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Inferring Neural Connectivity and the Underlying Network Dynamics from Spike Train Recordings

Valeri A. MAKAROV†, Oscar DE FEO‡, and Fivos PANETSOS†

†Neuroscience Laboratory, Department of Applied Mathematics, School of Optics, Universidad Complutense de Madrid;
Avda. Arcos de Jalon s/n, 28037, Spain.
‡Laboratory of Nonlinear Systems, Swiss Federal Institute of Technology Lausanne;
EPFL-IC-LANOS, CH-1015 Lausanne, Switzerland.
Email: vmakarov@opt.ucm.es, oscar.defeo@epfl.ch, fivos.panetsos@opt.ucm.es

Abstract—A novel method for the identification and modeling of neural networks using experimental spike trains is discussed. The method assumes a reference model of interconnected deterministic integrate-and-fire neurons and fit the parameters of the model to the observed experimental spike trains. The identification provides the properties of the individual synapses and neurons, hence extracting the functional connectivity between neurons. The method is shown to be effective when applied on simulated data.

1. Introduction

The qualitative and quantitative analysis of the spiking activity of individual neurons is a very valuable tool for the study of the dynamics and functional architecture of the neural networks in the Central Nervous System [1]. In particular, deducing the functional connectivity of neural networks from experimental data, usually restricted to spike trains, is of crucial importance in neuroscience: for the correct interpretation of the electrophysiological activity of the involved neurons and networks; and, more important, for correctly relating the electrophysiological activity to the functional tasks accomplished by the network. Here, the term *functional* stands for any observable, direct or indirect, interaction between neurons which alters their spike timings.

The measured activity of a neuron is not the result of its solely intrinsic properties, but stems from the direct and indirect influences of the other neurons of the network, leading to network behaviors far beyond the simple combinations of those of the isolated neurons. On the other hand, the measured time instants of spike occurrences (point events) do not allow any direct insights about the subthreshold and/or intrinsic membrane dynamics of the neurons. Nonetheless, spike trains can be used to identify the functional characteristics and effective architecture of the neural network they originated from, e.g [2, 3].

The most common and standard methods for identifying the synaptic connections between neurons assume a stochastic nature of the spike trains, and the functional bond between two neurons is extracted from the statistical inference of the discharges times, usually deducing it from the shapes of cross-correlograms [2, 3]. Though widely understood, this tool provides a very limited knowledge about the functional properties of the neural networks, and it cannot distinguish direct from indirect connections among neurons. Recently, more sophisticated statistical methods [4, 5, 6] have overtaken this problem. However, these methods still fit into a stochastic framework and lack a compact description of the estimated interactions. Furthermore, since they assume a stochastic nature of the spike trains, they do not provide considerations about the dynamics of the involved neurons, nor about the nature of the intrinsic processes that are responsible for such behavior.

In contrast to a purely statistic approach, a deterministic one can be considered, with the main advantage of providing a mathematical model for inferring single neuron or neural network properties indirectly. In this direction, methods for extracting a dynamical system out of the interspike intervals have been recently proposed [7, 8], however these methods assume neurons to be isolated; hence, they do not provide insights about the neural network structure and its relationships with the observed dynamics.

Here a new model based method for the identification and modeling of *whole* neural networks from experimental spike trains is proposed. A description of the method is given in Sec. 2, whilst in Sec. 3 numerical tests of it are presented and then discussed in Sec. 4.

2. Identification Method

The identification method, despite being quite mathematically convoluted, is rather transparent in its principle. The reference model adopted in the identification process is a network of interconnected integrate-and-fire neurons. All the parameter values necessary to univocally define it, *i.e.* the connectivity matrix of the network, the synaptic time scales, and the intrinsic parameters of the neurons, are derived from the recorded spike trains by an optimization procedure which minimizes the difference between the predicted and measured timings of spike episodes.

Precisely, given N spike series from as many neurons, the reference model is a network composed of N interconnected single-compartment leaky integrate-and-fire models. The connections between neurons are represented by a $N \times N$ matrix W whose elements w_{kn} are the weights of the synapses directed from the k^{th} to the n^{th} neuron. Schematically, it results in a graph of N vertices representing the neurons, whose spike trains are experimentally observed, where the links between vertices match functional synapses between the corresponding neurons.

