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Validation of task-related excess of spike coincidences based on NeuroXidence

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Abstract

One of the key findings supporting the assembly hypothesis was found in recordings from the primary motor cortex of behaving monkeys involved in a delayed pointing task [A. Riehle, S. Grün, M. Diesmann, A. Aertsen, Spike synchronization and rate modulation differentially involved in motor cortical function, Science 278 (1997) 1950–1953]. Based on the unitary event ('UE') method, the authors have shown that excess coincidences between simultaneously recorded neurons occur dynamically at behaviorally relevant points in time. However, sensitivity of the UE method for non-stationarities and regularity of spike trains caused fear that the results presented might be, at least in part, false positives. We reanalyzed the same data with the new non-parametric method NeuroXidence, which is robust against firing-rate modulations, rate changes across trials, regularity or burstiness, as well as low rates. Our results based on NeuroXidence confirm the results presented in Riehle et al. Spike synchronization and rate modulation differentially involved in motor cortical function, Science 278 (1997) 1950–1953 and demonstrate behaviorally modulated excesses of coincidences on a time scale of 3–5 ms.

Keywords: Spike synchronization; Statistical significance; Non-parametric; Surrogate data; NeuroXidence; Monkey motor cortex

1. Introduction

In recent years, there has been a great deal of controversial discussion about the assembly hypothesis. On the one hand, evidence for fine-temporal structure in spiking activity is accumulating. On the other hand, there are still concerns about the appropriate analysis techniques to demonstrate the existence of precise temporal coordination of spiking activities of neurons and to diminish the fear of false positives due to violations of inherent assumptions of the analysis method [2,5,13]. One of the key findings that supports the assembly hypothesis was found in recordings from the primary motor cortex of behaving monkeys involved in a delayed pointing task [12]. It was shown that excess joint-spike activity of simultaneously recorded neurons occurs dynamically at behaviorally relevant points in time. The analysis of the data was based on the unitary event analysis method ('UE' ; [3,4]).

2. UE method

The core idea of the UE method is based on a statistical hypothesis test that compares the amount of empirically measured coincidences within simultaneously recorded neurons with the expected number. The latter is estimated based on the null-hypothesis (H_0) that assumes that the recorded spike trains within the analysis window can be described by independent and stationary Bernoulli processes [3]. To compare the expected and the empirical numbers by a statistical significance test, the UE method assumes the expected numbers to be Poisson distributed [3]. Thus, a violation of H_0 can have different causes: spikes of the simultaneously recorded neurons are correlated, or individual spike trains violate inherent assumptions of the method. Of course, the latter has to be avoided because this

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may lead to false positives and thus, to false interpretation of the data. Specifically, features of experimental data, like non-stationarity in time or across trials [4,5], latency (co-)variation [2,5], and/or deviation from Poissonian processes that may be induced by temporal structures within individual spike trains ('auto-structure') [1,4,7,8,10], may lead to false-positive results.

This caused the concern that experimental evidence of precise temporal coordination of spiking activities might actually be based on false positives. Therefore, we developed a number of additional procedures to increase the robustness of the UE method by reducing the number of assumptions. We introduced the shuffling of spike trains, in combination with bootstrapping, to account for the auto-structure of spike trains and their consequences for the distribution of the expected coincidences used for the significance test [10]. The drawback, however, is that the shuffling of spike trains assumes rate stationarity across trials.

To account for non-stationarity across trials, we suggested estimating the expected coincidences and their distribution by estimating the firing rates on a trial-by-trial approach. Numerically this can be accounted for by shuffling the individual spike times within each trial and analysis window for each neuron [5]. This approach also compensates for co-variation of firing rates across trials. However, it does not consider the auto-structure of individual spike trains, e.g. a tendency for regularity or burstiness. As a consequence, both additional procedures [5,10] are not fully robust against features of experimental spike trains, since they assume either stationary processes across trials or do not account for the full auto-structure. This motivated the development of a new approach, called NeuroXidence [11], that accounts for both features simultaneously and is completely non-parametric.

