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Estimation and Statistical Validation of Event-Invariant Nonlinear Dynamic Models of Hippocampal CA3-CA1 Population Activities

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***Abstract*—To develop hippocampal prosthetic devices that can restore the memory-dependent cognitive functions lost in diseases or injuries, it is essential to build a computational model that sufficiently captures the transformations of multiple memories performed by hippocampal sub-regions. A universal model with a single set of coefficients for all memories is desirable, since it can transform the memories without explicitly knowing what those memories represent and thus avoids switching between multiple models for multiple memories in implementation. In this study, we test the feasibility of such universal models of hippocampal CA3-CA1 by estimating the multi-input, multi-output (MIMO) nonlinear dynamic models using input (CA3) and output (CA1) spike trains recorded during multiple behavioral events representing multiple memories from rats performing a delayed nonmatch-to-sample task. We further statistically evaluated the model performances of the MIMO models on the different events. Results show that the models accurately replicate the output spike patterns during those events, and thus can be used as event-invariant nonlinear dynamic models that continuously predict the ongoing CA1 spatio-temporal patterns as the ongoing CA3 spatio-temporal patterns unfold.**

I. Introduction

Performing the memory-dependent delayed-nonmatch-to-sample (DNMS) task involves multiple long-term memories such as the memories of lever position and task phase [1, 2]. In the hippocampus, these memories are represented as spatio-temporal patterns of spikes associated with behavioral events and propagating from the upstream brain regions, e.g., CA3, to the downstream regions, e.g., CA1. To develop prosthetic devices that can restore the memory-dependent cognitive functions of a hippocampal region, it is essential to build a computational model that sufficiently describes the transformation of multiple memories during different behavioral events performed by this region. One approach of solving such modeling problem is to build separate models specific for each memory/event, i.e., event-specific models (Fig. 1, Left). Alternatively, a single event-invariant model may be attempted for multiple memories/events (Fig. 1, Right). The latter approach is more desirable for developing hippocampal prostheses because it generates a universal model that transforms the memories without explicitly knowing what those memories represent and thus avoids switching between multiple models based on the discrimination or monitoring the precise timings of those memories/events. The goal of this study is to test the feasibility of such modeling approach by estimating and statistically validating the multiple-input multiple-output nonlinear dynamic model of CA3-CA1 using input (CA3) and output (CA1) spike trains corresponding to the various events during the DNMS task.

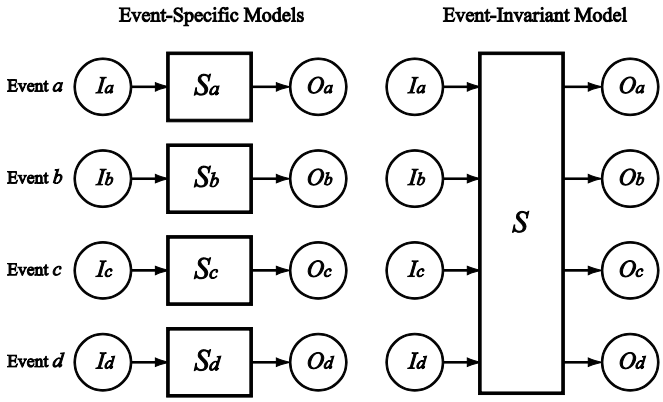

Figure 1. Event-specific models vs. event-invariant model. An event-specific model describes the input-output transformation during a single event. An event-invariant model describes the input-output transformations with the same set of coefficient during multiple events. *I*: input signals; *O*: output signals; *S*: MIMO models.

