

# Analysis of higher-order neuronal interactions based on conditional inference

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**Abstract.** Higher-order neural interactions, i.e., interactions that cannot be reduced to interactions between pairs of cells, have received increasing attention in the context of recent attempts to understand the cooperative dynamics in cortical neural networks. Typically, likelihood-ratio tests of log-linear models are being employed for statistical inference. The parameter estimation of these models for simultaneously recorded single-neuron spiking activities is a crucial ingredient of this approach. Extending a previous investigation of a two-neuron system, we present here the general formulation of an exact test suited for the detection of positive higher-order interactions between  $m$  neurons. This procedure does not require the estimation of any interaction parameters and additionally optimizes the test power of the statistical inference. We apply the approach to a three-neuron system and show how second-order and third-order interactions can be reliably distinguished. We study the performance of the method as a function of the interaction strength.

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## 1 Introduction

Thanks to advances in neurophysiological recording technology, it has now become feasible to investigate interactions between cortical neurons on the basis of simultaneous multiple single-neuron recordings (Aertsen et al. 1987; Nicolelis 1998). Such analyses of the joint spiking activity of several neurons are of fundamental importance for the understanding of neural cooperativity in cortical networks. They are particularly relevant for the experimental assessment of a number of different conceptualizations of temporal neural coding schemes,

such as “correlational cell assemblies” (Aertsen and Gerstein 1991, Gerstein et al. 1989; von der Malsburg 1981), “coherent oscillations” (Singer 1993; Singer and Gray 1995; Singer 1999), “precise firing patterns” (Abeles 1982; Abeles and Gerstein 1988; Abeles 1991; Abeles et al. 1993; Baker and Lemon 2000; Prut et al. 1998), and “unitary events” (Grün et al. 2002a,b; Riehle et al. 1997; Roy et al. 2000). In this context, the study of higher-order neural interactions, i.e., interactions that cannot be reduced to interactions between pairs of cells, has received increasing attention (e.g., Raz et al. 1996). However, because of the stochastic appearance of neural response patterns in the cortex (Palm et al. 1988), the main challenge of these approaches is to develop an adequate stochastic framework for the statistical evaluation of the interaction structure in the observed data. Recently, several contributions have proposed the use of log-linear models for binary random variables to describe the joint spiking of several neurons and to characterize the interaction structure of the recorded neurons (Amari 2001; Martignon et al. 1995, 2000; Nakahara and Amari 2002). In these models, the logarithms of the joint spike probabilities are linear functions of the model parameters (e.g., Bishop et al. 1975). Applying these models to neuronal data, it has been illustrated how higher-order neural interactions can be estimated and how their significance can be statistically tested. Likelihood-ratio tests have been employed for statistical inference, and hence the estimation of the corresponding interaction parameters were a crucial ingredient of these approaches.

In this paper, we treat the frequently encountered situation where only the presence of significant interactions of a given order is to be inferred, and the quantitative estimation of interaction parameters is only of secondary importance. In this case, an exact statistical test exists under the same assumptions that underlie an application of the log-linear model. As a consequence, the estimation of the model parameters can be entirely omitted. A major conceptual difference between the likelihood-ratio tests and the exact theory is that the latter does not make use of the data sample to estimate

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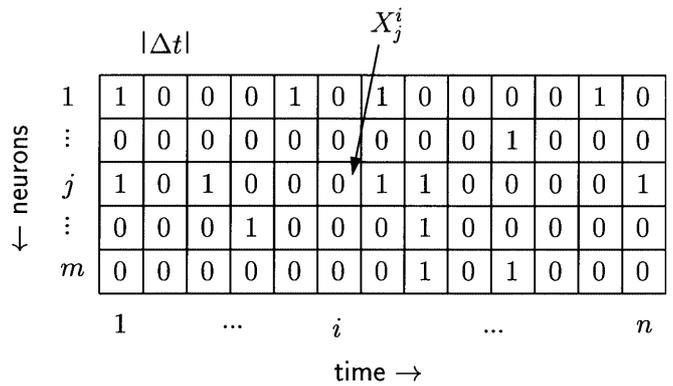
the interaction parameters of the model. Rather, one works with the distribution of the test statistic for a given interaction order, conditional on the lower-order spike patterns in the neuronal data. Then, under the null-hypothesis of no interaction at the order of interest, the distribution of the test statistic becomes independent of the lower-order model parameters.

We illustrate the application of this procedure to the problem of decomposing the orders of interaction in simulated data of three neurons that contain either pair or triple interactions. In this study, we will also quantify the test power of the proposed procedure for the three-neuron system, i.e., the probability of correctly detecting a neuronal interaction of a given order and strength. It is a well-established result of mathematical statistics that the randomized version of the exact test used here (Gütig et al. 2002) is uniformly most powerful unbiased (Lehmann 1986). As we have shown previously for the case of pairwise interactions, the gain in test power of the exact test compared to the corresponding binomial test (Grün et al. 2002a) based on the maximum-likelihood estimators of the distribution parameters can be of considerable practical importance (Gütig et al. 2002).

