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Multi-neuronal activity and functional connectivity in cell assemblies

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Our ability to collect large amounts of data from many cells has been paralleled by the development of powerful statistical models for extracting information from this data. Here we discuss how the activity of cell assemblies can be analyzed using these models, focusing on the generalized linear models and the maximum entropy models and describing a number of recent studies that employ these tools for analyzing multi-neuronal activity. We show results from simulations comparing inferred functional connectivity, pairwise correlations and the real synaptic connections in simulated networks demonstrating the power of statistical models in inferring functional connectivity. Further development of network reconstruction techniques based on statistical models should lead to more powerful methods of understanding functional anatomy of cell assemblies.

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Introduction

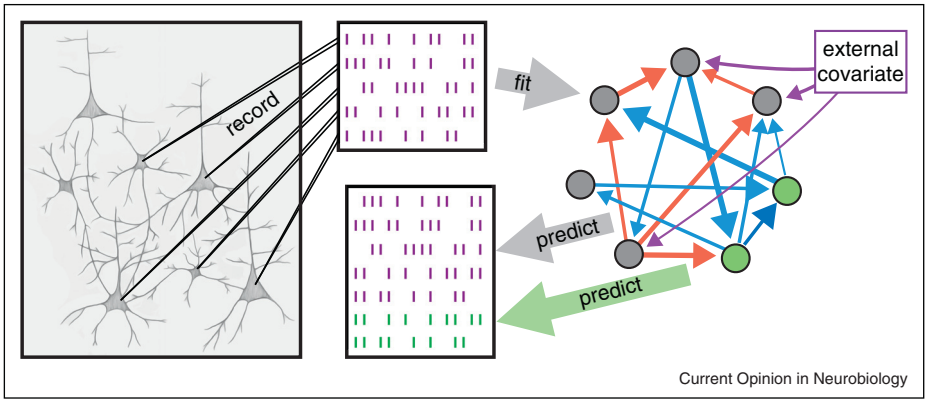
In lower species, single neurons or small circuits with stereotyped connectivity patterns are studied as computational building blocks of the nervous system. In higher species, such as mammals, on the other hand, populations of neurons, or cell assemblies, are probably the closest thing to a computational unit [1]. A familiar example is the Hebbian cell assembly [2]: a group of neurons with stronger connections between the cells within the group than with other cells. The stronger connections between the neurons in the Hebbian assembly leads to the attractor dynamics that is believed to underlie a variety of neuronal computations [3]. Other examples of cell assemblies include groups of neurons that share functional similarities, such as color, form and motion selective cells in primary visual areas [4], or the barrels in the rat barrel cortex [5]. Functional cells assemblies also exist in higher cortical areas. An example is that of grid cells in the medial entorhinal cortex [6]. As an animal runs in a two-dimensional environment, each grid cell fires maximally at locations that form a hexagonal pattern. Grid cells form a functional cell assembly and are coupled to cells in the same anatomical location that belong to other assemblies, for example, border cells [7] and head directional cells [8]. To understand computation in the mammalian nervous system, one has to characterize these assemblies and their relationship to each other and to identify the anatomical and molecular features associated with specific assemblies.

Although the theoretical concept of cell assemblies is not new, tools for analyzing them have only recently emerged in systems neuroscience. Experimentalists can now record the activity of many cells at the same time, and the spatial and temporal resolution with which these recordings can be done is increasing rapidly [9,10]. With new recording technology, even areas previously inaccessible to simultaneous multi-cell recording are becoming available. In addition, optogenetic [11] and other molecular and genetic techniques [12,13] now allow experimentalists to stimulate specific kinds of cells during their recordings. All these advances have shifted the focus of efforts to understand neural computation from single-neuron recordings to simultaneous recordings of many neurons. In parallel, there has been significant progress on theoretical and computational tools for analyzing such recordings. Although, so far, these methods have been applied almost exclusively to data from sensory or motor areas, we can anticipate their exploitation in higher cortical areas, leading to new ways of thinking about information processing at the population level. In this paper, we review the main modern approaches for modeling multi-unit recordings and discuss future avenues that can be explored using these methods.