II. Methodology

A. Behavioral Task

Male Long-Evans rats were trained to criterion on a two-lever, spatial DNMS task with randomly occurring variable delay intervals [1]. Animals performed the task by pressing (sample response) a single lever presented in one of the two positions in the sample phase (left or right); this event is called the "sample response" (Fig. 2, Left). The lever was then retracted and the delay phase initiated; for the duration of the delay phase, the animal was required to nose-poke into a

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lighted device on the opposite wall. Following termination of the delay the nose-poke light was extinguished, both levers were extended and the animal was required to press the lever opposite to the sample lever; this act is called the "nonmatch response" (Fig. 2, Right). If the correct lever was pressed, the animal was rewarded and the trial was completed. A session included approximately 100 successful DNMS trial that each consisted of two of the four behavioral events, i.e., left sample (LS) and right nonmatch (RN), or right sample (RS) and left nonmatch (LN).

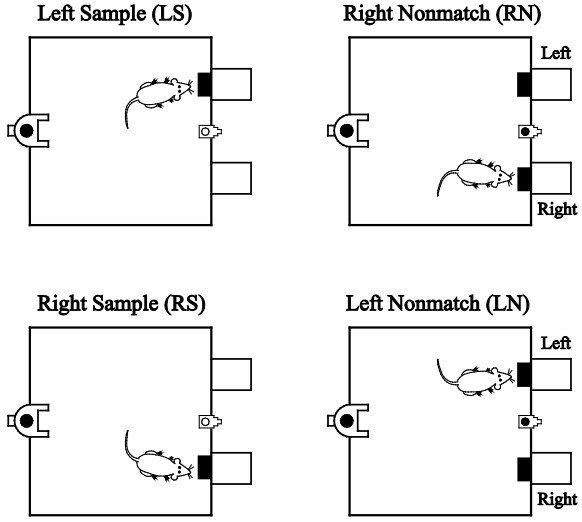

Figure 2. Major behavioral events during the DNMS task. Each successful DNMS trial consists of either LS and RN (top), or RS and LN (bottom).

B. Recording and Preprocessing of Spike Trains

Spike trains were obtained from both hippocampal CA3 and CA1 regions of rats performing the DNMS task using a multi-electrode array. Spikes were sorted, timestamped, and discretized with a 2 ms bin size.

C. Model Configuration and Parameter Estimation

A general, Volterra kernel-based strategy is used to model the MIMO nonlinear dynamics underlying hippocampal CA3-CA1 spike train-to-spike train transformations [3-5]. In this approach, the identification of spatio-temporal pattern transformations from the hippocampal CA3 region to the CA1 region is formulated as the estimation of a MIMO model that can be decomposed into a series of multi-input, single-output (MISO) models with a physiologically plausible structure that can be expressed by the following equations:

$$w = u(k,x) + a(h,y) + \varepsilon(\sigma), \quad y = \begin{cases} 0 & \text{when } w < \theta \\ 1 & \text{when } w \geq \theta \end{cases}$$

The variable x represents input (CA3) spike trains; y represents output (CA1) spike trains. The hidden variable w represents the pre-threshold membrane potential of the output neurons. It is equal to the summation of the post-synaptic potential u caused by input spike trains, the output spike-triggered after-potential a, and a Gaussian white noise ε with standard deviation σ. When w exceeds threshold, θ, an output spike is generated and a feedback after-potential (a) is triggered and then added to w. The transformation from x to u is expressed as a MISO Volterra series with a set of feedforward kernels k. The transformation from y to a is expressed as a single-input, single-output Volterra series with a feedback kernel h.

In order to estimate event-invariant models, input-output data during the four major events (-2s to 2s) are extracted and concatenated to form the training data for parameter estimation.

Due to the Gaussian noise term and the threshold, this model can be considered a special case of the Generalized Laguerre-Volterra Model (GLVM), which employs a *probit* link function [4, 5]. All model parameters, i.e., k, h, σ, and θ, can be estimated simultaneously with an iterative re-weighted least-squares method and a simple normalization procedure. To avoid overfitting and reduce model complexity, a statistical procedure is used to select the significant inputs and model terms [4, 5]. The resulted sparse MIMO model achieves maximal out-of-sample likelihood.