## 2 Stochastic model

Following Amari (2001), Nakahara and Amari (2002), and Martignon et al. (2000), we use a log-linear model to describe the joint spike activity of  $m$  simultaneously recorded neurons within an analysis window comprising  $n$  discrete time bins of duration  $\Delta t$  (but see Grün et al. 1999 for a critical discussion of discrete time models in multiple spike train analysis). In order to keep the number of model parameters manageable, previous contributions have restricted their treatments to neural interactions of coincident bins only, and assumed all noncoincident bins to be stochastically independent. Adopting the same assumption here, it is important to realize that while the log-linear models themselves can be generalized in a straightforward manner, this restriction is crucial for the application of the exact test proposed here, and a generalization would be substantially more demanding. Nevertheless, the approach suffices to treat the standard situations including the occurrences of precise spatiotemporal spike patterns (Abeles and Gerstein 1988, Prut et al. 1998) where all interactions of interest have a fixed temporal relationship and can be treated as coincident after the spike trains have been appropriately shifted in time.

The spike patterns across  $m$  neurons in each time bin  $i$  are described through  $m$  binary random variables  $X_j^i$  ( $i = 1, \dots, n$ ;  $j = 1, \dots, m$ ), with the values “0” and “1” denoting, respectively, the absence or presence of a spike (cf. Fig. 1). Because of the assumed independence of noncoincident bins, we first describe the probability distributions of the spike patterns for each bin  $i$  separately and then obtain the description of the complete analysis window by forming the product space over all bins. As explained in Amari (2001) and Nakahara and Amari (2002), we define the interaction structure



**Fig. 1.** Spike train model. Binary activity of  $m$  simultaneously recorded neurons in an analysis window comprising  $n$  discrete time bins of duration  $\Delta t$ . The activity of each neuron  $j = 1, \dots, m$  in a given bin  $i = 1, \dots, n$  is modeled by the binary random variable  $X_j^i$

between the  $m$  neurons through the parameters of a log-linear model by writing the probability distribution of the spike patterns  $\mathbf{X}^i$  of the  $m$  neurons in the  $i$ th bin as

$$P_{\theta^i}(\mathbf{x}^i) = \exp \left[ \sum_j \theta_j^i x_j^i + \sum_{j < k} \theta_{jk}^i x_j^i x_k^i + \dots + \theta_{1 \dots m}^i x_1^i \dots x_m^i - \psi^i \right]. \quad (1)$$

In this model, an interaction between a given subset of the recorded neurons, e.g., the units  $j, k, \dots, l$ , is specified through the interaction parameter  $\theta_{jk \dots l} \in \mathbb{R}$ , whose indices correspond to the combination of neurons in the subset, and  $\psi^i$  normalizes the distribution. As can be seen from Eq. 1, each interaction parameter only affects the probability of the spike pattern  $\mathbf{x}^i$  if all neurons that appear in the indices of the parameter contribute a spike to the pattern, i.e., if  $x_j = x_k = \dots = x_l = 1$ . The order of an interaction is therefore given by the number of indices of the corresponding interaction parameter. A given interaction  $j, k, \dots, l$  is said to be absent (Martignon et al. 2000) if the corresponding parameter vanishes ( $\theta_{jk \dots l} = 0$ ), i.e., if the joint spike activity of all  $m$  recorded neurons can be described without a parameter specifically weighing the coincident occurrence of spikes from units  $j, k, \dots, l$ . It is clear from Eq. 1 that if the interaction is positive ( $\theta_{jk \dots l} > 0$ ), such that the factor  $\exp[\theta_{jk \dots l}] > 1$ , the probability of all spike patterns containing the spike constellation  $jk \dots l$  is increased with respect to the case where the interaction is absent. Likewise, negative interactions ( $\theta_{jk \dots l} < 0$ ) reduce the probability of occurrence of all spike patterns that contain the associated spike constellation as subset. In the present work, we will deal only with the detection of positive interactions.

