

# Chapter 9

## Spatio-Temporal Spike Patterns



### Searching for Significance of Repeating Spike Patterns

*Moshe Abeles*

I met George for the first time in 1969 at the Second Intensive Study Program organized by Francis O. Schmitt in Boulder Colorado. I was a very young faculty at the Hebrew University of Jerusalem and was invited as such to attend the program. At the registration, there were several bins each with a range of participant names. After getting my badge and program, a young person approached me and with a kind smile asked “how did you like that?” pointing to the registration desk stating “Abeles to Goy.” At first, I did not get what was the punch. But, after a short pause I got it. “GOY” is the Hebrew word for a non-Jewish believer and also has a connotation of a simple minded person. That was George who was recruited to help with the organization of the program. His presence, the young physicist who moved into “wet” neurophysiology but used very sophisticated analysis tools, was evident throughout the workshop.

His kind and friendly attitude spanned our entire encounters. Back in Jerusalem, I started to record from auditory cortex using advanced spike sorting techniques for isolating in parallel several spike trains (Abeles and Goldstein 1977). I used extensively the analysis methods devised by Don Perkel and George to quantitatively study the dynamic firing properties of single neurons and pairs of neurons (Perkel et al. 1967a,b; Gerstein and Perkel 1969). However, I felt there is room for studying

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M. Abeles (✉)  
Hebrew University, Jerusalem, Israel  
Bar-Ilan University, Ramat Gan, Israel  
e-mail: [Moshe.Abeles@biu.ac.il](mailto:Moshe.Abeles@biu.ac.il)

more complex interactions. Looking at the literature, the only thing I found was their “snowflake” method for studying 3-fold interactions (Perkel et al. 1975).

When measuring times of 3 spikes, say at  $t_1, t_2, t_3$ , there are 3 intervals to be considered:  $(t_2 - t_1)$ ,  $(t_3 - t_2)$ , and  $(t_1 - t_3)$ . However, they are not independent as:  $(t_2 - t_1) + (t_3 - t_2) + (t_1 - t_3) = 0$ . They found an elegant way to present the 3 intervals on a plane by using the Einthoven’s Triangle (used in medicine to present the activity vector of the electrocardiogram). If the maximal allowed delay was some fixed value, the dots fall within a hexagonal area looking similar to a “snowflake.” This display provided a qualitative impression of the relations among the 3 spike trains. I could convert this display into a quantitative one by tessellating the area with triangular bins, counting the number of points that fell in each bin, and finding various ways of normalization (Abeles 1983).

While studying the 3-fold correlations with this method, I encountered several cases in which 1 or 2 bins stood up with a lot of counts. Such cases represented a situation where 3 spikes were repeating again and again with almost precisely the same intervals (see Abeles (1982 Chapter 6)). While searching the literature for such phenomena, I found the impressive work of Dayhoff and Gerstein (see also Chap. 5 this Volume). They looked on intervals between successive spikes within a spike train as “characters” and searched for “words” that repeated many times.

George was interested in my way of quantifying the “snowflakes,” while I was interested in his method of finding repeating structures within a spike train. So, I paid him a visit in Philadelphia to discuss these issues. I felt this to be very useful and asked whether he would host me for a sabbatical. George agreed and very kindly offered to supplement my somewhat inadequate university salary from his grant money.

George was also very kind in helping us to find a house to rent at Haverford just outside Philadelphia. We (my spouse, two little daughters, and me) spent a wonderful year there. My main interest was to find a way for detecting complex spatio-temporal patterns that repeat many times. I had numerous discussions with George in which we examined several alternatives. But, they all seem too cumbersome to implement with the computing power available at the time.

One morning George came up with the following analogy: Suppose we represent the spike times of a neuron as holes along a line in a punched paper tape. If we recorded several neurons in parallel, their spiking times would be represented as holes along parallel lines. Take two copies of such a punched paper tape and slide them past each other. Any repeated patterns of holes will show up at some point of sliding. I coded this magnificently simple idea in Fortran and added ways to estimate what might be found by chance. When data was analyzed this way, it often showed a significant excess of repeating spatio-temporal firing patterns (Abeles and Gerstein 1988). This algorithm serves me for detecting such patterns to this very day (although the Fortran was replaced by C and now by Matlab).

A couple of years later, in an international workshop in Jerusalem, I presented my synfire chain model and the results on repeated spatio-temporal patterns. As supporting evidence, I showed the number of patterns found in surrogate spike trains

that were very close to the estimated chance occurrence. At the end of my talk, van Essen said:

– Can you show the table for the surrogate data?

I showed it.

– The numbers you found are too close to the expected, and this cannot be true.

I was stunned! A famous scientist accuses me, a young and unknown researcher, of faking data. It took me a while to recover and then.

– Here the expected was 39 patterns and I found 38. I assume that had I found 31 you would be happier.

– Ah hah.

– But the probability of finding 31 when the expected is 39 is much smaller than the probability of finding 38 when 39 is expected.

– Silence.

A somewhat similar case arose many years later in an international workshop in France where both George and I participated. The organizers scheduled a talk by Roger Lemon to immediately follow mine, without warning me of what is coming. After giving my talk about repeated spatio-temporal patterns in recordings from the cortex of behaving monkeys, Roger described his very elegant experiments on recording pyramidal tract neurons in monkeys performing a precision motor task. In these data, he searched for repeating spatio-temporal patterns and found many with a high number of repetitions. This number was much higher than expected based on surrogate trains generated with Poisson statistics. However, Roger claimed, the spike trains are not Poissonian. When using the appropriate Gamma distribution of inter-spike intervals (ISI), the number of patterns found was much larger than the number in the experimental data. All my “friends” were happily grinning. The fallacy of these results was immediately clear to me. But now, being more mature, I did not want to offend him publicly. So I suggested we discuss his findings over lunch. At lunch, I told him that he showed an expected number of  $\approx 100$  patterns, while in the data there were only 35. The probability of finding 35 or less when 100 is expected is well below  $10^{-13}$ . (Note: I do not recall the exact numbers, but the principle of the above description is correct). Thus, if the surrogates were appropriate, there should be some special mechanism that avoids the repetition of any firing patterns that were already generated.

The moral of these two incidences is: Do not mess with statistics and probabilities unless you have a profound grasp of these issues.

Following that talk, George told me you gave a hell of a lecture. Maybe I am taking an unjustified credit, but following this incident, George took enhanced interest in synfire chains and the precisely repeating spatio-temporal patterns. One of the first studies he made was to find what would be the appropriate statistics to use for surrogate spike trains (Gerstein 2004), followed by work on how to decompose complex patterns into sub-patterns and several works with Markus Diesmann, Sonja Grün, and their students on how to detect repeated patterns in massively parallel spike trains (see also Chap. 14 in this Volume).

For me, the most illuminating conclusion that emerged from these studies was that if multiple synfire chains were embedded in a small cortical volume you would

need to record from at least 200 neurons in parallel to detect such synfire activities. Recording from over 100 neurons in parallel is now available, and getting to over 200 is coming. However, such recordings are now either spread over a too large of area or have a too low time resolution. Yet the time that such recordings will be possible from a small volume of cortical tissue is fast approaching. Only then it will be possible to establish or refute the synfire chain model.

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## Detecting Spatiotemporal Firing Patterns Among Simultaneously Recorded Single Neurons

MOSHE ABELES AND GEORGE L. GERSTEIN

*Department of Physiology, School of Medicine, Hebrew University, Jerusalem 91010, Israel; and Department of Physiology, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104*

### SUMMARY AND CONCLUSIONS

1. A particular firing pattern among simultaneously observed neurons represents a particular sequence of activity. If any multineuron pattern repeats significantly more than expected by chance, we may be observing a repeated state of a neural assembly as it processes similar units of information.

2. We present here an algorithm that rapidly finds all single or multineuron patterns that repeat two or more times within a block of data, as well as equations for calculating the number of patterns of given length and repetition that would be expected. The complexity of patterns for which it is practical to compute expected numbers is three to six spikes (inclusive).

3. Confidence limits are based on these expected numbers of patterns, so that it is possible to identify groups of patterns that are worthy of further analysis.

4. These methods are tested against simulated multineuron data that has various types of known nonstationarities, with good agreement between observed and expected values.

5. Application to real spike trains shows a large excess of observed repeating patterns, of which some, but not all, are shown to be due to bursts of high frequency firing.

6. It should be possible to apply the new method as a filter in real time in order to search for an association between repeated pattern events and externally observable events (stimulus, behavior, etc.). Any repeated pattern events which cannot be so associated may represent a new indicator of internal events in the nervous system.

### INTRODUCTION

In 1949, Hebb (8) suggested that cell assemblies are the building blocks that carry out higher brain functions. According to Hebb, cell assemblies are formed by strengthening of particular synaptic connections between cells, thereby forming circuits in which only some of the neurons in a given region may participate. Such cell assemblies are dynamic entities that become functional when activated by the appropriate spatiotemporal firing patterns at their input. When activated, the cell assembly produces some appropriate spatiotemporal firing patterns at its output.

