Analyzing Functional Connectivity Using a Network Likelihood Model of Ensemble Neural Spiking Activity

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Analyzing the dependencies between spike trains is an important step in understanding how neurons work in concert to represent biological signals. Usually this is done for pairs of neurons at a time using correlation-based techniques. Chornoboy, Schramm, and Karr (1988) proposed maximum likelihood methods for the simultaneous analysis of multiple pair-wise interactions among an ensemble of neurons. One of these methods is an iterative, continuous-time estimation algorithm for a network likelihood model formulated in terms of multiplicative conditional intensity functions. We devised a discrete-time version of this algorithm that includes a new, efficient computational strategy, a principled method to compute starting values, and a principled stopping criterion. In an analysis of simulated neural spike trains from ensembles of interacting neurons, the algorithm recovered the correct connectivity matrices and interaction parameters. In the analysis of spike trains from an ensemble of rat hippocampal place cells, the algorithm identified a connectivity matrix and interaction parameters consistent with the pattern of conjoined firing predicted by the overlap of the neurons’ spatial receptive fields. These results suggest that the network likelihood model can be an efficient tool for the analysis of ensemble spiking activity.
1 Introduction

A major goal of neural data analysis is to characterize how neurons that are part of an ensemble interact with each other (Espinosa & Gerstein, 1988; Gochin, Gerstein, & Kaltenbach, 1990; Eggermont, 1991; Gochin, Miller, Gross, & Gerstein, 1991; Lindsey, Hernandez, Morris, & Shannon, 1992; Wilson & McNaughton, 1994; Vaadia et al., 1995; Skaggs & McNaughton, 1996; Li, Morris, Baekey, Shannon, & Lindsey, 1999; Schoenbaum, Chiba, & Gallagher, 2000; Shannon, Baekey, Morris, Li, & Lindsey, 2000; Louie & Wilson, 2001; Lee & Wilson, 2002). With the advent of the multielectrode recording technology, it is now possible to record the activity of several hundred neurons simultaneously (Wilson & McNaughton, 1993; Nicolelis et al., 2003). This has underlined the need for developing analysis methods that can process these data quickly and efficiently (Brown, Kass, & Mitra, 2004). Statistical dependencies between spike trains may be represented using cross-intensity functions (Cox & Lewis, 1972; Brillinger, 1976a, 1992), product densities, cumulant densities, cumulant spectra, method of moments (Bartlett, 1966; Brillinger, 1975a, 1975b), cross-correlation (Perkel, Gerstein, & Moore, 1967; Moore, Segundo, Perkel, & Levitan, 1970; Aertsen & Gerstein, 1985; Palm, Aertsen, & Gerstein, 1988; Brody, 1998, 1999a, 1999b), coherence (Brillinger, 1976b, 1992), and joint peristimulus time histogram (JPSTH) (Gerstein & Perkel, 1969, 1972; Aertsen, Gerstein, Habib, & Palm, 1989). These methods are usually applied to characterize the dependencies between pairs of neurons at a time, ignoring possible effects from other neurons, although techniques such as partial coherence (Brillinger, 1976b, 1992), conditional cross-correlogram (Eggermont, 1991), and JPSTH (Kristan & Gerstein, 1970) have been applied to the simultaneous analysis of triplets. Logical extension of these methods to the simultaneous analysis of more than three spike trains faces the problem of exponentially increasing number of bins to calculate. This problem is avoided in methods that detect particular spike timing relations among multiple neurons. These include the gravitational clustering algorithm, which is used for the detection of synchronous cell assemblies (Gerstein & Aertsen, 1985; Gerstein, Perkel, & Dayhoff, 1985; Baker & Gerstein, 2000), and spike pattern classification methods, which are used to detect precisely timed spatiotemporal firing patterns or search for a particular sequential firing pattern within the ensemble spiking activity (Abeles & Gerstein, 1988; Louie & Wilson, 2001; Pipa & Grün, 2003; Lee & Wilson, 2004).

Statistical methods based on the maximum likelihood (ML) principle have been proposed as alternative techniques for the simultaneous analysis of neural interactions (Borisuyk, Borisuyk, Kirillov, Kovalenko, & Kryukov, 1985; van den Boogaard, 1986; Brillinger, 1988a, 1988b, 1992; Chornoboy, Schramm, & Karr, 1988). The applicability of the ML method to the analysis of spike trains of more than a few neurons has been limited due to
the difficulties in computing the ML estimates in large models. Chornoboy et al. (1988) addressed the issue of easy computability of the estimates for large models and proposed iterative estimation algorithms for a class of additive-linear and multiplicative conditional intensity function models. In this article, we explore the computational properties of the algorithm associated with the multiplicative model and use it to analyze both simulated and real neural data. The original formulation of the algorithm is in continuous time. Here we formulate a discrete-time implementation and describe a method that reduces the number of operations. We derive a principled method for computing a good initial parameter vector to start the algorithm. We also derive a data-specific stopping rule to terminate the iteration. We apply this algorithm to the analysis of simulated spike trains and show that it successfully recovers the true time course of the excitatory and inhibitory interactions among simulated neurons. We propose a method to determine optimal connectivity matrices for neural ensembles using a combination of the likelihood ratio test and the Akaike information criterion or the Bayesian information criterion (AIC or BIC; Box, Jenkins, & Reinsel, 1994). We show that this method discovers the correct connectivity matrices in simulations. We apply these methods to the analysis of simultaneously recorded spike trains of a population of rat hippocampal place cells. We determine an optimal connectivity matrix for these cells and analyze its relationship to the degree of overlap between their place fields.

2 Theory

In this section, we introduce the network likelihood model and the iterative algorithm for the ML estimation of the model parameters. We derive a method to compute a starting vector for the algorithm and a stopping rule to terminate the iteration. Finally, we describe how the ML estimates are used to determine a connectivity matrix that describes the data optimally.

2.1 Network Likelihood Model. Our method is based on the point process representation of spike trains (Brillinger 1988a, 1992; Chornoboy et al., 1988; Brown, Barbieri, Ventura, Kass, & Frank, 2002; Brown, Barbieri, Eden, & Frank, 2003). Define an interval \((0, T]\), and let \(0 < u_{i,1} < u_{i,2} < \ldots < u_{i,n-1} < u_{i,n} \leq T\) be a set of spike times from the spike train of neuron \(i\), for \(1 \leq i \leq C\), where \(C\) is the total number of neurons in the ensemble. For \(t \in (0, T]\), let \(N_i(t)\) be the sample path of the counting process associated with the spike train of neuron \(i\). The sample path is a right continuous function that jumps 1 at the spike times and is constant otherwise (Snyder & Miller, 1991). In this way, \(N_i(t)\) counts the number and location of the spikes of neuron \(i\) in the interval \((0, t]\). We model the spiking activity of a neuron (target) as a point process that depends on a finite spiking history of
all the neurons in the ensemble (triggers). Let $H_t$ denote this finite spiking history, which is defined in the interval $[t - MW, t)$. This interval is divided into $M$ nonoverlapping rectangular windows of duration $W$. Using $\chi_m(u)$ as the indicator function for $u \in ((m-1)W, mW]$, with $1 \leq m \leq M$, define the process $I_{c,m}(t)$ as the number of spikes fired by neuron $c$ in window $m$, such that

$$I_{c,m}(t) = \int_0^t \chi_m(t - \tau) dN_c(\tau).$$  \hfill (2.1)$$

The duration $W$ of the spike counting window and the duration $MW$ of the history are constant and the same for all cell pairs. The firing propensity of the target neuron is computed as a function of these processes using the following conditional intensity function (Brillinger, 1975b; Chornoboy et al., 1988),

$$\lambda_i(t | \alpha_i, H_t) = \exp \left( \alpha_{i,0} + \sum_{c=1}^C \sum_{m=1}^M \alpha_{i,c,m} I_{c,m}(t) \right).$$  \hfill (2.2)$$

where, $\alpha_{i,0}$ represents the component of the firing probability that is not correlated with the available history and $\alpha_{i,c,m}$ represents the effect of $I_{c,m}(t)$ on the firing probability of cell $i$ at time $t$. The probability that neuron $i$ fires a spike in a brief time interval $(t, t + \Delta]$ is then given by $\lambda_i(t | \alpha_i, H_t) \Delta$. The vector $\alpha_i$ is the row vector of parameters

$$\alpha_i = [\alpha_{i,0}, \alpha_{i,1,1}, \ldots, \alpha_{i,1,M}, \alpha_{i,2,1}, \ldots, \alpha_{i,C,M}].$$  \hfill (2.3)$$

