Acta Neurobiol Exp 2004, 64: 203-207

Searching for significance in spatio-temporal firing patterns

George L. Gerstein

Department of Neuroscience, University of Pennsylvania, 210 Stemmler Hall,
3450 Hamilton Walk, Philadelphia, PA 19104-6074, USA

Short communication

Abstract. We examine a specific candidate for temporal coding of information by spike trains, the occurrence of a temporal firing pattern among some number of neurons that repeats more often than expected by chance. Methods for detection of repeating patterns have long been available, but there are no analytic methods for calculating the expected numbers of repeating patterns to enable assignment of significance to the results from the experimental data. The expected numbers can be calculated by Monte-Carlo methods by repeatedly modifying the original data spike trains. Ideally the surrogates produced by such changes should destroy all patterns and cross-correlations but preserve other aspects of the trains such as rate, interval structure etc. We present here a novel variant of the "dither surrogate" (Date et al. 1998) and use surrogates generated by this algorithm to evaluate repeating pattern significance in data recorded in monkey motor cortex during behavior. Although we can demonstrate high statistical significance for the excess repetition of some spike patterns, it is not obvious that this has physiological meaning or that such patterns are used for information transfer.

Key words: neuron firing patterns, multi-neuron, synchrony, cortex, synfire-chains, coding, statistical significance

The basic problem. The nervous system certainly uses firing rate coding to represent information, but it is not clear whether and to what extent specific spike timing is used despite many papers on this topic. Perhaps the simplest timing structure would be firing synchrony of two or more neurons. This can have an amplified effect on downstream neurons because of nonlinear addition of the EPSPs. The extent and circumstances in which such "unitary" synchrony events exceed expected rates by significant amounts have been thoroughly investigated in a series of papers by Grün et al. (2001) with the conclusion that excess synchrony can be temporally associated with behavioral events. In this paper we will examine a more complicated type of temporal firing structure consisting of a firing pattern of some length among some number of neurons that repeats more than expected by chance. Such repeating patterns are at least potentially a carrier of information. Also in terms of Abeles' concept of synfire chains (Abeles 1991) they could represent the repeated activation of a particular synfire chain from which we record some number of neurons.

Available methods. Short patterns consisting of two intervals among the firings of one to three neurons (i.e., three successive spikes) have been studied by a variant of the Joint Peri-Stimulus Time Histogram (JPSTH) (Aertsen et al. 1989, Gerstein and Perkel 1972) where the occurrence of a spike in a particular train is used as reference (instead of stimulus) and the delayed occurrence of the next two spikes (of the other trains being analyzed) are represented along the x and y axes of the JPSTH. If a particular interval pattern is repeating more than other interval sequences there will be a hot spot in this variant JPSTH. The method and appropriate significance tests were worked out in a series of papers by Prut et al. (1998). Again it was possible to demonstrate a fairly loose time locking of such excess pattern repetitions to behavioral events. (Note that the "snowflake" (Perkel et al.1975) could be used in a similar way.)

Repetitions of more complex patterns of arbitrary length and membership can be found by a method of Abeles and Gerstein (1988). This is easily visualized by representing the data as an old fashioned punched paper tape. Each line of holes along the tape represents the firing of a particular neuron, quantized time (bins) represented along the tape. Simultaneous firings to within the bin time are represented by more than one hole across the tape at a particular temporal location. Now make a second copy of the tape. With the two tapes superimposed over a light source, start shifting one relative to the other in steps of one bin. We choose a window for maximum pattern length, and at each shift we scan the entire overlaid tapes for superimposed holes. For each tape shift and widow position we keep track of the number and identity of superimposed holes. This identifies patterns of any complexity (number of firings involved) and with any temporal structure within the chosen pattern length window that repeat two or more times in the data. In the original paper significance of counts was obtained by analytic calculation on Poisson and inhomogeneous Poisson trains. This is a poor match to most real data, so that other tests for significance are needed.