Note that any probability distribution of binary patterns can be expanded in the exponential form of Eq. 1, on the condition that no pattern has a probability of zero. Since zero probabilities can be approximated with arbitrarily small values through Eq. 1, this restriction does not seem of practical importance for the

applications of log-linear models to neuronal data. For compactness of notation we introduce the vector  $\theta^i = (\theta_1^i, \theta_2^i, \dots, \theta_{12}^i, \theta_{13}^i, \dots, \theta_{1\dots m}^i)$  to denote all  $2^{m-1}$  interaction parameters pertaining to the  $i$ th time bin. In the example of two neurons, an elementary calculation shows that if the second-order interaction vanishes ( $\theta_{12}^i = 0$ ), the firing of the two neurons becomes independent, i.e.,  $P_{\theta^i}(X_1^i = 1, X_2^i = 1) = P_{\theta^i}(X_1^i = 1)P_{\theta^i}(X_2^i = 1)$ . A detailed account of the advantages of the parameterization of the log-linear model in the context of an information theoretic treatment is given in Amari (2001) and Nakahara and Amari (2002).

Assuming serial independence, the probability distribution of the joint spike activity  $\mathbf{X} = (X^1, X^2, \dots, X^n)$  of the  $m$  recorded neurons over all  $n$  bins of the analysis window is given by

$$\begin{aligned} P_{\theta}(x) &= \prod_{i=1}^n \exp \left[ \sum_j \theta_j^i x_j^i + \sum_{j<k} \theta_{jk}^i x_j^i x_k^i + \dots \right. \\ &\quad \left. + \theta_{1\dots m}^i x_1^i \dots x_m^i - \psi^i \right] \\ &= \exp \left[ \sum_{i=1}^n \left( \sum_j \theta_j^i x_j^i + \sum_{j<k} \theta_{jk}^i x_j^i x_k^i + \dots \right. \right. \\ &\quad \left. \left. + \theta_{1\dots m}^i x_1^i \dots x_m^i - \psi^i \right) \right]. \end{aligned} \quad (2)$$

A second important assumption commonly made in previous treatments of the subject is that the interaction parameters of the log-linear model remain stationary across the analysis window. Adopting this assumption as well, we hereinafter omit the superscript  $i$  of the interaction parameters. As a consequence, the sum over all interaction orders in Eq. 2 depends on the bin index  $i$  only through the spike variables  $x^i$ . Thus, when performing the summation over  $i$ , we obtain each interaction parameter  $\theta_{jk\dots l}$  simply weighted by the number of times  $k_{jk\dots l}$  a spike pattern  $x^i$ , including the constellation  $x_j = x_k = \dots = x_l = 1$ , occurred within the analysis window. For example, the coincidence count  $k_{124}$  denotes the number of time bins in which neurons 1, 2, and 4 fired together, regardless of the activity of all other neurons. Hence, the probability of a realization of spikes  $\mathbf{x}$  in the entire analysis window with corresponding coincidence counts  $\mathbf{k} = (k_1, k_2, \dots, k_{12}, k_{13}, \dots, k_{1\dots m})$  reduces to

$$\begin{aligned} P_{\theta}(\mathbf{x}) &= \exp \left[ \sum_j \theta_j k_j + \sum_{j<k} \theta_{jk} k_{jk} + \dots \right. \\ &\quad \left. + \theta_{1\dots m} k_{1\dots m} - n\psi \right]. \end{aligned} \quad (3)$$

Note that this expression depends only on the realization of spikes  $\mathbf{x}$  through the coincidence counts  $\mathbf{k}$  and, in particular, is independent of the temporal sequence of the spike patterns. As a consequence, the probability of observing a coincidence count vector  $\mathbf{k}$  is given by the product of the corresponding  $P_{\theta}(\mathbf{x})$  times the number of

all possible permutations of realizations of spikes with coincidence counts  $\mathbf{k}$ . Denoting this number of possible realizations by  $\mathcal{N}_{\mathbf{k}}$ , we obtain

$$P_{\theta}(\mathbf{k}) = \mathcal{N}_{\mathbf{k}} e^{k \cdot \theta - n\psi}, \quad (4)$$

where we abbreviated the weighted sum over the interaction parameters appearing in the exponent of Eq. 3 by the scalar product notation  $\mathbf{k} \cdot \theta$ .

### 3 Conditional inference

Whereas the general analysis of higher-order interactions based on the log-linear model requires the estimation of the parameters  $\theta$ , the important special case where only the presence of interactions of a specific  $g$ th-order is to be inferred can be treated by using an exact test, without knowledge of the model parameters. The basic idea of this exact test was introduced by Fisher almost 70 years ago (Bishop et al. 1975) and elaborated in the statistical literature throughout the 1960s and 1970s in the context of the analysis of contingency tables (Birch 1964; 1965; Weiß 1978; Zelen 1971). Despite their “intuitive (as well as theoretical) appeal” (Bishop et al. 1975), numerical limitations in the computation of the required conditional distributions have then restricted their applicability.

