



Short communication

Statistical significance of sequential firing patterns in multi-neuronal spike trains

Casey O. Diekman^a, P.S. Sastry^b, K.P. Unnikrishnan^{c,*}^a Dept. of Industrial & Operations Engineering and Center for Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, MI 48109, USA^b Dept. of Electrical Engineering, Indian Institute of Science, Bangalore 560012, India^c Department of Computer Science, Wayne State University, 5143 Cass Avenue, Detroit, MI 48202, USA

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ABSTRACT

Sequential firings with fixed time delays are frequently observed in simultaneous recordings from multiple neurons. Such temporal patterns are potentially indicative of underlying microcircuits and it is important to know when a repeatedly occurring pattern is statistically significant. These sequences are typically identified through correlation counts. In this paper we present a method for assessing the significance of such correlations. We specify the null hypothesis in terms of a bound on the conditional probabilities that characterize the influence of one neuron on another. This method of testing significance is more general than the currently available methods since under our null hypothesis we do not assume that the spiking processes of different neurons are independent. The structure of our null hypothesis also allows us to rank order the detected patterns. We demonstrate our method on simulated spike trains.

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1. Introduction

Detection of temporal firing patterns among groups of neurons is an important task as these patterns are potentially indicative of functional cell assemblies or microcircuits present in the underlying neural tissue (Hebb, 1949; Brown et al., 2004). Computational methods (e.g., the two-tape algorithm; Abeles and Gerstein, 1988) which discover repeating occurrences of precise firing sequences in simultaneous recordings from multiple neurons have been used to assess activity patterns in cortical structures *in vivo* (Nadasdy et al., 1999), in slice preparations (Ikegaya et al., 2004), and in cultures of dissociated cortical neurons (Rolston et al., 2007). Methods such as the two-tape algorithm count the occurrences of a precisely timed pattern (e.g., the 3-neuron pattern $A[T_1]-B[T_2]-C$ where a spike from neuron A is followed by a spike from neuron B after a delay of T_1 time units and a spike from neuron C after a further delay of T_2 time units) by finding correlations among time shifted spike trains. Several methods have been developed to determine the statistical significance of such patterns based on how many times they occur (Prut et al., 1998; Tetko and Villa, 2001; Abeles and Gat, 2001). To assess significance, often one employs a null hypothesis that assumes that all neurons spike as (possibly non-homogeneous) Poisson processes and that different neurons are independent. In a class of empirical methods (Hatsopoulos et al., 2003; Amarasingham, 2004; Gerstein, 2004), one generates many

surrogate data streams by systematically perturbing the spikes in the original data. The significance of a pattern is then determined by noting the difference in correlation counts (or in any other statistic derived from the counts) for these patterns in the original data and in the surrogate streams. These “jitter” methods allow for a lot of flexibility regarding the assumed statistical model for a spike train because the perturbations can be designed to preserve any assumed distribution for inter-spike intervals. However, the implicit null hypothesis here amounts to assuming independence because spike trains of different neurons are independently perturbed to obtain the surrogate spike trains. In this paper we present a method for analyzing the statistical significance of sequential firing patterns that goes beyond the currently available techniques by allowing the null hypothesis to include “weak dependence” among neurons and by rank ordering significant patterns according to the “strength of influence” among participating neurons. The ability to discriminate significant patterns representing strong influences from those representing weak influences is a useful feature considering that the cortical network has been described as a skeleton of strong connections in a sea of weaker ones (Song et al., 2005).

2. Methods

2.1. Correlation count

For simplicity of exposition, we first explain the method for a pattern of only two neurons, $A[T]-B$. Suppose we find the number of repetitions of this pattern in the data using simple correlation as follows. Let t_1, t_2, \dots, t_n denote all time instants at which there is a

* Corresponding author. Tel.: +1 248 635 9862.

