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Boolean Modeling of Neural Systems with Point-Process Inputs and Outputs

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Abstract—**This paper presents a novel modeling approach for neural systems with point-process inputs and outputs (binary time-series of 0's and 1's) that utilizes Boolean operators of modulo-2 multiplication and addition, corresponding to the logical AND and OR operations respectively. The form of the employed mathematical model is akin to a "Boolean-Volterra" model that contains the product terms of all relevant input lags in a hierarchical order, where terms of order higher than first represent nonlinear interactions among the various lagged values of each input point-process or among lagged values of various inputs (if multiple inputs exist) as they reflect on the output. The coefficients of this Boolean model are also binary variables that indicate the presence or absence of the respective term in each specific model/system. Simulations are used to explore the properties of such models and the feasibility of accurate estimation of such models from short data-records in the presence of noise (i.e. spurious spikes). The results demonstrate the feasibility of obtaining reliable estimates of such models, even in the presence of considerable noise in the input and/or output, thus making the proposed approach an attractive candidate for modeling neural systems in a practical context.**

I. Introduction

The study of the manner in which information is processed by neuronal ensembles is a problem that has been studied extensively for many years. Its solution has been hindered by the fact that neural systems are nonlinear, dynamic, highly interconnected and subject to stochastic influences/variations. In the case of point-process input and output data (sequences of action potentials recorded from individual neurons), the complexity of the mathematical analysis is compounded by the binary signal modality. Although considerable progress has been made by numerous efforts over the last 50 years in the development of modeling methods appropriate for point-process inputs and outputs ([1], [2], [3], [4]), much remains to be done in order to improve the efficacy and reduce the complexity of such methods.

This paper introduces a new approach of modeling neural systems with point-process inputs and outputs that utilizes Boolean operations (logical AND and OR operations corresponding to modulo-2 multiplication and addition, respectively).

This approach offers a general methodological framework that exhibits the advantages of parsimonious representation (i.e. relatively compact models) and computational efficacy (i.e. robust estimation from short data-records in the presence of noise or measurement inaccuracies).

Although a vast mathematical literature exists in the context of Boolean operations, few attempts have been made to apply this mathematical approach to biological problems. Some of these attempts have been made in the research areas of molecular/cellular modeling [5], associative memories [6] and network dynamics [7]. Note that the term *Boolean model* is used therein with a different meaning and bears no essential relation with the work presented herein.

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II. Methods

For point-process data, the general mathematical form of the proposed kth-order Boolean model in the single-input/single-output case is given by the expression:

$$\begin{aligned} y(n) &= h1(1)\otimes x(n-1)\oplus h1(2)\otimes x(n-2)\oplus\ldots \\ &\oplus h1(M)\otimes x(n-M)\oplus h2(1,2)\otimes x(n-1)\otimes x(n-2)\oplus\ldots \\ &\oplus h2(m1,m2)\otimes x(n-m1)\otimes x(n-m2)\oplus\ldots \\ &\oplus h2(M-1,M)\otimes x(n-M+1)\otimes x(n-M)\oplus\ldots \\ &\oplus hk(m1,\ldots mk)\otimes x(n-m1)\otimes\ldots\otimes x(n-mk)\oplus\ldots \end{aligned} \quad (1)$$

where *y(n)* and *x(n)* denote the binary output and input data, respectively, as time-series of 0's and 1's in discrete-time intervals (bins) of bin-width equal to the refractory period of the neuron (with 1 indicating the presence of an action potential at the respective bin). The model coefficients/parameters h_k $(m_1, \ldots, m_k)$ are binary variables that are estimated from input-output data as described below. The Boolean operators ⊗ and ⊕ denote the modulo-2 operations of multiplication (logical AND) and addition (logical OR) respectively.

It is evident in this model form that the terms on the right-hand side (RHS) are structured in a hierarchical manner representing various orders of nonlinear interactions in the subject system (of course, the first-order terms represent the linear portion of the model). The set of existing terms of kth order may be viewed as the kth-order "Boolean-Volterra (B-V) kernel" of the system, in analogy to Volterra models of systems with continuous inputs and outputs [2].

In each specific neuronal system, only some of the additive terms on the RHS of Eq. (1) exist (a fact that is expressed mathematically by the respective coefficient being 1). The finite memory of the system implies that the system performs a mapping of a vector of input past and present values (equal in length to the system memory and termed the "input epoch") onto the output present value at each discrete time n.