Although the concept of information processing by such cell assemblies is popular, there has been very little direct experimental research on the level of cell assemblies. The reason for this deficiency is probably the difficulty and relatively primitive capabilities of current experimental methods for identifying and analyzing neural assemblies. Standard recording of single neurons sequentially is of little help because with such data it is impossible to detect the interactions between individual neurons that are part of the assembly process. With such data only the timing relations between a single neuron and external events may be studied, as with the peristimulus time histogram. Even this fails if the process of interest is not accurately time locked to an external event. (This would be the case for internal processes like recalling a memory or planning a movement.)

In principle, a cell assembly could be studied experimentally by monitoring the activity of all its members simultaneously. This is an

impractical goal with the present recording techniques because the number of neurons involved in (mammalian) neural assemblies is likely to be very large, perhaps many thousands. Present techniques do allow recording from about 30 single neurons in parallel [see (7) and (11) for reviews]; this is a small and usually a relatively random sample of the putative neuronal assembly.

Let us now assume, whenever an assembly is engaged in a particular computational process (which need not be time locked to any external event), that a unique wave of activity passes among the neurons. If the same information is repeatedly processed, we would expect some particular wave of activity to appear repeatedly, representing some particular repeated "state" of the assembly. Conversely if a particular wave of activity is observed to repeat, we might assume that this is an indicator that the neural assembly is repeatedly in some particular state, corresponding to the repetition of some particular computational process. Note that this one-to-one relationship is probably an oversimplification: We might expect that some *range* of processes will correspond to some *range* of patterns or states, i.e., that these are noisy quantities. Let us assume, however, that these ranges of similarity are small, so that the one-to-one relationship is approximately valid. We are deliberately leaving the nature of the underlying computational process vague at this point; a partial strategy for identifying the type of information that is involved will be proposed in the DISCUSSION.

In the context of practical simultaneous recording, only a small part of the repeated wave of activity could be observed. This sample would take the form of a repeated sequence of firing among some of the observed neurons. Thus by experimentally detecting (possibly noisy) repetitions of multineuronal firing patterns, we mark the occurrence of particular repeated states in the underlying neuronal assembly.

Detection of repeating patterns per se is only the beginning of such investigations. Patterns can and do repeat by chance, so that it is essential to develop a significance test for the experimental detections. If the entire analysis process becomes fast enough, it is in principle possible to search for the repeated sensory or behavioral event which in some

cases might be associated with the repeated pattern.

There have been some previous investigations of repeating patterns in both single and parallel spike train recordings in which some repeating patterns were found in each case. Some investigators (4, 5, 9) studied only patterns generated by intervals between successive spikes in a recording of one single unit. In Ref. 9 patterns were defined in terms of relative size of successive intervals rather than in the more usual terms of absolute interval lengths. Other investigators (2, 3) have studied single unit patterns made up only of 3 spikes. Still others (6, 12) have started with simple seed patterns of 2 or 3 spikes (across two neurons) and looked for more complex patterns in which the seeds were embedded. Legendy and Salzman (13) examined firing bursts in each of several spike trains and found that occasionally they contained embedded multineuron patterns. However, the detecting techniques used by most of these investigators required enormously prolonged computations (many hours) and did not even detect all the repeating patterns. Basically, the brute force calculations for this problem are intrinsically unsatisfactory. We note that in parallel to the new work reported here, two other groups have made alternate approaches to the pattern problem (Perkel, private communication of working notes and Johannesma, private communication); it is premature to compare and contrast these different ideas.

In the present paper we describe a new algorithm that detects all possible patterns that repeated twice or more within a section of recorded multineuron data. The algorithm is fast enough to be carried out during an experiment, so that it is possible to consider an interactive search for the events associated with given repeated patterns. We also describe methods for statistical estimation of the number of patterns of a given length and repetition that is expected to appear by chance.

## METHODS

### *The detection algorithm*

The detection of all patterns that repeated at least twice may be described by the following metaphor. Suppose the multineuron spike data were represented in the form of a long punched-paper

tape. Each row represents the activity of a particular neuron, and each of its spikes is represented by a hole; time runs along the tape. (Old-fashioned paper teletype tape could represent the activities of 8 neurons in this metaphor.) Let us take a second copy of the same tape and slide it past the stationary original tape. At a given displacement we examine the superimposed tapes against a light source. A region which contains *any* pattern that repeats at this particular tape displacement will be much brighter than average. Note that by selecting appropriate thresholds for length (duration) of region and brightness (number of spikes matched), any pattern can be investigated for match to any degree of accuracy, including both extra and omitted spikes. Note also that regions of very fast (burst) activity will tend to match *any* pattern; we will deal with this problem separately below.

A straightforward application of this algorithm with a digital computer will consume a lot of time. As an illustrative example, take a case where 10 single neurons are observed in parallel for 100 s. The average firing rate in each spike train is 5/s, and the spike times are measured with accuracy of 1 ms. (These are typical values for single neurons recorded in mammalian cortex.) The sliding copy of the tape has to be shifted by 100,000 steps (number of ms in 100 s), and after each such shift the position of all 5,000 spikes (10 spike trains  $\times$  5/s  $\times$  100 s) would have to be examined for pattern matches with the stationary copy. This means 500 million comparisons. Even a supermini computer which is dedicated to this process would take many minutes to make all these comparisons.

In order to expedite this search process, we have developed the following algorithm. Let us construct interval histograms for the time between every spike in the stationary tape and the next spike of the same train in the sliding copy. This creates  $N$  histograms, one for each of the simultaneously observed spike trains.

Initially, when the two tapes are in exact register, the histograms are identical to ordinary interspike interval histograms. Note that at each subsequent step in the tape sliding process, the entries in each bin remain unchanged, but the time value of each bin is reduced by one bin time. In other words, at each sliding step each current histogram is shifted left by one bin. At a given step, the entries that have just reached zero time (i.e., the leftmost bin) correspond to all those spikes of the stationary tape that fall exactly over a spike (of the same train) in the sliding tape. The final step in updating the histograms after each sliding step is to recalculate interval values only for the spikes to which the zero bin points.

For each such spike in the stationary tape, we measure the time to the next spike of the same train in the sliding tape, and increment the appropriate bin of the corresponding histogram.

Now, instead of just keeping a tally for each bin of a histogram, we also maintain a pointer list. These pointers define the location along the tape (i.e., the time of occurrence) of all the events (intertape spike intervals) of a particular length for a particular spike train) that contributed to that tally. The pointers also identify which particular spike train they describe.

As a final step of the algorithm, we merge the  $N$  histograms, bin by bin, into a single compound histogram. In this process all pointers belonging to each particular bin of the compound histogram are sorted into a time ordered list. The new pointers created in updating the events in the zero bin must of course be inserted at the correct place into whichever of these lists (bins) is appropriate.

It is now trivial to examine the time ordered pointer list at the zero bin with a sliding time window whose duration is the chosen pattern duration. Whenever the count of pointers falling within such a window exceeds the criterion chosen to define pattern "complexity", we have identified a repeated pattern. Its location and details are spelled out by the pointers.

For the typical data situation described above, on the average only 25 spikes would overlap at each sliding step. Thus only 2.5 million rather than 500 million comparisons are needed. On a Data General MV 10000 it takes  $\sim 1$  min to detect all the repeating patterns in such typical data, a calculation time comparable to the data collection time. Thus a typical personal computer will not suffice for this purpose.

If one wishes to use bins wider than the time resolution at which the data was collected, one can use one of the following methods: 1) convert the data into coarser time grain, or 2) use the spikes that are within the first  $n$  bins of the interval histograms as pointers to patterns whose match is within  $n$  time units.

#### *Simulated data*

In order to evaluate our detection scheme and to obtain some experience with the numbers of patterns that might be generated by chance, we simulated the activity of 10 spike trains in the following form. The simulation advanced in 1-ms steps. After each step the probability of firing for each cell was determined (so as to generate various types of nonstationarity and correlations, as described in *A* through *G*, below), and then a decision of whether the cell fired at this step was taken by drawing a random number.

It is important to be cautious with random number generators. Using the commercial random number generator supplied with our computer produced huge numbers of repeated patterns. Only when we wrote a special random generator which combines an additive generator (Eq. 7, p. 26 of Ref. 10) with randomizing by shuffling

(Algorithm B, p. 32 of Ref. 10) did the results seem random. (Note that we did not experiment extensively with various forms of random number generators; we used the first satisfactory generator we came across.) A recent review article on the merits and testing of random number generators can be found in Ref. 14.

Seven simulations were used for the data described in this paper. All the simulations were run for 100 s of simulated time with 10 parallel spike trains.