After normalization, the dynamics at node k can be written as:

$$\dot{v_k} = -\frac{v_k}{\tau_k} + i_k^0 + i_k^s(t)\,,\ \text{if}\ v_k = 1\ \text{then}\ v_k = 0 \wedge \text{spike}, \quad (1)$$

where v_k is proportional to the neural membrane potential, τ_k is the membrane time constant, $i_k^s(t)$ is the synaptic current induced by the spikes from the other neurons of the network, and the constant current i_k^0 allows neurons to fire periodically when uncoupled. Whenever the membrane potential v_k reaches the threshold $v_k = 1$ a spike is fired and v_k is instantaneously reset to the initial state $v_k = 0$.

The synaptic current provided to neuron k by a spike from neuron n is well approximated by:

$$i^s(t) = \frac{w_{nk}}{\lambda_n} \exp\left(-\frac{t-t'}{\lambda_n}\right),$$

where t' is the time instant when a spike from the presynaptic neuron arrives; w_{nk} accounts for the synaptic strength and polarity (weight); and λ_d is a time constants determining the synaptic time scale. Hence, between two spikes of neuron k, the total synaptic current can be accounted by the sum over all spikes, within the interspike interval of neuron k, generated by all the presynaptic neurons:

$$i_k^s(t) = \sum_{\substack{n=1 \\ n \neq k}}^{N} \left[\frac{w_{nk}}{\lambda_n} \sum_j \exp\left(-\frac{t-t_{nj}}{\lambda_n}\right)\right]. \quad (2)$$

Given the spike events, the identification of all the parameters is guaranteed by the decomposition of the fitting problem according to two nested independencies of the integrate-and-fire (reset) model: first, the dynamical equation of each neuron remains independent from the others; second, the dynamics of each neuron within an interspike interval is independent from the dynamics within the other intervals. Hence, the identification proceeds neuron- and interval-wise. In particular, the working principle is outlined in Fig. 1. Let us assume that a neuron k receives two synaptic inputs of different polarity, *i.e.* excitatory and inhibitory, *cf.* two upper spike trains. For each one of the two synapses, an input spike induces an exponential current and the sum of them gives the postsynaptic current I_{syn}. The amplitude and the sign of the two components of the postsynaptic current are defined by the corresponding weights of the connectivity matrix W, in this case with only two synapses let call them shortly w_1 and w_2; the decay of the current, duration of the synaptic transmission, is defined by the parameters λ_1 and λ_2, in general different. Between each two spikes of neuron k, in absence of external input, the membrane potential evolves according to

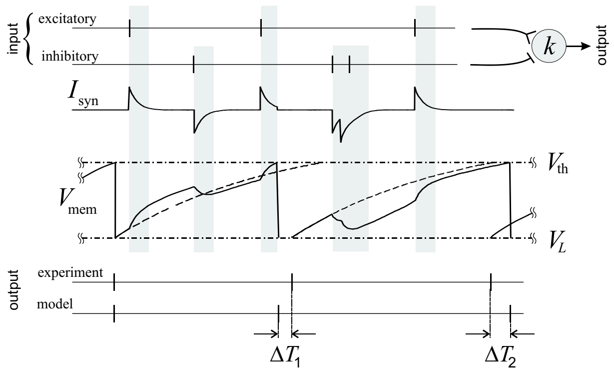

Figure 1: Operating scheme of the identification algorithm.

its intrinsic dynamics (dashed line). When external spikes income, the membrane potential deviates from the intrinsic behavior, highlighted in gray, and, each time the membrane potential reaches the threshold, the neuron fires a spike and v is reset to the initial state. Given the input spike trains, the parameter set $p = \left\{i^0, \tau, \lambda_1, \lambda_2, w_1, w_2\right\}$ of Eqs. (1) and (2) define uniquely the dynamics of neuron k within two of its successive spikes. Hence, the parameters can be adjusted to minimize the sum of squared differences ΔT_i between the experimentally observed firing of the neuron ("experiment output") and the firing predicted by the model ("model output"). The resulting parameter set p^* gives the best (predictive) estimate of the intrinsic parameters and of the entries in the connectivity matrix corresponding to the modeled neuron.

Finally, it should be noted that this algorithm consents also the inclusion of any a priori knowledge of the parameter values, which may be provided by physiology, morphology, etc., simply constraining to the given values or ranges of the corresponding parameters. Furthermore, recurring to a preprocessing of the spike trains, the method handles bursting neurons; all is needed is to specify the minimal time interval for which two spikes are considered to be separated events and not a burst.

3. Numerical Tests

The method has been validated on three artificial test beds (neuron networks): i) a network of two probabilistic Spike Response Model (SRM) neurons [9] with low firing rates; ii) a network of two tonic Regularly Spiking (RS) [10] neurons; and iii) a mixed SRM-RS three neurons network.