E-mail address: k.p.unnikrishnan@gmail.com (K.P. Unnikrishnan).

spike from any neuron in the data. Let:

$$f_{AB} = \sum_{i=1}^n I_A(t_i) I_B(t_i + T) \quad (1)$$

where for any neuron x , $I_x(t) = 1$ if there is a spike from x at time t and zero otherwise. Note that f_{AB} is simply a correlation integral which counts the number of spikes from A that are followed by a spike from B with a delay of exactly T time units, and hence counts the number of repetitions of our pattern. If we want to allow for some small random variations in the delay we can define the indicator variable $I_x(t)$ to take value 1 if there is a spike in a time interval of length Δ centered around t . (For example, we can take Δ to be the time resolution in our measurements. From now on we assume that Δ is small enough so that the probability of getting more than one spike from the same neuron in Δ is negligible.) Most current methods for detecting sequential firing patterns rely on correlation counts as described above. Since the focus of this paper is on statistical significance (and not on computational efficiency), we simply assume that one can calculate such counts for pairs of neurons and for various delays T of interest. The question of interest is “how large should the count be to conclude that the pattern represents a significant positive influence of A on B ?” (By a positive influence of A on B , we mean that A and B are correlated in the sense of having a high value for the count given by Eq. (1). We do not mean to imply that A causes B to fire, since any method that relies only on correlations cannot distinguish between true causation and accidental correlation.)

Since we want to address this question in a classical hypothesis testing framework without assuming independence, we need to choose a null hypothesis that includes as many models as possible of interdependent neurons without any “strong” positive influences between pairs of neurons. In addition, we want the null hypothesis to contain a parameter to denote the strength of influence so that we can rank order all significant patterns.

2.2. Significance test

Here we characterize the strength of influence between any pair of neurons in terms of a conditional probability as proposed in Sastry and Unnikrishnan (2008). Let $e(B|A, T, t)$ denote the conditional probability that B will fire at time $t+T$ (or more precisely, in a time interval $([t+T - \Delta/2, t+T + \Delta/2])$) given that A has fired at time t . We assume that $e(B|A, T, t)$ is same for all t and hence denote it by $e(B|A, T)$. (The implications of this and other assumptions are discussed in Section 2.3.) We employ the following composite null hypothesis: *any model of interacting neurons is in our null hypothesis if it satisfies $e(Y|X, T) \leq e_0$ for all neurons X, Y and a set of specified delays T , where e_0 is a user-chosen constant.* The parameter e_0 is essentially a threshold on the conditional probability below which positive influences are deemed “weak”. For example, if all neurons are independent homogeneous Poisson with rate 5 Hz and $\Delta = 1$ ms, the conditional probability for any pair is about 0.005. Hence, if we choose $e_0 = 0.05$, it means that when we reject the null hypothesis we can say that the influences represented by the pattern are at least 10 times stronger than those in the case of independence.

To get a test for statistical significance we need to calculate a bound on the probability that, under this null hypothesis, the count f_{AB} is above a given threshold. For this, we proceed as follows. Suppose L is the total time duration of the data and let the random variable $N_A(L)$ denote the total number of spikes by neuron A during this time. Define:

$$S_{AB} = \sum_{i=1}^{N_A(L)} X_i \quad (2)$$

where X_i are independently and identically distributed 0–1 random variables with $\Pr[X_i = 1] = (1 - \Pr[X_i = 0]) = p$. If we take $p = e(B|A, T)$, it is easy to see that S_{AB} is equivalent to f_{AB} since every time there is a spike from A , with probability p a spike from B would follow with the appropriate delay. Now we assume that the spiking of A is Poisson. This implies that, since the X_i s are 0–1 random variables, S_{AB} is also a Poisson random variable (Ross, 1996). The mean and variance of S_{AB} are given by (Ross, 1996):

$$\begin{aligned} E[S_{AB}] &= E[N_A(L)]E[X_i] \\ \text{Var}[S_{AB}] &= E[N_A(L)]E[X_i^2] \end{aligned} \quad (3)$$

Since under the null hypothesis, $e(B|A, T) \leq e_0$, taking $p = e_0$ will allow us to get a bound on the probability of S_{AB} exceeding a threshold.

The test of statistical significance is as follows. Let e_0 be the bound on conditional probability that we choose for our null hypothesis and α be the allowed Type I error. Let λ_A be the rate of firing for the first neuron in the pattern and L be the total time duration for the data. Set $\lambda_Z = e_0 L \lambda_A$. Using the cumulative distribution of a Poisson random variable with parameter λ_Z , we calculate the M needed to satisfy $\Pr[Z > M] \leq \alpha$. This M is the threshold on the count of the pattern for us to be able to reject the null hypothesis and declare the pattern to be significant. To calculate M , we need λ_A . This can be estimated from the data as the average rate of firing for neuron A . Fig. 1D shows the threshold M as a function of e_0 .

