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# Insights on synaptic paired-pulse response using parametric and non-parametric models

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***Abstract*— Paired-pulse protocol is a well-established stimulation pattern used to characterize short-term changes in synaptic potency. Due to the experimental difficulty in accessing and measuring responses and interactions between subsynaptic elements, understanding the mechanisms that shape synaptic response is extremely challenging. We already proposed to address this issue and gain insights on the matter using a complex integrated modeling platform called EONS (Elementary Objects of the Nervous System). The use of this parametric platform provided us with insightful information on the subsynaptic components and how their interactions shape synaptic dynamics. We herein propose to add and combine a non-parametric model to (i) simplify the modeling framework, the number of underlying parameters and the overall computational complexity while faithfully maintaining the desirable synaptic behavior and (ii) provide a clear and concise framework to characterize AMPA and NMDA contributions to the observed paired-pulse responses.**

## I. INTRODUCTION

Synapses are inherently characterized by use-dependent changes in the amplitude of their responses over a time scale of milliseconds to seconds. Such plasticity (referred to as short-term plasticity or STP) is believed to have a strong influence on learning and memory and brain function in general. STP responses are classified into two major categories: (i) facilitation, when the response to the subsequent pulses increases due to previous stimulation with prior pulses, and (ii) depression when the opposite effect is observed. The nature of such phenomena has often been linked to presynaptic mechanisms, the residual calcium hypothesis of facilitation and the depletion model (resulting in overall synaptic depressed response). Numerous experimental protocols were used throughout the years to understand the various mechanisms underlying these observations [1–4]. However, given the nanoscopic nature of the structures and time scale under consideration, it has proven challenging to assess the mechanisms at play solely with conventional experimental methods. Computational methods have proven effective in providing insights into the mechanisms that underlie such observations. To this end, several parametric models have been developed [3], [5]. The structure of these models and of parametric models in general consists in faithfully replicating the multitude of physiological mechanisms that occur in the synapse, thereby relying on numerous a-priori assumptions. The values of the parameters are then evaluated to optimally superimpose the experimental results to the simulated ones. On the contrary, non-parametric models are obtained directly from the input-output data collected from experimental results without relying on any structural bias or assumption. Instead, the non-parametric approach consists in finding optimal functions contained within the general model to represent the input-output relationship of the system.

Within this framework, the present study proposes to (i) use a parametric model to generate a broad input-output synaptic dataset where experimental results are difficult to obtain, (ii) generate non-parametric models for AMPA and NMDA receptors responses using this input-output and (iii) determine the contributions of both receptor types to overall STP synaptic response.

## II. MODELING FRAMEWORKS

The parametric model used is the EONS platform (Elementary Objects of the Nervous System) [6] which is a complex integrated model of a generic glutamatergic synapse that encompasses presynaptic mechanisms such as calcium buffering, neurotransmitter release diffusion and uptake, and postsynaptic elements, such as ionotropic AMPA and NMDA receptors, their distribution and synaptic geometry, as well as metabotropic glutamate receptors. The focus of the present study is the postsynaptic component, and more specifically the ionotropic AMPA and NMDA receptors on the postsynaptic membrane which mediate rapid glutamatergic transmission.

The AMPA receptor model we used is described in [7]. It faithfully captures the receptor dynamics using 16 transition

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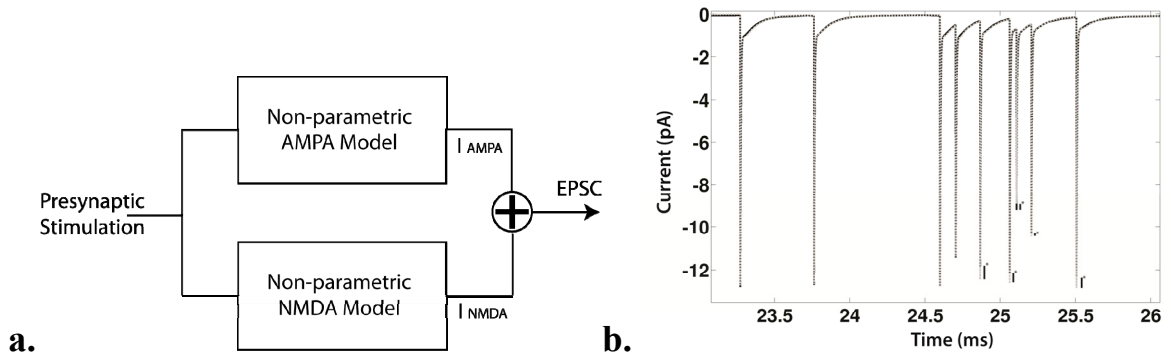