*A* (sim.002a): Spike trains were realizations of independent and stationary Poisson processes. All spike trains were firing at 5/s. *B* (sim.003a): Spike trains were realizations of independent and stationary Poisson processes. Firing rates were between 10 and 1/s. (Averaged over cells, the firing rate was 4.8/s.) *C* (sim.004a): Spike trains were realizations of independent and nonstationary Poisson processes. The firing rates in each spike train fluctuated slowly between 9 and 22 spikes/s (average firing rate 3.8/s and standard deviation of the fluctuations 4.1/s). The time constant of the firing rate fluctuations was 2 s. *D* (sim.005a): Spike trains were realizations of independent but nonstationary Poisson processes. The firing rates in each spike train fluctuated rapidly between 0 and 50 spikes/s (average firing rate 4.0/s and standard deviation of the fluctuations 6.7/s). The time constant of the firing rate fluctuations was 0.05 s. *E* (sim.006a): Spike trains were realizations of correlated and nonstationary Poisson processes. The firing rates in each spike train fluctuated slowly just as in *C* above, but in addition the cells were divided into five pairs (1 and 2, 3 and 4, 5 and 6, 7 and 8, 9 and 10). In each pair the firing rate fluctuations as a function of time were precisely the same. *F* (sim.007a): Spike trains were realizations of correlated and nonstationary Poisson processes. The firing rates in each spike train fluctuated rapidly between 0 and 28 spikes/s (average firing rate 4.3/s and SD of the fluctuations 4.7/s). The time constant of the firing rate fluctuations was 0.05 s. The cells were divided into five pairs (1 and 2, 3 and 4, 5 and 6, 7 and 8, 9 and 10). In each pair the firing rates as a function of time were precisely the same. *G* (sim.007b): Spike trains were realizations of correlated and nonstationary Poisson processes. The spike trains were similar to those in *F* except that the rates of fluctuations were larger, as in *D*.

#### Experimental data

The detection scheme was applied to four 100-s recordings of spontaneous activity from eight single units measured in parallel. The recordings were made with metal microelectrodes inserted into the primary auditory cortex of a cat anesthetized with nitrous oxide. The eight units were recorded from six electrodes; at most two units could be isolated from a single electrode. The distance between ad-

acent electrodes was 2.5 mm, and the distance between the two furthest electrodes was 5.6 mm. Detailed description of the recording procedures and stimulus conditions between the periods of recording that are analyzed here are given in Ref. 3.

## RESULTS

### The expected number of repeating patterns

Even if there were no special brain processes that increase the occurrence of repeated firing patterns in the recorded data, some number of patterns might repeat just by chance. We have developed several equations for estimating the expected number of such repeating patterns, with detailed derivations given in the APPENDIX; here we shall describe some of the final equations and their applicability.

First let us assume a very simple random process in which there are  $n$  spike trains each firing at  $\lambda$  spikes per second. The firing times follow a stationary Poisson process and the spike trains are independent. Within this process we look for patterns made out of  $c$  spikes with  $r$  repetitions of the pattern in the  $T$  seconds of recording. Let us denote by  $w$  the maximum allowed delay between the first and last spike in a pattern and by  $\Delta$  the time accuracy with which the firing time is measured (e.g., 1 ms). In this case Eqs. A6 and A8 are reduced to

$$N_r^{(c)} = n^c [(w/\Delta)^{c-1} / (c-1)!] [T\Delta^{c-1}\lambda]^c e^{-T\Delta^{c-1}\lambda^c / r!} \quad (1)$$

where  $N_r^{(c)}$  is the expected number of patterns of complexity  $c$  that repeat  $r$  times.

Although the conditions for which this equation was derived hardly hold in any physiological recordings of real spike trains, it does illustrate several important properties of pattern repetition. The number of expected repetitions is most sensitive to the firing rate  $\lambda$ , since it depends on the firing rate raised to the power  $r \cdot c$ . (Note that the argument of the exponential is very small, about  $-10^{-2}$ , for typical parameter values). Thus if, for instance, the firing rate of the cells increases from 5/s to 8/s, the number of patterns of 4 spikes that repeat 2 times will increase 43-fold ( $(8/5)^8$ ). We must be extremely careful with data that involve high and variable spike rates.

The next critical parameter in Eq. 1 is the "bin width"  $\Delta$ , i.e., the time resolution used for defining spikes. The number of patterns



that repeat by chance is proportional to  $\Delta$  raised to the power of  $(c-1) \cdot (r-1)$ . This suggests using the highest possible time resolution (minimum  $\Delta$ ) that is physiologically reasonable. In all the examples illustrated in this paper we have used 1 ms.

Real spike trains frequently show firing rate fluctuations that exceed those predicted for a stationary Poisson process. Such large rate fluctuations may be interpreted as the result of nonstationary processes of some appropriate time scale. Note that *Eq. 1* predicts many more chance repeating patterns during periods of high firing rate. For real nonstationary neurons, the use of average firing rates in *Eq. 1* or *A8* would lead to a gross underestimate of the expected number of patterns that repeat by chance. Accordingly, for real spike trains we have developed two alternate ways to estimate the expected number of repeating patterns: the "ad hoc" method for triplet and quadruplet patterns, and the "bootstrap" method for patterns made up of five or more spikes. A brief description of these methods follows.

**AD HOC METHOD.** Rather than assuming some kind of Poisson process as a basis for calculation, this method actually counts the number of patterns that occur in a given piece of data. If, for example, we are interested in patterns of 3 spikes (2 intervals) we should count the number of patterns composed of 3 firings, respectively from neurons (1, 1, 1), (1, 1, 2), . . . , etc. (i.e., all combinations of three names). For each such set of ordered names we can calculate the number of possible different time combinations (including intervals of zero) that could occur in a pattern window duration  $w$  and time resolution  $\Delta$ . For pattern complexity (length) 3 *Eq. A3* becomes

$$n(\mathcal{D}_3) = (w/\Delta)^2/2$$

where  $\mathcal{D}_3$  is the set of all possible time combinations for a particular ordered name list of complexity 3. For the present example, if we have a time resolution of 1 ms and we are interested in triplet patterns that may last up to 500 ms, then we could have 125,000, i.e.,  $500 \cdot 500/2$  different possible time delays between firings of, e.g., neurons 1, 2, and 3 in that order.

Assume that the observed counts are distributed uniformly among all the possible

different time delay combinations that can occur for each set of names. (The assumption is testable if we wish.) For every list of neuron names  $S_c$ , we divide the number of patterns actually observed for these ordered names,  $m(S_c)$ , by the number of possible different time delays  $n(\mathcal{D}_c)$ . This yields  $x(S_c)$ , the expected number of occurrences of any one particular delay pattern with these names in this particular data set. (This calculation is similar to sampling with replacement in an urn problem.) For instance, if we observed 1,250 cases where neurons (1, 2, 3) fired in that order within 0.5 s, then the expected number of occurrences for any particular delay pattern of this same firing sequence will be 0.01 (i.e.,  $1,250/125,000$ ) under the uniform distribution assumption. From this small expected count we can compute the probability of seeing a given pattern  $r$  times, using *Eq. A1*. For our example, the probability of seeing a particular pattern twice is 0.00005. By adding up such probabilities over all possible  $c$ -fold names, we can find the expected number of all  $c$ -spike patterns which repeat  $r$  times (again for this particular data set)

$$N_c^{(r)} = \frac{(w/\Delta)^{c-1}}{(c-1)!} \sum_{S \in \mathcal{I}_c} e^{-x(S)} \cdot x(S)^r / r! \quad (2)$$

**THE BOOTSTRAP METHOD.** The ad hoc method described above requires counting the number of times that every possible pattern  $S_c$  occurs. Such a counting process is not practical for patterns which are longer than 4 spikes. With the bootstrap method we calculate the expected number of repeating 5-spike patterns from the expected number of repeating 4-spike patterns. In turn the expected number of 6-spike patterns is calculated from the expected number of 5-spike patterns. Although this method might be carried on also to patterns of  $\geq 7$  spikes, it is not advisable to do so, because the inaccuracies (introduced by the assumption that the added spike trains are Poissonian) accumulate and yield an underestimate of the expected numbers. Thus for cortical units the bootstrap method is useful only for two steps beyond what is obtained with the ad-hoc method. The APPENDIX describes *Eqs. A18* and *A19* which are used for these computations.