This vector represents the dependency of neuron $i$ on a finite firing history $H_t$ of all neurons in the ensemble. It specifies the functional connections that neuron $i$ receives from these neurons. To specify the pair-wise connections among all neurons simultaneously, we consider the following parameter vector, which is obtained by concatenating the vectors $\alpha_i$ for all $i$:

$$\alpha_{1:C} = [\alpha_1, \alpha_2, \ldots, \alpha_C].$$  \hfill (2.4)$$

We assume that neurons are conditionally independent given $\alpha_{1:C}$ and $H_t$. Given the ensemble spiking activity in $(0, T]$, provided that neurons do not fire simultaneous spikes, the likelihood function of the parameter vector
\( \alpha_{1:C} \) is (Jacod, 1975; Chornoboy et al., 1988)

\[
L_T(\alpha_{1:C}) = \exp \left( \sum_{i=1}^{C} \left\{ \int_{0}^{T} \log(\lambda_i(u|\alpha_i, H_u)) \, dN_i(u) + \int_{0}^{T} [1 - \lambda_i(u|\alpha_i, H_u)] \, du \right\} \right).
\] (2.5)

Since the vector \( \alpha_{1:C} \) specifies the functional interactions among all neurons, it can be viewed as the description of a fully interconnected network. It follows that \( L_T(\alpha_{1:C}) \) is the likelihood function of this network. The network log-likelihood function is

\[
l_T(\alpha_{1:C}) = \sum_{i=1}^{C} \left\{ \int_{0}^{T} \log(\lambda_i(u|\alpha_i, H_u)) \, dN_i(u) + \int_{0}^{T} [1 - \lambda_i(u|\alpha_i, H_u)] \, du \right\}.
\] (2.6)

2.2 Maximum Likelihood Estimation Algorithm. Our goal is to compute the parameter vector \( \hat{\alpha}_{1:C} \), the ML estimate of \( \alpha_{1:C} \), which maximizes the network log-likelihood function. This function is uncoupled with respect to the index \( i \). Therefore, the ML estimate can be computed by maximizing the log-likelihood function \( l_T(\alpha_i) \) separately for each \( i \), where

\[
l_T(\alpha_i) = \int_{0}^{T} \log(\lambda_i(u|\alpha_i, H_u)) \, dN_i(u) + \int_{0}^{T} [1 - \lambda_i(u|\alpha_i, H_u)] \, du. \] (2.7)

This is the log-likelihood function corresponding to the spike train of neuron \( i \). Equation 2.7 is actually the log of the ratio of the likelihood relative to a Poisson process model with unit rate (Karr, 1991). Because it differs from the log-likelihood by only the constant term \( T \), we do not make the distinction between it and the actual log-likelihood function (Brown et al., 2003; Daley & Vere-Jones, 2003). To reduce the number of subscripts used for indexing the parameters, we combine the indices \( c \) and \( m \) in a new index \( j \) given by

\[
j = (c - 1)M + m. \] (2.8)
Using this new index in equation 2.2, the conditional intensity function for neuron $i$ is written as

$$\lambda_i(t|\alpha_i, H_t) = \exp \left( \sum_{j=0}^{D} \alpha_{i,j} I_j(t) \right), \quad (2.9)$$

where $D = CM$, and $I_0(t) = 1$. The definition in equation 2.3 of the parameter vector $\alpha_i$ is rewritten accordingly:

$$\alpha_i = [\alpha_{i,0}, \alpha_{i,1}, \ldots, \alpha_{i,D}]. \quad (2.10)$$

Using equation 2.9 in equation 2.7, the log-likelihood function of $\alpha_i$ is given by

$$l_T(\alpha_i) = \int_0^T \left( \sum_{j=0}^{D} \alpha_{i,j} I_j(u) \right) dN_i(u) + \int_0^T \left[ 1 - \exp \left( \sum_{j=0}^{D} \alpha_{i,j} I_j(u) \right) \right] du. \quad (2.11)$$

Chornoboy et al. (1988) proposed an iterative algorithm to compute the ML estimates. Here, we describe a discrete-time formulation of this algorithm. The algorithm is designed to compute the ML estimate of $\gamma_i = [\exp(\alpha_{i,j})]$. For this reason, the model is often expressed as a function of $\gamma_i$ in the following analysis. The ML estimate $\hat{\gamma}_i$ of $\gamma_i$ is computed iteratively using the following equations:

$$\gamma^{(n+1)}_{i,j} = \gamma^{(n)}_{i,j} \left[ \frac{\sum_{k=0}^{K-1} I_{j,k} N_{i,k;k+1}}{\sum_{k=0}^{K-1} I_{j,k} \left[ \prod_{l=0}^{D} \left( \gamma^{(n)}_{i,l} \right)^{I_{l,k}} \right] \Delta} \right]^{\beta_{i,j}} \quad (2.12)$$

$$\beta_{i,j} = \frac{\sum_{k=0}^{K-1} I_{j,k} N_{i,k;k+1}}{\sum_{k=0}^{K-1} I_{j,k} \left[ \sum_{l=0}^{D} I_{l,k} N_{i,l;k+1} \right]} \quad (2.13)$$

where $I_{j,k} = I_j(k\Delta)$, $N_{i,k;k+1} = N_i((k+1)\Delta) - N_i(k\Delta) \approx dN_i(k\Delta)$, $K$ is the smallest integer larger than $T/\Delta$, and we choose $\Delta = 1 \text{ ms}$ such that $N_{i,k;k+1} \leq 1$. The ML estimate of a parameter $\gamma_{i,j}$ cannot be computed using the iteration if $\beta_{i,j}$ is zero. Therefore, such parameters are excluded from the model. In the following, it is assumed that $\beta_{i,j} > 0$ for all parameters.

If the duration of the spike counting window $W$ is short relative to the average interspike interval in the data, the processes $I_{j,>0}$ are zero at
most time points. This allows computing the denominator in equation 2.12 by executing the summations and multiplications only at the time points where $I_{j,k}$ are nonzero. In the following, we develop the notation needed to achieve this simplification. We define the set $Q_j$ of all time points $k$ at which $I_{j,k} > 0$. With this definition, the denominator in equation 2.12 is given by $\sum_{k \in Q_j} I_{j,k} N_{i,k,k+1}$.

This expression can be further simplified since the products can be computed by multiplying only the parameters that have a nonzero exponent. This can be achieved by defining a set, at each time point, to index these parameters. We thus define the sets $J_k = \{l | 0 \leq l \leq D, I_{l,k} > 0\}$ for $0 \leq k \leq K - 1$.

With these sets, equations 2.12 and 2.13 may be written as

\[
\gamma_{i,j}^{(n+1)} = \gamma_{i,j}^{(n)} \left[ \sum_{k \in Q_j} I_{j,k} N_{i,k,k+1} / \sum_{k \in Q_j} I_{j,k} B_{i,k}^{(n)} \Delta \right]^{\beta_{i,j}}, \tag{2.14}
\]

\[
P_{i,k}^{(n)} = \prod_{l \in J_k} \left( \gamma_{i,l}^{(n)} \right)^{I_{l,k}}, \tag{2.15}
\]

\[
\beta_{i,j} = \frac{\sum_{k \in Q_j} I_{j,k} N_{i,k,k+1}}{\sum_{k \in Q_j} I_{j,k} \left[ \sum_{l \in J_k} I_{l,k} \right] N_{i,k,k+1}}. \tag{2.16}
\]

Only the denominator of equation 2.14 needs to be recomputed at each iteration. The product $P_{i,k}^{(n)}$ is not computed anew for each parameter. It is computed once per iteration, and its values are looked up during the computation of the denominator for individual parameters. Precomputing the sets $Q_j$ and $J_k$ for later look-up reduces the computation time substantially, especially considering that the parameters are reestimated under several different contingencies during connectivity analyses.

The ML estimate $\hat{\alpha}_{i,j}$ of $\alpha_{i,j}$ is computed as $\hat{\alpha}_{i,j} = \log(\hat{\gamma}_{i,j})$ using the invariance principle of the ML estimation (Pawitan, 2001). For large $T$, the probability density function of the statistic $\sqrt{T}(\hat{\alpha}_{i} - \alpha_{i}^0)$ is multivariate normal with mean 0 and covariance $\Sigma^{-1}$, where $\alpha_{i}^0$ is the true value of the parameter vector and $\Sigma_{jl} = -\frac{1}{T} \frac{\delta^2 \ln L(\alpha)}{\delta \alpha_{i,j} \delta \alpha_{i,l}} \bigg|_{\alpha_i = \alpha_{i}^0}$. We use this relationship to compute the 100 $(1 - \alpha)\%$ confidence interval of $\hat{\alpha}_{i,j}$ as $\hat{\alpha}_{i,j} \pm \sqrt{\frac{1}{T} (\Sigma^{-1})_{jl} \Phi^{-1}(1 - \frac{\alpha}{2})}$, where $0 \leq \alpha \leq 1$ is the significance level, $\Phi(\cdot)$ is the standard normal distribution function, and $\Sigma$ is evaluated at $\alpha_i = \hat{\alpha}_i$.