The method is easily generalized to longer patterns. Consider pattern $A[T_1] - B[T_2] - C$. We get counts f_{ABC} by 3-point correlations. We define S_{ABC} as before but with $p = e(B|A, T_1)e(C|B, T_2)$. S_{ABC} would be same as f_{ABC} if all influence of A on C comes through B . Even otherwise, S_{ABC} would be a lower bound on the correlation count and hence it is enough to bound the probability of S_{ABC} exceeding a threshold. Since all conditional probabilities are bounded above by e_0 under our null hypothesis, we can calculate the needed threshold by taking $\lambda_Z = e_0^2 L \lambda_A$. For a pattern involving n neurons, we calculate the threshold M needed to satisfy $\Pr[Z > M] \leq \alpha$ where $\lambda_Z = e_0^{n-1} L \lambda_A$.

2.3. Discussion of methodology

We assume that the conditional probability $e(B|A, T, t)$ is independent of t . This conditional probability is well defined whether or not A is connected to B . If most of the contribution to this conditional probability comes from the A to B synapse then this assumption amounts to saying that the synaptic strength does not change much during the time interval of data recording. On the other hand, if A is not connected to B , then the assumption is essentially an assumption on the stationarity of some relevant network-level statistics of joint probabilities of relevant groups of neurons. Under such a stationarity assumption, even patterns that are due to network activity rather than microcircuits can be handled using our method.

Our null hypothesis does not assume that the spiking processes of different neurons are independent. When we reject the null, we can assert with a high confidence that the count for this pattern cannot be this high unless the strengths of influences among these neurons (measured in terms of conditional probabilities) are above the threshold e_0 . One value for e_0 corresponds to independence of neurons which is what is assumed in the null in existing methods. Our method of user-chosen e_0 allows the user another dimension of flexibility to discover patterns significant at different levels of strength of influence. This we feel is the main novelty of the method proposed here.

To derive our test of significance we assumed that the first neuron in the pattern is Poisson. This allowed us to show that the count of a pattern is Poisson even if the neurons are not independent. For our method, the essential thing is that the pattern count is Poisson. Other researchers have also assumed that the count is Poisson, as long as the occurrences of patterns are stochastically independent