3. NeuroXidence

NeuroXidence is, likewise the UE method, based on a hypothesis test that compares the expected and the empirical numbers of coincidences occurring in simultaneously recorded spike trains [11]. It detects fine-temporal cross-structure on a time scale τ_c (e.g. $\tau_c = 5\,\text{ms}$) that is not explained by either the auto-structure of individual spike trains or the cross-structure, which may exist on a time scale slower than τ_r (e.g. $\tau_r = 15\,\text{ms}$). NeuroXidence utilizes surrogate data to derive the statistical significance of the empirical number of joint-spike events. The surrogate data sets are obtained from the original spike trains by displacing each spike of an individual spike train by the same time interval $\varepsilon_{t,n}$. The random variable $\varepsilon_{t,n}$ is drawn independently for each neuron (n) and for each trial (t) from a uniform distribution between $-\tau_r/2$ and $\tau_r/2$. Thus, random displacements $\varepsilon_{t,n}$ are bounded by a lower and an upper limit:

$$p(\varepsilon_{t,n}) = \begin{cases} \dfrac{1}{\tau_r} & \text{for } -\dfrac{\tau_r}{2} < \varepsilon_t < \dfrac{\tau_r}{2}, \\ 0 & \text{else.} \end{cases} \quad (1)$$

In contrast to the random temporal displacement (or 'dithering') of each individual spike [6], which applies changes to the original temporal structure of the spike trains, NeuroXidence preserves the original auto-structure. Thus, fine-temporal cross-structure on a time scale τ_c is mainly destroyed in the surrogate data, while cross-structure slower than the time scale τ_r (e.g. rate or latency covariation), as well as the full auto-structure of each individual spike train, is preserved. To assess a deficiency or an excess in the frequency of coincidences for a particular set of neurons, we compare the frequency of their occurrence in the original data set $f_t(org)$ to their frequency in the surrogate data set $f_t(sur)$ by computing the difference Δf_t. Δf_t is determined for each trial to assess its variability across trials:

$$\Delta f_t = f_t(org) - f_t(sur) \text{ for trial } t = 1 \ldots T \quad \text{and}$$

$$\bar{\Delta} f_t = \frac{1}{S} \sum_{s=1}^{S} \Delta f_{t,s}. \quad (2)$$

To improve the sampling of the chance frequency occurring in surrogate data that reflects H_0, NeuroXidence allows the use of multiple (S) surrogates. Thus, for $S > 1$, the difference Δf_t becomes the average difference between the original data and the S surrogates $\bar{\Delta} f_t$. A value of $\bar{\Delta} f_t$ larger than zero indicates an excess of coincidences in the original data set. In the case of the evaluation of coincidences between one pair of neurons, the value of $\bar{\Delta} f_t$ is equivalent to the difference of the area under the curve of the cross-correlogram between $-\tau_r/2$ and $\tau_r/2$ of the original spike trains and the more smooth cross-correlogram obtained from the surrogate data. To test if coincidences are reliably increased across trials, NeuroXidence tests if the median of $\bar{\Delta} f_t$, obtained for all trials $t = 1 \ldots T$, is significantly larger than zero (Wilcoxon-test). Testing the median rather than the mean or total number of JSE across M trials makes NeuroXidence robust against rare events and outliers. This provides, in contrast to the UE method, a conservative hypothesis test in the case of low rates and non-stationarity across trials.

In summary, NeuroXidence allows one to detect an excess of precise temporal coordination of spiking activity of multiple neurons on a time scale of a few milliseconds. Since the estimation of the chance frequency considers the complete auto-structure of each individual neuron and trial as well as cross-structure slower than τ_r, it shows robustness against features of neuronal data that were discussed to induce false positives [2,5,8], such as any firing-rate modulations of individual neurons and covariations of firing rates across neurons that are slower than τ_r, possible regularity or burstiness, non-stationary rates across trials, and low rates. Thus, NeuroXidence provides a robust method to test the assembly hypothesis.