In Table 1, for data taken from control simulations *A-G*, we compare the number of repeating patterns that are actually found

TABLE 1. Comparison between the number of repeating patterns that were found and the expected number for simulated spike trains

Complexity:	3				4		5	6
	2	3	4	5	2	3	2	2
<i>A</i> found	9,710	48	0		402	0	13	0
<i>A</i> expected	9,515	39.7	0.125		400	0.008	12.5	0.3
<i>B</i> found	21,703	390	4	0	1,367	0	53	2
<i>B</i> expected	21,640	353	5.34	0.073	1,327	0.18	53.1	1.74
<i>C</i> found	11,443	103	4	0	814	0	45	2
<i>C</i> expected	11,970	95.4	0.83	0.0078	877	0.069	23	0.48
<i>D</i> found	4,357	14	0		175	0	3	
<i>D</i> expected	4,171	13.1	0.034		169	0.003	3.64	
<i>E</i> found	8,868	59	0		721	0	51	2
<i>E</i> expected	8,961	68.5	0.60		750	0.076	15.45	0.25
<i>F</i> found	4,120	13	0		150	0	2	0
<i>F</i> expected	4,108	11.7	0.025		150	0.002	3.33	0.059
<i>G</i> found	7,133	28	0		359	0	13	
<i>G</i> expected	6,538	24.7	0.074		294	0.007	7.68	

For patterns of 3 and 4 spikes the expected number was computed by the ad hoc method, whereas for 5 and 6 spikes it was computed by the bootstrap method. The parameters of the simulations *A* through *G* were described in METHODS. Window length was 0.5 s. Data were included only when the expected number of repeating patterns was  $>0.001$  or when patterns were actually found.

with the number of repeating patterns that are expected from the calculations described here. In most cases the estimates are quite accurate, even though various forms of nonstationarity were included in the simulations. Thus we should be able to detect excess numbers of repeating patterns in real data if they are present.

The assumptions used to derive the ad hoc method held only in simulations *A*, *B*, and *C* where the firing rates were either stationary or changed slowly. In the other simulations, the firing rates were changing rapidly, or pairs of spike trains had (various independent) covariation of rate, or both. Nevertheless, the estimations of counts are quite good. The assumptions used to derive the bootstrap method held only in simulations *A* and *B*, where the firing rates were stationary. Indeed, the bootstrap method gives inaccurate prediction in simulations *C* and *E* where the firing rates fluctuated slowly but with large amplitudes (0–22 spikes/s).

Figure 1 gives some insight into the degree of fluctuation and correlation (from covariation of rates) that can be tolerated by these calculations. Satisfactory results were obtained with the degree of cross-correlation (from covariation of rate in pairs of neurons)

as in Fig. 1, *A* and *C*, or alternatively, in the absence of cross-correlation with the degree of auto-correlation shown in Fig. 1*B*. Inaccurate (low) predictions of the expected number of repeating patterns occurred if the firing of the individual neurons showed the degree of autocorrelation shown in Fig. 1*B* and in addition there was cross-correlation (from covariation of rates in pairs) of the degree in Fig. 1*D*.

#### *Finding which patterns did not appear by chance*

In simulation *G* (Table 1), we found 13 quintuplet patterns that repeated twice, whereas only 7.68 were expected to repeat twice. Is this difference significant? Those quintuplet patterns that did appear twice are an extremely small fraction of the many possible quintuplet patterns (given a time resolution and window duration). For the particular values in this example there are  $1.3 \cdot 10^{17}$  possible quintuplet patterns; each of these has an extremely low probability of appearing twice. These are appropriate conditions for using the Poisson formula (Eq. A1) to compute the probability of getting  $\geq 13$  repeating patterns when 7.68 are expected. The result is 2.5%, so that these numbers represent a not

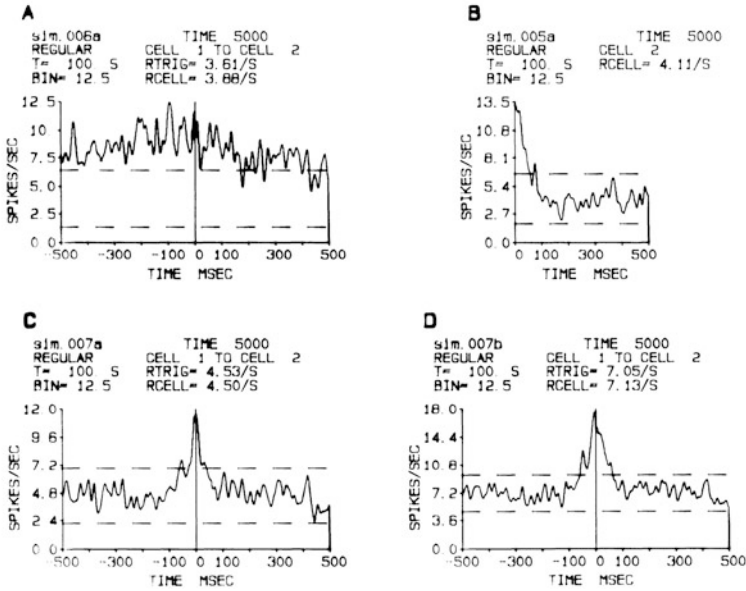


FIG. 1. Auto (*B*) and cross-correlations (*A*, *C*, *D*) of spikes in the several simulations with rate fluctuations. The cross-correlations are from simulations in which pairs of "neurons" had covarying rates. The auto-correlation is from a simulation where each neuron had independent rate fluctuations. Dashed lines show the 99% confidence limits for a comparable correlogram of a stationary Poisson process of the same mean rate. The expected number of repeating patterns calculated by the ad hoc method agreed with the observed number of all simulations that had less covariation of pair rates than shown in *D*.

very significant excess in the number of repeating quintuplet patterns.

Confidence limits for any expected number of patterns can be obtained by calculating the corresponding probabilities for all possible observed numbers of patterns with the Poisson formula. For 99% confidence limits we would sum the probabilities for low numbers until we achieve a total probability of 0.005; we would then continue summing probabilities for higher counts until we reach a total probability of 0.995. This determines the upper and lower integers that set the 99% confidence limit. When the expected number of patterns is large, the normal approximation to the Poisson formula was used (see Ref. 1 for a more detailed description).

We emphasize that Fig. 2 and all similar figures in this paper compare observed and

expected *number of patterns* that meet the stated criteria of repetition, complexity, window, and in some cases specific name or delay list. The expected counts are calculated from the number of single occurrences of the patterns that meet the same stated criteria (except, obviously for the repetition). These figures do not show the observed and expected counts of repetitions for particular patterns; such measure are not appropriate at this stage of the analysis.

Normally we would plot vertical bars (e.g., for 99% confidence limits) of each point in these graphs. If such a bar does not reach the line where observed and expected numbers are equal, then the observation falls outside the stated limits. Since this procedure would produce a rather messy graph we have instead plotted a vertical 99% confidence region

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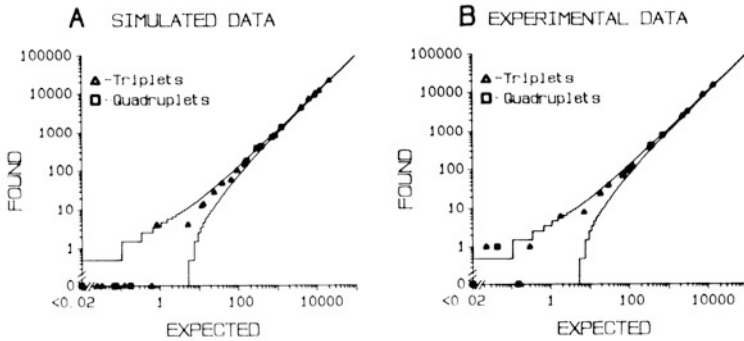


FIG. 2. Comparison of the number of patterns found versus the expected number that repeated two or more times. The triangles describe triplets; the squares describe quadruplets. The jagged lines give the 99% confidence limits. *A*: 7 simulations described in Table 1. *B*: 4 experimental data files described in Table 3.

around the observed equals expected line. The limit values are indicated as next outer half integers, so that there is no doubt when a particular point (which must have an integral observed value) falls beyond the confidence limits. Fig. 2*A* shows in this manner the triplets and quadruplets of the simulation data in Table 1. Only a few points (mostly from Simulation *G*) fall outside the 99% limits. These results suggest that the ad hoc and the bootstrap methods give reasonable estimates for the expected number of repeating patterns in "random" control data. The confidence limits, in turn, can therefore be used on unknown data to focus our attention on those types of repeating patterns that appear in excessively large numbers.

When the number of repeating patterns is small, the confidence limits may be sufficient to point out candidate patterns which do not occur by chance. However, when the number of repeating patterns is very large, the mere knowledge that there is an excess number of such patterns is not enough. For example, in Table 1 we see that in simulation *G* there were 7,133 different triplets that appeared twice, while the expected number was 6,538. This difference is certainly significant, but we wish to know which of the 7,133 triplets are most likely to be nonrandom. This can be done by dividing the 7,133 triplets into subgroups and looking whether there are sub-

groups in which the number of triplets exceeds the confidence limits. One way for such a division is to separate the triplets by the names of the single units that make up these patterns (e.g., all triplets made of single units 1, 2, and 3; all triplets made of single units 1, 2, and 4; etc.). Equation *A5* can be used for getting an estimate of the expected number of occurrences for any particular list of single unit names. This expected count can then be used to compute confidence limits.

