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At what time scale does the nervous system operate?

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Abstract

A novel statistical strategy, the spike jitter method, was developed to assess temporal structure in spike trains from neuronal ensembles. Its key feature is the introduction of a null hypothesis that assumes a uniform relative likelihood of observing a spike at one temporal location versus another within a small temporal window. We applied the method to simultaneously recorded motor cortical neurons in behaving monkeys and examined the occurrence of finely timed synchrony between neuron pairs. Evidence was found for millisecond synchrony that could only be accounted for by assuming fine temporal structure in the constituent neurons' spike trains. The method was also applied to higher-order patterns.
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1. Introduction

The temporal coding hypothesis states that fine spike timing in the nervous system occurs and forms an important part of the representational substrate for thought and action. It remains a controversial issue, partly because there are few mathematical methods for directly and quantitatively assessing the temporal structure in spike trains. Many existing methods are either qualitative, sensitive to artifactual sources of fine temporal structure, or limited to examining lower-order structure. For example, cross-correlation methods can be used to assess fine temporal structure between cells but are somewhat descriptive and restricted to second-order structure between pairs

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of cells. Moreover, quantitative techniques used in conjunction with cross-correlations such as the shift predictor can overestimate the number of expected synchronous spikes due to slow rate covariations which are known to exist [1,2,4]. To address these problems, we developed a statistical method that allows us to quantitatively test specific spike timing hypotheses without the pitfalls that plague other methods. The key feature of this novel method is to test an explicit null hypothesis regarding the operating time scale of single neurons or groups of neurons.

2. Method

The *spike jitter* method is a general statistical method that can be used to assess any statistic based on an ensemble of neuronal spike trains. In this work, we have restricted ourselves to examining the number of spikes in one spike train (the target train) that occur within a certain time interval centered on each spike occurring in a second simultaneously recorded spike train (the reference train). This time interval defines the temporal resolution of synchrony and is called the synch width, $+/- \mathbf{w}$ (from $+/- 0.5$ to $+/- 2$ ms).

The method tests a null hypothesis which states that given the reference train, the target train is generated from an inhomogeneous Poisson process whose rate function is constant in a collection of small windows, $+/- \mathbf{J}$ (from $+/- 1$ to $+/- 4$ ms) centered on each spike in the reference train. The occurrence of significant synchrony is assessed by randomly and uniformly jittering each spike in the target train within the $+/- \mathbf{J}$ window and counting the number of synchronous spikes (Fig. 1a). This is repeated multiple times (1000 times) to create a distribution of synchronous spikes under the null hypothesis. The significance is then determined by the location of the unjittered synchronous count in the distribution (Fig. 1b).
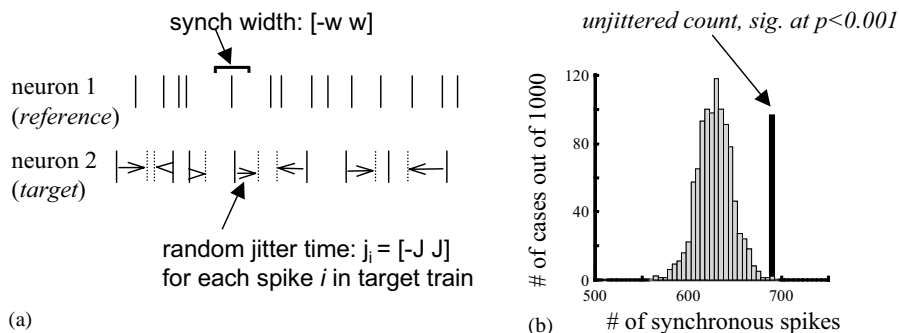

Fig. 1. (a) The spike jitter procedure involves shifting the timing of each spike in the target train by a random amount within the $+/- \mathbf{J}$ interval. The parameter, $\mathbf{w}$, defines the synchrony resolution. (b) A Monte Carlo procedure for estimating the distribution of synchronous spikes under the null hypothesis. Each realization in this distribution is the number of synchronous spikes observed after randomly jittering all the spikes in the target train once. The unjittered synchrony count is shown as a vertical line and falls to the right of the distribution in this example.

2.1. Experimental recordings and procedures

We recorded simultaneously from up to 11 neurons in primary motor cortex (MI) using silicon-based electrode arrays [3]. Four macaque monkeys were trained to perform two different reaching tasks with the hand. The first task involved moving a cursor, whose position was controlled by a two-link manipulandum in the horizontal plane, from an initial target in the center of the screen to different targets positioned around the initial target in different directions (center-out task). In the second task, the monkey was required to perform a movement sequence by moving the cursor from an initial target at the bottom of the screen, though an intermediate target, to a final target either to the left or to the right (sequence task). Information regarding the type of sequence to generate (i.e. leftward or rightward) was provided to the animal either before movement began (pre-planned) or as the intermediate target was approached (unplanned). This task also contained a control condition in which the monkey was required to stop at the intermediate target. A total of 224 cell pairs were analyzed from single units in MI based on data collected from 60 neurons recorded on 8 separate recording sessions. For both reaching tasks, data were taken from a 400 ms window centered on the start of movement and pooled over all behavioral conditions (i.e. direction in the center-out task and sequence-type, pre-planned or unplanned, and control in the sequence task).