2.3 Formulation of the Starting Vector and the Stopping Rule. It is desirable to start the iteration using a parameter vector that is as close to the solution as possible. Here, we present two equations that can be used to compute such a vector (see the appendix for details). In the following, the
starting vector for neuron $i$ is denoted by $\gamma_{i}^{(1)}$. For $j > 0$, the components $\gamma_{i,j}^{(1)}$ of this vector are computed by solving the following equation:

$$p \left( \gamma_{i,j}^{(1)} \right) = \sum_{r=0}^{R_{j}} \text{card}(Q_{j}^{r}) (r v_{i,0} - v_{i,j}) (\gamma_{i,j}^{(1)})^{r} = 0. \quad (2.17)$$

Here, $v_{i,j} = \sum_{k \in Q_{j}} I_{j,k} N_{i,k+1}$, $Q_{j}^{r}$ is the set of all time points $k$ at which $I_{j,k} = r$, $\text{card}(Q_{j}^{r})$ is the cardinality of $Q_{j}^{r}$, and $R_{j} = \max(I_{j,k})$. By Descartes’ sign rule, at most one of the roots of the equation $p(\gamma_{i,j}^{(1)}) = 0$ is strictly positive (Struik, 1986). If this root exists, we use it as $\gamma_{i,j}^{(1)}$. If it does not exist, then some $\gamma_{i,j} > 0$ that minimizes $|p(\gamma_{i,j})|$ may be used as $\gamma_{i,j}^{(1)}$. We compute $\gamma_{i,0}^{(1)}$ as the average firing rate,

$$\gamma_{i,0}^{(1)} = \frac{v_{i,0}}{K \Delta}. \quad (2.18)$$

We stop the iteration when the change in the parameter values is below a certain threshold. This is achieved by terminating the iteration when the following inequality is achieved:

$$\delta \gamma_{i,n} = \max_{j} \left( \frac{\gamma_{i,j}^{(n+1)}}{\gamma_{i,j}^{(n)}} - 1, \frac{\gamma_{i,j}^{(n)}}{\gamma_{i,j}^{(n+1)}} - 1 \right) < \theta. \quad (2.19)$$

When the iteration is stopped using the rule $\delta \gamma_{i,n} < \theta$, the change in the log likelihood is around $\theta^2 \Omega$, where $\Omega = \sum_{j=1}^{D} \sum_{t=0}^{T} I_{j}(u) I_{i}(u) dN_{j}(u)$ (see the appendix for details). $\Omega$ is completely specified given the ensemble spike train data. Therefore, this relationship can be used to select a data-specific threshold $\theta$. $\Omega$ was smaller than $4.8 \times 10^{4}$ for all place cells in our study. In our analysis, we used $\theta = 10^{-5}$, which resulted in a change in the log likelihood of less than $4.8 \times 10^{-6}$ at the end of the iterations.

2.4 Computing an Optimal Connectivity Matrix. We used a combination of the likelihood ratio test and the AIC or the BIC to determine the optimal order of the network model, which in this case corresponds to the optimal number and configuration of connections to include. Minimizing the AIC or the BIC strikes a balance between maximizing the log likelihood and reducing the number of parameters in the model (Box et al., 1994). We use these criteria and the likelihood ratio test as follows (see the appendix for details). We first compute the significance of each connection using the likelihood ratio test. This test determines whether the removal of one pair-wise connection from the network changes the likelihood significantly. Therefore, it computes this significance by taking into account all other pair-wise interactions. We obtain a new network configuration by discarding the
connections whose significance is lower than a variable threshold. We compute the AIC and the BIC for such configurations by reestimating the surviving model parameters. We find the thresholds that minimize these criteria. The optimal parameter vector that minimizes the AIC (BIC) is denoted by $\alpha_{AIC}^1$ ($\alpha_{BIC}^1$). These vectors constitute optimal representations of the changes in the firing probability of neurons following a spike in any neuron in the network. They also imply the optimal connectivity matrices $G_{AIC}$ and $G_{BIC}$. In these binary matrices, a 1 at the entry $(i, c)$ indicates that the functional connection from neuron $c$ to neuron $i$ was kept in the optimal model. Here, the term connection refers to statistical dependencies between spike trains (neurons) and does not necessarily imply the existence of an anatomical connection between the corresponding neurons.

3 Applications

3.1 Simulation of Ensemble Spiking Activity. To demonstrate that the method successfully recovers inhibitory and excitatory interactions among neurons, we generated spike trains that had known interaction matrices using both types of interactions. We simulated the ensemble spiking activity as a multivariate point process using the discrete version of the time rescaling method, with a temporal resolution of $\Delta = 1$ ms (Brown et al., 2002). The simulated ensembles consisted of 4, 8, and 20 model neurons. These are shown in Figures 1A, 4A, and 6A, respectively. The firing probability of each neuron depended on the activity of other neurons through inhibitory and excitatory interactions. Each neuron inhibited itself and had at least one inhibitory and one excitatory interaction with other neurons. These interactions are shown in Figure 1B and are described by the following functions,

$$\alpha_0(u) = -2 \sin(2\pi 0.08^{-1}u) \exp(-0.04^{-1}u),$$
$$\alpha^+(u) = 2 \sin(2\pi 0.06^{-1}u) \exp(-0.04^{-1}u),$$
$$\alpha^-(u) = -3 \sin(2\pi 0.12^{-1}u) \exp(-0.04^{-1}u),$$

where $u$ is in seconds and $\alpha_0(u)$, $\alpha^+(u)$, and $\alpha^-(u)$ represent the auto-inhibitory, excitatory, and cross-inhibitory interactions among neurons, respectively. In addition, each neuron had a spontaneous firing rate of 5 Hz. These functions are dimensionless and represent the logarithm of dimensionless multipliers of the spontaneous firing rate. They represent statistical dependencies between neurons without reference to physiological processes.

To generate the simulated spike trains, we computed the firing probability of neuron $i$ in the time interval $(t, t + \Delta]$ as $\lambda_i(t | \alpha_i, H_i)\Delta$ using equation 2.9 with a history duration of 120 ms and a spike counting window of $W = 1$ ms. This resulted in $M = 120$ parameters for each pair-wise
interaction. We now explain how the parameters for neuron 1 were obtained from equation 3.1 in the network of four neurons, which is shown in Figure 1A. In this network, each neuron excites its neighbor in the clockwise direction and inhibits its neighbor in the opposite direction. Using equation 2.8 with $M = 120$, the component $\alpha_{1,(c-1)M+m}$ of the parameter vector $\alpha_1$ describes how the number of spikes fired by neuron $c$ in the interval $[t - mW, t - (m - 1)W]$ influences the firing probability of neuron 1 at time $t$. In the present case, this interval contains at most one spike because $W = 1$ ms. When neuron 1 fires a spike at time $t - mW$, its effect on its own firing probability at time $t$ is computed as $\alpha^0(mW)$ using the auto-interaction function in equation 3.1. The effect of a spike that occurs within the interval $[t - mW, t - (m - 1)W]$ may be represented by the mean value of the...
function \( \alpha^0(u) \) for \( u \in ((m - 1)W, mW] \). Since \( \alpha^0(u) \) does not change by a large amount within 1 ms intervals, we approximated this mean by the value of the function at the beginning of the interval. Therefore, the value of the parameter \( \alpha_{1,m} \) was computed as \( \alpha_{1,m} = \alpha^0((m - 1)W) \) for \( 1 \leq m \leq 120 \). Similarly, for \( 1 \leq m \leq 120 \), the parameters that describe the influence of neurons 2 and 4 on neuron 1 are computed as \( \alpha_{1,M+m} = \alpha^-(m - 1)W \), and \( \alpha_{1,3M+m} = \alpha^+(m - 1)W \), respectively. On the other hand, the parameters \( \alpha_{1,2M+m} \) are all zero since neuron 3 does not directly influence the firing of neuron 1. The parameter \( \alpha_{1,0} \) is equal to \( \log(5) \) since the spontaneous firing rate is 5 Hz for all neurons. Model parameters were obtained in an identical fashion for the other simulated neurons. The simulations were stopped after each neuron fired at least 5000 spikes. An absolute refractory period of 1 ms was enforced by preventing spikes from being generated in adjacent time steps.