Figure 3*A* shows graphically such a division of all the triplets that repeated twice in simulation *B*. The jagged line gives, as in Fig. 2, the 99% confidence limits. In simulation *B* there were 10 single units, so that there were 1,000 different triplet names [such as (1, 1, 1), (1, 1, 2), (1, 1, 3), . . . , (10, 10, 10)]. When using 99% confidence limits one can expect that 10 out of the 1,000 points will exceed the limits. This is roughly what happens in Fig. 3*A*. Note also, that even the points that fall outside the confidence limits are not placed very far away from the limits.

#### Experimental data

When experimental data were analyzed it became evident immediately that the number of repeating patterns was far beyond what could be expected by chance. Table 2 shows the data for 100 s of "spontaneous" activity of eight single units which upon shallow ex-

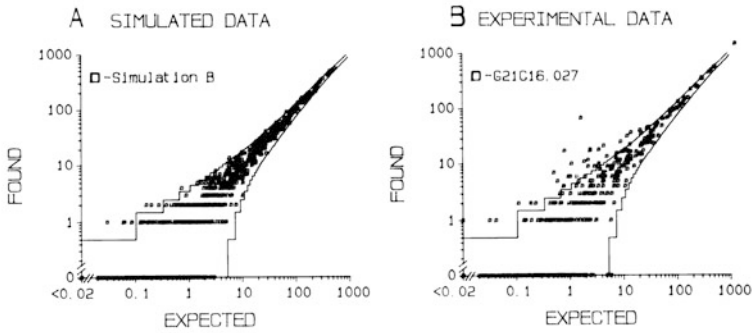


FIG. 3. Breaking triplets into subgroups. All the patterns of 3 spikes that appeared twice are divided into subgroups according to the names of the single units that participated in the patterns. *A*: simulated data (1,000 subgroups). *B*: experimental data (512 subgroups).

amination looked reasonably stationary and not heavily correlated. Among the striking differences between the observed and the expected number of repeating patterns were one pattern of seven spikes that repeated twice, a pattern of four spikes that repeated four times and two patterns of three spikes that repeated seven (!) times.

Figure 3*B* shows the division of 9,330 triplets that occurred twice in this record, into all possible triplet names. Both Fig. 3*B* and Ta-

ble 2 show great excess of repeating patterns. Close examination of these unusual patterns revealed that they are associated mostly with bursting cells. For instance the two triplets that repeated seven times were (using the nomenclature  $S_c$ ,  $D_c$  of the APPENDIX, in which a pattern is defined by a list of single unit names followed by a list of delays from the first spike): (4, 4, 4), (0, 2, 4) and (4, 4, 4), (0, 2, 6). This means that when single unit 4 emits a high-frequency burst, the detailed

TABLE 2. Effect of eliminating bursts and high firing rates on the number of patterns found

Complex.	Patterns Repeat	All spikes		Filtering	
		Found	Expected	Found	Expected
3	2	9,330	8,785	3,134	3,011
	3	263	195	39	30
	4	12	4.7	1	0.29
	5	4	0.1	0	0.003
	6	2	0.0023		
	7	2	<0.0001		
	4	2	635	554	94
3		8	0.159	0	0.007
4		1	<0.0001		
5	2	70	15.3	2	2.6
6	2	9	0.337	0	0.05
7	2	1	0.0062		

Data taken from a record containing 100 s of spontaneous activity of 8 single units. Filtering means eliminating all spikes around which (within 500 ms) there were >10 other spikes from the same single unit (i.e., all time sections in which a single unit fired at a high rate) and all the spikes before which another spike from the same single unit occurred within 5 ms (i.e., eliminating all but the first spike in a burst).

structure of the burst tends to repeat. It is possible that such a burst is a highly significant event in the overall activity. Its detailed structure may reflect some interesting organization of the excitation which drives the cell, but it may be also a reflection of the internal changes of excitability in the driven unit itself. If the latter mechanism is true, excessive numbers of patterns associated with high frequency bursts may obscure other patterns which are more likely to represent significant organization of activity in the cortical network.

Periods in which a spike train fired at high rates contributed a large fraction of the repeating patterns produced by these neurons. For instance in another recording from the same single units as described in Table 2 we got >120,000 triplets that repeated twice. About 100,000 of these came from periods in which some single unit(s) fired at rates > 20/s. We can detect that there is an excess number of repeating patterns under the particular conditions, but it is obviously quite difficult to identify which patterns are candidates for further analysis in these circumstances.

We have examined the effect of eliminating bursts and periods of high firing rates from the data. This elimination, which will be called filtering, was carried out in the following manner: a burst was defined as a group of spikes from the same single unit following

each other with interspike intervals that did not exceed some minimal time (e.g., 5 ms). When a burst was found, only the first spike was considered in the search for patterns. The low-pass frequency filtering was achieved by setting a window (e.g., 500 ms) around each spike and counting how many more spikes from the same single unit occurred within this window. If the number of spikes exceeded some threshold (e.g., 10) the spike around which the window was set was not considered by the pattern searching routines.

The right half of Table 2 shows what happens when such a filtering scheme is applied to experimental data. The number of observed patterns at each complexity and repetition are very close to what can be expected by chance. Figure 4*B* shows the separation of the 3,134 triplets that occurred twice according to single unit names. Figure 4*A* shows the data from the same record when all the spikes were considered. It is evidence that most of the excessive patterns were removed by this filtering scheme. However some of the cell combinations still tend to produce more patterns than can be expected by chance.

For instance, the single units (3, 1, 4) generated one pattern that appeared twice [at delays (0, 177, 266)], while the expected number of patterns appearing twice by chance was 0.021, or the single units (4, 2, 2) generated two patterns that repeated twice [at delays (0,

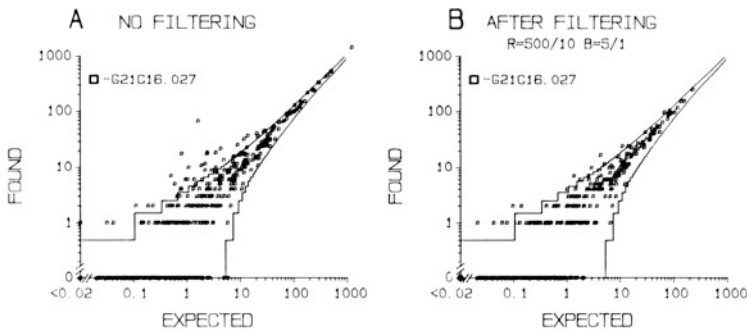


FIG. 4. The effect of filtering on the number of triplets that repeated twice. *A*: all the spikes in the recordings were considered when searching for patterns. *B*: only spikes which were not embedded in periods of high firing rates or which were not embedded in a burst were considered. See legend of Table 2 for the exact definition of the spikes that were filtered out.

TABLE 3. *Observed and expected repeating patterns*

Complexity:	3				4		5	6
	2	3	4	5	2	3	2	2
1 found	8,209	120	6	1	396	1	13	0
1 expected	7,789	119	1.74	0.023	358	0.044	26.5	1.57
2 found	3,134	39	1	0	94	0	2	0
2 expected	3,011	30	0.29	0.003	95	0.007	2.6	0.05
3 found	14,542	355	8	0	759	0	27	1
3 expected	13,710	328	7.1	0.14	701	0.15	30	1.03
4 found	2,406	24	0	0	69	0	0	
4 expected	2,248	18.5	0.14	0.001	70	0.004	3.74	

Data from 4 records of "spontaneous" activity each of 8 single units in the primary auditory cortex of cat. All records were filtered as described in the legend of Table 2.

160, 182) and (0, 317, 332)], while the expected number of patterns appearing twice by chance was 0.097.

Table 3 and Fig. 2*B* show the number of repeated patterns found in 4 recordings of experimental data after filtering (as described in Table 2). When comparing Table 3 to Table 1, Fig. 2, *A* to *B*, and Fig. 3*A* to 4*B*, it is evident that the experimental data tend often to have more repeated patterns than were found in comparable simulations. One may wonder whether more drastic filtering would cause these patterns to disappear. We found that although one can reduce the number of repeating patterns by more strict filtering of the data, there are always some single-unit combinations that generate excess numbers of repeating patterns.

At this stage one cannot say whether this excess is due to large deviation from the assumptions made while developing the equations used to compute the expected number of patterns that repeat themselves by chance, or due to the presence of some special neural processes that make the cells fire repeatedly in the same pattern. Some clue as to whether the excess of patterns is real may be obtained by merging the list of detected patterns from all four records and looking for patterns that were detected in more than one record. When this procedure was carried out on the data described in Table 3, it was found that indeed some patterns appeared twice (or three times) in more than one record. For example, the pattern (2, 2, 2), (0, 14, 23) appeared three times in record 1 and twice in record 2; the pattern (1, 6, 1), (0, 125, 234)

appeared twice in record 1 and twice in record 3. Altogether there were 51 patterns of this sort.

