
BRAIN THEORY

SPATIO-TEMPORAL ASPECTS
OF BRAIN FUNCTION
A. AERTSEN / EDITOR



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Neuronal Interaction in the Cortex – Quantitative Characterization by Cross-Interval Statistics

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Abstract

In view of the relatively poor temporal precision which is generally observed for the generation of action potentials in cortical neurons, we argue that a certain amount of “stochasticity” may be immanent to single neuron function in the cortex. This fact seems to hamper many attempts at a quantitative assessment of neuronal interaction by means of cross-correlation analysis, especially in higher cortical areas. We give arguments why it might be advantageous to look at cross-interval histograms of low order separately from each other. In fact, theoretical considerations within the framework of *interacting stochastic point processes* suggest how certain characteristics of neuronal interaction may be inferred from spike trains that were recorded extracellularly from several neurons simultaneously under circumstances where “fluctuations” seem to dominate the signals.

1. RANDOMNESS IS IMMANENT TO CORTICAL NERVE CELLS

The *temporal precision* in the generation of action potentials in single cortical neurons seems to be relatively poor. This may be concluded from electrophysiological recordings *in vivo* as well as from *in vitro* experiments, where parameters are better under control. For the *in vivo* case it appears to be a general rule that a neuron’s response to repeated presentations of identical sensory stimuli shows a considerable amount of variability over different stimulus presentations (for examples, see [16, 30]). Moreover, even under the most controlled *in vitro* conditions the timing of action potentials is far from being “exact” and reproducible (see also the contribution by Heck et al., this Volume). In the simple experiment, where constant input into the cell under otherwise stationary conditions can be achieved by intracellular DC-current injection, the interval histograms are still

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remarkably broad. For example, in layer II/III neurons in an acute slice preparation of rat visual cortex, we found standard deviations for the interval histograms ranging up to tens of milliseconds [25] (see Fig. 1).

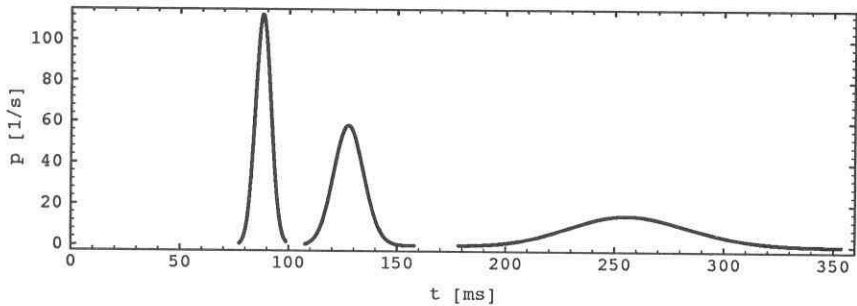


Figure 1. Fits to interval histograms for the repetitive discharge of a cortical neuron under intracellular injection of DC-currents using γ -distributions [8, 10]. We show examples for the respective probability density functions p (scaled in counts/second) from an acute slice preparation of rat visual cortex, the injected current was 320, 390 and 480 pA, respectively. Each sample contained about 800 action potentials, the mean intervals were 88, 128, 258 ms with standard deviations of 3.6, 6.7, 27.4 ms, respectively. A more detailed description of the experiments is given in [15, 25].

Such findings lead us to the even more drastic view that some sort of *random principle* might be a fundamental property of single cell function in the cortex [23, 24]. If this was true, the following questions would immediately arise (see also the contribution by Abeles et al., this Volume): How can the brain perform efficient information processing on the basis of devices whose output is so much “contaminated” by random fluctuations? How is it possible to represent information on a time scale down to the millisecond range with units being one order of magnitude less precise?

It is our feeling that this apparent randomness of cortical single neuron firing deserves specific attention from experimentalists. At the same time, it is of considerable interest to explore the functional implications of randomness as a theoretical concept [17, 19, 23, 24]. In this context, the mathematical theory of *interacting stochastic point processes* seems to provide a suitable framework for an approach to the questions stated above (see also [7]). Here, we discuss certain implications from this theory concerning the quantitative assessment of neuronal interaction in stochastic settings.

