Peri-event Cross-Correlation over Time for Analysis of Interactions in Neuronal Firing

António R. C. Paiva, Il Park, Justin C. Sanchez and José C. Príncipe

Abstract— **Several methods have been described in the literature to verify the presence of couplings between neurons in the brain. In this paper we introduce the peri-event cross-correlation over time (PECCOT) to describe the interaction among the two neurons as a function of the event onset. Instead of averaging over time, the PECCOT averages the cross-correlation over instances of the event. As a consequence, the PECCOT is able to characterize with high temporal resolution the interactions over time among neurons. To illustrate the method, the PECCOT is applied to a simulated dataset and for analysis of synchrony in recordings of a rat performing a go/no go behavioral lever press task. We verify the presence of synchrony before the lever press time and its suppression afterwards.**

I. Introduction

An important problem in neurophysiological studies is how to assess and measure the temporal dynamics of neural couplings. This is fundamental to understand the underlying principles of information transmission by a population of neurons [1]. Many studies have reported on encoding by populations of neurons either by modulation of the firing rate of neurons [2], the precise timing of the neuronal firings [3], [4], or both [5]. In the case of synchronous firings [3], [4] the dependence on correlation over time is implicit since, by definition, synchrony can only asserted between at least two neurons. But this is equally important for population representations in terms of rate modulations [6].

Therefore, several methods have been proposed on how to verify and quantify the presence of interactions in neuronal firings. Some well known examples are cross-correlation, joint peri-stimulus time histogram (JPSTH), unitary events, partial directed coherence (PDC), among others. The cross-correlation function [7] is probably the most widely used technique to measure the interaction between spike trains. Cross-correlation as a statistical measure was "imported" from random processes and can only be applied to point processes by first transforming uncertainty in time onto amplitude variability. Moreover, to address non-stationarity, the cross-correlation is averaged over windows of time which greatly compromises the time resolution and limits its usefulness as a descriptor of the evolution of correlation as a function of time. The JPSTH [8], [9] is another widely used tool to characterize the evolution of synchrony over time between two neurons. However, the approach rapidly becomes unmanageable for more than just a few neurons since the analysis is does in pairs (e.g., 16 neurons requires 120 JPSTH plots). Unitary events [10], [11] is a statistical method to detect coincident joint spike activity above chance. But, like other methods, is also sensitive to binning and employs a large moving window analysis for statistical reliability. Similar to the cross-correlation, the PDC [12] and the method by Hurtado et al. [13] operate over windows of data in the frequency domain, and thus do not provide an effective description of the evolution of the interactions over time.

For analysis of interactions among neurons we need a method capable of characterizing the evolution of correlation as a function of time, that can easily scale with an increasing number of neurons, and may be applicable either the experimenter is seeking for correlation in firing rate modulations or synchronous firing. However, all the above mentioned methods are limited in at least one of these issues.

In this paper we propose the *peri-event cross-correlation over time* (PECCOT) to analyze and visualize the evolution of synergistic information over time in a convenient way. The PECCOT is computed by averaging the cross-correlation over multiple realizations of an event. Therefore it allows to infer the relation between interactions among neurons and the event onset. Because the averaging is done over the realizations instead of over time, the PECCOT is able to characterize the interactions among neurons with high temporal resolution. Moreover, because it is formulated in terms of the ideas of the generalized cross-correlation (GCC) [14] it is applicable regardless of timescale of analysis. To validate and illustrate the method, the PECCOT is first applied to a simulated dataset where it is known which neuron pair is coupled and at what time the connectivity is in effect. Then, it is utilized for analysis of synchrony in recordings of a rat performing a go/no go behavioral lever press task. It is easily verifiable the presence of synchronous firings immediately before the lever is pressed and their suppression afterwards.

II. Peri-event cross-correlation over time

Cross-correlation of two spike trains, say A and B, is typically expressed in terms of their binned counterparts as,

$$C_{AB}^{bin}[n] = \frac{1}{M} \sum_{n=1}^{M} N_A[n] N_B[n], \qquad (1)$$

where M is the number of bins and $N_A[n]$, $N_B[n]$ are the number of spikes in the nth bin for spike train A and B,

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respectively. But, binning is an estimator of the firing rate (apart from a normalization by the bin size) [15]. Therefore, cross-correlation of spike trains should be expressed directly in terms of the intensity functions of the underlying point processes; that is,

$$C_{AB}(t) = E\left[\lambda_A(t)\lambda_B(t)\right] \tag{2}$$

where $\lambda_A(t)$ and $\lambda_B(t)$ denote the intensity functions for spike trains A and B, respectively. Clearly, the generalized cross-correlation (GCC) [14] definition in equation (2) expresses the cross-correlation in more fundamental principles than equation (1).