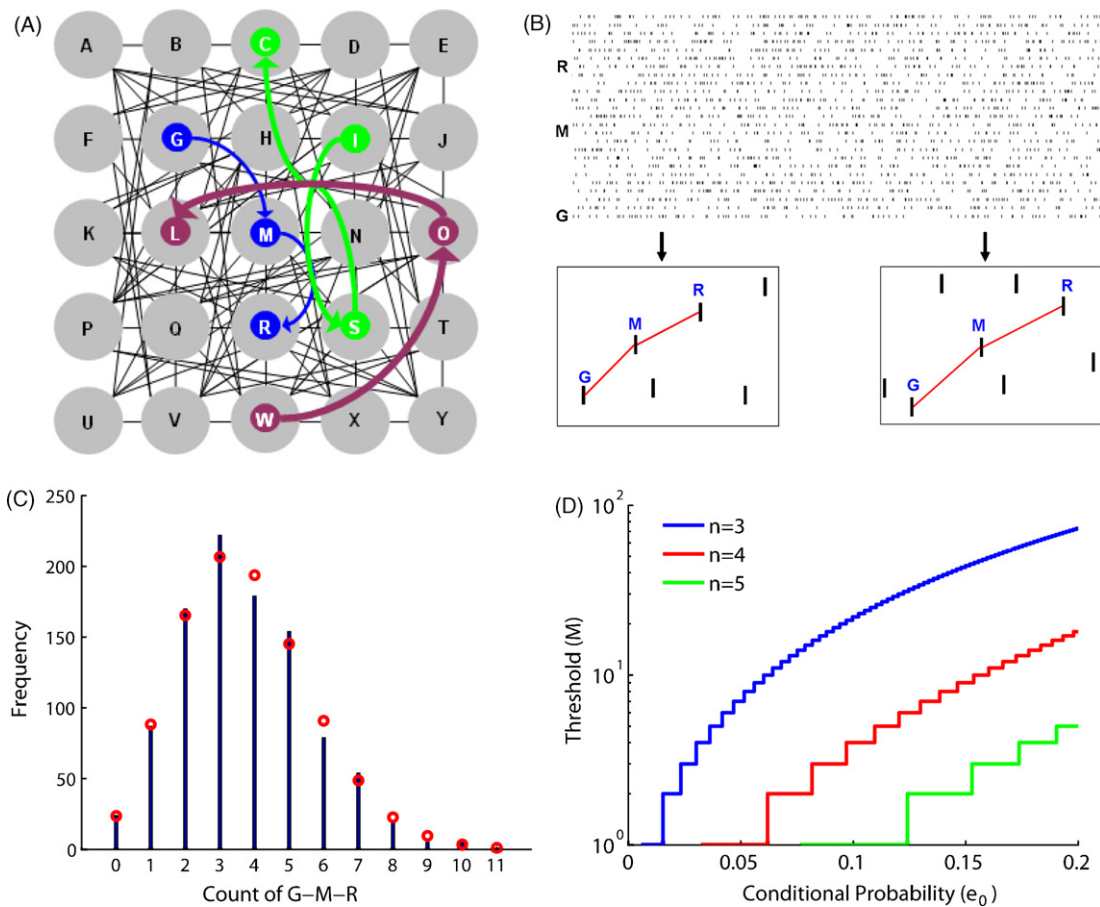


Fig. 1. Network simulation, pattern count, and count threshold characteristics. (A) Schematic of a 25-neuron network with three 3-neuron chains of strong excitatory connections. The delays (in ms) and strengths (as conditional probabilities) in the chains are (denoted as Neuron 1 [delay, strength]–Neuron 2, ...): G[3, 0.05]–M[7, 0.05]–R; I[8, 0.1]–S[4, 0.1]–C; and W[5, 0.15]–O[6, 0.15]–L. Simulation settings: $L = 300$ s, $\lambda = 5$ Hz, refractory period 1 ms, random connections as described in text, firing rates updated every 1 ms. (B) Raster plot of 20 s worth of data from the simulation. There are two occurrences of the pattern G–M–R in the data shown here, but one cannot easily identify the patterns using visual inspection. (C) Count histogram of the pattern G–M–R over 1000 simulations demonstrating that the count of a pattern is approximately Poisson distributed. Red circles are the Poisson distribution with $\lambda = (0.05^2)(300)(5) = 3.75$. (D) Threshold calculated for $n = 3$ -, 4-, and 5-neuron patterns with Type I error $\alpha = 0.05$ as a function of pattern strength for $\lambda_A = 5$ Hz and $L = 300$ s. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

as one would expect them to be under most physiological conditions (Abeles and Gat, 2001). In this sense we do not feel that our assumption is too restrictive. In practice, we found that the analytically derived threshold of our method works well even when the Poisson assumption is not strictly satisfied.

3. Results

3.1. Network simulations

We simulated a network of 25 neurons, labeled A through Y, with three embedded patterns (G–M–R, I–S–C, W–O–L). A schematic of the network and details of the patterns are given in Fig. 1A. The synaptic strengths of these patterns (expressed as a conditional probability) ranged from 0.05 to 0.15 in accordance with the range of strengths found in typical recordings from the cortex (Abeles, 1991). The nominal firing rate of each neuron (5 Hz) was modulated at time intervals of $\Delta = 1$ ms based on all inputs the neuron received (details of how the network was simulated are given in Supplemental Material). All neurons had an absolute refractory period of 1 ms, and all synapses had delays between 1 and 10 ms. In addition to the embedded patterns, each neuron was randomly connected to 25% of the other neurons in the network with strengths chosen uniformly from the interval [0.0025, 0.01]. With an average firing rate of 5 Hz, the unconditional probability of a neuron firing in an interval of

length Δ is about 0.005, which is also the conditional probability if the neurons are independent. Hence the interval from which the strengths of the random connections was chosen spanned a factor of 2 on either side of the independent case and modulated the firing rate of the neurons from 2.5 Hz to 10 Hz based on the input received.

Our method of assessing significance assumes that the number of times a pattern occurs is Poisson distributed. Due to the absolute refractory period and the modulation of firing rates based on spiking of other neurons, the spiking processes of individual neurons are not approximately Poisson (Suppl. Fig. S1). However, the count for one of the embedded patterns, G–M–R, was approximately Poisson (Fig. 1C and Suppl. Fig. S1). Indeed, in simulations with $L = 300$ s, the count of G–M–R was still approximately Poisson distributed when random connections spanned a factor of 5 on either side of independence (Fano factor for count of G–M–R was 0.97 ± 0.04 (mean \pm S.E.M.) based on 20 trials of 50 simulations. See Suppl. Fig. S1).