We designed the simulated networks to have nontrivial connectivity while avoiding excessive visual complexity. These examples are intended to show that for increasingly complex networks under no a priori assumption about the connectivity, our algorithm has a high likelihood of identifying whatever connectivity is in the system. The network model generates both stationary and nonstationary spike trains depending on whether its parameters satisfy certain constraints. Since our simulation and analysis methods do not impose any specific constraints on the parameters, the application of our method is not restricted to stationary spike trains.

3.2 Analysis of the Simulated Ensemble Spiking Activity. We use the four-neuron network as a simple example to illustrate our method. Figure 1C shows the interspike interval (ISI) distribution (top) and the power spectral density (PSD) of the spike train for neuron 1. The exponential function superimposed on the ISI distribution shows the distribution that would be obtained from a 5 Hz Poisson spike train. These plots are representative of all neurons in this and the other simulated networks due to the symmetry and the use of the same interaction functions in each network. It can be seen that the neuron has a certain tendency to fire with ISIs of about 60 ms, which shows up as a peak at around 16 Hz in the PSD. This structure can be explained in terms of the temporal distribution of excitation within the interaction functions (see Figure 1B). Namely, the auto-inhibition has an excitatory rebound that peaks at around 56 ms, and the excitation has two excitatory peaks separated by 60 ms. The former results in an interval of increased firing probability at around 56 ms after each firing of neuron 1, and the latter results in two intervals of increased firing probability, separated by about 60 ms, after each firing of an excitatory trigger neuron, which is the neuron 4 in this case.

For the parameter estimation, we used a history duration of 120 ms and \( W = 10 \) ms, which resulted in 12 parameters per connection. An optimal value of \( W \) can be found by trying different values and selecting the one
that minimizes the AIC or the BIC. This is done in the analysis of the place cell data in section 3.3. Here, the value of 10 ms was chosen intuitively to obtain a relatively small number of parameters per connection while maintaining the temporal resolution sufficiently high to capture the important features of the interaction functions.

Figure 2A shows $\hat{\alpha}_{1:4}$, the ML estimate of the parameter vector $\alpha_{1:4}$, superimposed on the actual interaction functions. The ML estimates are shown by the black dots, and each estimate is plotted at the center of the 10 ms window that it is associated with. The error bars show the 99.99% confidence intervals of the estimates. The asterisks indicate the parameters that are significantly different from zero ($p < 0.0001$). The diagonal plots show the auto-inhibitory interaction estimates. The connectivity pattern implied by Figure 2A matches the actual diagram in Figure 1A. It can be seen that the temporal evolution of the interactions is captured in the parameter values accurately. The estimates of the spontaneous firing rates for each cell are shown in Figure 2B.

Figure 2A shows that the parameters that represent the connections between the neuron pairs (1, 3) and (2, 4) are close to zero. As a result, these were the least significant connections in the network. Both the AIC and the BIC were minimized when these connections were removed from the model. The resulting optimal vectors $\alpha_{1:4}^{\text{AIC}}$ and $\alpha_{1:4}^{\text{BIC}}$ were identical. In these vectors, the parameters that correspond to the removed connections are zero. The other parameters are reestimated under this constraint, and their values were found to be very close to the values shown in Figure 2A. In other words, the optimal parameter vectors correctly identified the true matrix of excitatory and inhibitory interactions among the simulated neurons. The connectivity matrices $G^{\text{AIC}}_{1:4}$ and $G^{\text{BIC}}_{1:4}$ that are implied by $\alpha_{1:4}^{\text{AIC}}$ and $\alpha_{1:4}^{\text{BIC}}$ were also identical and are shown in Figure 2C. In this matrix, connections that were kept in the optimal model are indicated by the black squares. The diagonal entries represent the dependence of the cells on their own activity history. This matrix corresponds to the true connectivity matrix of the network in Figure 1A. Note that the optimal connectivity matrices do not show a connection between neurons that do not have direct interactions, even though they have indirect interactions. For instance, neuron 1 has a bidirectional interaction with neuron 3 through neuron 2. In other words, neuron 2 acts as an “interneuron” between neurons 1 and 3. This relation is successfully detected in Figures 2A and 2C without mistakenly concluding that neurons 1 and 3 are in direct interaction.

For comparison, we also computed the interaction estimates using auto- and cross-intensity functions (Brillinger, 1976a). The estimates for neuron 1 are shown in Figure 3. These estimates are representative for the other neurons of this network as well. Here, the square root of the instantaneous firing rate of neuron 1 is shown as a function of time after a trigger spike. Assuming that the neurons do not fire simultaneous spikes and that the bivariate point processes that consist of the spike trains of neuron 1 and each of
Figure 2: (A) The ML estimates of the parameter vectors computed using the algorithm, superimposed on the actual interaction functions. The estimates are shown by the black dots. The error bars show the 99.99% confidence intervals of the estimates. The asterisks indicate the parameters that are significantly different from zero ($p < 0.0001$). The interaction estimates are dimensionless and represent the logarithm of dimensionless numbers that modulate the spontaneous firing rate. (B) The spontaneous firing-rate estimates. (C) $G^{AIC}$ and $G^{BIC}$ were identical and corresponded to the true connectivity matrix. Black squares indicate the presence of a connection.

the four trigger neurons are stationary, the square root of the auto- or cross-intensity function has a nearly normal asymptotic distribution (Brillinger, 1976a). In each graph, the thick curve shows the transformed true interaction function. For instance, in the top left graph, this curve is the function $\sqrt{5} \exp(\alpha^0(u))$ for $0 \leq u \leq 120$ ms, where $\alpha^0(u)$ is given by equation 3.1 and
5 Hz is the true spontaneous firing rate of neuron 1. The curves that show the true cross-interactions between neuron 1 and neurons 2 and 4 were obtained similarly, using \( a^-(u) \) and \( a^+(u) \), respectively, in place of \( a^0(u) \). For neuron 3, the thick curve shows \( \sqrt{5} \text{ s}^{-1/2} \), which is the square root of the spontaneous firing rate. In each graph, the dashed line indicates the square root of the estimated average firing rate of neuron 1, which has the same value in all plots. Of the three parallel curves, the middle curve shows the square root of the intensity function estimate. We computed this function using a bin size of 10 ms such that its value at time \( \tau \) represents the square root of the average intensity in the interval \( (\tau - 5 \times 10^{-3}, \tau + 5 \times 10^{-3}] \) (Brillinger, 1976a). Therefore, these estimates can be directly compared with the interaction estimates computed using our method (see Figure 2A). The upper and lower curves show the 99.99% confidence interval around the estimates. The two raster traces below the curves show the points where the estimates differ significantly from the true interactions in 16% to 35% of the 120 ms interval.
significantly differ from the estimated average firing rate (top raster trace) or the true interaction functions (bottom raster trace) \( p < 0.0001 \). It can be seen that the interaction estimates are significantly different from the true interaction functions in certain segments of the 120 ms interval. These segments cover 16% to 35% of the 120 ms interval. This coverage is 40% to 60% using 95% confidence intervals (not shown). In contrast, the true interaction functions are within the confidence intervals of all parameters in Figure 2A. These results show that although the auto- and cross-intensity functions provide a descriptive estimate of the interactions, they could not recover the true interaction functions accurately.

To test our algorithm on a larger network with a denser connectivity pattern, we designed a network of fully interconnected eight neurons. All neurons had the same properties as those in the previous network. In this network, each neuron receives only one excitatory connection, which is from the previous neuron in the clockwise direction, and six cross-inhibitory connections from the remaining neurons. This network is shown in Figure 4A, where only the connections made to three neurons are shown for clarity. The spontaneous firing-rate estimates and the best and worst cases of the interaction estimates, based on the mean squared error, are shown in Figures 4B and 4C, respectively. Even in the worst case, the estimates were very close to the true values of the parameters.

Figure 5 shows \( \hat{\alpha}_{1:8} \), the full matrix of the interaction estimates. The diagonal plots show the auto-inhibitory interactions. Each neuron is seen to have one excitatory interaction with the proper neuron and inhibitory interactions with the remaining neurons, in agreement with the true network connectivity. All entries in \( G^{AIC} \) and \( G^{BIC} \) were 1’s, indicating that the optimal connectivity matrices corresponded to a fully interconnected network. It also follows that the optimal parameter vectors \( \alpha^{AIC}_{1:8} \) and \( \alpha^{BIC}_{1:8} \) were identical to \( \hat{\alpha}_{1:8} \).