2. CROSS-INTERVALS AND CROSS-CORRELATION FUNCTION

Cross-correlation is the commonly used tool to assess the interaction between two simultaneously recorded neurons. It estimates the probability density for an action potential in neuron A as a function of the time lag to an action potential in neuron B [18, 22]. In fact, an evaluation of the relative timing of action potentials remains the only possibility

to approach questions on neuronal interaction when intracellular signals are not available, as is most often the case in the *in vivo* situation. The experimental literature provides a large number of examples where cross-correlation analysis led to valuable insights into the functional organization of cortical structures [1-3, 10, 27-30]. In view of the fluctuations omnipresent in neuronal signalling, however, we assert that it may be advantageous to use a more refined tool for analysing the experimental data.

The method we propose is based on a selection of action potentials by their "order". Using a spike in neuron B as a point of reference, each spike in neuron A is attributed a number accounting for its proximity to the reference spike: the first spike following is of order $+1$, the second one following is of order $+2$, and so on. Likewise, the first spike in neuron A preceding the reference spike in neuron B is of order -1 , the second one is of order -2 , and so forth. Thus, using all action potentials in neuron B 's spike train as a reference spike, one ends up having as many intervals of any order k as there were reference spikes. We consider their distribution by forming appropriate normalized histograms $p_{AB}^k(\tau)$ which have been called *cross-interval histograms* [22]. From this construction it is obvious that we get the usual cross-correlation function $c_{AB}(\tau)$ as the sum of all cross-interval histograms, if one takes care of the proper sign for the interval

$$c_{AB}(\tau) = \sum_{k=1}^{\infty} (p_{AB}^{+k}(\tau) + p_{AB}^{-k}(-\tau)). \quad (1)$$

Separate inspection of the cross-interval histograms and comparison to the respective expectation for zero-interaction may reveal quite detailed information about range and dynamics of interaction between the two neurons. In fact, theory suggests a way to compute the approximate zero-interaction expectation for the cross-interval histogram of any order from the data. In the case of (total) cross-correlation this zero-interaction expectation is simply the "flat" correlation

$$c_{A0}(\tau) \equiv \frac{1}{\mu_A}, \quad (2)$$

where μ_A is the average length of the intervals in neuron A 's spike train. Instead of giving the expectation for the cross-interval histograms analytically [18, 22], we process the data in a way which provides additional valuable information on the *significance* of any deviation from the zero-interaction case. To this end, we *shuffle* neuron B 's intervals and force them into a pseudo-random order. Again, we compute the cross-interval histograms from the randomized spike train with neuron A 's original spike train. Shuffling will destroy all the intricate timing relations which might have existed between neuron B and neuron A . By this procedure, neuron A is left untouched, whereas neuron B 's interval distribution remains the same. In fact, if B 's firing could be described as a renewal process [8, 10], which is often not too far from reality, shuffling would not change B 's statistical characteristics at all. The shuffling procedure is performed a reasonable number of times (in our case, 20 times) to enable a reliable estimation of the statistical fluctuations occurring in the estimation of the cross-interval histograms. For each entry of the cross-interval histogram, we determine the average value and the standard deviation of the zero-interaction histogram estimates gained by shuffling. This is done by applying conventional formulas to each set of 20 values, respectively. Fig. 2 shows an example of the outcome of this procedure.