It is critical to note that the presence of a first-order term at some lag i eliminates the possibility of having a higher order term with a lag i. Likewise, the presence of a second-order term at some pair of lags (i, j) eliminates the possibility of a higher order term with this pair of lags etc. We refer to this fact as the *occlusion effect* (i.e. the fact that a non-zero value of a B-V kernel at some combination of lags prevents the possibility of non-zero values of higher order B-V kernels at those locations that contain the same combination of lags). This fundamental fact follows from the definition of the RHS of the Boolean model as an OR logical conjunction of combinations of input past spikes with the ability to cause an output spike in the specific neural system. This notion of *sufficiency* of each term on the RHS of the Boolean model leads to the occlusion effect.

We also observe that no terms can exist with a multiplicity of lag indices (e.g. the diagonal elements of the second-order B-V kernel defined by m1=m2) because an input event cannot be considered as interacting with itself.

The meaning of the proposed Boolean model is that, depending on the specific input-epoch data at each discrete time n, the activation of *at least one* of the existing terms on the RHS of the model will cause an event (action potential) at the output. If more terms happen to get activated, then the result will be the same. The nonzero terms on the RHS of the model indicate the possible binary input patterns that can trigger an event at the output. The mathematical and physiological notion of the triggering input pattern is far more general in this context (because it includes possible high-order nonlinear interactions) than the customary first-order notion. Furthermore, the extraction of this general model from input-output data is mathematically rigorous, robust and computationally efficient (i.e. short data-records suffice for accurate estimation of nonlinear models, even in the presence of considerable noise that is manifested as spurious spikes), as illustrated with simulated data in the Results section.

The extension of this modeling approach to multiple inputs and outputs is straightforward and remains computationally efficient, although the notational complexity of the model inevitably increases as the number of inputs increases in order to accommodate the interactions among the multiple inputs.

It is important to note that the estimated Boolean model can be used for predicting the output in response to *any point-process* input (or set of inputs in the multi-input case). The estimation of the Boolean model from input-output data is straightforward and computationally efficient following the procedure described below.

To estimate the Boolean model, we count the number of times each possible term on the RHS of the model may have contributed to the generation of an output event. For instance, in the single-input/single-output case of Equation (1), we count the lagged input events and their product combinations (as they are defined by the additive terms on the RHS of the model equation) that precede each output event within a memory window of M lags. The resulting *incidence index* for each term (the number of all possible causal contributions of the specific term after all output events have been considered, divided by the total number of output events) is compared to a properly selected threshold (the *estimation threshold*) and the respective term is included in the estimated model if, and only if, its incidence index exceeds this threshold.

The selection of the estimation threshold (which is distinct for each order of B-V kernel and depends on the statistics of the specific input process) is a critical task that can be performed either by setting statistical confidence bounds for the computed value of the incidence index at each lag of every B-V kernel of the system/model, based on Type I and Type II errors (at specified significance levels) for rejecting/accepting the null hypothesis that the true kernel values are zero, or from computed Receiver Operating Characteristic (ROC) curves – commonly used in detection studies – using an "optimal threshold" criterion [2].

The value of the estimation threshold generally depends on the mean firing rate (MFR) of the input, as well as the prevailing noise conditions. Specifically, in the noise-free case of the singe-input/single-output system, extensive simulations (Monte Carlo runs) have shown that the estimation threshold for the first-order B-V kernel is proportional to the square-root of the input MFR, and the estimation threshold for the second-order B-V kernel is proportional to the input MFR. We postulate that, in general, the estimation threshold is proportional to the (k/2)-th power of the input MFR for the kth-order B-V kernel.

Although the size of the required data-record for satisfactory estimation of the B-V kernels generally depends on the characteristics of each specific system (i.e. the number and type of terms in its model) and the ambient noise conditions, our initial results from simulated data indicate that a few hundred input-output spikes ought to be adequate in most cases. This implies that the required length of experimental data-records will be on the order of a few minutes, depending on the input/output MFR.

In the case of input and/or output noise point-processes (i.e. spurious spikes superimposed randomly on the input and/or output point-processes), the presence of the spurious spikes increases the respective MFR and affects the incidence index potentially for all terms in the model, depending on the specific statistical characteristics of the noise point-process. As we will illustrate in the Results section, this estimation procedure is remarkably robust in the presence of spurious spikes (defining "noise" in this context) in the input and/or output.

Since the statistical distribution of the incidence index under the null hypothesis (of zero B-V kernel values) depends on the statistical characteristics of the specific input point-process and the ambient noise, we believe that the method of the ROC curves offers a practical advantage. Nonetheless, if the statistical characteristics of the specific input point-process and ambient noise are known (or can be reliably measured), then the statistical distribution of the incidence index under the null hypothesis can be determined for each order of B-V kernel and, from this, the confidence bound at the selected significance level that becomes the estimation threshold for the respective kernel values.

Another important issue in the kernel estimation procedure is the aforementioned *occlusion effect* that is due to the fact that a non-zero value of a B-V kernel at some combination of lags prevents the possibility of non-zero values of higher order B-V kernels at those locations that contain the same combination of lags. This reduces the computational burden and the likelihood of nonzero B-V kernels of order higher than second or third in actual applications.