#### DISCUSSION

We began this paper with the notion that excessively repeating patterns could be used to indicate some sort of repeating state of the nervous system. Since we are examining only a very limited number of neurons, any repeating pattern which we detect probably is a (small) portion of a larger pattern which involves neurons that are not under observation. It is entirely possible that different states (different large patterns) could be associated with the same observed subpattern. This is an intractable sampling problem and ultimately sets limits on the breadth of inference that can be drawn from detection of repeating patterns in the spike trains of a limited number of simultaneously observed neurons.

We have presented algorithms and confidence limit methods that detect all repeating spatiotemporal firing patterns in a given stretch of multineuron data and which subsequently show which pattern classes are appearing in excess. It should be noted that our method seeks exact pattern matches (to within the time resolution). A missing spike in a "repetition" would cause the remaining spikes to be treated as a different pattern, possibly of another class. On the other hand, our matches ignore extra spikes; this means that firing bursts cause excess and possibly meaningless matches. We have demonstrated the effects of filtering bursts out of the data.

It is possible, of course, to take the view that firing bursts are themselves highly significant events whose pattern of occurrence marks particular states of information processing. In this case one can implement a reversed scheme for selection of the data: filter out the isolated spikes and leave the bursts. The methods of this paper can then be used to study patterns made up of or within bursts. Identification of bursts for purposes of elimination, as in this paper, can be made simply on a criterion of spikes following each other with interspike intervals shorter than some minimal delay. If instead the bursts are to be kept and studied, it would probably be more appropriate to use a more rigorous method to define bursts in the context of an ongoing spike train. One excellent approach to this is the Poisson surprise calculation used by Legendy and Salzman (13).

Other approaches to the repeated pattern detection problem can be envisioned. For example, during the detection phase, matches could be made "inexact" according to some continuous measure so that missing and excess spikes are both equally penalized (Perkel, private communication of working notes). This approach is computationally expensive. However, once templates have been made out of candidate patterns detected rapidly by the methods presented here, such continuous measures of fit are feasible and appropriate.

When the various algorithms described here were developed, we had the following experimental situation in mind. Suppose that the activity of several single units is being recorded in parallel. Initially the units are studied, possibly under some set of stimulus conditions, for a period of about 100 s. These recorded data are submitted to the pattern searching routines. The computer compares the number of observed repeating patterns of a given description (repetition, complexity, name, or delay list, etc.) with the number of such patterns expected by chance. Presumably repeating patterns of certain descriptions will be singled out as occurring in excess numbers.

If the number of such patterns of a particular description is relatively small, then all of them can be chosen as candidates for further attention. For instance, if we examine the results of expt. 1 in Table 3, we see that only 1.74 patterns of 3 spikes were expected to re-

peat 4 times while 6 were found. All these 6 patterns are candidates to serve as templates for further search. Similarly, by looking at Fig. 4B we see that in this experiment there were 4 points outside the 99% confidence limits at the level of 1. That means that there were 4 different unit combinations [these were (1, 2, 3), (3, 4, 5), (1, 8, 1), and (7, 7, 7)] for which <0.1 patterns are expected to repeat twice but for which 1 pattern actually repeated twice. These 4 patterns are also candidates for templates. The experience of one of us (M. Abeles) from analysis of records obtained from the auditory and the prefrontal cortex of unanesthetized monkeys is that such patterns can be singled out in about half of the records.

If, however, the number of patterns of a particular description is large, it is impractical to designate them all as candidates for further analysis. The experimenter must devise external criteria to make a selection. Alternatively, different subgroupings in the analysis can be attempted (as in the breakdown by name list in Fig. 3) which might single out repeating patterns which are in excess, but which form a smaller group. This selection process is extremely important and deserves considerable future attention.

Once the list of candidate patterns is determined, the computer can generate a corresponding set of templates; all further incoming data from the experiment is examined against the templates with some appropriate criterion of fit. The computer is programmed to announce the further occurrences of any of the candidate patterns (e.g., with a beep). The experimenter may now manipulate the environment (stimuli, behavioral conditions, motor responses, etc.) in a search for the situation, if any, in which some of the candidate patterns reappear.

This type of experiment is analogous to the early experiments on single neurons. Once the single unit was isolated, the experimenter tried to determine the adequate stimulus for firing of that unit. In our case, instead of studying the conditions that result in single unit firing, the experimenter studies the "receptive field" properties of the generator producing the repeated spatiotemporal firing pattern events.

There is no technical difficulty in building several tens of templates that would detect



the reappearance of candidate firing patterns in real time, assuming that we solve the selection problem discussed above. The algorithm described here for detecting repeating patterns is very fast and will automatically recognize all patterns that repeat twice or more. The confidence limits developed here should help focus the experimenter's attention on those patterns which are less likely to be generated by chance. The entire process of detecting patterns, sorting them according to spike names, and computing confidence limits for a typical multineuron recording would take  $\sim 10$  min on a fast minicomputer. This is a vast improvement on past approaches to this problem.

The next step, then, is to install the pattern detecting "machine" as a routine filter in ongoing multineuron experiments. This will allow a continual study of temporal association between repeating patterns and externally observable events. Repeating patterns which continue to occur in an experiment, but for which such an association can not be found, may be a new indicator of repeating internal events in the workings of the observed portion of the nervous system.

#### APPENDIX

##### Symbols

$c$	Complexity of a pattern. The number of spikes in a pattern. $c = 1, 2, \dots$
$D, D_c$	A list of $c$ delays, $D_c = (0, \tau_2, \tau_3, \dots, \tau_c)$ . The delay $\tau_n$ is the time elapsed from the first to the $n$ th spike in a pattern. Therefore $\tau_1$ is always 0
$\mathcal{D}_c$	The set of all possible $D_c$ . E.g., $\mathcal{D}_3 = \{(0, 0, 0), (0, 0, \Delta), (0, 0, 2\Delta), \dots\}$
$\Delta$	The accuracy of the time measurement in seconds. E.g., 0.001 s
$\lambda_i$	The firing rate of the $i$ th single unit, in spikes per second
$m(S_c)$	The total number of cases in which the spike sequence $S_c = (i_1, i_2, \dots, i_c)$ appeared regardless the delays, except that the total duration of the pattern was less than $w$
$n$	The number of recorded single neurons.
$n(D_c)$	The number of different time delays $D_c$ that can be fitted in a time window $w$ seconds wide
$N^{(r)}(S_c)$	The expected number of patterns made from spike trains $S_c = (i_1, i_2, \dots, i_c)$ which repeated $r$ times
$N_c^{(r)}$	The expected number of patterns of complexity $c$ which repeated them-

	selves $r$ times. All possible ways of writing $c$ names are allowed
$r$	The number of repeated appearances of the same pattern. $r = 2, 3, \dots$
$S, S_c$	A list of $c$ single unit names, $S_c = (i_1, i_2, \dots, i_c)$ . E.g., $S_4 = (1, 5, 6, 1)$ . The $i_j$ can be assigned any names from among the $n$ recorded neurons
$\xi_c$	The set of all possible $S_c$ . E.g., $\xi_3 = \{(1, 1, 1), (1, 1, 2), (1, 1, 3), \dots\}$
$T$	The total duration of single unit recording, in seconds. E.g., 100 s
$t$	Time
$\tau_i$	The delay between the first and the $i$ th spike, in seconds
$x, x(S)$	The expected number of repetitions of a particular pattern $S, D$
$w$	The window duration. The maximal allowed delay between the last and first spikes in a pattern, in seconds. E.g., $w = 0.5$ s

##### Expected number of repeating patterns

In this section we shall develop equations for evaluating the number of different patterns that are expected to appear repeatedly. We shall assume that for any particular predetermined pattern (e.g., a spike from cell 1 followed, after 0.015 s, by a spike from cell 3, etc.) we can compute the expected number of occurrences  $x$ . In the following sections we shall develop several ways to estimate this  $x$ ; here we assume that  $x$  is known.

Let us denote the list of single-unit names that appear in a pattern of  $c$  spikes by  $S_c, S_c = (i_1, i_2, \dots, i_c)$ , and the list of delays between these spikes and the first spike by  $D_c, D_c = (0, \tau_2, \tau_3, \dots, \tau_c)$ , where  $i > j$  implies  $\tau_i \geq \tau_j$  and  $\tau_c < w$ . Let us denote the expected number of appearances of the pattern  $S_c, D_c$  by  $x(S_c, D_c)$ .