D. Statistical Validation of the Event-Invariant Model

Due to the stochastic nature of spike firing, estimated models are validated using an out-of-sample Kolmogorov -Smirnov (KS) test based on the time-rescaling theorem [6]. In short, this method directly evaluates the continuous firing probability intensity predicted by the model with the recorded output spike train. According to the time-rescaling theorem, an accurate model should generate a conditional firing intensity function that can rescale the recorded output spike train into a Poisson process with unit rate. By further variable conversion, inter-spike intervals (ISIs) should be rescaled into independent uniform random variables on the interval (0, 1). The model goodness-of-fit then can be assessed with a KS test, in which the rescaled intervals are ordered from the smallest to the largest and then plotted against the cumulative distribution function of the uniform density. If the model is accurate, all points should be close to the 45-degree line of the KS plot. Confidence bounds (e.g., 95% or 99%) can be used to determine the statistical significance.

In order to test the event-invariability of an estimated model, the prediction performances of the model on the multiple events need to be assessed and compared. By definition, an event-invariant model should be able to capture accurately the input-output properties of the system during different events. Thus, the first criterion (Criterion A) requires the KS plots of the estimated model to be close to the 45-degree line in all events. A model that meets Criterion A can be called an *event-invariant model*. However, it is quite possible that a model is event-invariant simply because there is no event-specificity in the system to begin with. For example, the firing characteristics of the modeled CA1 neuron may remain the same across different events, i.e., the CA1 neuron does not belong to any functional cell type (FCT) [1]. In order to rule out this possibility, we introduce

Criterion B that requires (i) the distributions of ISIs during different events to be different, and (ii) the distributions of the ISIs rescaled by the model to be similar. Statistically, (i) can be tested by comparing the KS plots of the ISIs with a trivial model (e.g., zeroth-order model or "no model"), and (ii) can be tested by comparing the KS plots of the ISIs with the estimated MISO nonlinear dynamic model. The zeroth-order model is simply a homogeneous Poisson model taking only the mean firing rate of the output into account (without including the inputs and the past output activities). A model that meets *both* Criterion A and B will be called a *true event-invariant model*. Obviously, a true event-invariant model is nothing else but an event-invariant model of a FCT.

III. Results

We estimate and validate MISO models with multi-event input-output datasets using the method described in the Methodology Section.

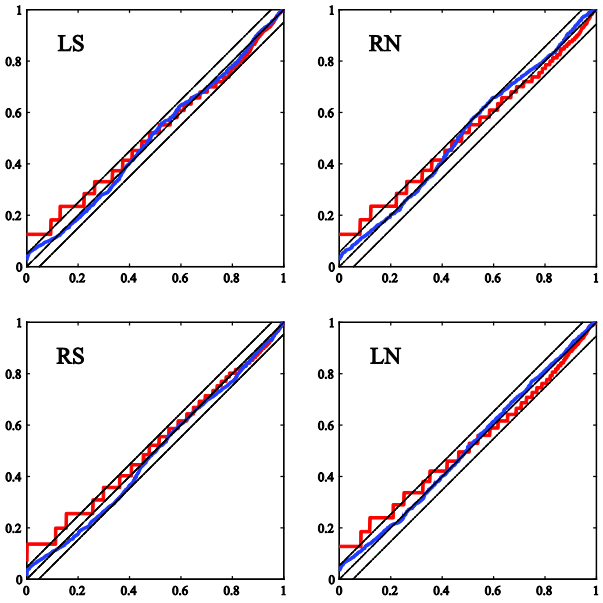

Figure 3. KS plots of a MISO model in the four major events (case #1). Red lines: KS statistics of ISIs without applying the MISO model; blue lines: KS statistics of ISIs after applying the MISO model; Black lines: 95% confidence bounds and the 45-degree line. 99% confidence bounds are not shown.