To try a network of nontrivial size, we constructed a network of 20 neurons using the four-neuron network as a building block, as shown in Figure 6A. This network contains 10 neuron triplets, such as the triplets \( (4 \leftarrow 3 \rightarrow 5) \) and \( (2 \leftarrow 6 \rightarrow 5) \), in which two neurons receive a shared input without having direct interactions. Therefore, this network can be used to test whether the method can differentiate between direct interaction and shared input.

The optimal connectivity matrices \( G^{AIC} \) and \( G^{BIC} \) were identical and corresponded to the true connectivity matrix shown in Figure 6B. In this case, \( G^{AIC} \) corresponded to this matrix when the interactions were estimated at \( W = 5 \) ms resolution instead of 10 ms. At 10 ms resolution, \( G^{AIC} \) had three false-positive connections. This suggested that 12 parameters per connection did not provide a sufficiently accurate representation of the interactions, which caused the model to overfit the data by forcing some parameters to be significantly different from zero even though they were part of the connections that did not exist in the original network. Indeed, after doubling
the number of parameters per connection to 24 (a resolution of 5 ms), $G^{AIC}$ corresponded to the true connectivity matrix. Also, the minimum AIC was smaller at 5 ms resolution, indicating that the true connectivity matrix was indeed the optimal solution across temporal resolutions, as expected. This suggests that in an unknown experimental situation, a range of values for $W$ should be tried, and values that minimize the AIC or the BIC (or both) should be used in the analysis. On the other hand, $G^{BIC}$ corresponded to the true connectivity matrix at both temporal resolutions, and the minimum BIC was lower at 10 ms resolution. Figure 6B shows that $G^{AIC}$ and $G^{BIC}$ do not indicate direct interactions between the neuron pairs that receive shared input without direct interaction, while the fact that they receive a shared input is visible in these matrices. This shows that the method can make this
distinction successfully, provided that the shared input source is accurately modeled in the conditional intensity functions of the neurons. The spontaneous firing-rate estimates and the best and worst cases of the interaction estimates using a 10 ms resolution are shown in Figures 6C and 6D, respectively. As for the other networks, the estimates were highly accurate even in the worst case.

The interaction estimates in Figures 2 and 4 through 6 show that the model fit the true interactions with high accuracy. The goodness-of-fit of the conditional intensity functions may be assessed by using Kolmogorov-Smirnov (KS) plots. The KS plots are obtained by rescaling the spike times of a spike train using the conditional intensity function that is fit to that spike train and comparing the distribution of the intervals between the rescaled times (rescaled ISIs) to the ISI distribution of a Poisson process with unit rate. The rescaling is done using the following formula,

$$\Lambda(u_{i,k}) = \int_0^{u_{i,k}} \lambda(u|H_u)du,$$

(3.2)
Figure 6: (A) The 20-neuron network. Same properties as in Figure 1. (B) $G^{AIC}$ and $G^{BIC}$ were identical and corresponded to the true connectivity matrix. Black squares indicate the presence of a connection. (C) The spontaneous firing-rate estimates. (D) The best and the worst cases of the interaction estimates based on the mean squared error. Same figure properties as in Figure 2.

where, $u_{i,k}$ is the time at which the $k$th spike of neuron $i$ occurs, $\Lambda(u_{i,k})$ is the rescaled time, and $\lambda(u|H_u)$ is a conditional intensity function satisfying $0 < \lambda(t|H_u)$ for all $t \in (0, T]$. According to the time rescaling theorem, if the spike times are rescaled using the true intensity function of the spike train, the rescaled times constitute a Poisson process with unit rate (Brown et al.,
The quality of the fit would then be assessed by comparing the distribution of the rescaled and transformed ISIs to the uniform distribution using the KS statistic. As a result, in KS plots, the quality of the fit is measured by the proximity of the plot to the 45 degree line. Figure 7 shows the best and worst KS plots across all neurons in all simulated networks. All plots were within the 95% confidence intervals, indicating that the conditional intensity functions fit the spike trains very well. These plots were obtained using the interaction estimates that were computed with 10 ms resolution.

### 3.3 Analysis of the Place Cell Ensemble Spiking Activity

To illustrate the application of the method to the analysis of real neural data, we analyzed
the spiking activity of an ensemble of hippocampal place cells. A given place cell fires only when the animal is in a certain subregion of the environment, termed the neuron’s place field (O’Keefe & Dostrovsky, 1971). The data were recorded from a Long-Evans rat in a familiar open circular environment 70 cm in diameter with walls 30 cm high and fixed visual cues. A multiunit electrode array was implanted into the CA1 region of the hippocampus of the animal. The simultaneous activity of 33 place cells was recorded from the electrode array for 23 minutes while the animal was freely foraging in the environment for randomly delivered food pellets. The cells were clearly separated even though there were more than one cell per tetrode. Spike sorting was done by visual cluster cutting and ambiguous spikes were eliminated. The position of the animal was also recorded simultaneously using a camera (Brown, Frank, Tang, Quirk, & Wilson, 1998).

We divided the recording session into two equal parts and analyzed the ensemble spiking activity independently in each part. In this way, we obtained two independent estimates of the optimal connectivity matrices of the cells. There were up to 3000 spikes available per neuron in each part of the recording session. In a preliminary analysis, we selected a history duration of 120 ms, with a spike counting window of $W = 1$ ms. We observed that significant auto- and cross-interactions among the neurons occurred first within an approximately 30 ms window, and then again at the next cycle of the hippocampal theta rhythm (data not shown). For this analysis, we chose a history duration of 30 ms to analyze the early phase of the functional interactions. We estimated the interactions at the resolutions of $W = 1$ ms, 3 ms, and 5 ms for the first part of the session. The lowest AIC was obtained at the resolution of 3 ms. We therefore used this resolution in analyzing the data.

Examples of the interaction estimates for the place cells are shown in Figure 8. Note that the estimates are very similar in the first (black lines) and second (red lines) parts of the recording session. This level of similarity was observed for most auto-interactions and a few cross-interactions.

The estimates $G_1^{BIC}$ and $G_2^{BIC}$ of $G^{BIC}$ in the first and second parts of the session are shown superimposed in Figure 9. The stars and the disks indicate the connections that were present only in the first and second parts of the session, respectively. The black squares show the connections that were present in both parts. Note that almost all of the diagonal entries are black squares, indicating that the auto-interactions were significant throughout the session.

The optimal connectivity matrix among the place cells is represented by the off-diagonal entries. The relative number of off-diagonal black squares is a measure of how similar the matrices were in the two parts of the session. We computed the significance of this similarity under the null hypothesis that each of the $C(C - 1)$ connections in an ensemble of $C$ neurons has the same probability $p_o$ of being present in the optimal connectivity matrix, and that $p_o$ is the same in both parts of the session. The ML estimate of the probability $p_o$ is then given by $p_o = (m_1 + m_2)/(2F)$, where $F = C(C - 1)$,
Figure 8: Examples of the interaction estimates for the place cells. Each plot shows the interactions estimated in the first (black lines) and second (red lines) parts of the recording session for a given cell (left), or cell pair (right). The dashed lines are the 99.99% confidence intervals. Asterisks indicate the parameters that were significantly different from zero (\(p < 0.0001\)).

and \(m_1\) and \(m_2\) are the numbers of off-diagonal entries in the optimal connectivity matrices obtained from the first and second parts of the recording session, respectively. Denoting the observed number of off-diagonal black squares by \(m_c\), we propose that given \(p_o\) and \(F\), the probability of observing \(m_c\) or more of the off-diagonal entries in both matrices can be used as the significance of the similarity between these matrices. This probability is given by

\[
\Pr(S \geq m_c \mid F, p_o) = \sum_{\mu_1=m_c}^{F} \sum_{\mu_2=m_c}^{F} \sum_{s=\max(m_c, r-F)}^{\min(\mu_1, \mu_2)} \frac{F!}{\mu_1! \mu_2!} \left( \frac{\mu_1}{s} \right) \left( \frac{F - \mu_1}{\mu_2 - s} \right) p_o^s (1 - p_o)^{2F - \tau},
\]

where, \(\tau = \mu_1 + \mu_2\) and the random variable \(S\) represents the number of common off-diagonal entries in the two matrices. Using this equation, we found that the similarity of the optimal connectivity matrices in the two
1948 M. Okatan, M. Wilson, and E. Brown

Figure 9: The optimal connectivity matrices $G_1^{BIC}$ and $G_2^{BIC}$, computed in the first and second parts of the recording session, respectively, are shown superimposed. The stars and the disks indicate the functional connections that were present only in the first and second parts of the session, respectively. The black squares show the functional connections that were present in both parts of the session. The diagonal entries represent the cells’ dependence on their own spiking activity history. The relative number of off-diagonal black squares measures the similarity of the optimal connectivity matrices among neurons in the two parts of the session.

parts of the session was highly significant ($p < 10^{-22}$). Table 1 shows the data used for this computation. In either case, the assumption that $p_0$ is the same in both parts of the session was not rejected on the basis of the observed numbers of off-diagonal connections ($\Pr(|m - E p_0| \geq |m_1 - m_2|/2) > 0.45$, where $m$ is the random variable that represents the number of off-diagonal connections).