The main difficulty in estimating cross-correlation is that in practice only stochastic estimates of the intensity functions of the spike trains are available. The traditional approach is to average the instantaneous cross-correlation in the argument of expectation over a time interval. The problem with this approach is that it trades time resolution for statistical reliability. Instead, for experimental paradigms with multiple realizations, we propose to average the instantaneous cross-correlation of the estimated intensity functions over the trials, similarly to how the peri-event time histogram (PETH) is obtained, thus retaining the full temporal resolution.

For estimation of the intensity functions the conventional approach in the statistical literature is kernel smoothing [16], with clear advantages over binning. Denote the spike times of spike train A in the time interval $[0,T]$ as $\{t_i^A : i = 1,\ldots,N_A\}$, where N_A is the number of spikes of A in the interval. The estimated intensity function is given by

$$\hat{\lambda}_A(t) = \sum_{m=1}^{N_A} h(t - t_m^A), \tag{3}$$

where h is the smoothing function. For intensity estimation this function h must integrate to one. The primal advantage of this approach for intensity estimation compared to binning is that no discretization in time is introduced and therefore the resolution is not decreased even if larger timescales of analysis are intended.

Therefore the algorithm for estimation of the PECCOT is as follows:

1) For each realization of the event,
   a) Estimate the intensity function of each neuron in an time interval around the event onset, $[-T,T]$ (zero corresponding to the event onset), according to equation (3).
   b) Compute the instantaneous cross-correlation for each pair of neurons. At the kth realization, between neurons i and j, the instantaneous cross-correlation is,
   $$c_{ij}^{(k)}(t) = \hat{\lambda}_k^i(t)\hat{\lambda}_k^j(t),$$
   where $\hat{\lambda}_k^i(t), \hat{\lambda}_k^j(t)$ are the estimated intensity functions for the realization.
2) Average the instantaneous cross-correlation for each pair of neurons across realizations.

Careful examining the method one may recognize the same form that leads to the main diagonal of the JPSTH [9]

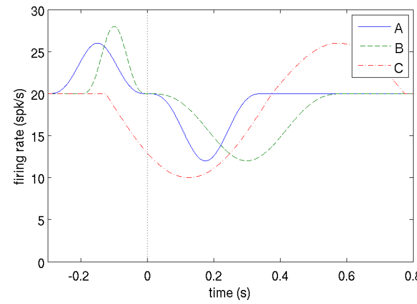

Fig. 1: Modulation of intensity with the event for each neuron.

which typically expresses the neural interactions. The difference however is that here the computation is done explicitly, and thus much more efficient. Also, by focusing only on this function, analysis of the overall result is much simpler since the result of all pairs of neurons may be summarized in a single plot. Nevertheless, as for the JPSTH, it is also possible to compute other diagonals by introducing the dependency to a lag between $\hat{\lambda}_k^i(t)$ and $\hat{\lambda}_k^j(t)$. Moreover, the statistical procedure proposed by [9] for normalization of the JPSTH can be applied for normalization of the PECCOT, with intensity estimation by kernel smoothing.

III. Results

A. Simulated experiment

To illustrate and validate the method just proposed we consider a simple simulated example. Three neurons with base firing rate 20 spk/s were generated. All of these neurons modulated their firing rate in the time vicinity of the event, as shown in figure 1, and here generated with an inhomogeneous Poisson model. In addition, neurons A and B tended to fire synchronously approximately 0.12s before the event. This coupling was introduced in the generated spike trains by selecting the nearest spike of A to 0.12s before the event as a reference and moving the closest spike in B to the same time (with a 1ms zero mean Gaussian jitter added), if the two spikes differ by less than 50ms (baseline inter-spike interval). Neuron C spiked independently of both A and B. A total of 100 event realizations (trials) where generated.

The constructed dataset was analyzed by PECCOT with a Gaussian smoothing function of width $\sigma = 5$ms. The computed result is shown in figure 2. The result was centered by removing the expected coincidence levels merely due to rate modulations. The PECCOT marks the presence of synchronous activity between neurons A and B with a strong peak in the cross-correlation roughly 0.12s before the event onset, as expected given the construction of the dataset. Moreover, the instantaneous cross-correlation between neuron C and others does not show any significant peak, only the effect of firing rate modulations.

