

At what time scale does the nervous system operate?

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Abstract

A novel statistical strategy, the 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 specifies the relative likelihood of observing a spike or spike pattern at one temporal location versus another. 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 whole spike patterns. The method can also be applied to higher order patterns.

The temporal coding hypothesis states that fine spike timing in the nervous system occurs and is an important part the representational substrate for thought or 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 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 [1,2,3,4,6]. 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.

Method

The *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 pairs of cells and have examined 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, $\pm\mathbf{w}$ (typically ± 1 or ± 2 ms).

Spike-jitter

The spike-jitter method tests a null hypothesis which states that 1) the target train is generated from a inhomogeneous Poisson process whose rate function is constant in a collection of small windows, $\pm\mathbf{J}$ (typically ± 2 to ± 4 ms), and 2) conditioned on that rate parameter, the target train is independent of the reference train. The occurrence of significant synchrony is assessed by randomly and uniformly jittering each spike in the target train within the $\pm\mathbf{J}$ window and counting the number of synchronous spikes (Figure 1a). This is repeated multiple times (~ 1000) to create a distribution of synchronous spikes under the null hypothesis. The significance is then determined by the location of theunjittered synchronous count in the distribution (Figure 1b).

Pattern-jitter

The pattern-jitter method was developed to address two unreasonable restrictions imposed on the null hypothesis as defined in the original spike jitter method. 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 [6]. For example, neurons have an absolute refractory period and bursting properties that can impose millisecond precision on spike trains. Second, the original null hypothesis assumes that the rate parameter is exactly constant within the $\pm\mathbf{J}$ jitter window.

To address these two problems, the pattern-jitter method accommodates the temporal precision of whole patterns of spikes by preserving the inter-spike intervals between spikes in the pattern. Moreover, the null hypothesis defines some value, Δ , for the relative likelihood of observing a whole spike pattern at one temporal location versus a neighboring location (in millisecond steps) within a $\pm\mathbf{J}$ window. For example, if Δ is 1.05, the change in the likelihood of observing a pattern in one temporal location versus the following/previous millisecond location can be as high as 5%. In performing the hypothesis test, spike patterns are not actually jittered since a closed-form solution for the null distribution can be computed using dynamic programming.

Experimental recordings and procedures

We recorded simultaneously from up to 28 neurons in primary motor cortex (MI), dorsal premotor area (PMd), and supplementary motor cortex (SMA) using silicon-based electrode arrays [5]. Four macaque monkeys were trained to perform two different reaching tasks with the hand or sit quietly. The first task involved moving a cursor, whose position was controlled by a two-arm 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. 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.

Results

A total of 506 cell pairs were analyzed from recorded single units in MI, PMd, and SMA based on data from four separate recording sessions. All results are from application of the pattern-jitter method with $\mathbf{w}=2$ ms, $\mathbf{J}=22$ ms. For all reaching tasks (the first 3 data sets), data were taken from a 600 ms window, 200 ms before to 400 ms after start of movement over all trials. In the 4th data set in which the monkey was sitting quietly and not behaving, a 500 second window was used. 10% (8/77) of cross-validated cell pairs engaged in synchronous interactions ($p<0.01$) when Δ was 1.02, or 2% change per millisecond. This implies that the fine temporal synchrony we observed cannot be accounted for by assuming that the exact temporal placement of spike patterns is irrelevant. In fact, the observed synchrony tells us about the relative likelihood of observing a spike pattern in the target train in one temporal location versus another. There is strong evidence that the chance of observing a spike pattern in one temporal location versus a neighboring location differs by at least 2% per millisecond. 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. It remains to be determined whether this temporal structure is functionally relevant to the animal. The statistical method we introduced provides specific information as to the operating time scale of the nervous system and can be applied to higher-order patterns among neuronal ensembles.

References

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[1] Brody, C. (1998). Slow covariations in neuronal resting potentials can lead to artefactually fast cross-correlations in the spike trains. *Journal of Neurophysiology*, 80, 3345-3351.

[2] Brody, C. (1999) Disambiguating different covariation types. *Neural Computation*, 11, 1537-1551.

[3] Brody, C. (1999) Correlations without synchrony. *Neural Computation*, 11, 1553-1577.

[4] Hatsopoulos, N.G., Harrison, M.T., & Donoghue, J.P. (2001). Representations based on neuronal interactions in motor cortex. In M. Nicolelis (ed.). *Progress in Brain Research*, 130, 230-244.

[5] Maynard, E.M., Hatsopoulos, N.G., Ojakangas, C.L., Acuna, B.D., Sanes, J.N.,

Normann, R. A., & Donoghue, J.P. (1999). Neuronal interactions improve cortical population coding of movement direction, *Journal of Neuroscience*, 19, 8083-8093.

[6] Oram, M.W., Hatsopoulos, N.G., Richmond, B.J., & Donoghue, J.P. (2001). Excess synchrony in motor cortical neurons provides direction information that is redundant with the information from coarse temporal response measures, *Journal of Neurophysiology*, 86, 1700-1716.

Figure Legends

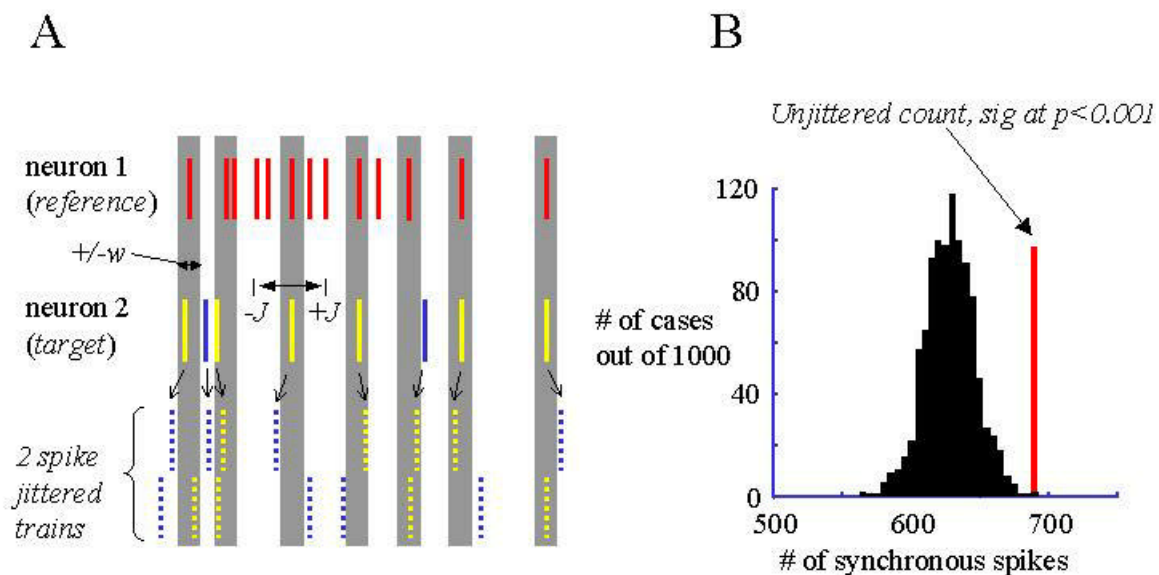


Figure 1

Figure 1. A. The spike jitter procedure involves shifting the timing of each spike in the target train by a random amount within the $\pm J$ interval (typically ± 2 to ± 4 ms). The parameter, w , defines the synchrony resolution which was typically either 1 or 2 ms. 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. Theunjittered synchrony count is shown as a vertical red line and falls to the right of the distribution.