**Fig. 1.(a)** Diagram representing the non-parametric modeling framework containing AMPA and NMDA non-parametric models. **(b)** Superimposed EPSC responses of parametric EONS model and non-parametric model (dashed line) to a random interval train of 2Hz mean frequency. Noticeable differences in responses between parametric and non-parametric models are outlined with a bar next to them which length corresponds to the amplitude of the difference observed.

states, from resting to open, desensitized and deeply desensitized states. Our model of NMDA receptor is also a detailed kinetic model and was described in [8]. It consists of 15 states, which include interactions due to the binding of glutamate and a co-agonist glycine. The open state conductances are modulated by the concentration of magnesium within the extra-cellular environment. The open state transition probabilities multiplied with the conductance of the channels give an estimate of the postsynaptic current. Both models have been validated with experimental results, and the details of the kinetic constants of the hidden Markov processes are reported in [7], [8]. 80 AMPA receptors and 20 NMDA receptors were used, consistent with experimental results for AMPA expressing (non-silent) synapses [9]. Receptors were placed at median locations along the postsynaptic membrane, with AMPA receptors placed at an average distance of 80nm from the release site, and NMDA receptors at a distance of 60nm. Simulations were run in voltage-clamp situation, i.e. with postsynaptic voltage held constant thereby allowing the use of single-input single-output non-parametric framework (input being the presynaptic pulse stimulation, and output being the receptors-associated currents).

Non-parametric modeling (using Volterra models) through use of specific functions called Laguerre functions has already been proven to qualitatively and quantitatively reproduce nonlinear dynamics underlying synaptic STP [10] and will be used in this study. Within the Volterra modeling approach, the results are segmented in a hierarchy of orders representing the rising combination of multiple preceding events. Responses are derived from the Volterra kernels which describe the dynamics of the system. The first order response represents the amplitude and shape attributed to a single stimulation event, i.e. in the absence of any preceding input pulse within a specific time window (defined as the memory of the model). The second-order response represents the change in amplitude caused by a prior event on the response to the latest event. Similarly, the third order corresponds to the change in amplitude caused by third-order interactions between the present input event and any two preceding input pulses within the memory window. For brevity reasons, the Volterra model estimation is not described in this paper, but readers are advised to read [11], [12] for more details. The non-parametric framework we propose consists of the summation of two Volterra models, one for AMPA and one for NMDA receptor models as described in Fig. 1a.

To calibrate our non-parametric models, we subjected the parametric model to a random interval train of stimulation pulses (RIT) at a mean frequency of 2Hz with a Poisson distribution during 100 seconds. This generates a series of input-output data that allowed us to determine the coefficients of the Volterra kernels. A series of two simulations were launched, a first with NMDA receptors blocked and a second with AMPA receptors blocked to calibrate the two non-parametric models for the two receptors independently, and allow for optimal estimation of their respective p value.

## III. RESULTS

| | AMPA-R only | NMDA-R only | Global framework |
|---|---|---|---|
| NRMSE | 3.98% | 9.36% | 5.0% |

**Table 1.** Normalized mean square error for all non-parametric models with respect to parametric data.

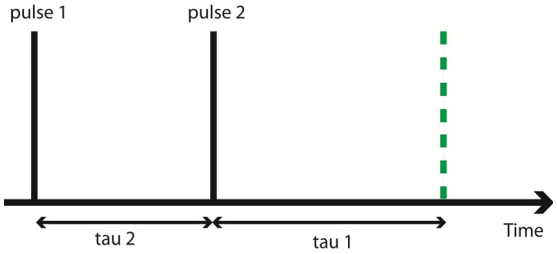


**Fig. 2.** Illustration explaining the significance of the two variables tau1 and tau2 for the second order response. The green dashed line corresponds to the point of measure.