For comparison, we also computed the JPSTH for the same neuron pairs (shown in figure 3) using NeuroExplorer (Littleton, MA). For ease of comparison, the bin size was set to 5ms. Again, we observe a strong peak between A and B approximately 0.12s before the event. Several interactions are

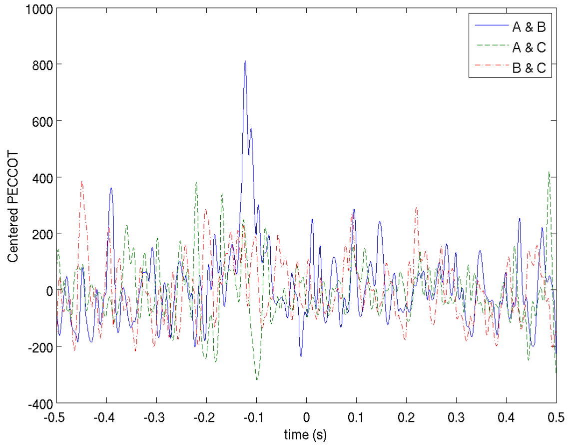

Fig. 2: Centered PECCOT for the three neuron pairs around the lever.

visible for the other two pairs. However, carefully examining the scales one notices that the peak is about two times higher in the first case. These results highlight the difficulty in analyzing multiple JPSTH plots, especially with an increasing number of neuron pairs. On the other hand, by displaying the result of all neuron pairs in a single plot under the same scale, the PECCOT greatly simplifies this analysis.

B. Behavioral experiment

1) Data description: In this study we utilized multi-electrode array recordings collected from male Sprague-Dawley rats performing a go-no go lever pressing task. Array configurations of two rows of eight tungsten electrodes (2×8), spaced 250μm between columns and 500μm between rows, were chronically implanted in the forelimb region of M1 (+1.0mm anterior, 2.5mm lateral of bregma). Neuronal activity was collected with a Tucker-Davis recording rig with sampling frequency of 24414.1Hz and digitized to 16 bits of resolution. In this dataset, 29 channels had action potentials above the noise floor from which, after spike sorting and removing neurons firing slower that one spike per second, we retained 39 spike trains from single neurons, 24 from the left hemisphere of the brain and 15 from the right hemisphere. The queue and lever press signals were recorded simultaneously with the neural activity with sampling frequency 381.5Hz.

2) Data analysis: The PECCOT is now demonstrated for the analysis of couplings in the neuronal firings of neurons in forelimb region of M1 of a rat performing a behavioral task. Specifically, we wanted to verify if the neurons' synchronous firing patterns modulated with movement onset. This question is of high relevance, for example, for brain-machine interfaces (BMIs) since it may suggest that additional information is being conveyed about the movement through synergistic correlations among neurons.

To test this hypothesis the centered PECCOT[1] was computed in a neighborhood of two seconds before and after the lever presses. The smoothing filter was a Gaussian function with width $\sigma = 5$ms. For visualization purposes, the centered PECCOT was smoothed with a Gaussian window of width, $\sigma = 10$ms. To analyze possible differences in synchrony modulation between left and right lever presses (since the two levers are usually pressed with different paws) and between hemispheres, the situations are considered separately. A total of 93 left lever presses and 45 right lever presses were used for averaging. The results are shown in figure 4. We opted to display the results in the form of a color coded figure due to the large number of neuron pairs, making it easier to visualize the overall modulation and identify the most relevant neuron pairs.

It can be observed that the synchrony among neurons in the left hemisphere is far more widespread than in the right hemisphere, for both left or right level presses. It can be clearly observed that in all situations there is considerable

[1]Centering was utilized to remove the effect of very different firing rates and their modulations.