3.2. Assessing and rank ordering significance of patterns

We simulated our network for 1000 replications and compared the distribution of actual pattern counts in the simulated data to our analytically calculated thresholds for the patterns to be significant at different values of e_0 . Fig. 2A demonstrates our method

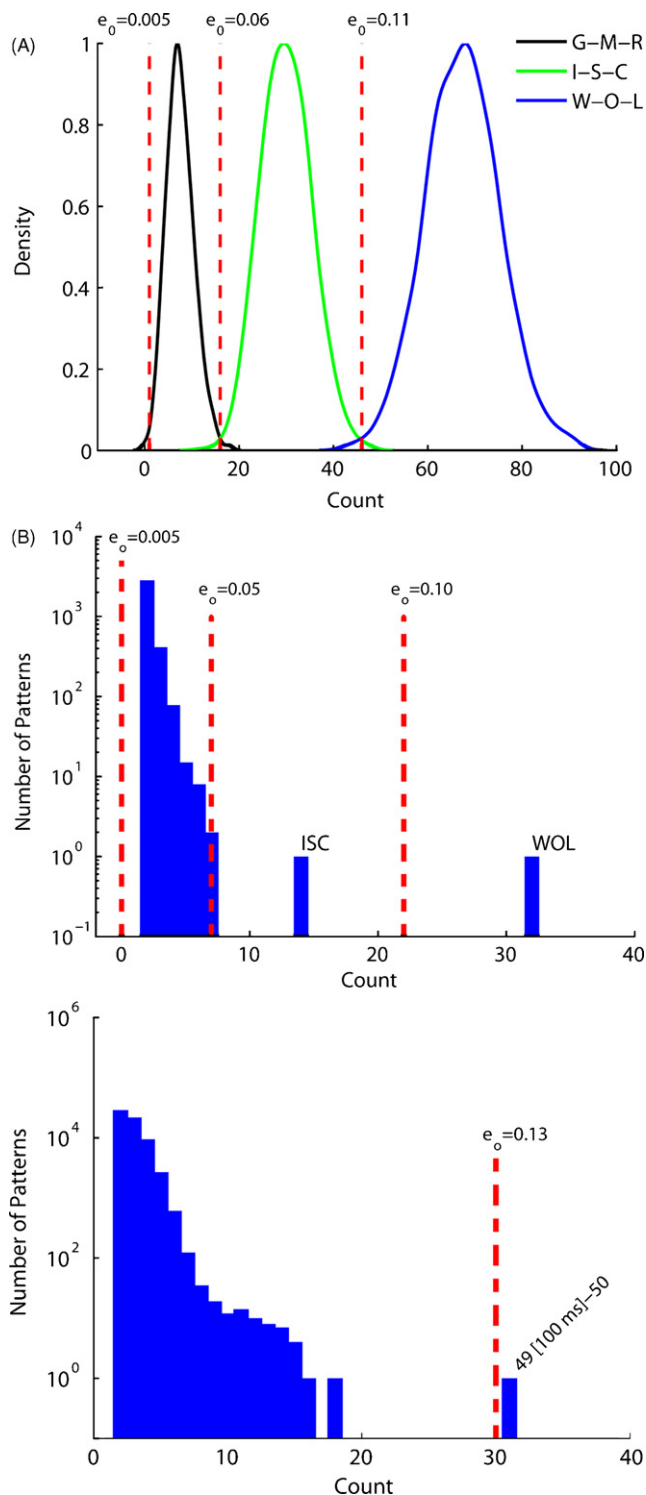


Fig. 2. Rank ordering of patterns discovered in network simulations by connection strength. (A) Count densities of embedded patterns over 1000 replications of a 600 s simulation of the 25-neuron network with random connections and strong connections as shown in Fig. 1A. Thresholds corresponding to $e_0 = 0.005$ (independence), 0.06, and 0.11. (B) Two-tape algorithm counts of all patterns that occur more than twice in 300 s of simulation. Simulation settings as in Fig. 1A, with only two strong patterns embedded (*I-S-C* with strength 0.1, and *W-O-L* with strength 0.15). Thresholds corresponding to $e_0 = 0.05$, 0.05, and 0.10 demonstrate the ability to discriminate strong significant patterns from weaker ones. (C) Two-tape algorithm counts of all patterns that occur more than twice in 20 s of the “network activity” simulation as described in Section 3.2, demonstrating the usefulness of our method for patterns generated by mechanisms other than microcircuits.

was effective in assessing the varying strengths of the embedded patterns via the user-chosen parameter e_0 .