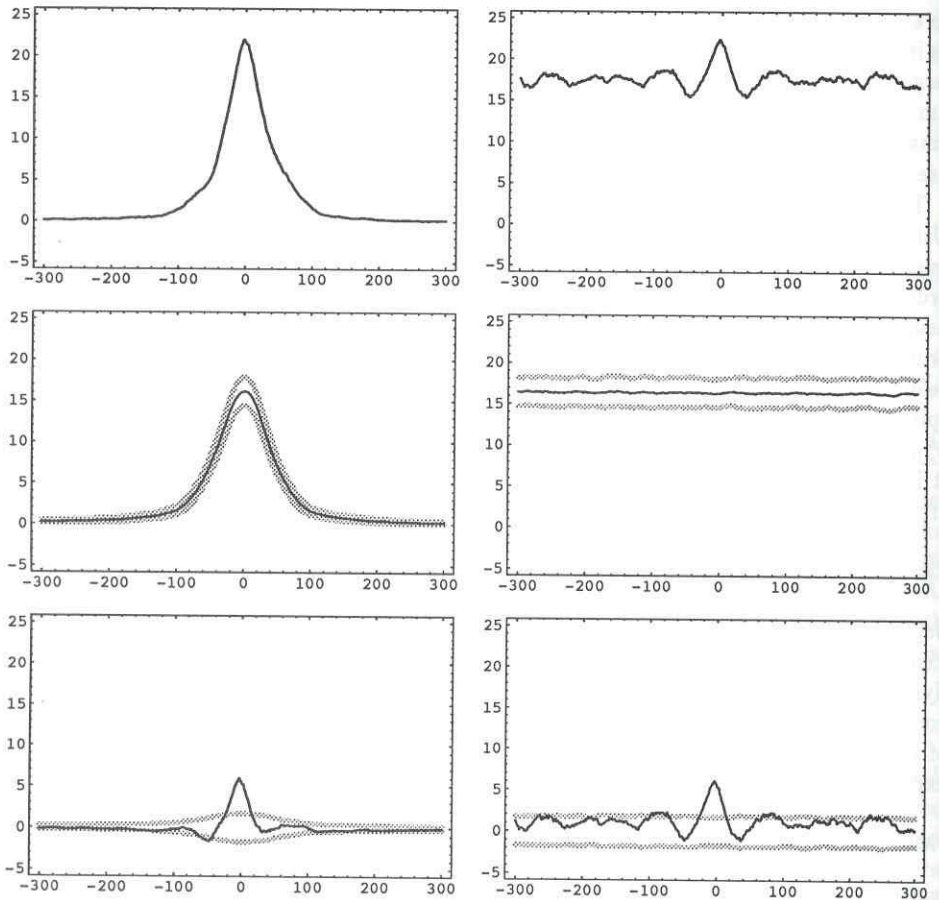


Figure 2. Example for the decomposition of correlation functions between two cortical neurons on the basis of the shuffling procedure described in the text. The data are from two simultaneously recorded neurons in the prefrontal cortex of an awake, behaving monkey [30]. The plots show a first order cross-interval histogram (top left) and a cross-correlation function (top right), their zero-interaction parts (center, dark lines) and the residuals (bottom, dark lines), respectively. The vertical scaling is counts/second. The residual may be interpreted as the net effect of interaction due to direct synaptic interaction and/or more complex cooperative network effects. The plots also show one standard deviation from the mean, both in positive and in negative direction (grey lines), thus providing a measure for the "significance" of deviations from the zero-interaction case. All curves shown were smoothed by a moving average of width 20 ms.

3. INTERPRETATION OF CROSS-INTERVAL HISTOGRAMS

There is a great interest in detailed information on the relation between direct synaptic interaction and synchronized inputs into a cortical nerve cell. Especially the question what mechanism(s) of interaction contribute to the main features of the correlation structure in neuronal signals continues to give rise to considerable debate. Even partial answers to this question would enable substantial progress in the elaboration of more global ideas on the meaning of cortical spike activity, such as *neuronal assemblies* [13, 14], *synfire chains* [1, 2], *response synchronization* [9, 11, 20] and related concepts. It seems that the point process approach can indeed give new hints on the interpretation of observations made in simultaneous recordings from several neurons. As an example, we will discuss what can be inferred from the distribution of cross-intervals, rather than from the usual cross-correlation function.

Typical post-synaptic currents induced by transmitter release at cortical synapses from neuron *B* to neuron *A* in response to a presynaptic action potential have durations of up to some tens of milliseconds [12]. Hence, in view of the low firing rates in the cortex, leading to intervals of length 100 ms and more on average, it is generally only the generation of the first spike following the trigger spike which is eventually influenced by direct synaptic effects. Therefore, we expect that the action potentials in neuron *A* immediately following an action potential in neuron *B* are the ones carrying most information on direct synaptic interaction. All the successors are indirectly influenced in terms of a sustained time shift in *A*'s spike train and, in addition, may reflect the effects of more complex forms of interaction between the two neurons due to ensemble synchronization effects.

The first action potential following a trigger spike is, of course, included in the cross-correlation function. However, there are more or less serious conceptual and statistical complications arising while adding the higher order spike events:

- The serial correlations *internal* to neuron *A*'s spike train are also included and may mask the interaction effects. For neurons with a prolonged dead time there is no obvious way to correct the cross-correlation function for such effects [26].
- The effects on mutual timing induced by interaction are corrupted by fluctuations. The first spike in neuron *A* following the trigger spike is least affected by this, higher order spikes are subject to random displacements increasing more or less linearly with the order.