Using the observed  $g$ th-order coincidence count  $k^* = k_{1\dots g}$  as test statistic for the presence of the corresponding higher-order interaction  $\theta_{1\dots g}$ , the core concept of the exact test is to compute the probability distribution of  $k^*$ , conditional on all lower-order coincidence counts  $\mathbf{k}' = (k_1, k_2, \dots, k_{12}, k_{13}, \dots, k_{1\dots g-1}, \dots, k_{2\dots g})$  in the data. Hence, statistical significance in this approach is not defined with respect to estimated model parameters but rather with respect to the actual observed lower-order coincidence counts. The conditional  $g$ th-order coincidence count distribution is given by

$$\begin{aligned} P_{\theta}(k^* | \mathbf{k}') &= \frac{P_{\theta}(\mathbf{k})}{P_{\theta}(\mathbf{k}')} = \frac{P_{\theta}(\mathbf{k})}{\sum_{c=0}^{k_{\max}^*} P_{\theta}(\mathbf{k}', c)} \\ &= \frac{\mathcal{N}_{\mathbf{k}} e^{k \cdot \theta - n\psi}}{\sum_{c=0}^{k_{\max}^*} \mathcal{N}_{(\mathbf{k}', c)} e^{c\theta^* + \mathbf{k}' \cdot \theta' - n\psi}} = \frac{\mathcal{N}_{\mathbf{k}} e^{k^* \theta^*}}{\sum_{c=0}^{k_{\max}^*} \mathcal{N}_{(\mathbf{k}', c)} e^{c\theta^*}} \end{aligned} \quad (5)$$

where, in analogy to the coincidence counts  $k^*$  and  $\mathbf{k}'$ ,  $\theta^*$  and  $\theta'$  denote, respectively, the  $g$ th and the lower-order interaction parameters. The summation limit  $k_{\max}^*$  denotes the maximum number of  $g$ th-order counts possible for the observed lower-order counts  $\mathbf{k}'$ . As defined above,  $\mathcal{N}_{(\mathbf{k}', c)}$  denotes the number of possible realizations of the analysis window with  $\mathbf{k} = (\mathbf{k}', c)$  coincidence counts. Under the null-hypothesis of a vanishing  $g$ th-order interaction parameter, i.e.,

$$H_0 : \theta^* = 0,$$

Eq. 5 above reduces to the simple form

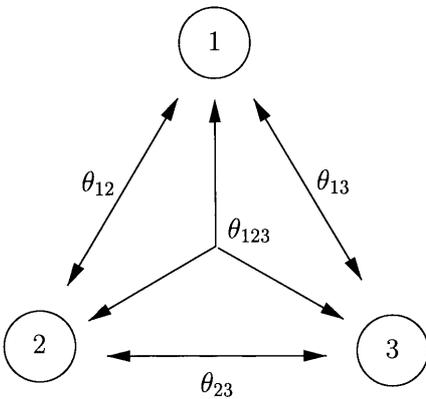
$$P_{\theta}(k^*|k') = \frac{\mathcal{N}_k}{\sum_{c=0}^{k^*_{\max}} \mathcal{N}(k',c)}, \quad (6)$$

with the numbers  $\mathcal{N}_k$  readily given by multinomial coefficients (cf. Appendix). Based on this conditional distribution of the  $g$ th-order coincidence count, the test for the presence of a  $g$ th-order interaction can be constructed in a straightforward manner by using the standard p-value as significance measure. Hence, the problem of detecting the presence of a higher-order interaction reduces to the combinatorial problem of computing  $\mathcal{N}_k$ ; this can be solved with the help of standard mathematical software packages.

#### 4 Decomposition of neural interactions

As a demonstration of the analysis technique proposed above, we treat here the longstanding problem of decomposing the interactions of a simple three-neuron system such that pairwise interactions become distinguishable from triple interactions (Gerstein and Aertsen 1985; Raz et al. 1996; Martignon et al. 2000). The application of the general equations given above to more neurons is straightforward although numerically more demanding. The general idea is to investigate a given data set by testing all orders of interaction and identifying the highest significant order. Once interactions of a specific order have been found to exist, all lower orders cannot be interpreted as pure but are known to be confounded with the higher-order interaction.