For each of the three "experimental" arrangements, the method has been applied to identify the connectivity pattern and intrinsic parameter values of the model neural network. Afterwards, the identified models have been simulated. Though, in the case of a few neurons the considered reference model possess rather simple dynamics, demonstrating a kind of synchronization phenomenon in spite of the strong variability of the measured data. Hence, in the simulations a white modeling noise has been added to the deterministic equations to model all the unmeasured phenomena, including entrances from unobserved neurons and noisy environment. The simulation of the identified model

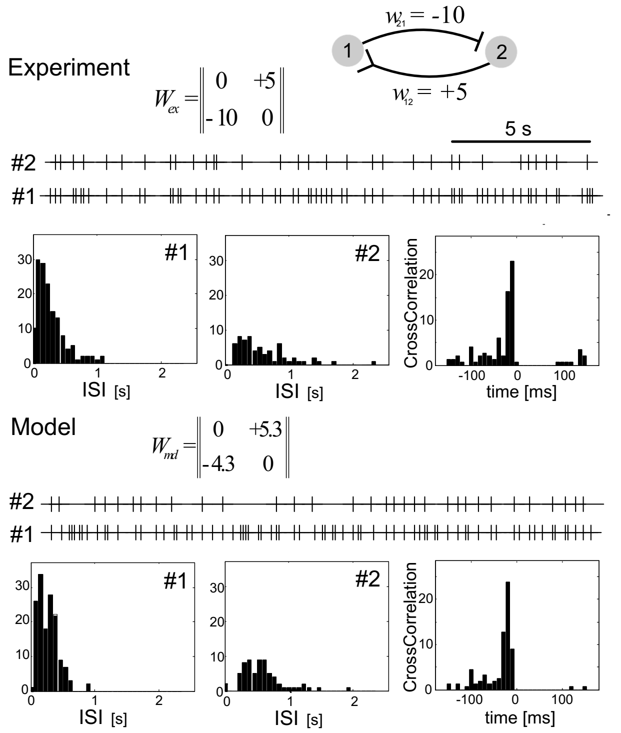

Figure 2: Identification and modeling of a two-neuron network with an excitatory-inhibitory coupling loop between two SRM neurons. The upper part marked "Experiment" shows the experimental spike trains and their ISI and cross-correlation histograms. The lower part marked "Model" illustrates the identified connectivity matrix, W_{md}, which captures correctly the experimental connectivity pattern, and the modeled spike trains with their ISI and cross-correlation histograms, which are similar to those from the experiment.

allows crosschecking statistical properties, *e.g.* interspike intervals (ISI) and cross-correlation histograms, of modeled and "experimental" spike trains, besides comparing the connectivity patterns.

The details of the test beds and results are summarized in Figs. 2–4.

Figure 2 shows the results for the case of two neurons forming an excitatory-inhibitory loop. The "V" and "T"-like link ends mark excitatory and inhibitory synapses, respectively. The spike trains from the two neurons are not trivially interrelated. The presence of the excitatory synapse is pointed out by the experimental cross-correlation histogram, which shows a peak. However, the presence of an inhibitory synapse is not obvious. On the contrary, the identification method provides the correct connectivity pattern, and the simulation of the network results in a satisfactory statistical accordance of experimental and model produced data. Though, it should be noted that the "experimental" and identified coupling matrices can be compared only qualitatively, as the absolute values of their entries are incommensurable referring to two completely different mathematical models.

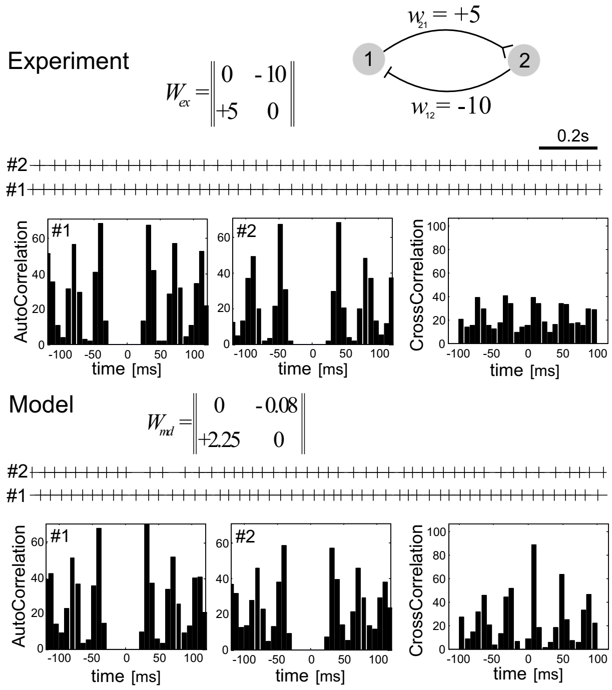

Figure 3: Same as in Fig. 2 for the case of a two-neuron network of mutually interconnected RS neurons.