First, we examine the model goodness-of-fit during the events. Figure 3 and 4 show two cases of the models. Before applying the MISO models, the KS plots of the ISIs (red lines) all fall out of the 95% or 99% confidence bounds in all four behavioral events in both datasets. After applying the MISO models, the KS plots (blue lines) become much closer to the 45-degree lines in all events. In Case #1, KS plots with the model are within the 95% confidence bounds in 3 of 4 events (in the RN, the KS statistics is slightly out of the 95% bounds but within the 99% bounds); in Case #2, KS plots with the model are all within the 95% confidence bounds. These results show that these MISO models can capture the hippocampal CA3-CA1 nonlinear dynamics in all events. With 95% as the significance threshold, Model #2 is an event-invariant model; with a more relaxed 99% threshold, both Model #1 and #2 are event-invariant models.

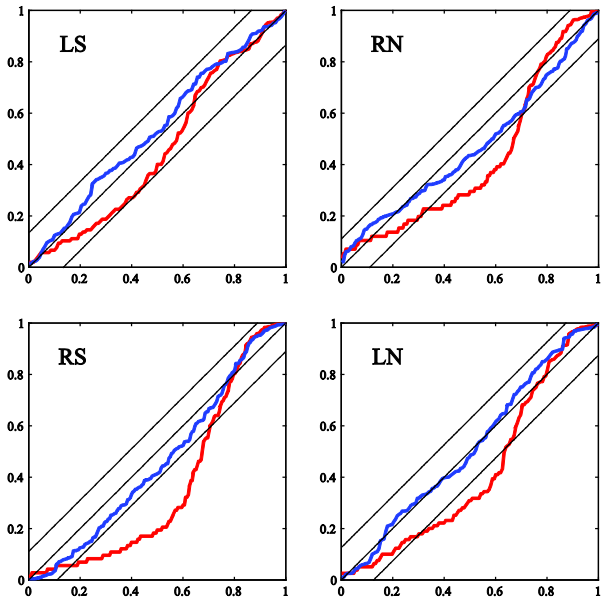

Figure 4. KS plots of a MISO model in the four major events (case #2).

TABLE I
Pair-Wise Kolmogorov-Smirnov Test Results

Case #1

	LS-RN	LS-RS	LS-LN	RN-RS	RN-LN	RS-LN
NM	2.3×10^{-4} ***	1.9×10^{-4} ***	6.9×10^{-5} ***	5.2×10^{-3} **	2.8×10^{-3} **	2.1×10^{-3} **
M	0.13 -	0.55 -	0.46 -	0.05 -	0.27 -	0.12 -

Case #2

	LS-RN	LS-RS	LS-LN	RN-RS	RN-LN	RS-LN
NM	0.15 -	5.2×10^{-4} ***	0.25 -	5.0×10^{-6} ***	7.3×10^{-2} -	4.8×10^{-3} **
M	6.6×10^{-2} -	4.2×10^{-2} *	0.72 -	2.6×10^{-2} *	0.16 -	0.22 -

NM: no model; M: with model. The numerical values are the p-values of the two-sample KS tests. The symbols -, *, **, and *** indicate $p > 0.05$, $p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively.

Secondly, we conduct pair-wise comparisons between the KS plots during different events, with and without applying the MISO models. The results are shown in Table I. In Case #1, the KS plots without the model (i.e., no model, or NM) are significantly different from each other in all pairs of events. With the model (i.e., M), there is no significant difference between any pair of the events. In Case #2, the KS plots without the model are significantly different in 3 of the 6 possible pairs of events. With the model, 0 or 2 pairs of events show significant differences (with the significance threshold value α set at 0.05 or 0.01, respectively). In both cases, the p-values of the null hypotheses are markedly increased from "no model" to "with model", indicating that

the differences in the distributions of ISIs during different events are greatly reduced by the models. With $\alpha = 0.05$, Model #1 is a true event-invariant model; with $\alpha = 0.01$, both Model #1 and #2 are true event-invariant models.