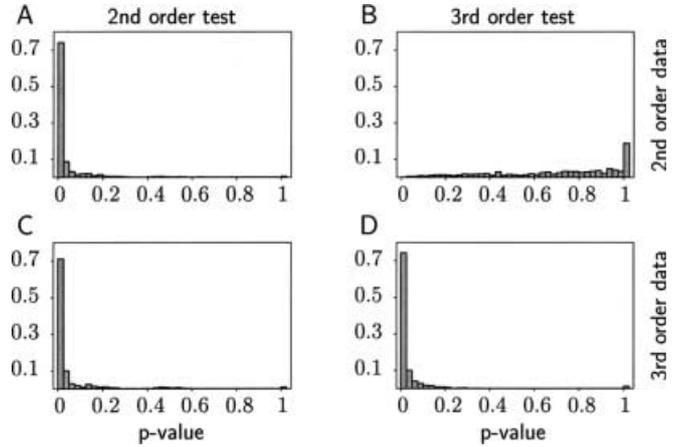
As is schematically depicted in Fig. 2, we investigated two types of simulated data from a three-neuron system. Assuming a typical value of  $\Delta t = 2$  ms for the bin size, we adjusted the binwise firing probabilities of all neurons to obtain single-neuron firing rates  $r$  of 10 Hz in both data sets. Corresponding to 40 trials of a typical 100-ms analysis window, we set  $n = 2000$ . In addition,



**Fig. 2.** Higher-order interactions. Schematic diagram of a three-neuron system contrasting second-order vs. third-order neural interactions. While the second-order interaction parameters  $\theta_{12}$ ,  $\theta_{13}$ , and  $\theta_{23}$  depict pairwise interactions between the neurons, the triple interaction involving the activity of all three neurons is denoted by the third-order parameter  $\theta_{123}$

we required both types of data to have a pairwise spike correlation of  $\rho = 0.1$  (cf. Eq. A6 for all possible pairs among the three neurons). Hence, both sets were statistically identical with respect to the individual neuron firing rates and the pairwise correlations. However, while one type of data was generated with second-order interactions only, the pairwise correlations in the other one originated from a pure third-order interaction. Specifically, the second-order interaction data stemmed from a model with no third-order interactions whatsoever, i.e.,  $\theta_{12} = \theta_{13} = \theta_{23} > 0$  and  $\theta_{123} = 0$ . In contrast, the third-order interaction data were generated from a model with no second-order interactions, i.e.,  $\theta_{12} = \theta_{13} = \theta_{23} = 0$  and  $\theta_{123} > 0$  (see Appendix for details). For the following analysis, 1000 independent realizations of each type of data were generated.

For each of the realizations of both data types, we computed all p-values for the null-hypotheses of  $\theta_{12} = 0$ ,  $\theta_{13} = 0$ ,  $\theta_{23} = 0$ ,  $\theta_{123} = 0$  against the one-sided hypotheses of each interaction being positive. Figure 3 shows the relative frequencies of the p-values for one of the two identical second-order interactions (panels A and C) and for the third-order interaction  $\theta_{123}$  (panels B and D). While the upper row (panels A and B) corresponds to the data generated with second-order interactions, the lower row (panels C and D) refers to the data sets corresponding to the third-order model. The histograms clearly show that in both types of data, second-order interactions are reliably detected (panels A and C), i.e., almost all p-values are very small. Hence, in most

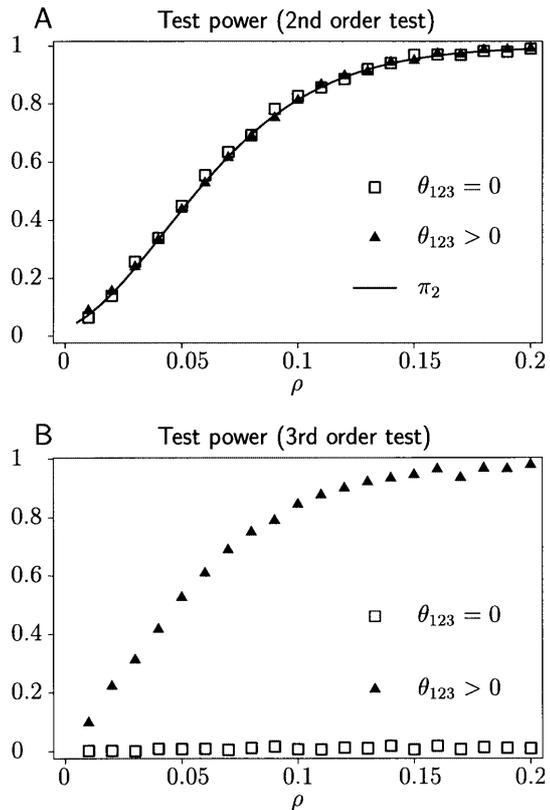


**Fig. 3.** P-value histograms. The histograms depict the relative frequencies of p-values obtained by testing 1000 independent realizations of the analysis window for the presence of a given interaction order. Each analysis window was simulated over  $n = 2000$  discrete bins with the spike probabilities of the three simulated neurons adjusted such that the single-neuron firing rates were  $r = 10$  Hz assuming a bin size of 2 ms. In all data sets, the interaction parameters of the generating models (see text for details) induced a pairwise spike correlation of  $\rho = 0.1$  for all pairs of neurons. Panels A and C show the results of testing for the presence of a second-order interaction ( $H_0 : \theta_{12} = 0$ ), panels B and D correspond to tests for a third-order interaction ( $H_0 : \theta_{123} = 0$ ). While the data underlying panels A and B were generated by second-order interactions only, i.e.,  $\theta_{12} = \theta_{13} = \theta_{23} > 0$  and  $\theta_{123} = 0$ , panels C and D refer to data sets in which the pairwise correlations  $\rho$  were induced by a purely third-order interaction, i.e.,  $\theta_{12} = \theta_{13} = \theta_{23} = 0$  and  $\theta_{123} > 0$