We then ran the two-tape algorithm (Abeles and Gerstein, 1988) on a simulated dataset to count the occurrences of all 3-neuron patterns that occurred at least twice (with a maximal delay of 200 ms between the first and last spikes in any pattern). We found 3340 3-neuron patterns that occurred at least twice (Fig. 2B). Since so many patterns exceed the threshold, we need some additional criteria to select which of these individual patterns are the best candidates for further analysis. Abeles and Gerstein (1988) remarked that this selection process is very important, and called for future research to be conducted in this area. Using our framework, by having different values for e_0 in the null hypothesis, we can ask what patterns are significant at what value of e_0 and thus rank order patterns. This is easily seen from Fig. 2B, where we show count thresholds corresponding to different values of e_0 . For example, if we chose $e_0 = 0.05$ (i.e., conditional probability is 10 times that in the case of independence), then the number of candidates came down to 4. Thus, our compound null hypothesis with the user-chosen parameter e_0 helps one distinguish the most interesting patterns for further investigation, e.g., to correlate to behavioral events, from weaker patterns that may only be marginally significant. The commonly used “jitter” methods of determining significance of patterns are not useful in this regard. Of the 3340 3-neuron patterns that occurred more than twice, creating 100 surrogate data streams using spike jitter as in Date et al. (1998) tells you that 808 patterns have a p -value less than 0.05, but gives little information about which of these patterns are the best candidates to select for further analysis. (For another example demonstrating how the parameter e_0 in our null hypothesis provides a convenient handle for further analysis of the significant patterns see Suppl. Fig. S2.)

The patterns discovered as significant as shown in Fig. 2B are “rare”, in the sense that only a very small fraction of the spikes of the neurons (less than 1%) contribute to the occurrence of patterns. The raster scan of part of the data on a typical simulation run of our network is shown in Fig. 1B, where we also highlight a couple of occurrences of one of the patterns. The embedded patterns are not obvious upon visual inspection. In the full data for Fig. 2B (which is of 300 s duration), the patterns *W-O-L* and *I-S-C* occur 32 and 14 times, respectively. The total number of spikes from neurons *W*, *O*, *L*, *I*, *S*, and *C* are, respectively, 1486, 1733, 1753, 1579, 1692, and 1646.

In Section 2.3, we mentioned that the conditional probability, $e(B|A,T)$, is well defined even when A is not connected to B . We show, in Fig. 2C, how our method can be useful in analyzing certain patterns that result due to network activity rather than two neurons directly influencing each other. We used a network of 50 neurons where each neuron was randomly connected to 25% of other neurons with strengths between 0.0025 and 0.01. Neurons 1–48 were each connected to both 49 and 50 through weak connections (strength 0.01). All connections into 49 had delays of 100 ms, all connections into 50 had delays of 200 ms, and the random connections had delays between 1 and 200 ms. The connections strengths were such that input from a subset of the 48 neurons was enough to make both 49 and 50 likely to fire. Synchronous firing of a random subset of the 48 neurons (7.2 of them on average) was induced via an external input that fired with a rate of 5 Hz. Thus the pattern 49[100 ms]–50 was expected to occur often even though there is no connection between 49 and 50. The pattern 49[100 ms]–50 had the highest count and was significant, by our analytical method, at $e_0 = 0.13$ (Fig. 2C), while no other 2-neuron patterns were significant at this e_0 . Note that this pattern has a long delay, which is typical of the precisely timed patterns that have been found to repeat in experimental recordings (Abeles, 1991). (See Suppl. Figs. S3 and S4 for an example showing the use of our method to detect patterns arising from network activity in the form of synfire chains (Abeles, 1982, 1991)).