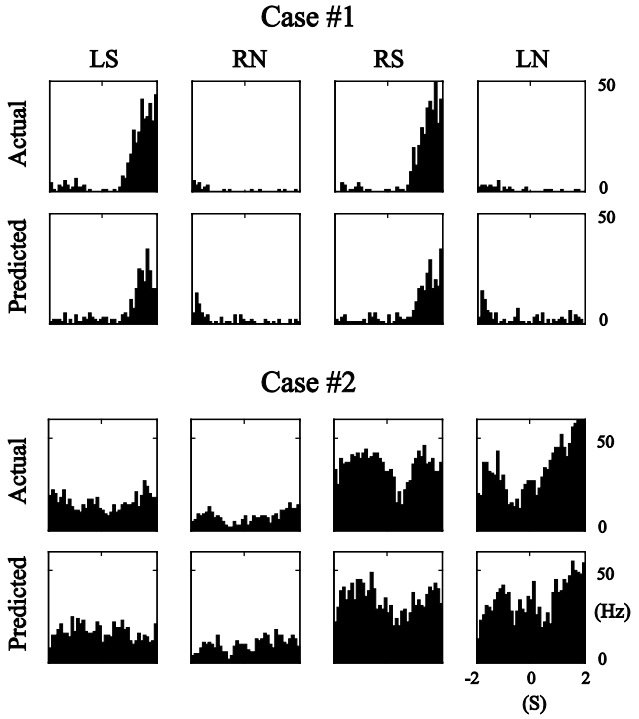

Figure 5. Perievent histograms of actual output spike train and predicted spike trains. Case #1 presents a phase-type cell; Case #1 presents a trial-type cell. In both cases, the MISO models accurately replicate the markedly different per-event histograms with a single set of coefficients. Bin size is 50 ms in all histograms.

Lastly, we examine the performances of the models in terms of replicating the peri-event histograms of the four major events. The peri-event histograms allow more direct appreciations of the averaged firing patterns during the events. Single-trial output spike trains are predicted from the estimated MISO models and the input spike trains using a simulation procedure [3, 4]. Peri-event histograms of predicted spike trains are then calculated and compared with the peri-event histograms of the actual spike trains. Figure 5 shows two representative cases. Case #1 presents a phase-type cell, i.e., a FCT that has high firing during the phase events (LS and RS). Case #2 presents a trial-type cell, i.e., a FCT that has high firing during two events that constitutes a success trial (LS and RN, or RS and LN in this case). It is evident that the MISO model can not only replicate the salient characteristics in firing rates during different events (e.g., in Case #1, the firing rates are high in LS and RS, and low in RN and LN; in Case #2, the firing rate are high in RS and LN, and low in LS and RN), but also capture some of the more subtle features in the temporal patterns of the spike trains (e.g., the prominent single peak in Case #1, and the multiple peaks in Case #2).

IV. Discussion

We estimate and validate event-invariant models of hippocampal CA3-CA1 for the development of hippocampal prostheses. The estimation of even-invariant model is straightforward – it simply requires using the input-output data during multiple events of interest to estimate the model coefficients. In this study, we include the four most critical events, i.e., LS, RN, RS and LN, during the DNMS task for the sake of efficiency. Other events, even the entire sequences of the input-output spike trains, can also be included in estimation, depending on the purpose of the model.

Furthermore, the event-invariabilities of the estimated models are evaluated with two statistical criteria. The purpose of using these criteria is to ensure that the models can not only predict accurately the output spike trains during multiple events, but also indeed capture the *differences* between the output spike trains during different events. The examples shown in this paper indicate that it is possible to build even-invariant models of hippocampal CA3-CA1. These results also suggest that the nonlinear dynamic transformational properties of the hippocampal CA3-CA1 remain constant across different forms of memories during the DNMS task in those well-trained animals.

Obviously, the event-invariabilities of the CA3-CA1 models depend on two factors: (i) the richness of information about CA1 firings in the ensemble firings of the CA3 neurons, and (ii) the generality of the nonlinear dynamic models, since CA1 outputs are predicted by the models based on the CA3 inputs. Natural questions to ask are how exactly such event-invariability is achieved and what the relative contributions of these two factors are. We aim to answer these questions in our future studies.

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