realizations the null-hypothesis of no second-order interaction ( $H_0 : \theta_{12} = 0$ ) would be correctly rejected. It is clear that, since both data sets were by definition identical in firing rate and pairwise spike correlations, no difference should be seen through the second-order tests in panels A and C. In contrast, when testing the null-hypothesis of no third-order interaction, the two distinct generating models of the data sets can be faithfully distinguished: while the second-order-type data hardly show any low p-values (panel B), the hypothesis of no third-order interaction ( $H_0 : \theta_{123} = 0$ ) would be rejected in most third-order data sets on the basis of low p-values (panel D). In practice, such a result would clearly indicate that the significant second-order interactions found in these data sets originate, at least in part, from an interaction between all three neurons.

Finally, we note the peculiar shape of the p-value histogram shown in panel B, corresponding to the test for third-order interactions in the second-order data. Since in this scenario the null-hypothesis of zero third-order interaction is correct, one would expect a uniformly distributed p-value histogram if the test statistic were a continuous variable. However, because of the finite number of bins  $n$ , the p-value histogram reflects the discrete nature of the triplet count  $k_{123}$  used as test statistic. Specifically, the peak at the p-value of exactly 1 corresponds to realizations of the analysis window with no triplet whatsoever ( $k_{123} = 0$ ). As shown in Gütig et al. (2002), a randomized version of such a test can be used to prevent a reduction of the effective significance level due to the discreteness of the p-values.

To quantify the dependence of the test power (the probability to correctly detect a deviation from the null-hypothesis) on the strength of the nonzero interaction, we repeated the above analyses for different pairwise correlations  $\rho$ . Evaluating the power for a significance threshold of  $\alpha = 0.05$ , Fig. 4 shows the relative frequencies of data sets in which the statistical test led to a rejection of the null-hypothesis of no interaction. Consistent with the findings displayed in Fig. 3A and B, the second-order interactions were detected with similar probability in both data sets (panel A). For the number of bins and firing rates used in our simulation, i.e.,  $n = 2000$  and  $r = 10$  Hz, the power curves exceed the value of 0.8 for correlations  $\rho \gtrsim 0.1$  in both types of data sets. The full dependence of the power of the exact test for second-order interactions on the neuronal firing rates and the number of bins in the analysis window was treated analytically in Gütig et al. (2002). Using this treatment as a check of robustness of our simulation results, the solid line in 4A shows a close agreement between the simulation results and the analytical evaluation of the test power. The test power results of the test for the third-order interaction for both types of data are shown in panel B. Again, as expected from the generating models, the third-order interaction is consistently classified as absent in the second-order interaction data, whereas the test power values for the detection of the third-order interaction in the third-order data reach comparable magnitudes as the second-order power results.



**Fig. 4.** Test power. Relative frequencies of classifying the interactions of a given order as significant ( $\alpha = 0.05$ ) as a function of the pairwise spike correlations  $\rho$  between the simulated spike trains. With parameters  $n$  and  $r$  corresponding to Fig. 3, the power results are based on 1000 independent realizations of the analysis window for each correlation strength. While *open squares* correspond to the data generated by the second-order interaction model, *gray triangles* depict the results stemming from the third-order data sets. **A** Test for presence of second-order interaction ( $H_0 : \theta_{12} = 0$ ). The *solid line* ( $\pi_2$ ) depicts the corresponding power curve calculated analytically with the procedure described in Gütig et al. (2002). **B** Test for presence of third-order interaction ( $H_0 : \theta_{123} = 0$ ). Here, numerical limitations prevented an analytical evaluation

## 5 Discussion

We have presented an exact statistical test to infer the presence of higher-order interactions among simultaneously recorded neurons. By avoiding the need to estimate the parameters of the log-linear model defining the interaction structure, this approach greatly simplifies the statistical testing procedure. In addition, this test is uniformly most powerful unbiased. Thus, in the frequent case where the numerical values of the interaction parameters are not of primary interest, this procedure presents a very useful tool – based on the same statistical assumptions as made in preceding works – to investigate the interaction structure that governs the spiking activity of simultaneously recorded neurons. Alternatively, it may be used as an effective pre-screening method to explore large amounts of data before more demanding quantitative methods (Martignon et al. 2000; Nakahara and Amari 2002) are applied to data sets that were identified as interesting.