We can think of the appearances of the sequence  $S_c, D_c$  as successes of a trial that is repeated many times in the following way. At time  $t = 0$  we look whether this particular pattern occurred, that is whether spike  $i_1$  fired during the time interval  $[0, \Delta)$  and spike  $i_2$  fired during the time interval  $[\tau_2, \tau_2 + \Delta)$  and spike  $i_3$  fired during the time  $[\tau_3, \tau_3 + \Delta)$ , etc. Then we try again to find this pattern at times  $t = \Delta$  and so on for  $T/\Delta$  times. The probability of getting these spikes at any one trial is very low, but since we repeat this trial many times, we may succeed sometimes.

Because the few successes that we might get are due to repeating the experiment a great many times with an extremely low probability of success on any one trial, we may compute the probability of getting  $r$  successes in this experiment by the Poisson probability density which tells the probability of getting  $r$  successes when  $x$  successes are expected

$$pr\{r, x\} = e^{-x} x^r / r! \quad (A1)$$

It is important to note that the validity of Eq. A1 does not rest on the assumption that the spike trains behave like Poisson processes, but just on the assumption that at any time instance  $t$  the probability of getting one prespecified pattern is very low.

Under the conditions of interest to us (low firing rates, small and weak correlations between the cells) this  $pr\{r; x\}$  will be always very small. Thus, there is no point in asking what is the probability of finding  $r$  repetitions of one particular pattern  $S_c, D_c$ . But we can ask what is the expected number of different patterns made out of spikes from cells  $S_c = (i_1, i_2, \dots, i_c)$  that appeared repeatedly  $r$  times in our record. This expected number  $[N^{(r)}(S_c)]$  can be obtained by adding Eq. A1 over all possible delays  $D_c$

$$N^{(r)}(S_c) = \sum_{D \in \mathcal{D}_c} [e^{-x(S_c, D)} x(S_c, D)^r / r!] \quad (A2)$$

Note that since time is measured with a finite accuracy,  $\Delta$ , and the maximal delay is limited to  $w$ , the total number of terms on the summation is finite and is given by the following considerations: if we combine together all spike patterns  $S_c$  starting with the same  $(i_1)$  spike we shall have  $(c - 1)!$  different  $S_c$ s included. In this set of patterns each of  $\tau_2, \tau_3, \dots, \tau_c$  may obtain  $w/\Delta$  different values. There would be  $(w/\Delta)^{c-1}$  different delay lists. Thus for each particular  $S_c$  there are

$$n(\mathcal{D}_c) = \frac{(w/\Delta)^{c-1}}{(c-1)!} \quad (A3)$$

different time delays.

If we wish to know what is the expected number of patterns of complexity  $c$  (regardless of which particular spikes are involved in the pattern) which appeared  $r$  times in our record we would have to sum Eq. A2 over all possible spike names  $S_c$

$$N_c^{(r)} = \sum_{S \in \mathcal{I}_c} N^{(r)}(S) \quad (A4)$$

In some situations it may be possible to show that the expected number of occurrences  $x(S, D)$  is independent of  $D$ . That is, all time delays between the spikes in a pattern are equally probable. In such cases we may write:  $x(S, D) = x(S)$ , and the sum over  $D$  in Eq. A2 is just this expectation times the number of different time delays that one can have among  $c$  cells

$$\sum_{D \in \mathcal{D}_c} x(S, D) = n(\mathcal{D}_c) x(S)$$

By using Eq. A3 we get from Eq. A2 that the expected number of patterns from cells  $S_c$  that repeated  $r$  times is

$$N^{(r)}(S_c) = \frac{(w/\Delta)^{c-1}}{(c-1)!} e^{-x(S_c)} x(S_c)^r / r! \quad (A5)$$

and from Eq. A4 we get that the expected number of patterns of  $c$  spikes that repeated  $r$  times is

$$N_c^{(r)} = \frac{(w/\Delta)^{c-1}}{(c-1)!} \sum_{S \in \mathcal{I}_c} e^{-x(S_c)} x(S_c)^r / r! \quad (A6)$$

Equations A2 and A4 or A5 and A6 give a straightforward way of estimating the number of repeating patterns that one expects to get by chance, but they rely on a valid way for getting  $x(S_c, D_c)$  the expected number of occurrences of every specific pattern  $S_c, D_c$ . In the following four sections we develop ways to estimate this  $x$ .

*Stationary Poisson processes*

In this section we assume that our record is a realization of  $n$  parallel stationary Poisson processes, recorded for  $T$  seconds. Let us denote the firing rate of the  $i$ th single unit by  $\lambda_i$ . We assume also that the single units fire independently. The time of events is assumed to be quantized by units of  $\Delta$  seconds. We assume that  $\Delta$  is small enough so that the probability of getting two spikes from the same train within  $\Delta$  seconds is negligibly small.

At every time  $t$  we can ask what is the probability of getting the pattern  $S_c, D_c$ . This probability is given by multiplying the probabilities of getting the first spike exactly at  $t$  by the probability of getting the second spike during the interval  $[t + \tau_2, t + \tau_2 + \Delta)$  by the probability of getting the third spike during the interval  $[t + \tau_3, t + \tau_3 + \Delta)$  and so on. We get the following probability

$$pr\{S_c, D_c, t\} = \lambda_{i_1} dt \cdot \lambda_{i_2} \Delta \cdot \lambda_{i_3} \Delta \cdot \dots \cdot \lambda_{i_c} \Delta \quad (A7)$$

Note that here we assumed that the pattern started exactly on  $t$  and therefore the probability of finding there the first spike  $(i_1)$  is  $\lambda_{i_1} dt$  and not  $\lambda_{i_1} \Delta$ .

By integrating Eq. A7 over all the available time ( $T$ ) we get the expected number of occurrences of  $S_c, D_c$  during  $T$

$$x(S_c, D_c) = x(S_c) = T \Delta^{c-1} \prod_{i \in S_c} \lambda_i \quad (A8)$$

Note that the expected number of occurrences  $x$  is not a function of the delays  $D_c$ . This is so because we assumed that the spike trains behaved like independent and stationary Poisson processes. Thus we can substitute the expected count of Eq. A8 in A5 to get, for any list of single unit names  $S_c$ , the expected number of patterns made of  $S_c$  which repeated  $r$  times.

Similarly, by substituting Eq. A8 in A6 we get a simple way to compute the expected number of patterns of  $c$  spikes that repeated  $r$  times by chance.

However, these equations are of limited value for physiological spike data, mostly because the firing rates of neurons tend to fluctuate excessively so that stationary Poisson processes are poor ap-

proximations to the statistics of neuronal firing times.

#### Nonstationary Poisson processes

Let us assume that the firing times of the single units are realizations of independent Poisson processes with varying firing rates. Let us denote by  $\lambda_i(t)$  the firing rate of the  $i$ th single unit at time  $t$ . All the other assumptions are as stated in the previous section. Then the probability of getting a specific pattern  $S_c, D_c$  at time  $t$  is given by

$$pr\{S_c, D_c, t\} = \lambda_1(t)dt \cdot \lambda_2(t + \tau_2)\Delta \cdot \dots \cdot \lambda_c(t + \tau_c)\Delta \quad (A9)$$

and the expected number is given by integrating over  $t$ .

$$x(S_c, D_c) = \Delta^{-c-1} \int_0^T \prod_{j=1}^c \lambda_j(t + \tau_j) dt \quad (A10)$$

This is not a practical equation to compute for all possible  $D_c$  and  $S_c$ . If the fluctuations of the firing rates are slow (relative to the maximal pattern duration  $w$ ) then  $\lambda(t + \tau) \approx \lambda(t)$  and Eq. A10 can be simplified to

$$x(S_c, D_c) = x(S_c) = \Delta^{-c-1} \int_0^T \prod_{j=1}^c \lambda_j(t) dt \quad (A11)$$

Again in this form  $x(S_c, D_c)$  is not a function of  $D_c$ , or of  $t$ . Therefore, Eq. A11 can be used in A5 and A6 to get the expected number of patterns of cells  $S_c$  that repeated  $r$  times, or the expected number of patterns of  $c$  cells that repeated  $r$  times.

In most cases the firing rates  $\lambda_i(t)$  are not known a priori because they fluctuate in apparently random fashion. Evaluating them from the same record in which patterns are searched will usually result in under estimations of  $N$ . Nevertheless these equations can be useful for firing times obtained in simulations (where  $\lambda(t)$  are known), and for some cases where the only variations in firing rates are brought about by stimuli, the poststimulus time (PST) histograms for the stimuli are known, and the units respond in a stable fashion.