As described above, we modeled the place cell firing as being solely dependent on the 30 ms history of the ensemble spiking activity. The KS plots in Figure 10 show how well this model fit the place cell spike trains. These plots are representative of the best and worst fits across all cells in both parts of the session. Essentially, none of the KS plots were within the 95% confidence intervals, except for a few cells that fired relatively low numbers of spikes and thus had wide confidence intervals. These plots indicate that the 30 ms history of the ensemble activity did not contain all the information that is needed to account for the activity of these cells under the model. To determine whether increasing the amount of data would improve the goodness-of-fit, we reanalyzed the data without splitting the recording
Table 1: Data Used in Computing the Significance of the Similarity Between the Optimal Connectivity Matrices in the Two Parts of the Recording Session.

<table>
<thead>
<tr>
<th>Connections (BIC)</th>
<th>Part I</th>
<th>Part II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Off-diagonal, $m_1$ and $m_2$</td>
<td>45</td>
<td>35</td>
</tr>
<tr>
<td>Common, $m_c$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total possible, $F$</td>
<td>$33 \times 32 = 1056$</td>
<td></td>
</tr>
<tr>
<td>Probability, $p_0$</td>
<td>$(45 + 35)/2/1056 = 0.0379$</td>
<td></td>
</tr>
<tr>
<td>$\Pr (S \geq m_c</td>
<td>p_0, F)$</td>
<td>$10^{-23.93}$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Connections (AIC)</th>
<th>Part I</th>
<th>Part II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Off-diagonal, $m_1$ and $m_2$</td>
<td>255</td>
<td>250</td>
</tr>
<tr>
<td>Common, $m_c$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability, $p_0$</td>
<td>$(255 + 250)/2/1056 = 0.2391$</td>
<td></td>
</tr>
<tr>
<td>$\Pr (S \geq m_c</td>
<td>p_0, F)$</td>
<td>$10^{-22.12}$</td>
</tr>
</tbody>
</table>

Notes: The entries in the upper part of the table (BIC) are obtained from Figure 9. $\Pr (S \geq m_c | p_0, F)$ is given by equation 3.3.

Figure 10: The KS plots for the place cell data. These plots are representative of the best and worst fits across all cells in both parts of the session. Essentially, none of the KS plots were within the 95% confidence intervals (dashed lines), except for a few cells that fired relatively low numbers of spikes and thus had wide confidence intervals.

We next explored whether a model with a longer history would fit the data better. Reanalyzing the data using a 120 ms history at $W=3$ ms resolution resulted in better KS plots. However, these plots also were not within the 95% confidence intervals. The interaction estimates obtained using this longer history revealed that significant interactions occurred first within the initial session into two parts. This is equivalent to doubling the recording period, relative to analyzing the data from each part separately. There were no noticeable improvements in the KS plots under these conditions. In other words, doubling the amount of data did not improve the goodness-of-fit.
30 ms and then again at the next cycle of the hippocampal theta rhythm (data not shown). This suggests that the model with the longer history fit the data better because it implicitly represented the dependence of the firing of the place cells on the phase of the hippocampal theta rhythm. The optimal connectivity matrices that were obtained using the model with the longer history were also significantly similar in the two parts of the session ($p < 10^{-14}$). The strongest modulator of the place cell firing is the position of the animal in the environment. We anticipate that a conditional intensity function that models the firing probability as a function of the ensemble spiking activity history, the theta rhythm, and the position of the animal would fit the data better.

We tested whether the interactions that underlie the optimal connectivity matrices were linked to the degree of overlap between the place fields of the cells. We modeled the place fields and computed their areas of overlap as follows. Each spike of a given cell is associated with a spatial point on the circular area, which represents the location of the animal at the time of that spike. We used the center of mass of these points as the center of that cell’s place field. Using the principal component analysis (Jolliffe, 1986), we computed the principal axes of the distribution of these points. We represented the place field using an ellipse whose major and minor axes were parallel to the principal axes. The lengths of the major and minor axes were proportional to twice the standard deviation of the data along the corresponding principal axes. We used proportionality constants of $\rho = 0.25, 0.5, 1, 2,$ and $3$ to try different place field sizes. The overlap between a pair of place fields was computed as the area of the intersection of the corresponding ellipses. Place fields were determined using the data from the entire recording session. Using this analysis, we found that the cell pairs that were part of the optimal connectivity matrices in both parts of the session had significantly larger areas of overlap between their place fields, compared to other cell pairs ($p < 0.005$; Wilcoxon rank sum test; Lehmann, 1975). This was true for all values of $\rho$ and for the optimal connectivity matrices found using AIC or BIC.

As part of the analysis of place cell ensemble spiking activity, we tested whether the starting vector given by equations 2.17 and 2.18 (reference vector) had any advantage over random vectors of comparable magnitude. For this, we reanalyzed the place cell data using random starting vectors that had 0.1, 1, and 10 times the magnitude of the reference vector. The components of the random vectors were uniformly distributed in $[10^{-10}, 1]$ prior to magnitude adjustment. We found that the algorithm took $10.70 \pm 1.36\%$, $9.79 \pm 1.38\%$, and $9.46 \pm 1.80\%$ more iterations to converge for the magnitude ratios of 0.1, 1, and 10, respectively (mean $\pm$ standard error of the mean (s.e.m.)); $n = 66$. Reference number of iterations: 109.94 $\pm$ 3.23. We also observed that the same ML estimate of the parameter vector was found for all random starting vectors for each cell. The average magnitude of the difference vectors between the ML estimate obtained using random starting
vectors and the reference ML estimate was $0.00312 \pm 0.00035\%$, $0.00314 \pm 0.00035\%$, and $0.00270 \pm 0.00032\%$ (mean $\pm$ s.e.m, in percentages of the magnitude of the reference ML estimate) for the above order of magnitude ratios. The average magnitude of the difference vectors between the random starting vectors and the reference vector was $96.08 \pm 0.12\%$, $106.06 \pm 1.11\%$, and $960.83 \pm 1.18\%$ (mean $\pm$ s.e.m, in percentages of the magnitude of the reference) for the same order of magnitude ratios. These results indicate that the algorithm converged to the same ML estimates starting from widely different initial conditions.

4 Discussion

Analyzing the functional interactions among multiple spike trains is an important and challenging problem in computational neuroscience. In this study, we examined certain computational properties of a maximum likelihood method and demonstrated its application to the analysis of functional interactions among simulated and real spike trains. The method estimates pair-wise interactions among neurons simultaneously by taking into account the activity of all neurons in the ensemble. It allows simultaneous estimation of a large number of interaction parameters by maximum likelihood. We demonstrated that the algorithm successfully recovered both inhibitory and excitatory interactions among simulated spike trains that had known interaction matrices (Figures 2 and 4–6). Our method of computing the optimal connectivity matrix recovered the true connectivity in all simulated networks. This method successfully distinguished between direct interaction (e.g., synaptic), indirect interaction (e.g., via an interneuron), and shared input. The connectivity of the simulated networks did not make it easier or favor the application of our algorithm in any way. The analysis suggests that whatever connectivity is in the underlying system, given the assumptions of the model, our method would have a high likelihood of identifying that connectivity. Further simulation and real data analysis studies will be needed to explore how the accuracy of the connectivity inference depends on the topology of the underlying network or the properties of the interaction functions.

We computed the auto- and cross-intensity function estimates of the simulated interactions and showed that they were significantly different from our estimates and the true interaction functions. By design, these methods are suitable for the analysis of two interdependent stationary spike trains that do not depend on other spike trains. In our simulations, each spike train depended on the history of at least three spike trains. As a result, the auto- and cross-intensity functions could not estimate the interactions accurately. Statistical dependency of one spike train on multiple spike trains is common in real data. Figure 9 shows that the activity of certain place cells depended on up to five spike trains simultaneously (e.g., cells 6 and
This underlines the importance of using methods that analyze multiple interactions simultaneously.