The results presented above suggest a satisfactory performance of the method in decomposing the interactions of a three-neuron system. However, further studies are needed to clarify how the properties of this approach scale with the number of neurons involved. Specifically, the behavior of the method for more general interaction structures, including mixing of different higher orders and inhomogeneous strengths of same orders, requires further study. The understanding of the dependence of the test power of the approach on other parameters, such as the size of the analysis window or the single neuron firing rates, will aid the design of experiments. In this context, it is also important to note that the common assumptions of stationarity and serial independence underlying the log-linear model are by no means trivially satisfied in experimental data sets and, therefore, require careful evaluation. Likewise, the robustness of the statistical procedure presented here with respect to violations of these assumptions needs to be assessed. These various issues are the subject of current work.

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## Appendix

### *Three-neuron system with homogeneous interactions*

In this Appendix we show how the interaction parameters underlying the simulated data used in Sect. 4 are computed and give an explicit expression for the number of realizations  $\mathcal{N}_k$  entering the conditional probability distribution (Eq. 6) of the exact test. Explicit expressions for the second- and third-order p-values are given. Since by definition of the activity scenario in Sect. 4, all three single-neuron firing rates  $r$  and all three pairwise spike correlations  $\rho$  in the three-neuron model system are the same, we abbreviate the first- and second-order interaction parameters by  $\Theta_1 \equiv \theta_1 = \theta_2 = \theta_3$  and  $\Theta_2 \equiv \theta_{12} = \theta_{13} = \theta_{23}$ , respectively. Writing analogously  $\Theta_3 \equiv \theta_{123}$  for the third-order parameter, we abbreviate the full interaction structure of the model by the vector  $\Theta = (\Theta_1, \Theta_2, \Theta_3)$ . Omitting the index  $i$  of the time bin, we obtain for the probability distribution of the joint spike activity  $\mathbf{x}$  in the  $i$ th bin from Eq. 1

$$P_{\Theta}(\mathbf{x}) = \exp \left[ \Theta_1 \sum_j x_j + \Theta_2 \sum_{j < k} x_j x_k + \Theta_3 x_1 x_2 x_3 - \psi \right]. \quad (\text{A1})$$

Inserting this expression into the elementary relations

$$\begin{aligned} P_{\Theta}(x_1 = 1) &= P_{\Theta}(x_2 = 1) = P_{\Theta}(x_3 = 1) \\ &= P_{\Theta}(x_1 = 1, x_2 = 0, x_3 = 0) \\ &\quad + P_{\Theta}(x_1 = 1, x_2 = 1, x_3 = 0) \\ &\quad + P_{\Theta}(x_1 = 1, x_2 = 0, x_3 = 1) \\ &\quad + P_{\Theta}(x_1 = 1, x_2 = 1, x_3 = 1) \end{aligned}$$

and

$$\begin{aligned} P_{\Theta}(x_1 = 1, x_2 = 1) &= P_{\Theta}(x_1 = 1, x_3 = 1) \\ &= P_{\Theta}(x_2 = 1, x_3 = 1) \\ &= P_{\Theta}(x_1 = 1, x_2 = 1, x_3 = 0) \\ &\quad + P_{\Theta}(x_1 = 1, x_2 = 1, x_3 = 1), \end{aligned}$$

of the binwise spike and spike-pair probabilities, respectively, we obtain

$$P_{\Theta}(x_j = 1) = \frac{e^{\Theta_1} + 2e^{2\Theta_1 + \Theta_2} + e^{3\Theta_1 + 3\Theta_2 + \Theta_3}}{1 + 3e^{\Theta_1} + 3e^{2\Theta_1 + \Theta_2} + e^{3\Theta_1 + 3\Theta_2 + \Theta_3}} \quad (\text{A2})$$

and

$$\begin{aligned} P_{\Theta}(x_j = 1, x_k = 1) \\ &= \frac{e^{2\Theta_1 + \Theta_2} + e^{3\Theta_1 + 3\Theta_2 + \Theta_3}}{1 + 3e^{\Theta_1} + 3e^{2\Theta_1 + \Theta_2} + e^{3\Theta_1 + 3\Theta_2 + \Theta_3}} \end{aligned} \quad (\text{A3})$$

where  $j, k \in \{1, 2, 3\}$ ,  $j \neq k$ , and we used the normalization condition

$$\exp[-\psi] = \frac{1}{1 + 3e^{\Theta_1} + 3e^{2\Theta_1 + \Theta_2} + e^{3\Theta_1 + 3\Theta_2 + \Theta_3}}. \quad (\text{A4})$$