#### Ad hoc method

We know from Eq. A11 that if the firing times behave like independent Poisson processes whose firing rates change slowly with time then  $x(S_c, D_c)$  (the expected number of occurrences of the pattern  $S_c, D_c$ ) is independent of  $D_c$ . Usually we cannot use Eq. A11 because we do not know the firing rate functions  $\lambda(t)$ . However, we may estimate  $x$  by counting all the occurrences of the sequence  $S_c$  (with delays that are less than  $w$  seconds) in the data. This number  $m(S_c)$  is approximately the sum of  $x(S_c, D_c)$  over all the possible delays  $D_c$ . If we assume that all the  $x(S_c, D_c)$  for a given sequence of spike names ( $S_c$ ) are identical, we have

$$x(S_c) \approx m(S_c)/[(w/\Delta)^{c-1}/(c-1)!] \quad (A12)$$

where  $m(S_c)$  is obtained by counting how many times  $S_c$  appeared in the data. When  $m(S_c)$  is large we may assume equality in Eq. A12 and substitute in A5 and A6. Thus we get an ad hoc estimation of the number of patterns made of  $S_c$  that repeated  $r$  times and of the total number of patterns of complexity  $c$  that repeated  $r$  times.

This ad hoc method of estimation was proven to be fairly accurate for both simulated and real data (see RESULTS). However, the process of counting all the occurrences of  $S_c$  for all possible combinations of  $c$ -spike names becomes very tedious for  $c \geq 5$ . Thus we found it practical to use the ad hoc method for patterns of 3 or 4 spikes, but had to resort on the next method for patterns of  $\geq 5$  spikes.

#### The bootstrap method

We shall develop here estimations for the expected number of patterns of complexity  $c + 1$  that appeared repeatedly  $r$  times from the expected number of patterns of complexity  $c$  that appeared repeatedly  $r$  or more times. This kind of estimation is possible because any pattern  $S_{c+1}, D_{c+1}$  can be generated from the pattern  $S_c, D_c$  by appending a spike name to  $S_c$  and a delay to  $D_c$ . Furthermore a pattern of complexity  $c + 1$  cannot appear  $r$  times unless the subpattern  $S_c, D_c$  (in which  $S_c$  is the list of the first  $c$ -spike names of  $S_{c+1}$  and  $D_c$  is the list of the first  $c$  delays from  $D_{c+1}$ ) appeared also for at least  $r$  times.

Therefore, we may compute for every pattern  $S_c, D_c$  that appeared  $k$  times, the probability that it would produce  $r$  ( $r \leq k$ ) repetitions of a particular pattern of  $c + 1$  spikes whose names are  $S_c, i_{c+1}$  and whose delays are  $D_c, \tau_{c+1}$ , where  $\tau_c \leq \tau_{c+1} < w$ . Given that a subpattern  $S_c, D_c$  has occurred at time  $t$ , what is the probability of finding a spike from  $i_{c+1}$  at the time interval  $[t + \tau_{c+1}, t + \tau_{c+1} + \Delta)$ ? To compute this probability we assume that the  $i_{c+1}$  single unit is firing according to Poisson statistics with a firing rate of  $\lambda_{i_{c+1}}$ .

Then the probability that it fired is

$$pr\{i_{c+1} \text{ fired}\} = \lambda_{i_{c+1}}\Delta \quad (A15)$$

and the probability that it did not fire is

$$pr\{i_{c+1} \text{ did not fire}\} = 1 - \lambda_{i_{c+1}}\Delta \quad (A16)$$

We know that the subpattern  $S_c, D_c$  occurred  $k$  times and we wish to know what is the probability that in exactly  $r$  times it was followed by a spike from  $i_{c+1}$  at the appropriate time. This probability is given by the binomial term

$$pr\{i_{c+1} \text{ fired exactly } r \text{ times}\} = \binom{k}{r} (\lambda_{i_{c+1}}\Delta)^r (1 - \lambda_{i_{c+1}}\Delta)^{k-r} \quad (A17)$$

On the average there are  $w/c\Delta$  different time delays after the last spike of  $S_c, D_c$  at which the  $i_{c+1}$  spike

might fire, and we expect to have  $N^{(k)}(S_c)$  cases in which the subpattern  $S_c$  repeated  $k$  times, so that the expected number of patterns  $S$  that repeated  $r$  times is

$$N^{(r)}(S_{c+1}) = \frac{W}{c\Delta} (\lambda_{c+1}\Delta)^r \sum_{k=r}^c \binom{k}{r} (1 - \lambda_{c+1})^{k-r} N^{(k)}(S_c) \quad (A18)$$

The term  $N^{(k)}(S)$  falls off very fast as  $k$  increases, so that there is no practical value for summing up all the way from  $r$  to infinity.

The total number of patterns of  $c+1$  spikes that repeated  $r$  times is computed as in Eq. A4, by adding all the  $S_{c+1}$  that repeated  $r$  times

$$N_{c+1}^{(r)} = \sum_{S \in \mathcal{I}_{c+1}} N^{(r)}(S) \quad (A19)$$

Now that we have  $N^{(r)}(S_{c+1})$  and  $N_{c+1}^{(r)}$  we can apply Eqs. A18 and A19 to these estimates to obtain  $N^{(r)}(S_{c+2})$  and  $N_{c+2}^{(r)}$ , and so on.

These estimates are based on the assumption that the  $c+1$  neuron in the pattern can be re-

garded as a Poisson process. As discussed earlier this is a poor approximation. However, when applied for only one or two steps beyond  $c$  and if the baseline estimates  $N^{(r)}(S_c)$  are good, the errors introduced by the Poisson approximations are not too bad. In the analysis discussed in the results we applied the ad hoc method for patterns of 3 and 4 spikes and the bootstrap method for patterns of 5 and 6 spikes. The agreement with the number of patterns found both in simulated and experimental data were quite good.

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## Searching for significance in spatio-temporal firing patterns

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George L. Gerstein

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

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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.

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

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**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) (Acertsen 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 superim-

posed 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 window 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 ( $\pm 8$  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 diago-

nal (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 be 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-

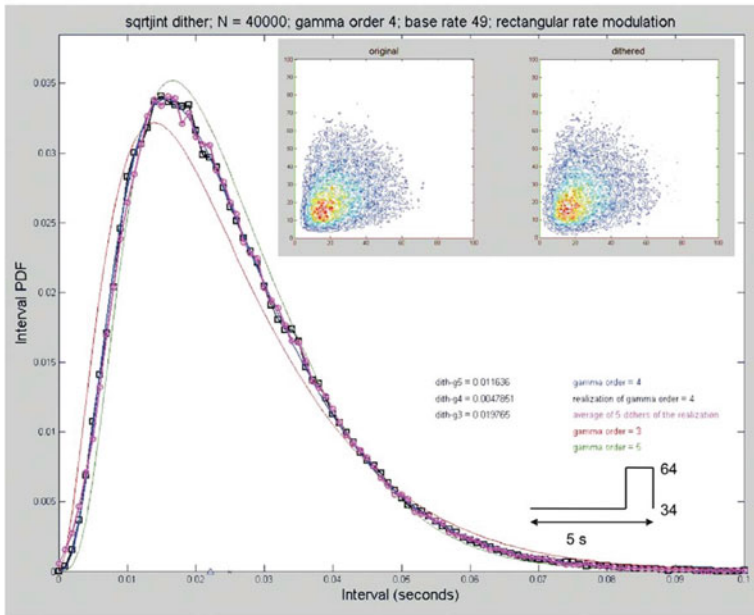


Fig. 1. Performance of the  $\sqrt{\text{JIH}}$  dither for data generated by a rate varying gamma process of order 4. The rate modulation cycle is indicated at lower right. Note that the theoretical IH, its realization and its dither all superimpose. Theoretical IH for gamma processes of order 3 and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



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mance of the  $\sqrt{J|H}$  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 Salzman 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

## Pattern Count Difference Spectrum

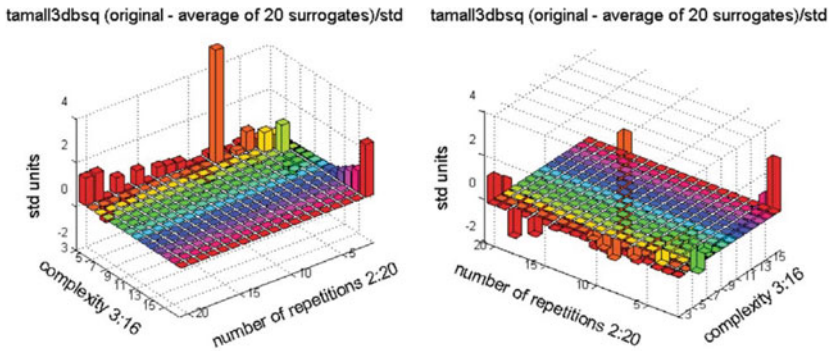


Fig. 2. An example of pattern count difference spectrum in units of standard deviation of the surrogate average. Data consisted of 6 well isolated neurons simultaneously recorded from left M1 of a monkey executing a repeating thumb-finger grasp task with both hands (Baker laboratory). Left panel shows 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 SURROGATE:	1,612,632
DIFFERENCE:	12,155
DIFFERENCE / $\sqrt{\text{SURROGATE}}$ :	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.

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