Analysis of neuronal interaction on the basis of first order cross-intervals can partially avoid such unwanted effects. In the presence of complex interactions between neurons, however, it is also of interest to examine higher order interval distributions. In fact, there is evidence that the time constants of ensemble synchronization effects may be in the range of hundreds of milliseconds or even seconds [1, 2, 4, 30] (see also Abeles et al., this Volume). Also, one would expect a quite different time structure for correlated activity as compared to the case of elementary synaptic interaction. Particularly the higher order interval distributions might exhibit a non-trivial structure reflecting these long-term interactions (see Fig. 3 for an illustration).

As a general rule, higher order cross-interval histograms from cortical recordings tend to be more and more corrupted by fluctuations. It is nevertheless instructive to successively

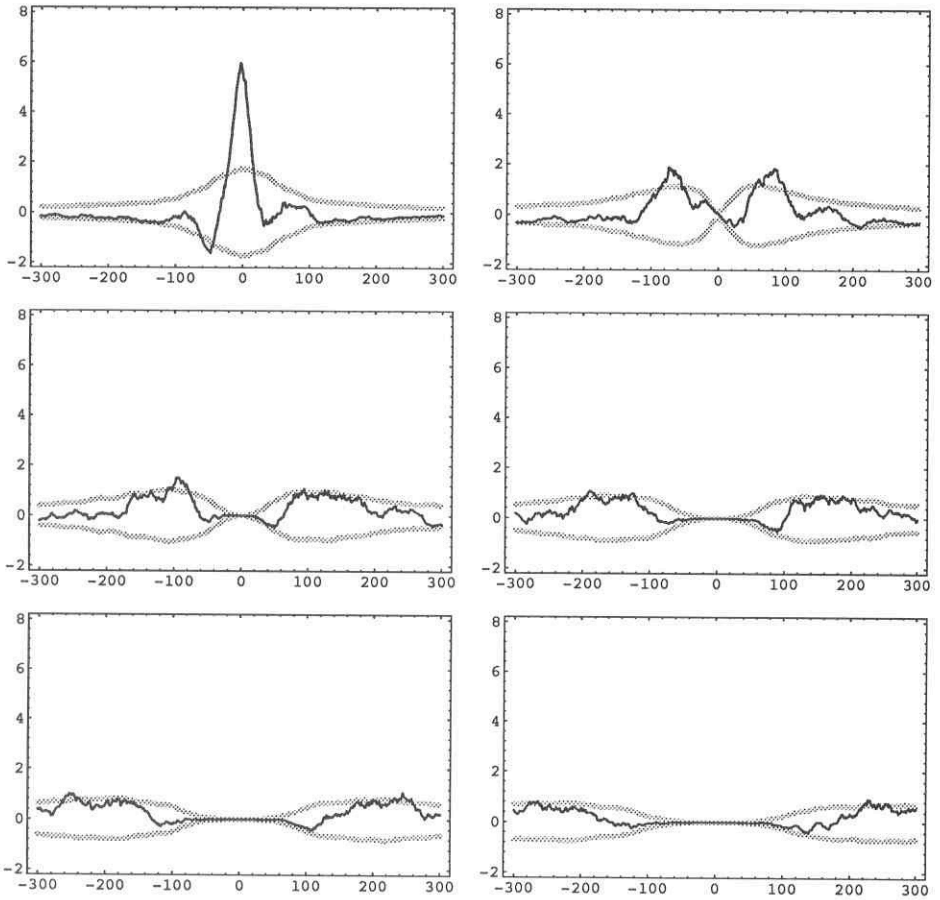


Figure 3. Residual cross-interval histograms up to order 6 from the same data as shown in Fig. 2, the zero-interaction expectation obtained by shuffling was subtracted. The grey lines indicate the respective plus/minus one standard deviation levels. Vertical scaling is again in counts/second. This is, in fact, a rather typical example, where the time structure in the cross-correlation function cannot be reduced to the first order cross-intervals alone (cf. Fig. 4). Generally, however, the “signal to noise ratio” appears to decrease rapidly with the order of the intervals.

