the results are quite similar. For the network with two neurons, the mean identified weights (and corresponding standard deviations) are $w_{1,2} = 7.03$ (2.14) and $w_{2,1} = -8.45$ (0.82). The mean identified biases (and corresponding standard deviations) are $b_1 = 5.52$ (0.32) and $b_2 = 5.00$ (4 10^{-3}). For the network with eight neurons, the mean values (and standard deviations) of $w_{1,2}$ and $w_{2,1}$ are 7.47 (1.99) and -8.49 (0.39). Among the other weights, the one with the largest variance (0.83) is once again $w_{4,3}$. The mean values (and standard deviations) of b_1 and b_2 are 5.48 (0.32) and 5.00 (2 10^{-3}). All the other biases are identified with variances in the order of 10^{-3}.

5. Scalability of the method

In the previous section, we applied the identification procedure to a deterministic LIF network (and a subnetwork) with fixed topology and neuron number. In this section, we apply the identification method to time series generated by two different kinds of networks (LIF and Izhikevic) with: stochastic elements, random one-to-all topology, and 2^p neurons, where $p = 1, \ldots, 7$. Our attention is focused once more on two neurons (the first two of each network), and especially on their mean firing frequency, by evaluating to what extent this feature is influenced by increasing the number of neurons in the network up to 128 elements. Since the network complexity scales linearly with the number of elements of the network, we expect that the method is able to identify reasonably well the connections between the neurons even for large networks. Moreover, since as far as the network size increases, the neurons tend to synchronize and to fire periodically also in the presence of stochastic terms in the original networks, we expect that the identification results get closer to the original ones for larger p values.

For each considered model (LIF and Izhikevic), we adopt the following protocol. For a fixed number of neurons (2^p, with $p = 1, \ldots, 7$) and for a fixed one-to-all topology, we sort 100 random configurations with Gaussian distribution for the weights ($\mu = 0$ and $\sigma = 10$). The output (spike timing) of each original network is used for a corresponding regression and the obtained weight matrix and bias vector are used to simulate a LIF (in any case) network according to our reference model. All the simulations are performed by using the forward Euler integration algorithm, with 50000 steps of length $\hat{h} = 10^{-3}$. The value of τ is assumed to be unitary. Finally, the ISIs first-order statistics for the first two neurons in the original and identified networks are compared.

For the LIF networks, the configuration is completed by extracting 2^p random biases according to a Gaussian distribution with mean 5 and variance 0.1. Moreover, we consider the presence of a stochastic neuron, spiking with a Poissonian distribution of the ISIs (with mean of 50 integration steps, so during the whole simulation the neuron generates about 1000 spikes) and

connected to the whole network by a random weight configuration with Gaussian distribution ($\mu = 0$ and $\sigma = 10$). The presence of this additive neuron counters the synchronization of the neuron networks and prevents the presence of linearly dependent columns in the regression matrix. The poissonian neuron weights are excluded from the regression, and during the simulation of the identified network the stochastic neuron is added again with the same statistics as before, but with different realizations of both the process and the coupling weights.

For the Izhikevic networks, the configuration is completed by using the model described in [8], with only excitatory neurons. Then, the bias current of each neuron is a stochastic Gaussian variable ($\mu = 0$ and $\sigma = 5$) during the time integration. In this case, the identified LIF networks may produce only regular spiking, then the ISI variance is negligible. On the contrary, owing to the presence of stochastic bias currents, the Izhikevic networks exhibit more complex behaviors, with significant ISI variances. Then, in principle, the identified LIF networks (being completely deterministic) can approximate only on average the behaviors of the Izhikevic networks. In order to introduce a stochastic term also in the LIF networks, one should add a stochastic component, to be identified *a posteriori*, on the basis of the model residuals.

5.1. Results

The black lines in Fig. 2 show, for different values of p, the mean values of the ISIs for the first (left panels) and second (right panels) neurons computed over 100 simulations in the LIF networks in the presence of a poissonian input neuron (upper panels) and in the Izhikevic networks (lower panels). The mean values in the identified LIF networks in both cases are represented in grey.

The comparison evidences that the identified networks, on average, reproduce quite accurately the ISIs mean values. Further first-order statistic measures, e.g., like those reported in [10], cannot be considered here, since (as stated before) the ISIs variance in the LIF models is negligible, even in the presence of the considered stochastic input neuron. We point out once more that, in order to model the ISIs variance of non regularly spiking reference networks, proper stochastic terms should be added to the identified LIF networks.

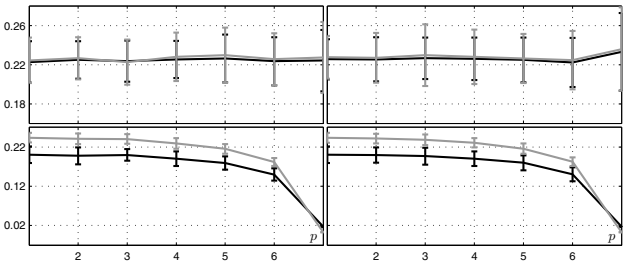

Figure 2

The regression for the network with 128 neurons takes about 200 seconds in the Matlab® environment on a PC equipped with an Intel® Core(TM)2 QUAD CPU Q6600 @2.4GHz and an 8GB RAM memory.

6. Concluding Remarks

In this paper we have proposed a modified version of an existing method for identifying networks of biological neurons. The main novelty element of the proposed version is the parameter identification based on linear regression. The method complexity scales linearly with the number of network elements, hence it is applicable to large size networks. To validate the viability of the method, we have proposed a series of preliminary tests, that produced encouraging results.

Future work will concern *in primis* the definition of a more organized and coherent set of tests, the inclusion in the identified models of a stochastic component (to be identified *a posteriori* on the basis of the model residuals), and the application of the method to real multi-electrode recording data.

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