The non-parametric model was successfully calibrated, with output faithfully reproducing the parametric results with a normalized root mean square error of 3.98% for the AMPA-R, 9.36% for the NMDA and 5% for the global non-

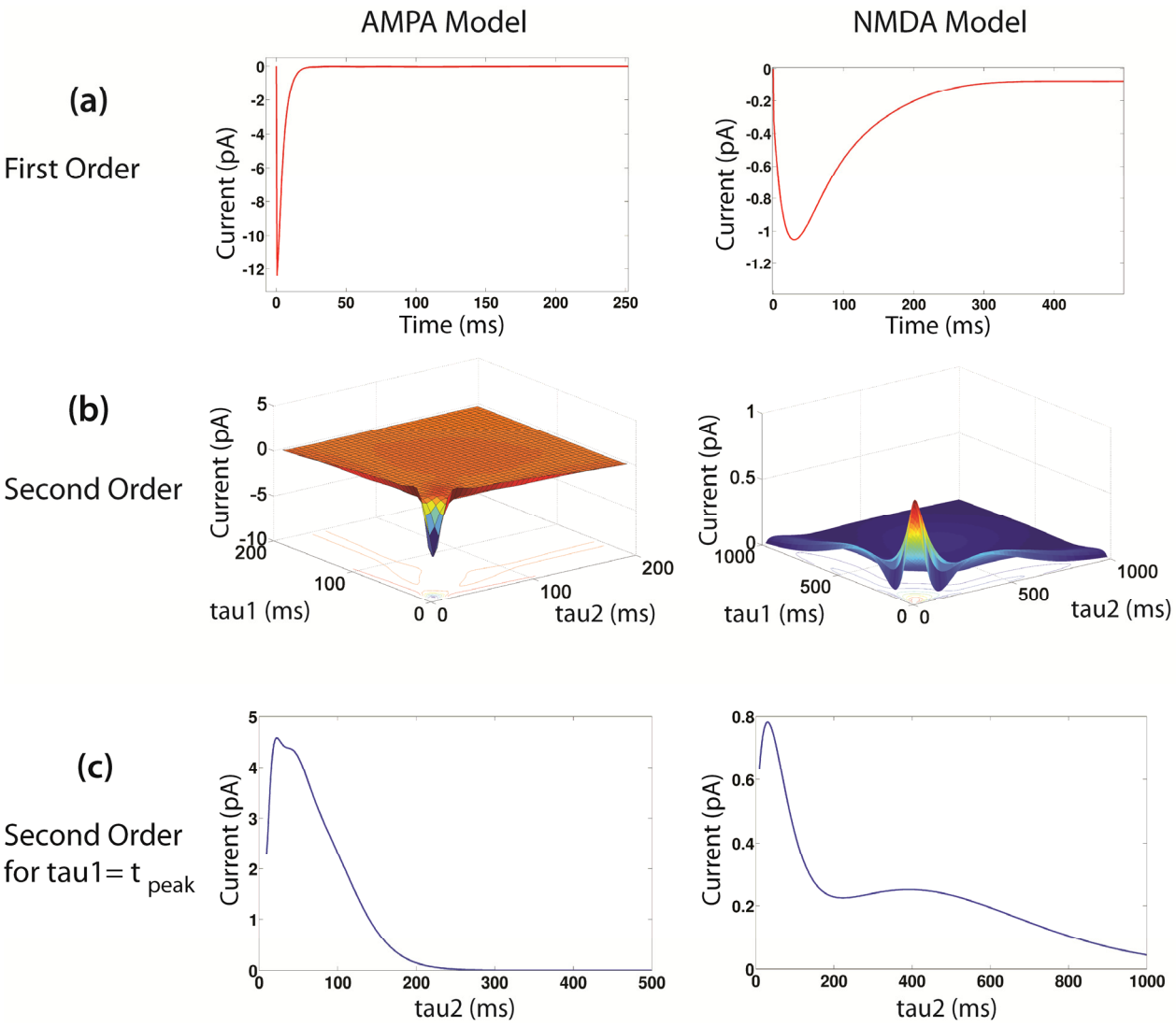


**Fig. 3.(a).** Responses derived from Volterra kernels for AMPA and NMDA-R (in amplitude of current going through the receptors, in pA). **(b)** Second order responses that modulate the first order response. **(c).** Second order responses at the maximum amplitude of the first order response, i.e. at the time of the peak of current (occurring at 2ms for AMPA-R and 30ms for NMDA-R). This curve corresponds to the modulation of amplitude as a function of the interpulse interval, providing a direct reading of the amount of depression induced due to the existence of a previous pulse. Please note the initial amplitudes are negative (current flows inside the cell) while their modulation is positive, thereby reducing the total amount of current.