Figure 3 illustrates the results for the case of two tonic spiking neurons connected into an excitatory-inhibitory loop. The auto-correlation clearly demonstrates equidistantly distributed peaks representative of the tonic spiking of both neurons, whilst the peaks in the cross-correlation highlight the presence of synaptic coupling. However, as in the previous experiment, the analysis of the histogram does not allow outlining the connectivity pattern, neither allows drawing any conclusion about the intrinsic spiking nature of the two neurons. On the contrary, the identified model provides the correct connectivity pattern and first order statistics. Furthermore, the simulation of the two iso-

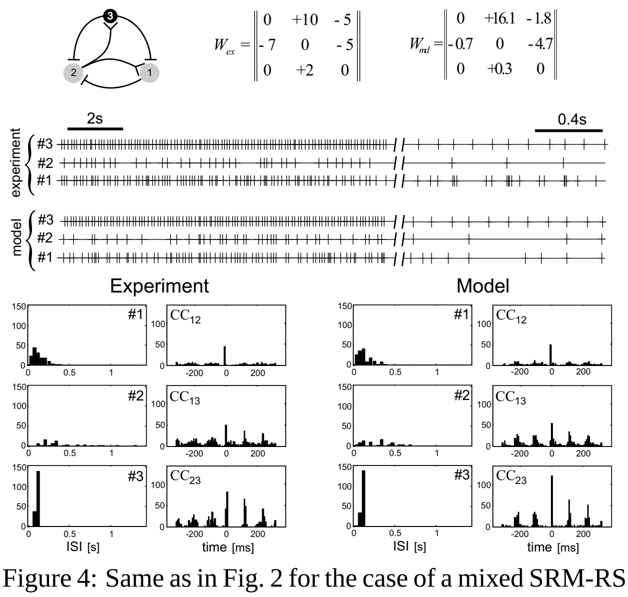

Figure 4: Same as in Fig. 2 for the case of a mixed SRM-RS three neurons network.

lated (modeled) neurons allows spotting exactly their intrinsic spiking nature, highlighting in this way the modeling ability of the method.

Finally, Fig. 4 summarizes the results obtained when applying the identification technique to a complex mixed RS-SRM three-neuron network: neuron 1 and 2 are SRM whilst the third is a RS neuron, *cf.* Fig. 4. Note that this case has different feedback loops and indirect connections, which makes problematic the study of the connectivity pattern by means of the conventional cross-correlations. However, also for this harder case the identified model provides the correct connectivity pattern and first order statistics. Again, the simulation of the three isolated (modeled) neurons correctly spots the intrinsic regularly spiking nature of one of the three neurons.

4. Discussion

The proposed method has been successfully tested on artificially generated data. In order to assess the robustness of the method, the generation of data has been performed considering neuron models denying the most restricting hypotheses on which the method trusts. Namely, considering networks combining statistical responding [9] and not renewal regularly spiking [10] neuron models, which deny the determinism and the resetting property of the modeled neuron, respectively. Furthermore, the three networks considered collect the main difficulties reported in literature about the identification of the neural connectivity, like mutual and indirect couplings and excessively regular interspike intervals; hence, providing a reliable platform for the assessment of the identification technique.

For all the considered networks, the method provided the correct functional connectivity pattern. Simultaneously, with reference to the modeling issues, the simulation of the identified networks has provided spike trains with first order statistics in satisfactory accordance with the experimental ones and, for the more complex considered networks, the mathematical analysis of the identified model has correctly spotted intrinsic features of the isolated neurons, which could not be inferred from the spike trains by statistical methods, highlighting in this way the strength of the modeling technique.

Finally, it should be mentioned that the network connectivity obtained may differ from the anatomical network from which the data are observed. Though, both of them are functionally equivalent for certain experimental conditions, *i.e.* they span the same dynamical behavior, which justifies the use of the term *functional synapse* or *functional network* used through all the text to indicate the equivalent neural dynamical systems that could generate the observed data.

5. Conclusions

The present paper has proposed a deterministic technique that, given the spike trains of N neurons, allows the extraction of a mathematical model describing the architecture of the underlined biological neural network and the dynamic behavior of its neurons. The method relies on the solely spike discharging times, and has been successfully applied on artificially generated data.

Acknowledgments

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