The predictive capability of the Boolean model can be quantitatively assessed by the relation of true positive and false positive predictions of output spikes, because the binary modality of the output hampers the use of the customary norm of output prediction mean-square error measurements for model performance evaluation.

The estimated Boolean model can be validated through its predictive capability for a set of input-output data that were not used during the estimation procedure but are proximal to the data-record used for model estimation (i.e. a data segment just before or just after the segment used for estimation). The ability of the estimated model to perform this "out-of-sample" prediction is predicated on the assumption of system stationarity and can be quantified by means of the ratio of the correctly predicted output spikes relative to the total number of actual output spikes (PTP: probability of true positives) and/or the ratio of the incorrectly predicted spikes in the model output relative to the total number of model-predicted spikes (PFP: probability of false positives). Note that the number of output spikes that are predicted correctly by the model (NTP: number of true positives) is given by the product of PTP with the total number of output spikes N_0, which is generally different from the total number of model-predicted spikes N_p. Thus, the probability of not predicting correctly an actual output spike is different from PFP and it is given by (1-PTP) in the absence of spurious spikes at the output.

The performance of the estimated Boolean model is evaluated by the relation of the PTP and PFP measurements in the context of the prevailing noise conditions (i.e. the number of spurious spikes at the input and/or output). Obviously, we seek *higher PTP and lower PFP* values, although the precise form of an appropriate "metric of performance" cannot be universally defined, since it depends on the relative importance of true positives versus false positives in each particular application. It must be also recognized that both values depend on the prevailing noise conditions and the selected estimation threshold. The latter fact leads to the evaluation tool of ROC curves that depict the relation between PTP and PFP for various values of the estimation threshold under given noise conditions.

III. RESULTS

As an illustrative example, consider the second-order single-input/single-output system defined by the two Boolean-Volterra (B-V) kernels shown in Figure 1.

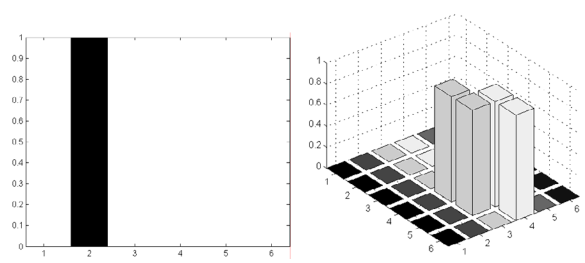

Fig. 1. The first-order (left) and second-order (right) Boolean-Volterra (B-V) kernels of the simulated second-order system/model. Note that the diagonal values of the second-order B-V kernel must be zero by definition, and its values along the lines at *m1=2 and m2=2* must be also zero in this case due to the occlusion effect (see text).

A Poisson point-process input with mean firing rate (MFR) of 20 sps (spikes per second) is used to simulate this system and generate the corresponding point-process output that has a MFR of 22 sps (determined by the specific form of the two B-V kernels). Illustrative segments of the input-output data-record over 10 sec are shown in Figure 2, where the output spikes that are due to the second-order interactions (defined by the second-order B-V kernel) are highlighted with thick dashed lines.

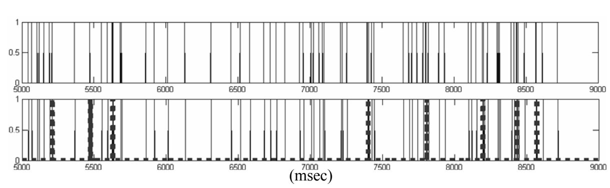

Fig. 2. Segments of the Poisson input point-process (top) and the corresponding output (bottom) over 10 seconds. The thick dashed spikes in the output are spikes due to the second-order interactions.

These input-output data are used to estimate the two B-V kernels following the procedure outlined in Methods. This procedure yields the “incidence indices” shown in Figure 3 for the two kernels that result in the correct B-V kernels upon thresholding with the appropriate estimation thresholds of 300 for the first-order kernel and of 40 for the second-order kernel.

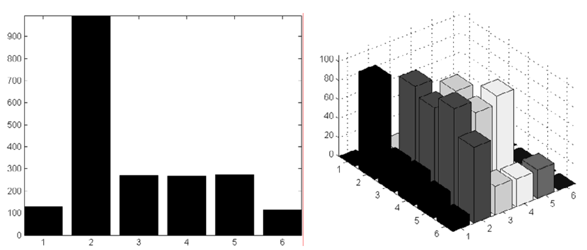

Fig. 3. The computed incidence indices for the two B-V kernels of the simulated second-order Boolean system/model of Figure 1. The occlusion effect dictates that we set the second-order B-V kernel values to zero along the lines at m1=2 and m2=2, because of the non-zero value of the first-order B-V kernel at m=2, and along the diagonal m1=m2.