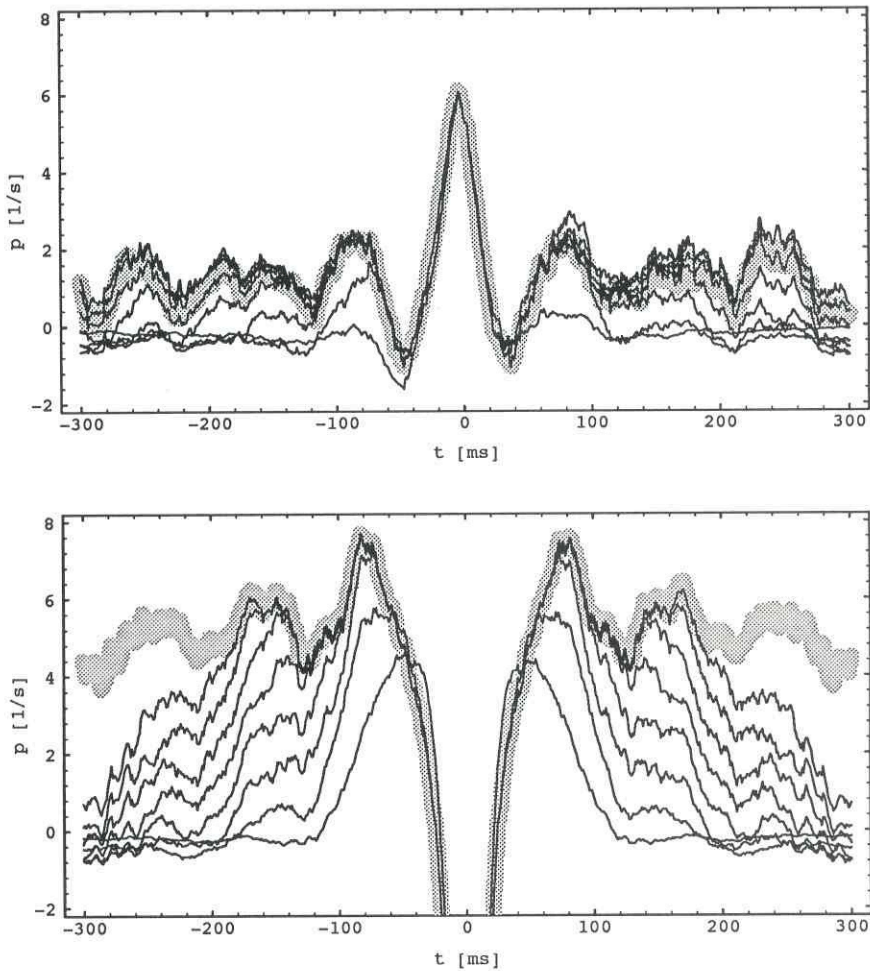


Figure 4. Successive summation of residual cross-interval histograms up to order 8 (top). The data are the same as before, vertical scaling is in counts/second. The result of this procedure adds evidence that the periodic bumps in the cross-correlation function are not just “noise” as might be inferred from the broad significance bands in Fig. 2. Rather, they indicate preferred times of occurrence for successive action potentials. A comparison with the net auto-interval histograms and the net auto-correlation function (bottom) reveals that the structure of higher order net cross-interval histograms cannot be induced by direct interaction alone. In particular, the difference in convergence of the summation of the two histograms suggests that more complex interactions may be involved.

add up the contributions of cross-intervals which have been kept apart so far. In this way, one can gradually reconstruct the average time course of the spike response of neuron *A* to an action potential of neuron *B* (see Fig. 4, top). One observes how the "bumps", which would hardly have been termed "significant" before, are slowly built up.

For an investigation to what extent this time structure is determined by neuron *A*'s dynamics – for theoretical reasons, *B*'s influence can be neglected – we employed the analogous procedure for auto-intervals, i.e., with reference points being the action potentials of neuron *A* itself (Fig. 4, bottom). One notices that bumps emerge with the same time structure as in the case of cross-intervals, but that it takes more higher order contributions until they are complete. This is true especially for longer time delays. The interpretation of this is twofold. First, it seems that the periodic structure in the cross-correlation function is already contained in *A*'s spike train and could have been predicted from it. The difference observed in the convergence of the summation, however, tells us that there is a tendency for neuron *A* to selectively omit spikes in those parts of its spike train which are in the vicinity of a spike in neuron *B*.

To summarize, it appears quite promising to consider cross-intervals of different orders separately. A systematic evaluation of effects as described in the example may help to further unravel functional details of the dynamics of neuronal interaction in cortical networks.

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