3. Results

The spike jitter method was applied using three sets of parameter values: (1) $\mathbf{w} = 0.5$ ms, $\mathbf{J} = 1$ ms; (2) $\mathbf{w} = 1.0$ ms, $\mathbf{J} = 2$ ms; and (3) $\mathbf{w} = 2.0$ ms, $\mathbf{J} = 4$ ms. 6.7%, 7.6%, and 3.6% of all cell pairs in MI exhibited significant synchrony ($p < 0.01$) using the three parameter settings, respectively. To account for multiple comparisons, a binomial test verified that these percentages were significantly larger than the expected 1%: $p < 1.2 \times 10^{-8}$, $p < 1.92 \times 10^{-10}$, and $p < 0.002$, for each parameter set, respectively. These results provide evidence for the first part of the temporal coding hypothesis by demonstrating that precise timing of spike patterns occurs in motor cortex.

To explore whether spike patterns such as synchrony might form a representational substrate for action, we applied the spike-jitter method to data that were parsed into different behavioral conditions. Fig. 2 shows an example of different patterns of synchrony among a group of eight neurons for leftward versus rightward movements in the center-out task. Each line connects pairs of neurons that exhibit significant synchrony. These data are only suggestive of differences in synchrony because the inability to reject the null hypothesis does not imply its acceptance.

One of the attractive features of this statistical method is that it can be applied to higher-order patterns among neuronal ensembles besides pair-wise synchrony. We examined the occurrence of significant triplet synchrony among groups of 3 neurons. Fig. 3 presents the same eight neurons as shown in Fig. 2 for leftward and rightward movements in which lines connect groups of three neurons that are engaged in significant triplet synchrony.
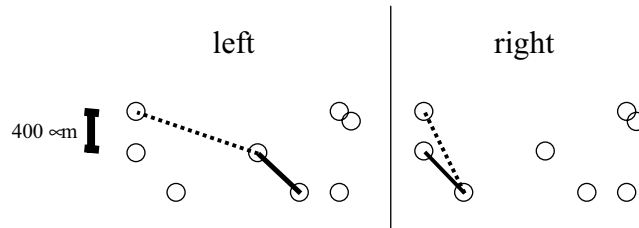
Fig. 2. The occurrence of pair-wise synchrony among an ensemble of eight simultaneously recorded motor cortical neurons arranged spatially according to the relative location of the electrode that recorded that neuron. Lines (solid and dashed) between neuron pairs indicate significant synchrony ($p < 0.01$) for leftward movements (left panel) and rightward movements (right panel). The parameters used were $\mathbf{w}=1.0$ and $\mathbf{J}=2.0$.
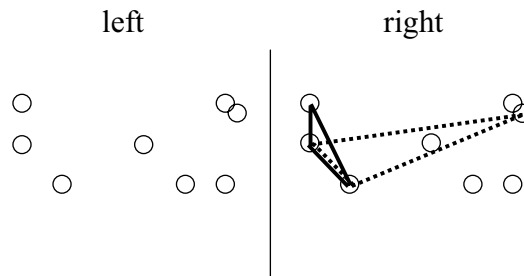

Fig. 3. The occurrence of triplet synchrony among the same ensemble of eight neurons as in Fig. 2 for leftward and rightward movements. The parameters used were $\mathbf{w} = 1.0$ and $\mathbf{J} = 2.0$.

4. Discussion

The spike-jitter method demonstrates that fine temporal synchrony as precise as $+/-$ 0.5 ms cannot be accounted for by assuming that the exact temporal placement of the spikes (in the target train) is irrelevant. A random jitter of each spike as small as $+/-1$ ms can disrupt the occurrence of the observed synchrony. This suggests that the motor cortex, at least, operates at a very fine temporal scale. Despite the well-formulated null hypothesis, the spike-jitter method imposes two restrictions on the null that may be viewed as unreasonable. First, there are intrinsic properties of neurons related to channel dynamics that can impose fine temporal structure in their spike trains and hence prevent these trains from being characterized as realizations of Poisson processes [4]. For example, neurons have an absolute refractory period and bursting properties that can impose millisecond precision on spike trains. This intrinsic temporal structure, albeit interesting, is a form of precise temporal structure that could result in excess synchrony or other higher-order patterns which we may not want to reject. Second, the null hypothesis assumes that the rate function that characterizes the generation of the target train is exactly constant within the $+/-\mathbf{J}$ jitter window. Although we have used very small jitter window lengths (as small as $+/-1$ ms), the null would be rejected

even for very slow varying processes characterizing the target train if enough data were collected. In future work, we will develop a modified method that will attempt to remove these restrictions.

References

[1] C. Brody, Slow covariations in neuronal resting potentials can lead to artefactually fast cross-correlations in the spike trains, J. Neurophysiol. 80 (1998) 3345–3351.
[2] C. Brody, Correlations without synchrony, Neural Comput. 11 (1999) 1553–1577.
[3] E.M. Maynard, N.G. Hatsopoulos, C.L. Ojakangas, B.D. Acuna, J.N. Sanes, R.A. Normann, J.P. Donoghue, Neuronal interactions improve cortical population coding of movement direction, J. Neurosci. 19 (1999) 8083–8093.
[4] M.W. Oram, N.G. Hatsopoulos, B.J. Richmond, J.P. Donoghue, Excess synchrony in motor cortical neurons provides direction information that is redundant with the information from coarse temporal response measures, J. Neurophysiol. 86 (2001) 1700–1716.