With Eqs. A2 and A3, the elementary definitions of the firing rate of neuron  $j$

$$r\Delta t = P_{\theta}(x_j = 1), \quad (\text{A5})$$

and the pairwise spike correlations of neurons  $j$  and  $k$

$$\begin{aligned} \rho &= \frac{\text{Cov}[X_j, X_k]}{\sqrt{\text{Var}[X_j]\text{Var}[X_k]}} \\ &= \frac{P_{\Theta}(x_j = 1, x_k = 1) - P_{\Theta}(x_j = 1)^2}{P_{\Theta}(x_j = 1)(1 - P_{\Theta}(x_j = 1))} \end{aligned} \quad (\text{A6})$$

establish two relations that need to be satisfied by the interaction parameters  $\Theta$  of the model. Adding these relations to the defining constraints of the second-order or third-order models, namely,  $\Theta_3 = 0$  or  $\Theta_2 = 0$ , respectively, calculation of the remaining two interaction parameters of each model is straightforward. Using the fully specified models, the spike patterns  $\mathbf{x}$  of all  $n$  bins are drawn independently according to the corresponding probability distribution Eq. A1.

To carry out the exact tests for each interaction order, the conditional distributions of the second-order and third-order coincidence counts  $P_{\Theta}(k_{12})$  and  $P_{\Theta}(k_{123})$ , respectively, need to be computed. Each coincidence vector  $\mathbf{k}$  uniquely determines the number of occurrences of each of the  $2^m$  possible spike patterns in the analysis window. For the three-neuron system we have

$$\begin{aligned}
c_{111} &= k_{123} \\
c_{110} &= k_{12} - k_{123} \\
c_{101} &= k_{13} - k_{123} \\
c_{011} &= k_{23} - k_{123} \\
c_{100} &= k_1 - k_{12} - k_{13} + k_{123} \\
c_{010} &= k_2 - k_{12} - k_{23} + k_{123} \\
c_{001} &= k_3 - k_{13} - k_{23} + k_{123} \\
c_{000} &= n - k_1 - k_2 - k_3 + k_{12} + k_{13} + k_{23} - k_{123} ,
\end{aligned}$$

where each  $c_{jkl}$  denotes the number of spike patterns ( $x_1 = j, x_2 = k, x_3 = l$ ) in the analysis window. Hence, the number of realizations  $\mathcal{N}_{\mathbf{k}}$  of the analysis window for each  $\mathbf{k}$  is given by the multinomial coefficient

$$\begin{aligned}
\mathcal{N}_{\mathbf{k}} &= \binom{n}{c_{111}, c_{110}, c_{101}, c_{011}, c_{100}, c_{010}, c_{001}, c_{000}} \\
&\equiv \frac{n!}{c_{111}!c_{110}!c_{101}!c_{011}!c_{100}!c_{010}!c_{001}!c_{000}!} .
\end{aligned}$$

Note that the full expression of the conditional coincident count distribution (Eq. 6) can be simplified by using elementary properties of binomial coefficients (e.g., Knuth 1973). Following the derivation in Gütig et al. (2002), we obtain for the p-value of the test for a zero second-order interaction among neurons  $j$  and  $l$  ( $H_0 : \theta_{jl} = 0$ )

$$J_2(k_j, k_l, k_{jl}, n) = 1 - \sum_{c=0}^{k_{jl}-1} \frac{\binom{k_j}{c} \binom{n-k_j}{k_l-c}}{\binom{n}{k_l}} . \quad (\text{A7})$$

Defining the auxiliary function

$$\begin{aligned}
\mathcal{A}(\mathbf{k}, n) &= \binom{k_1 - k_{13}}{k_{12} - k_{123}} \binom{k_2 - k_{12}}{k_{23} - k_{123}} \binom{k_3 - k_{23}}{k_{13} - k_{123}} \\
&\quad \times \binom{n - k_1 - k_2 - k_3 + k_{12} + k_{13} + k_{23}}{k_{123}} ,
\end{aligned}$$

the p-value of the third-order test ( $H_0 : \theta_{123} = 0$ ) can be reduced to the compact form

$$J_3(\mathbf{k}, n) = 1 - \frac{\sum_{c=0}^{k_{123}-1} \mathcal{A}(\mathbf{k}', c, n)}{\sum_{c=0}^{\min(k_{12}, k_{13}, k_{23})} \mathcal{A}(\mathbf{k}', c, n)} , \quad (\text{A8})$$

where, as defined in Sect. 3,  $\mathbf{k}'$  denotes the lower-order coincidence counts, and the minimum of the double coincidence counts  $\min(k_{12}, k_{13}, k_{23})$  implements the maximum number of triple coincidences possible for the observed lower-order counts.

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