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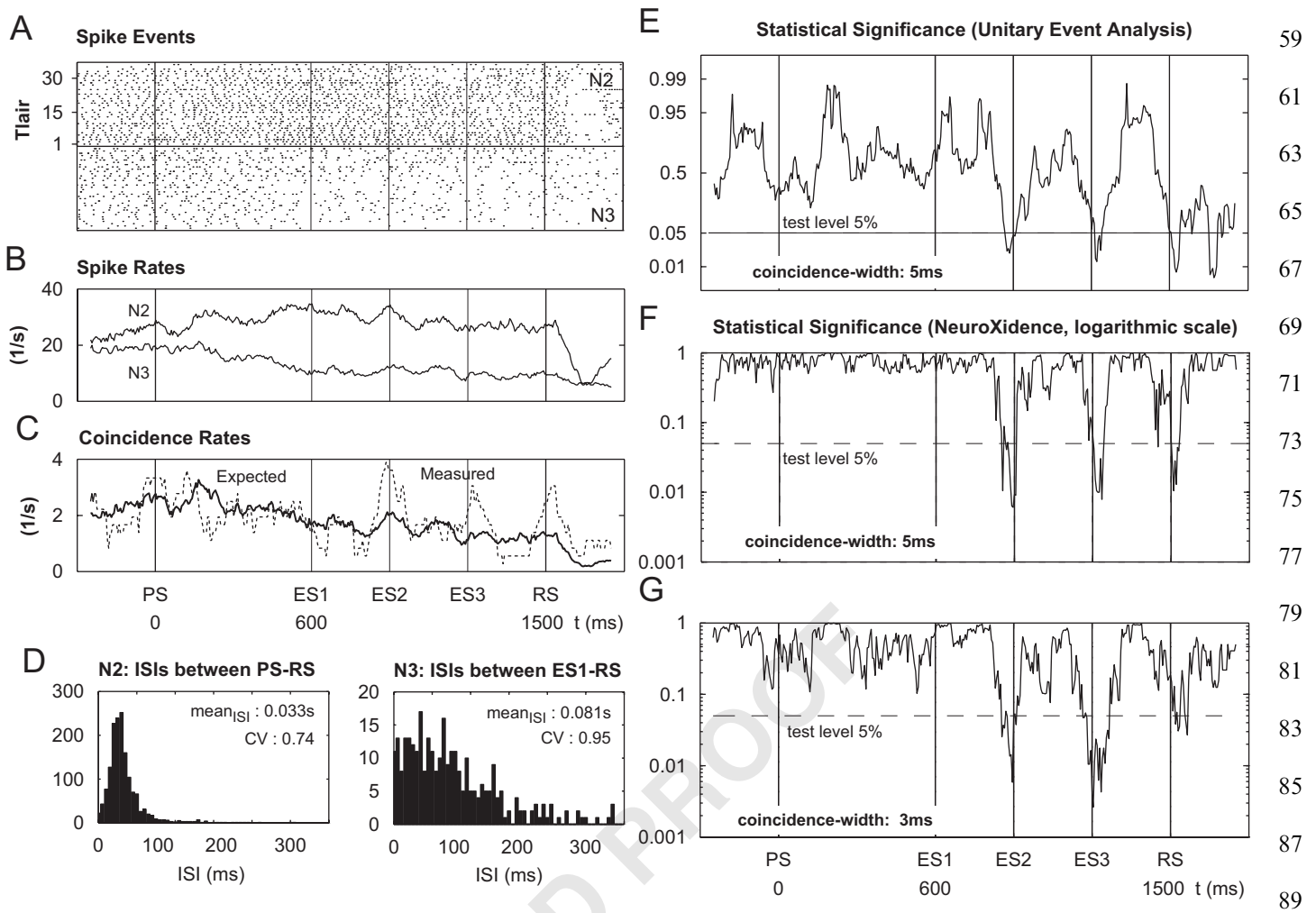