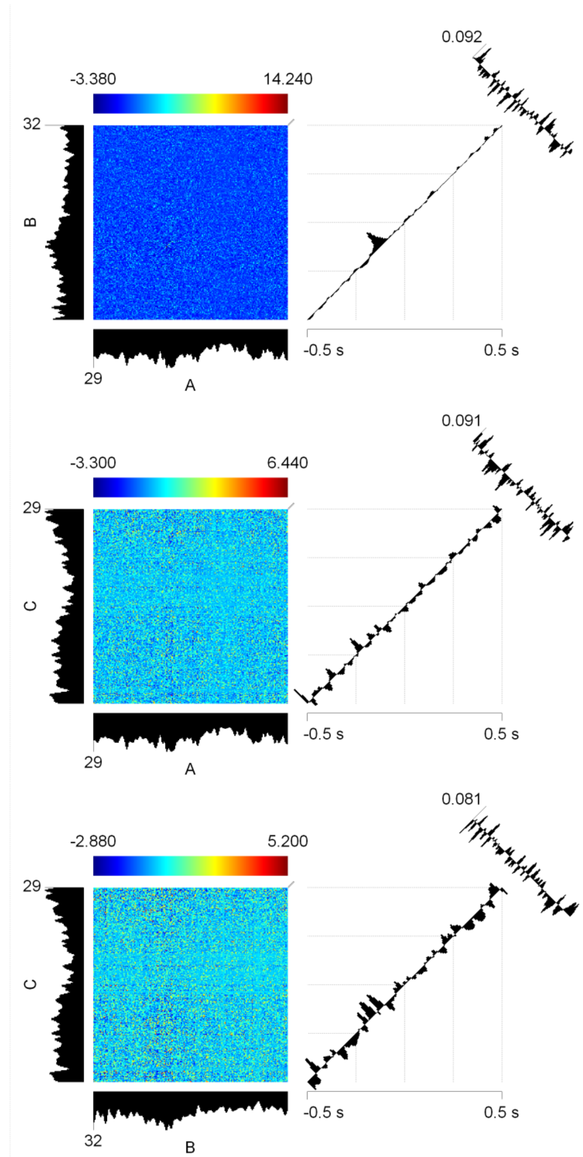

Fig. 3: Centered JPSTH for each neuron pair.

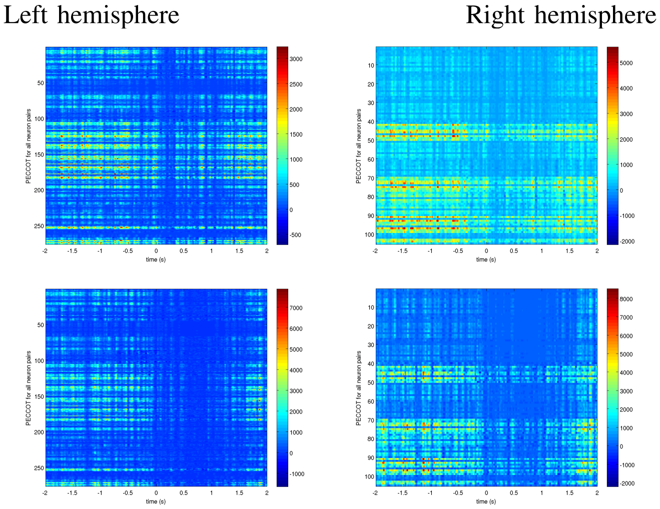

Fig. 4: Centered PECCOT around the lever press onset. The two columns correspond to neurons from the left and right hemispheres, respectively, and two rows correspond to the situation in which either the left or right lever was pressed, respectively.

interaction among neurons before the lever press instant and that these interactions are almost entirely suppressed immediately after. Approximately one second after the lever press instant the synchrony increases again. Interestingly, it should be remarked that this time interval corresponds approximately to the average duration of a lever press, after which the rat receives a water reward if the correct lever was pressed. Moreover, we notice lever press specific synchrony modulation with depressions around 1.4s, 0.95s, 0.8s, 0.45s and 0.3s before a left lever press, and a major depression around 1.25s before a right lever press. These modulations are present at the same time in both hemispheres. Also, in the images it is apparent that the interactions between neurons tend to be phase locked and have a periodic component in the theta range (3–8Hz). Although we have not investigated the reason for this periodic phase locking of synchrony, these results may provide further evidence on the role of low frequency rhythms commonly found in meso- and macroscopic recordings as "clock signals" for synchronization of multiple brain regions.

IV. Conclusion

In this paper we presented the PECCOT as a new tool to study interactions among neurons over time in the vicinity of an event in time. The key idea is to exchange averaging over time, as is usually done, by averaging over the realizations. This allows for high temporal resolution without compromising the variation in the estimation. Moreover, because the cross-correlation over time can be plotted together for all pairs of neurons, it is still easy to visualize the overall result as the number of neurons is increased. Although the method is perhaps most useful to verify interaction in the form of synchrony, the formulation is more general and the method can in principle also be applied to analysis of correlations in rate modulations.

The application of PECCOT for data analysis showed its importance to assess the presence of correlations around an event. In the behavioral experiment, we verified the presence and modulation over time of synchronous firings in the rat's motor cortex M1 in preparation for movement. These results suggest further studies to track the evolution of interactions between regions in brain. Furthermore, we found that synchrony is modulated in a somewhat periodic manner and thus the PECCOT may be an effective tool to relate meso- and macroscopic recordings, such as local-field potentials (LFPs) and electroencephalogram (EEG), to single neuron activity.

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