Significance tests. Other analytic tests have not yet been developed, so that it is necessary to use surrogate and Monte-Carlo calculation after the original data has been analyzed with the two tapes method. One such approach has been made by Baker and Lemon (2000). For each of the N neurons in the data they obtained firing rate function by convolution of the spike train with a suitable kernel. This rate function was used to generate a spike train with intervals drawn from rate modulated gamma functions of order 1 to 30. For each of these surrogate candidates an interval histogram (IH) was calculated, and the order which best matched the corresponding data IH was used in generating all further surrogates of that spike train. The process was repeated for each spike train in the data set. Unlike Poisson trains this approach replicates the refractory period and lack of short intervals that is typical of most data. The pattern search computation was then calculated for each set of N surrogates, and the process of generating surrogates and pattern search was repeated until adequate statistical significance could be assigned to events in the pattern analysis of the original data. Baker and Lemon's conclusion was that the number of repeating patterns in the surrogate data was the same as or even higher than in the original data, and therefore that patterns could not have any physiological significance (Baker and Lemon 2000).

However, Baker's method of generating surrogates has some problems. When we applied it to artificial data consisting of rate modulated gamma functions, the surrogate generating procedure always produced surrogates at least two orders larger than the original. The order parameter is connected to regularity – the higher the order the more repeating patterns are expected. Thus these were inappropriate surrogates and would produce inappropriately high pattern counts.

A completely different class of surrogates can be generated by dithering the time of each spike. This is an idea first developed by Date et al. (1998), Hatsopoulos et al. (2003) and used in Abeles and Gat (2001). Such a surrogate completely destroys any original patterns, but preserves the overall rate structure of the spike train. In this original formulation the distribution of dithers was flat over some appropriate window (± 8 ms). Such a surrogate however does change the original IH by adding short intervals and lowering the peak. In terms of gamma distributions, such a surrogate is a move to lower order and hence produces an inappropriately low number of patterns.

A modified result can be obtained by defining the dither distribution on the original Joint Interval Histogram (JIH) for adjacent intervals. Dithering a spike on such a 2 dimensional surface corresponds to movement along a trajectory perpendicular to the principal diagonal (for each three spikes as we dither the middle spike the first interval gets shorter and the second interval gets longer, or *vice versa*). The values of the JIH surface along this trajectory can are used to define the actual dither distribution. For typical parameter values the resulting surrogate also destroys any pattern structure, but creates an IH with less short intervals and a higher peak than in the IH of the original data. In terms of gamma distributions such a surrogate is a move to higher order and hence produces an inappropriately high number of patterns (as in the Baker and Lemon surrogate method).

It turns out that the same 2 dimensional procedure carried out on the surface which represents the square root of the JIH produces a surrogate with IH and JIH remarkably similar to the original. This version of dither algorithm has no obvious mathematical foundation, but because of the good IH fits we have used it extensively to make surrogates for pattern searches. The IH perfor-