Fig. 1. Spiking activity of two simultaneously recorded single MI neurons in 36 trials (same data as shown in Figure 2 in [12]). Marker on the time-axis in (A,B,C,E,F,G) correspond to the preparatory signal (PS) at 0 ms, the first expected signal ES1 at 600 ms, the second expected signal (ES2) at 900 ms, the third expected signal (ES3) at 1200 ms, and the reaction signal (RS) at 1500 ms. (A) Raster displays of spike discharges (top, neuron 2 ('N2') ; bottom, neuron 3 ('N3')). (B) Spike rate for each neuron (computed by a sliding window of 100 ms). (C) UE-based estimation of measured and expected coincidence rates (sliding window of 100 ms shifted by 5 ms, 5 ms coincidence width). (D) ISI histograms for N2 and N3. For N3, five intervals were larger than 300 ms and are not shown in the histogram. (E) Statistical significance for an excess coincidence rate based on the UE analysis (plotted as $\log_{10}[(1-p)/p]$, null hypothesis: independent Bernoulli processes). The larger the excess, the lower the p. (F) NeuroXidence-based estimation of the statistical significance for an excess coincidence rate (null-hypothesis: fine-temporal cross-structure between N2 and N3 is slower than 15 ms, log-scale). (G) The same analysis as in F but coincidence width was 3 ms instead of 5 ms. (E,F,G) Whenever the significance value was smaller than the test level of 5%, the analysis window defines an epoch with significantly more coincidences than expected by chance.

4. Results

We re-analyzed the data presented in [12] with both methods discussed above (UE, [3,4] and NeuroXidence, parameters: $S = 20$, $\tau_c = 5$ ms, $\tau_r = 15$ ms). We used the same parameters as those used in the original study (sliding window of 100 ms duration, shifted in 5 ms offset along the data, test level 5%, allowed coincidence width 5 ms). To describe the statistical properties of the recorded spike trains, we computed also the Inter-Spike-Interval ('ISI') distributions and the corresponding coefficient of variations ('CV') for periods with approximately stationary firing rates of the neurons (Fig. 1A–D). The dot-displays as well as the CV of 0.74 of neuron 2 indicate a more regular firing than expected by a Bernoulli process. In a former study, we found that, for moderate regularity in the spike trains, the significance test that utilizes the Poisson distribution may rather lead to a conservative significance level in the case of the UE method [9]. Only extremely high regularity may lead to false positives [3].

Since NeuroXidence fully accounts for the auto-structure in the data, we also applied that method to the very same data evaluated by the UE method [12] and rigorously compared the results. Fig. 1E,F compare the resulting p-values of the two methods (log-scale). The exact p-values resulting from the two methods show deviations, since NeuroXidence tests for an excess of coincidences based on a single-tailed test, while the UE method tests, by definition, on both. However, both methods agree on finding an excess of coincidences, specifically at the very

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same instances in time, i.e. at times when the monkey expected the go-signal to appear (at 0.9, 1.2, and 1.5 s).

Only during the period after RS do the results of both methods disagree. While the UE method indicates a significant excess, NeuroXidence indicates chance level. The reason may be that neuron 2 changed its activity locked to movement onset (not shown here), thereby creating a latency variability across trials, when aligned to signal occurrence (RS). Realignment of the trials to movement onset corrects for that (see [4, Fig. 8]). Another cause may be the extremely low firing rate at this time (Fig. 1A,B), a limitation for the UE method that is discussed in [13]. NeuroXidence is unaffected by both influences. Thus, the new analysis based on NeuroXidence validates the results reported in [12]: significant increase of precise coincident spikes beyond chance level is detected by both methods at times when the monkey expected the go-signal to appear at 0.9, 1.2, and 1.5 s.

To further investigate the time scale of the underlying spike coordination, we shrank the coincidence width from 5 to 3 ms (Fig. 1G, parameters: $S = 20$, $\tau_c = 3$ ms, $\tau_r = 9$ ms). As with the 5 ms coincidence width, the NeuroXidence analysis confirms an excess of coincidences with a precision of 3 ms at the same instances in time. We conclude that the results shown in [12] indeed indicate an excess of synchronized activity on a time scale between 3 and 5 ms, rather than false positives.

5. Conclusion

Taken together, we conclude that the results shown in [12] are not due to an effect of false positives. Indeed, our results based on NeuroXidence [11] confirm excess synchronized activity on a time scale of 3–5 ms at 0.9, 1.2, and 1.5 s after PS, at moments in time at which the monkey expected the occurrence of the GO signal. NeuroXidence does not assume specific properties of neuronal data and thus, is robust against features that may lead to false positives when using other methods. However, it is computationally more demanding e.g. compared to the base version of the UE method [3,4]. Thus, the UE method is a fast and useful tool to screen and analyze simultaneous spiking activity for the existence of synchronized spiking activity. However, the NeuroXidence method may be a better selection for validation of the results.

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