Existing methods for the simultaneous analysis of multiple spike trains include the gravitational clustering algorithm (Gerstein & Aertsen, 1985; Gerstein et al., 1985; Baker & Gerstein, 2000) and spike pattern classification methods (Abeles & Gerstein, 1988; Louie & Wilson, 2001; Pipa & Grün, 2003; Lee & Wilson, 2004). The gravitational clustering algorithm is useful for detecting synchronous cell assemblies. It can also be used to infer connectivity diagrams among a group of neurons using graphical methods (Gerstein & Aertsen, 1985). The significance of the clusters is determined using Monte Carlo methods (Baker & Gerstein, 2000). Spike pattern classification methods are useful for detecting precise spatiotemporal firing patterns (Abeles & Gerstein, 1988; Pipa & Grün, 2003), or searching for a particular sequential firing pattern within the ensemble spiking activity (Louie & Wilson, 2001; Lee & Wilson, 2004). The detection of precise spatiotemporal firing patterns involves the delicate statistical issue of formulating an appropriate null hypothesis to determine the correct significance level for the detected patterns. In some applications, the usual null hypothesis of inhomogeneous Poisson spike counts has been shown to overestimate the significance of the observed patterns when the actual spike count distributions differed from the Poisson distribution by even small amounts (Oram, Wiener, Lestienne, & Richmond, 1999). Combinatorial methods that search for a particular sequential firing pattern within the ensemble spiking activity are useful in applications where such an activity pattern is expected due to the design of the experiment (Louie & Wilson, 2001; Lee & Wilson, 2002), but may not be particularly useful in applications such as our place cell analysis where no particular sequential firing pattern is expected a priori. However, these methods can be used in combination with our method to test hypotheses of sequential firing that are suggested by the optimal networks. Our method provides an alternative approach for the simultaneous analysis of multiple spike trains. We construct a network likelihood model, which is a joint likelihood model for all pair-wise interactions among an ensemble of neurons. We compute the ML estimate of all interaction parameters simultaneously. The use of the likelihood is an optimal way of analyzing the data generated by a process if the probability model used in the ML method is a good approximation to that process (Pawitan, 2001).

We determined the optimal order of the network model by minimizing the AIC or the BIC. In the present application, this procedure determines the optimal number and configuration of the functional connections within the ensemble, given the assumptions of the method. These connections may reflect direct or indirect interactions among neurons (effective connectivity; Aertsen & Preissl, 1991; Friston, Frith, Liddle, & Frackowiak, 1993; Lee, Harrison, & Mechelli, 2003), as well as shared inputs to the recorded neurons from sources that are not represented in the network model. Distinguishing direct interaction from shared input is a long-standing problem in
connectivity analysis. Methods that have been used to make this inference for neuron pairs or triplets include the JPSTH (Aertsen et al., 1989), conditional cross-correlogram (Eggermont, 1991), partial coherence (Brillinger, 1976b, 1992), and ML methods (Borisyuk et al., 1985; Brillinger, 1988a, 1988b; Chornoboy et al., 1988). Our simulation results showed that our method could make this inference accurately if the network model is a close approximation to the true network underlying the data. In cases where such close approximations are not achieved, as may be indicated by a poor KS plot, the possibility that some of the inferred connections are due to shared inputs may not be ruled out.

In our analysis of the place cell data, we observed that the functional connectivity matrix of the place cells was significantly stable throughout the recording session (Figure 9 and Table 1). This stability is consistent with the facts that the place fields of CA1 place cells that are active in a familiar environment are stable throughout a given session, and over several days (Muller, Kubie, & Ranck, 1987; Wilson and McNaughton, 1993; Barnes, Suster, Shen, & McNaughton, 1997), and that cells with overlapping place fields exhibit correlated activity (Wilson & McNaughton, 1994; Skaggs & McNaughton, 1996, 1998). Indeed, we found that the place fields of the cell pairs that were part of the optimal connectivity matrices throughout the session had significantly larger overlaps compared to other cell pairs \( (p < 0.005) \). The significance of this relationship increased with increasing spatial selectivity of the place fields \( (p < 1.7 \times 10^{-9} \text{ for } \rho = 0.25) \). In analyzing the ensemble spiking activity, we explicitly ignored that the neurons have overlapping place fields. These results indicate that neurons that were found to be functionally connected corresponded to neurons that had overlapping place fields.

In this analysis, we have assumed that spikes have been sorted properly. The effect of improper spike sorting could significantly alter the results. We have discussed in detail the implications of correct spike sorting and the importance of developing algorithms to conduct spike sorting in a previous publication (Brown et al., 2004). As is the case with all single unit analyses, we are able to perform the analysis using the spike trains only from the neurons that are observed. The particular functional networks that we inferred from the data may change if cells are added to or removed from the ensemble. The results suggest that the new functional networks would be related to the overlaps of the place fields of the cells in the new ensembles and that they would be significantly stable throughout the session.

Several extensions of this work are possible. First, the derivation of the network likelihood model relies on the assumption that neurons do not fire simultaneous spikes. We will formulate a likelihood model that relaxes this assumption. Second, the activity of the place cells is modulated by covariates such as the animal’s velocity and the hippocampal theta rhythm in addition to position (McNaughton, Barnes, & O’Keefe, 1983; O’Keefe & Recce, 1993). We will construct more comprehensive place cell models that
incorporate these covariates explicitly into the model. Such models could be useful in spike train decoding applications. We found that including the network model in equation 2.2 into a place cell model similar to those used by Brown et al. (1998) and Barbieri et al. (2004) resulted in a smaller decoding error (unpublished result). Third, as in Wilson and McNaughton (1994), we plan to analyze the connectivity matrix of place cells during behavior and sleep episodes to study the reactivation of ensemble memories during sleep. Finally, we also see potential application of our methods to the analysis of ensemble spiking activity in cortical areas MI and 5d during reaching behavior in macaque monkey (Truccolo, Fellows, Eden, Brown & Donoghue, 2004). Precise time evolution of the functional interactions between these areas can be determined by analyzing large ensembles using our method.

In conclusion, we believe that the methods that we presented here may serve as fast and efficient tools that can be used to analyze the activity of a large number of neurons simultaneously. Such analyses are important for studying how the nervous system encodes information within the concerted activity of ensembles of neurons.

Appendix: Formulation of the Starting Vector and the Stopping Rule

We first derive a necessary condition that the solution vector satisfies. We then use this condition to solve for the maximum likelihood estimates under some simplifying assumptions and use this solution as the starting vector of the iteration. The log-likelihood function of \( \gamma_i = [\exp(\alpha_{i,j})] \) is obtained from equation 2.11:

\[
\begin{align*}
I_T(\gamma_i) &= \int_0^T \left( \sum_{j=0}^D \log(\gamma_{i,j}) I_j(u) \right) dN_i(u) \\
&+ \int_0^T \left[ 1 - \prod_{j=0}^D (\gamma_{i,j})^{I_j(\omega)} \right] du. 
\end{align*}
\]  

(A.1)

Since the vector \( \gamma_i \) is nonnegative, the maximization of \( I_T(\gamma_i) \) with respect to \( \gamma_i \) is a constrained optimization problem. Under this constraint, a parameter vector \( \hat{\gamma}_i \) is a ML estimate of \( \gamma_i \) if it satisfies the Kuhn-Tucker conditions (see Luenberger, 1984):

\[
\frac{\partial I_T(\gamma_i)}{\partial \gamma_{i,j}} \bigg|_{\hat{\gamma}_i} \leq 0, \quad \hat{\gamma}_{i,j} \geq 0, \quad \gamma_{i,j} \frac{\partial I_T(\gamma_i)}{\partial \gamma_{i,j}} \bigg|_{\hat{\gamma}_i} = 0, \quad 0 \leq j \leq D. 
\]  

(A.2)
Taking the partial derivative of the log-likelihood function with respect to the components of $\gamma_i$ we obtain

$$\frac{\partial l_T(\gamma_i)}{\partial \gamma_i} = \frac{1}{\gamma_i} \left\{ \int_0^T I_j(u)dN_i(u) - \int_0^T I_j(u) \left[ \prod_{l=0}^D (\gamma_{i,l})^{l(u)} \right] du \right\}. \quad (A.3)$$

We are interested in solutions where $\hat{\gamma}_{i,j} > 0$ for all $j$. For those solutions, the condition (A.2) yields $\frac{\partial l_T(\gamma_i)}{\partial \gamma_i} = 0$. Applying this to equation (A.3) and rearranging the terms, we obtain

$$\frac{\int_0^T I_j(u)dN_i(u)}{\int_0^T I_j(u) \left[ \prod_{l=0}^D (\hat{\gamma}_{i,l})^{l(u)} \right] du} = 1. \quad (A.4)$$