3.3. Comparison with other methods

The parameter e_0 in our compound null hypothesis helps in rank ordering significant patterns as shown in Fig. 2A. Initially this may appear unnecessary because in any significance analysis, a given value of count (or any other statistic) provides a p -value for rejecting the null and it might be possible to rank order significant patterns using their p -values. However, this is often not feasible because the p -values do not actually give proper indication of relative strengths of different patterns. To demonstrate this, we simulated our network with random connections and two embedded patterns of different strengths (I – S – C with strength 0.1, and W – O – L with strength 0.15). We then computed p -values for the significance of these two patterns using a variety of methods in the literature. The first method we considered (Abeles and Gat, 2001) is also based on the assumption that pattern counts are Poisson distributed, and significant 3-neuron patterns were detected as deviations from a smoothed version of a count matrix containing the triplet pattern counts for all delay combinations between 1 and 20 ms. We also considered three jitter-based methods: basic spike jitter (Date et al., 1998), pattern jitter (Harrison and Geman, 2009), and NeuroXidence (Pipa et al., 2008). With the parameters chosen, all four methods identified both I – S – C and W – O – L as significant (details on how each of these methods was implemented is given in Supplemental Material). The Abeles and Gat (2001) calculation, as well as spike jitter and pattern jitter, reported p -values of 0.000 for both patterns. NeuroXidence reported a p -value of 0.004 for I – S – C and 0.000 for W – O – L . Since the p -values are all close to zero for the two patterns with strong connections, these methods cannot be used for comparing relative strengths of significant patterns. Using our method, if we choose e_0 corresponding to independence as the null hypothesis, then the p -values are 0.000 for both patterns as well. However, using our analytically derived expression for count threshold, we can determine the maximum value of e_0 for which the observed count will make the pattern significant. This e_0 value is 0.07 for I – S – C and 0.12 for W – O – L , giving a relative strength ratio for the two patterns of 1.7, which is close to 1.5, the ratio of the true conditional probabilities.

While we have demonstrated that the p -values for the significant patterns cannot be used for rank ordering the strength of patterns, it may appear that the actual counts of the patterns themselves can be used for rank ordering. This would not be proper if the firing rates of the first neurons in the patterns are different. In a simulation with the same pattern strengths as before but where neuron I fired nominally at 5 Hz and neuron W fired nominally at 1 Hz, the count of I – S – C was 19 and the count of W – O – L was 9, even though W – O – L has stronger synapses. In this situation, our method of ranking patterns based on the highest value of the parameter e_0 at which the observed count is significant still correctly ranks W – O – L ($e_0 = 0.12$) ahead of I – S – C ($e_0 = 0.09$).

4. Discussion

In this paper we presented a method for assessing significance of sequential firing patterns using correlation counts as the statistic. We represent the “strength of influence” of A on B by the conditional probability that B fires after a prescribed delay following A . We state our composite null hypothesis in terms of a parameter e_0 which is an upper bound on all such pair-wise conditional probabilities. There are two attractive features of this method. Firstly, we can rank order significant patterns in terms the highest value of e_0 at which the pattern (which repeats a certain number of times in the data) is still significant. The second interesting feature of the method is that we can now include many models of interdependent neurons in our null hypothesis (based on the value chosen for e_0). When we declare a pattern such as $A[T_1]$ – $B[T_2]$ – C to be significant, we can conclude

that a spike by A has a “strong” chance of eliciting a spike from B with delay T_1 and a spike from C after a further delay of T_2 . Here “strong” would denote that the relevant conditional probabilities cannot be less than e_0 . Thus, our idea of casting the null hypothesis in terms of a bound on conditional probabilities allows for a richer level of significance analysis compared to other methods, as we demonstrated through simulation experiments.

The method presented can assess significance of sequential firing patterns only when the underlying influences are excitatory. Using a similar null hypothesis with a lower bound on a conditional probability which is much smaller than the case under independence, it may be possible to find how low the correlation count should be for us to conclude that there are significant inhibitory influences.

We have given a simple test of significance based on the counts calculated through multi-point correlations. As mentioned earlier, the motivation is that such correlations are what are presently used for detecting such patterns. However, using correlation counts to detect interactions among a large group of neurons is computationally intensive. Since our test will directly give the threshold needed for the count, given any pattern, we do not need to actually obtain the true correlation count which would be required if we wanted to estimate the conditional probability. We only need to ascertain whether a pattern occurs more than some number of times which leads to better computational efficiency. Further computational efficiency can be obtained by employing data mining algorithms for discovering patterns that count the *non-overlapped* occurrences of a pattern (Patnaik et al., 2008; Sastry and Unnikrishnan, 2008), rather than *all* occurrences as the method presented in this paper requires. We will be further studying the strengths and weaknesses of these data mining algorithms in our future work.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jneumeth.2009.06.018.

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