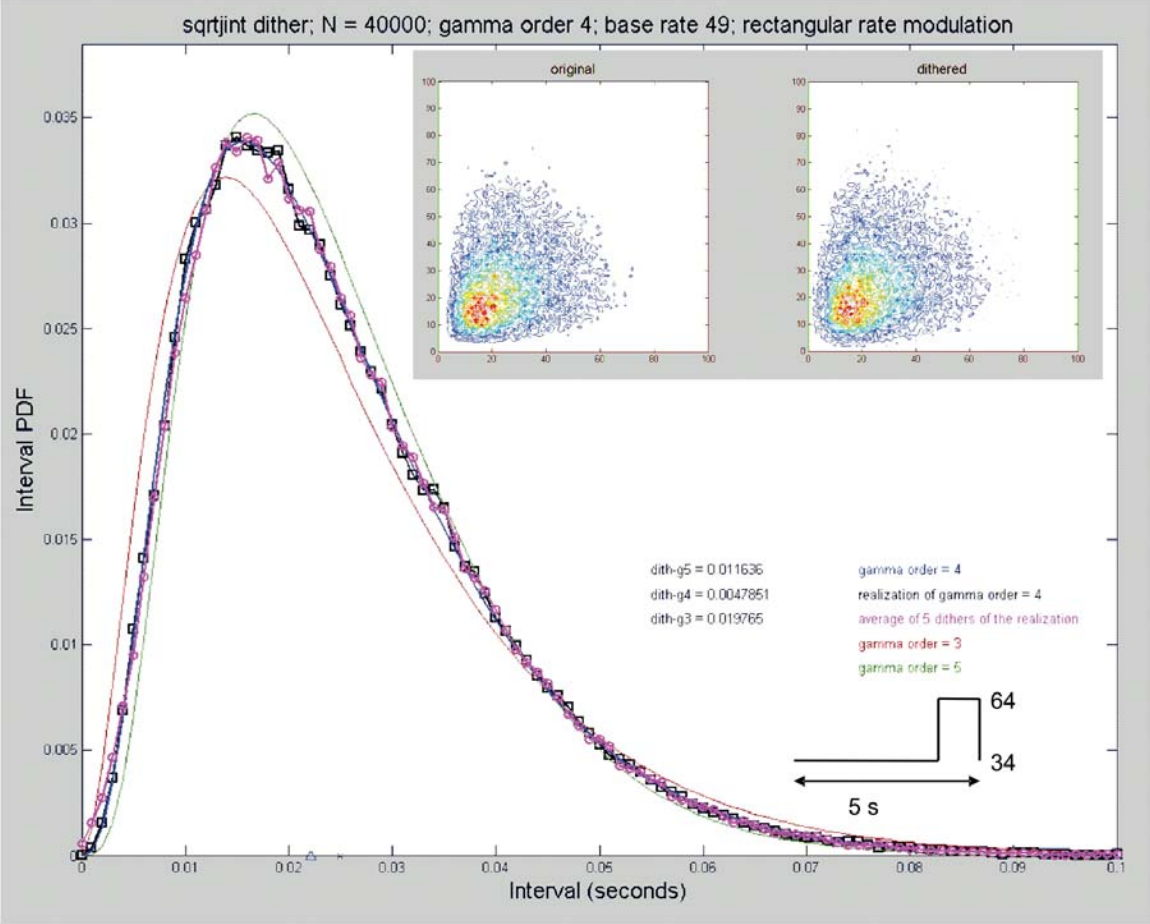

Fig. 1. Performance of the $\sqrt{\text{JIH}}$ dither for data generated by a rate varying gamma process of order 4. The rate modulation cycle is indicated at lower right. Note that the theoretical IH, its realization and its dither all superimpose. Theoretical IH for gamma processes of order 3 and 5 are included for comparison. Joint IH are shown at upper right for original and dithered, and also show little if any distortion.

mance of the $\sqrt{\text{JIH}}$ dither method for a data file generated with a rate modulated gamma process of order 4 is shown in Fig. 1. The superposition of theoretical, generated and dithered IH is obvious. The graph also shows theoretical IH for gammas of order 3 and 5 for calibration.

Pattern search results. Before analyzing the original data we filter it to remove bursts of activity. These may be defined as three or more consecutive intervals shorter than some criterion like 10 ms. Such bursts produce many repeating patterns that are essentially uninteresting (the recurrence of bursts *per se* as a potential carrier of information has been studied by Legendy and Salcman 1985). Application of the overlaid paper tape pattern search algorithm to burst filtered data is relatively straightforward, but this is a brute force computation that requires considerable time even with today's fast computers. We have generally processed the burst filtered original data and then made and processed 20 surrogate sets. Results can be summarized in a two dimensional histogram of number of patterns as a function of complexity (how many spikes are involved in the pattern) and of number of repetitions. We call this the pattern spectrum. Details of individual patterns, their repetition score and their location in time are of course also available for further analysis.

The pattern spectra for the 20 surrogates are averaged, and the standard deviation at each point is calculated. We then compute the difference between the pattern spectrum of the original data and this average surrogate spectrum, and express the final result normalized at each point by the corresponding standard deviation of the surrogate average.