This equation gives the relationship between the components of the ML estimate $\hat{\gamma}_i$ and can be used to compute approximate values for these components. To do this, we first compute the integrals in equation (A.4) using finite differences as in equation 2.12:

$$\frac{\sum_{k=0}^{K-1} I_{j,k} N_{i,k,k+1}}{\sum_{k=0}^{K-1} I_{j,k} \left[ \prod_{l=0}^D (\hat{\gamma}_{i,l})^{l_{i,k}} \right] \Delta} = 1. \quad (A.5)$$

For $j > 0$, we assume that the model consists of only the parameters $\gamma_{i,j}$ and $\gamma_{i,0}$ and set the other parameters to 1. Denoting the ML estimates of $\gamma_{i,j}$ and $\gamma_{i,0}$ under these conditions by $\gamma^{(1)}_{i,j}$ and $\gamma^{(1)}_{i,0}$, respectively, equation (A.5) gives the following equations corresponding to these estimates,

$$\frac{\sum_{k=0}^{K-1} I_{j,k} N_{i,k,k+1}}{\hat{\gamma}_{i,0} \sum_{k=0}^{K-1} I_{j,k} \left( \gamma^{(1)}_{i,j} \right)^{l_{i,k}} \Delta} = 1, \quad \frac{\sum_{k=0}^{K-1} N_{i,k,k+1}}{\hat{\gamma}_{i,0} \sum_{k=0}^{K-1} \left( \gamma^{(1)}_{i,j} \right)^{l_{i,k}} \Delta} = 1. \quad (A.6)$$

where we have used the fact that $I_{0,k} = 1$ for all $k$. The covariates $I_{j,0}$ are integer valued since they represent spike counts. Therefore, the denominators of these equations are polynomial functions of $\gamma^{(1)}_{i,j}$ and $\gamma^{(1)}_{i,0}$. Isolating $\gamma^{(1)}_{i,j}$ in these equations gives equation 2.17. For $j = 0$, we assume that the model consists of only the parameter $\gamma_{i,0}$ and set the other parameters to 1. Denoting the ML estimate of $\gamma_{i,0}$ under these conditions by $\gamma^{(1)}_{i,0}$, equation (A.5) gives equation 2.18, which is simply the average firing rate.

In other applications, the conditional intensity function may include continuous-valued covariates. The above method can also be used in those cases after discretizing such covariates. This discretization is necessary only for the computation of the starting vector. The original, continuous-valued covariates may be used in equations 2.14 to 2.16 without discretization.
We obtained the relationship between the stopping threshold $\theta$ and the change in the log likelihood using the following approximation. The log-likelihood difference $l_T(\gamma_i^{(n+1)}) - l_T(\gamma_i^{(n)})$ can be approximated by the following formula near the ML estimate, where the magnitude of the difference vector $\gamma_i^{(n+1)} - \gamma_i^{(n)}$ is sufficiently small,

$$l_T\left(\gamma_i^{(n+1)}\right) - l_T\left(\gamma_i^{(n)}\right) \approx \sum_{j=0}^{D} \left( \frac{\partial l_T(\gamma_i)}{\partial \gamma_i,j} \right) \left( \gamma_i^{(n+1)} - \gamma_i^{(n)} \right) \cdot \left( \gamma_i^{(n+1)} - \gamma_i^{(n)} \right),$$  
(A.7)

which gives

$$l_T\left(\gamma_i^{(n+1)}\right) - l_T\left(\gamma_i^{(n)}\right) \approx \sum_{j=0}^{D} \frac{\left( \gamma_i^{(n+1)} - \gamma_i^{(n)} \right)^2}{\partial \gamma_i,j} \cdot \sum_{i=0}^{L} l_i(u) \left[ \sum_{i=0}^{D} l_i(u) \right] dN_i(u) \leq (\delta \gamma_i,n)^2 \Omega, \quad (A.8)$$

where $\Omega = \sum_{j=0}^{D} \sum_{i=0}^{D} l_j(u) l_i(u) dN_i(u)$ and $\delta \gamma_i,n$ is given by equation 2.19. Therefore, when the iteration is stopped using the rule $\delta \gamma_i,n < \theta$, the change in the log likelihood is around $\theta^2 \Omega$.

A.1 Computing an Optimal Connectivity Matrix. We use the network log-likelihood function in equation 2.6 to find parameter vectors $\alpha^{AIC}_{i:C}$ and $\alpha^{BIC}_{i:C}$ that minimize the AIC and the BIC, respectively. For $1 \leq i, c \leq C$, define the sets

$$A_{i:C} = \{ \alpha_{1:C} = [\alpha_1, \alpha_2, \ldots, \alpha_C] \in \mathbb{R}^{1 \times (D+1)C} \}$$
$$\alpha_{i,j} = 0, \quad (c - 1)M + 1 \leq j \leq cM. \quad (A.9)$$

Here, $\alpha_i$, $1 \leq i \leq C$, is given by equation 2.10. The elements of the set $A_{i:C}$ specify networks in which the connection from neuron $c$ to neuron $i$ is absent. For large $T$, the likelihood ratio statistic $2[l_T(\hat{\alpha}_{1:C}) - \max_{\alpha_{1:C} \in A_{i:C}} l_T(\alpha_{1:C})]$ has a chi-squared distribution with $M$ degrees of freedom. Here $\hat{\alpha}_{1:C}$ is the ML estimate of the unconstrained parameter vector. The vector $\arg \max_{\alpha_{1:C} \in A_{i:C}} l_T(\alpha_{1:C})$ is the ML estimate of the constrained parameter vector and is computed using equations 2.14 to 2.16. The projection of $\hat{\alpha}_{1:C}$ into $A_{i:C}$ is used as the starting vector for the iteration. For $1 \leq i, c \leq C$, we compute the significance level $\sigma_{i:C}$ of the likelihood ratio statistic. Define the set $B = \{ 0, 1, \sigma_{i:C} | 1 \leq i, c \leq C \}$. We choose a variable threshold $\beta \in B$ and define the set

$$\Gamma_\beta = \{ \alpha_{1:C} \in \mathbb{R}^{1 \times (D+1)C} \}$$
$$\alpha_{i,j} = 0, \quad (c - 1)M + 1 \leq j \leq cM, \quad \sigma_{i:C} > \beta, \quad 1 \leq i, c \leq C. \quad (A.10)$$
The elements of the set $\Gamma_\beta$ specify networks in which connections whose significance is lower than $\beta$ are absent. For $\alpha_{1:C} \in \Gamma_\beta$, the AIC and the BIC are computed using the following equations,

\[
AIC_\beta = -2 \max_{\alpha_{1:C} \in \Gamma_\beta} (l_T (\alpha_{1:C})) + 2 \left[ (D + 1)C - M \sum_{i=1}^C \sum_{c=1}^C \psi_\beta (\sigma_{ic}) \right],
\]

(A.11)

\[
BIC_\beta = -2 \max_{\alpha_{1:C} \in \Gamma_\beta} (l_T (\alpha_{1:C}))
+ \left[ (D + 1)C - M \sum_{i=1}^C \sum_{c=1}^C \psi_\beta (\sigma_{ic}) \right] \log \left( \sum_{c=1}^C N_c (T) \right),
\]

(A.12)

where

\[
\psi_\beta (\sigma_{ic}) = \begin{cases} 
1, & \sigma_{ic} > \beta \\
0, & \text{otherwise}
\end{cases}
\]

(A.13)

This function indicates whether the connection from neuron $c$ to neuron $i$ is discarded from the model at threshold $\beta$. Finally, we define the set $\Gamma_B = \bigcup_{\beta \in B} \Gamma_\beta$. Then the vector $\alpha_{1:C} \in \Gamma_B$ that minimizes the AIC (BIC) is the optimal parameter vector $\alpha_{1:C}^{AIC} (\alpha_{1:C}^{BIC})$. The vector $\alpha_{1:C}^{AIC} (\alpha_{1:C}^{BIC})$ implies an optimal connectivity matrix $G_{AIC} (G_{BIC})$. Let $\beta \in B$ be the threshold that minimizes the AIC. Then the optimal connectivity matrix $G_{AIC}$ is defined by

\[
(G_{AIC})_{ic} = 1 - \psi_\beta (\sigma_{ic}).
\]

(A.14)

$G_{BIC}$ is defined similarly. In this way, these matrices indicate which connections are kept in the model after identifying the optimal order of the model.

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