parametric framework (superimposition of both AMPA and NMDA models). Qualitative results are presented in Fig. 1.b, and error values are summarized in Table 1. The optimal p values for both models were determined to be 0.07 and 0.01 for AMPA-R and NMDA-R respectively.

For this study, although three orders were used, we will focus our attention on the values of the second order as it describes the effect of a response to a previous stimulation on a second subsequent pulse, thereby providing some insights on the mechanisms at play during a response to paired-pulse protocol.

The second order response is a three-dimensional function which modulates the output due to the first order, and is dependent on two parameters: tau1 and tau2. Tau2 corresponds to the interpulse interval, while tau1 corresponds to the distance at which the modulation is recorded (Fig. 2).

The results obtained for the amplitudes of the first and second order responses are detailed in Fig. 3. Our first order responses show that the current generated by AMPA-R has a sharp rise and quick decay, returning back to baseline well before 50 ms. Meanwhile, the NMDA-R responses are much slower to rise and decay, returning to baseline about 400 ms past the event. These results indicate that the non-parametric model successfully captured the well known dynamics of fast acting AMPA and slower acting NMDA receptors in the case of a single event (Fig. 3a).

In the case of two events, we find that the major contribution of the first event on the response to the second one is overall a depressive effect (Fig. 3c). For AMPA receptors, we see this depressive effect if the second stimulation pulse is given within a 200 ms window after the initial (first) event; for NMDA the effects linger much

longer, showing minor but significant depressive effects up to 1 second after the initial pulse. The peak depression occurs at 22.5 ms and 30 ms for AMPA and NMDA, respectively. It is proposed that this depression is due to saturation of the channels. Indeed there appears to be a saturation limit that is most significantly seen in NMDA's dynamics: at its peak depression, over 70% of the second response's amplitude is silenced. AMPA, similarly, has a depressive effect although not as significant.

In addition to saturation, we observe that NMDA has a second dip in depression when the second event is given 300-500 ms after the first. Though the reason why such effect is not completely known and cannot be explained with our current results, we can speculate that this second order effect may be a result of the refractory period where the channels could be less responsive to a second event shortly after the first (i.e. desensitized).

## IV. DISCUSSION

Changes in synaptic dynamics are believed to have a strong impact on learning and memory and brain function in general. The non-parametric modeling framework developed allowed us to successfully replicate experimental observations as well as excitatory current from AMPA and NMDA receptors of our parametric platform. It inherently provides a clear interpretation of the impact of a past stimulation on the output to a current pulse. Further investigations using the parametric models of both AMPA and NMDA receptors and looking at details of their internal dynamics (and in particular their desensitized states) should provide further explanations as to the mechanisms that govern the phenomena observed, underlining the fact that a combined parametric-nonparametric modeling framework constitutes an insightful solution to shed some light on nanoscopic, experimentally challenging subsynaptic mechanisms such as the ones studied here.

Our non-parametric model replaces EONS to a high degree, with NRMSE of all models less than 10%, indicating that most of the dynamics have been captured by the non-parametric model. On occasional instances, peaks do not match up properly, possibly indicating higher order dynamics which were not covered within our third order model. However, it appears that the majority of the signal has been replicated faithfully and the framework presented was capable of characterizing the responses of the ionotropic receptors AMPA and NMDA to paired-pulse protocol and their respective contributions to overall depressed response following paired-pulse stimulation. Finally, this non-parametric modeling framework decreases dramatically the computational complexity as our latest benchmarking results suggest a 5000 fold decrease in simulation time compared to the reference parametric model. This outlines how such non-parametric framework can be used to help progress towards larger multi-scale simulations while producing biologically accurate models of networks and systems.

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