We show the analysis of a data set of six neurons simultaneously recorded in M1 cortex of a monkey doing a repetitive thumb-finger grasp task with both hands (Baker laboratory, methods as in Baker and Lemon 2000). Individual spikes within a pattern are defined to 2 ms, and total pattern duration is < 300 ms. The count difference plane in Fig. 2 at the left is shown from above (original pattern counts > average surrogate counts); the view from below the difference plane is at the right. Bar heights are in units of standard deviation of the average count at those coordinates. There are clearly more small differences in the positive direction (original > average of surrogates) than in the negative direction. Among the larger differences there is one bar at 5 SD and one bar at 3 SD in the positive direction; the largest bar in the negative direction is 2 SD

The 5 SD bar represents patterns of 4 spikes that repeat 8 times in the data set. There are 10 such patterns in the original data. We should now examine whether the

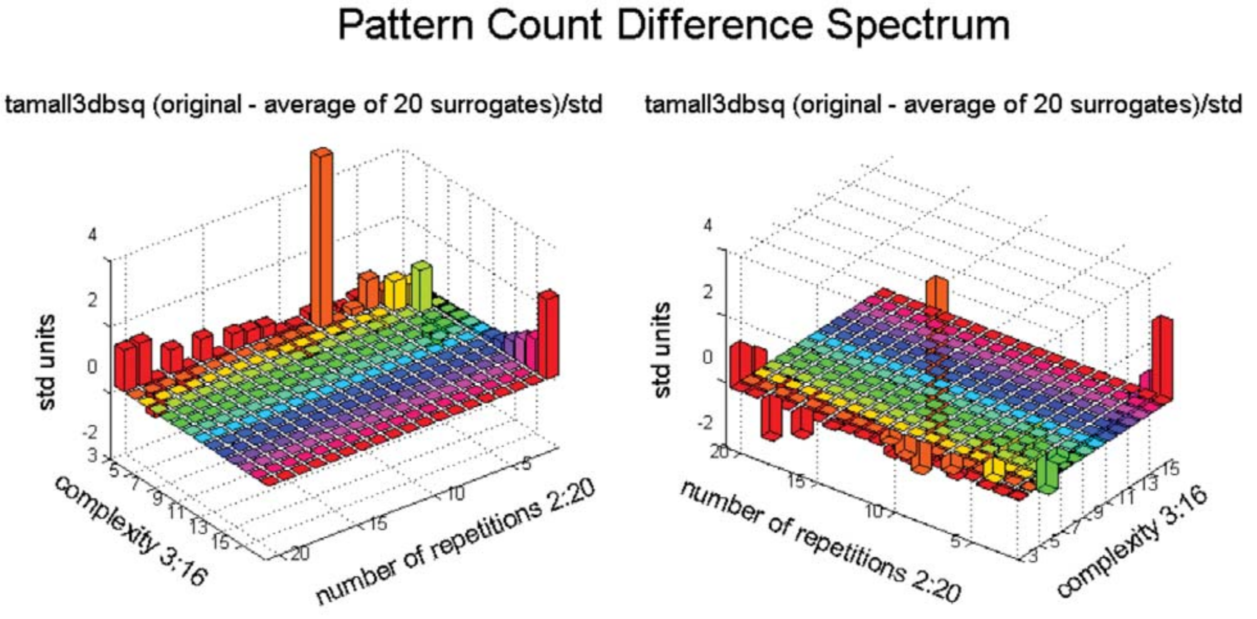

Fig. 2. An example of pattern count difference spectrum in units of standard deviation of the surrogate average. Data consisted of 6 well isolated neurons simultaneously recorded from left M1 of a monkey executing a repeating thumb-finger grasp task with both hands (Baker laboratory). Left panel shows view from above the plane, corresponding to original pattern counts > surrogate average counts; right panel is view from below the plane corresponding to original pattern counts < surrogate average counts. See text.

repeating occurrences of any of these patterns are related to particular behavioral events in the monkey's task.

Another test that compares the pattern occurrences in original and surrogate average is to compute the total number of repeating patterns, i.e., to sum all bars in the original and average surrogate pattern spectra. For the data set used for Fig. 2:

Total repeating patterns in ORIGINAL:	1,624,787
Total repeating patterns in $\overline{\text{SURROGATE}}$:	1,612,632
DIFFERENCE:	12,155
DIFFERANCE / $\sqrt{\text{SURROGATE}}$:	9.6

Thus the total number of repeating patterns in the original data set would seem to exceed those in the average of the surrogates by a statistically very significant amount.