In order to examine the dependence of the estimation thresholds on the input MFR, we repeat the simulation and estimation procedures for various input MFRs from 2 sps to 80 sps. The results are shown in Fig. 4 and confirm that the first-order estimation threshold depends on the square-root of the input MFR and the second-order estimation threshold is proportional to the input MFR.

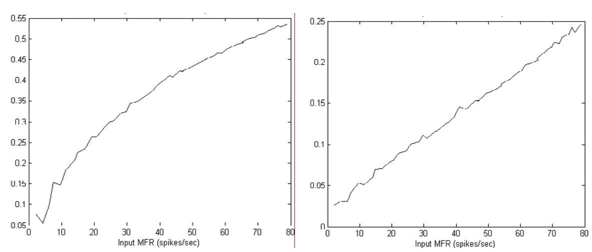

Fig. 4. The dependence of the estimation threshold on the input MFR for the first-order B-V kernel (left) and the second-order B-V kernel (right) as computed in independent runs.

In order to examine the robustness of the proposed modeling and estimation procedure in the presence of input and output point-process noise, we repeat the simulation and estimation procedures for a number of input (or output) spurious spikes equal to the actual input (or output) spikes in the noise-free data. The results in the two cases are shown in Figures 5 and 6 respectively, demonstrating the robustness of the proposed approach.

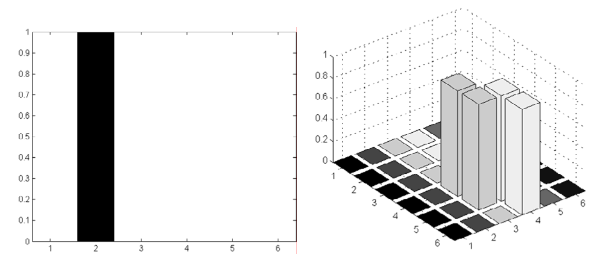

Fig. 5. The estimated first-order (left) and second-order (right) B-V kernels for the case of input spurious spikes, equal in number to the actual input spikes.

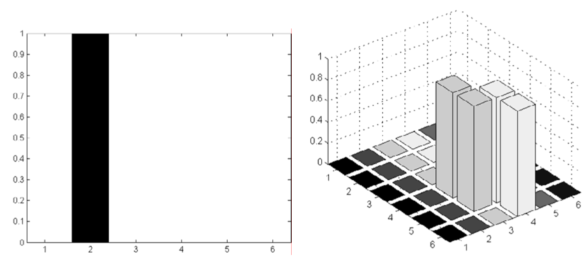

Fig. 6. The estimated first-order (left) and second-order (right) B-V kernels for the case of output spurious spikes, equal in number to the actual output spikes.

IV. DISCUSSION

The efficacy of the proposed Boolean modeling approach has been demonstrated with simulated data in a second-order single-input/single-output case. The dependence of the estimation threshold on the input MFR was examined and the robustness of this estimation and modeling approach in the presence of input or output spikes was also demonstrated. This approach can be extended to the multi-input/multi-output case. The next critical step is the validation of this approach with actual experimental data

REFERENCES

[1] F. Rieke, D. Warland, R. deRuytervanSteveninck and W. Bialek, *Spikes: Exploring the Neural Code*. Cambridge, MA: MIT Press, 1999.

[2] V. Z. Marmarelis, *Nonlinear Dynamic Modeling of Physiological Systems*. New York, NY: Wiley Interscience, 2004.

[3] V. Z. Marmarelis, T. W. Berger “General methodology for nonlinear modeling of neural systems with Poisson point-process inputs”, *Mathematical Biosciences,* vol. 196(1), pp. 1-13, July 2005.

[4] V. A. Makarov, F. Panetsos and O. de Feoo, “A method for determining neural connectivity and inferring the underlying network dynamics using extracellular spike recordings”, *Journal of Neuroscience Methods,* vol. 144(2), pp. 265-279, June 2005.

[5] C Farrow, J. Heidel, J. Maloney and J. Rogers, “Scalar equations for synchronous Boolean networks with biological applications”, *IEEE Trans. Neural Networks*, vol 15(2), pp. 348-354, Mar. 2004.

[6] A. G. D’yachkov, V. V. Rykov, “The capacity of the Boolean associative memory” in *1997 IEEE Int. Conf. Artificial Neural Networks*, pp. 158-160.

[7] J. C. Handley, E. R. Dougherty, “Optimal nonlinear filter for signal-union-noise and runlength analysis in the directional one-dimensional discrete Boolean random set model”, *Signal Processing,* vol. 51, pp. 147-166, 1996