Discussion. Does the pattern excess in the original data indicate that patterns are used for information transfer? The question of physiological significance is much harder to answer. In fact the numbers are rather discouraging. In the data example shown here there were more than 10^6 total patterns that repeated 2 or more times, with under 1% excess count over the corresponding surrogate average. What physiological mechanism could be used to single out this under 1% of excess patterning in order to use it for communication between neurons or domains?

Another possible interpretation of multi-spike patterns is that some such events are a signature of activity in an underlying synfire chain, while others are just random noise. Information would now lie in whether and which particular synfire chain is activated, not in the pattern *per se*. The numbers might be less daunting, since it is not unreasonable to suppose that many intersecting synfire chains could come through the region where the observed neurons are located.

One possible approach to testing the physiological significance of patterns, either directly or as evidence for a synfire chain, would be to perturb. If spikes are added (or subtracted) from a pattern by local electrical or chemical stimulation will there be any observable behavioral consequence? Certainly appropriate electrically imposed rate changes in cortical area MT can affect behavioral judgment of movement direction in the visual scene (Nichols and Newsome 2002). Related experiments to perturb specific patterns rather than rates have as yet not been carried out, are probably very difficult, and ultimately, because large populations of neurons are involved in typical task behavior, may produce effects far smaller than any observable behavioral changes.

So, for the present, although we have demonstrated a much better surrogate than previously used in such pattern computations, it is as yet impossible to assess the physiological significance of excess patterning. We might just be studying surrogates of different properties, some producing more, some fewer patterns than their original data.

Abeles M, Gerstein GL (1988) Detecting spatio-temporal firing patterns among simultaneously recorded single neurons. J Neurophysiol 60: 909-924.

Abeles M (1991) Corticonics: Neural circuits of the cerebral cortex. Cambridge Universtity Press, Cambridge, 280 p.

Abeles M, Gat I (2001) Detecting precise firing sequences in experimental data J Neurosci Methods 107: 141-154.

Aertsen AMHJ, Gerstein GL, Habib M, Palm G (1989) Dynamics of neuronal firing correlation: modulation of "effective connectivity". J Neurophysiol 61: 900-917.

Baker S, Lemon R (2000) Precise spatiotemporal repeating patterns in monkey primary and supplementary motor areas occur at chance level. J Physiol Lond 84: 1770-1780.

Date A, Bienenstock E, Geman S (1998) On the temporal resolution of neural activity. Technical report, Division of Applied Mathematics, Brown University (Available at: http://www.dam.brown.edu/people/elie/papers/temp–res.ps).

Gerstein GL, Perkel DH (1972) Mutual temporal relationships among neuronal spike trains. Biophysical J 12: 453-473.

Grün S, Diesmann M, Aertsen A (2001) Unitary events in multiple single-neuron spiking activity. I. Detection and significance. Neural Comput 14: 43-80.

Hatsopoulos N, Geman S, Amarasingham A, Bienenstock E (2003) At what time scale does the nervous system operate? Neurocomputing 52-54: 25-29.

Legendy C, Salcman M (1985) Bursts and recurrences of bursts in the spike trains of spontaneously active striate cortex neurons. J Neurophysiol 53: 926-939.

Nichols MJ, Newsome WT (2002) Middle temporal visual area microstimulation influences veridical judgments of motion direction. J Neurosci 22: 9530-9540.

Perkel DH, Gerstein GL, Smith MS, Tatton WG (1975) Nerve impulse patterns: a quantitative display technique for three neurons. Brain Res 100: 271-296.

Prut Y, Vaadia E, Bergman H, Haalman I, Hamutal S, Abeles M (1998) Spatio-temporal structure of cortical activity: Properties and behavioral relevance. J Neurophysiol 79: 2857-2874.

Received 3 February 2004, accepted 4 March 2004