Statistical modeling

Understanding a complex system is achieved through models, and the high variability of neuronal data requires that these models be statistical ones. Here, we describe how to build statistical models of multi-neuronal activity and show, using several examples, how they can help us understand the computational and physiological properties of cells assemblies, as well as the relationship between them.

Figure 1



Using spike trains recorded from neurons in a population (upper middle panel), one can learn a statistical model and the functional or effective connections (arrows in the right panel) between neurons (circles in the right panel) and between neurons and external factors that may influence the neuronal spike trains. This process can also include learning and inference of hidden variables, for example, unrecorded neurons (green circle in the right panel). The functional connections do not in general correspond to actual physical connections, though in some cases they may be very informative the presence or absence of connections [15,16•]; see also Figure 2. The inferred model can be used, for example, to generate synthetic data (lower middle panel) or to assign quantitative values for external covariates in explaining the data.

A statistical model is based on an assumed, parameterized form of some distribution, and its parameters are found by maximizing the likelihood of the data, that is, finding which model, among all those obtained by varying the parameters, is most likely to have generated the available data. The data we are thinking of here — spike trains, calcium imaging data, local field potential signals, or combinations of these — are very high-dimensional. Nevertheless, conceptually, this problem is no more abstract than the elementary one of fitting a Gaussian distribution to a set of measurements of a single variable. It is just of higher dimensionality (and technical issues therefore arise in making the fit), because the models have many parameters. Whatever the method for fitting the model, the outcome of this process is a statistical model with a set of functional connections (described in more details in the next section) which can be used for network reconstruction, generating synthetic data and/or assigning quantitative values to the role of unrecorded (hidden) neurons or external covariates in shaping multi-neuronal activity; see Figure 1.

Of course, there are many statistical models one can fit to data, and the choice of the model depends largely on the goal of the modeling effort and the available data. Common choices usually rely on prominent physiological features, such as the fact that single neurons usually integrate the input they receive over tens of ms, theoretical concepts such as the maximum entropy principle [14], or a combination of these. We will focus on two classes of models: so-called generalized linear models (henceforth abbreviated GLMs), and maximum-entropy (abbreviated max-ent) models. We describe their main features here; more details and key equations can be found in the accompanying Box 1.

GLMs assume that every neuron spikes at a time-varying rate which depends on earlier spikes (both those of other neurons and its own) and on 'external covariates' (such as a stimulus or other quantities measured in the experiment). The influence of earlier spikes on the firing probability at a given time is assumed to depend on the time since they occurred. For each 'pre-postsynaptic' pair i, j, it is described by a function $J_{ij}(\tau)$ of this time lag. In addition, there are more functions describing the effects of the external covariates. To fit the model, then, one finds those functions, out of all possible ones satisfying some reasonable smoothness constraints, for which the actual recorded spike history has the highest probability [17–19].

Statistical models of the max-ent type are different: One does not consider the likelihood of the recorded history. Rather, one takes, as the data, the set of observed simultaneous (i.e. within a single time bin) spike patterns, without regard to their temporal order. One then finds the distribution, within the class of distributions that have maximum entropy, given (for example) the measured firing rates and pairwise correlations [20–22], that maximizes the likelihood of finding these patterns. The reason for choosing the estimated distribution among the maximum-entropy class, is that this procedure, uniquely, makes minimal assumptions about the distribution of patterns (see Box 1).

Thus, one can say loosely that GLMs focus on predicting future spikes of a given neuron from past spikes of all neurons, while max-ent models aim at predicting spikes of a given neuron from the spike pattern of other neurons at the same time. Regardless of the chosen model, with the increasing availability of large data sets we are able to

Box 1 Two kinds of statistical models

Generalized linear models

A GLM assumes that a neuron spikes at a rate given by a nonlinear function $g()$ of an input that depends on past spikes, both its own and those of other neurons, and on some external covariates, such as the stimulus. Most frequently, the function $g()$ is taken to be an exponential or a logistic sigmoid, $1/(1+e^{-x})$. Usually the input (i.e. the argument of $g()$) is assumed to have the form

$$V_i(t) = b_i(t) + \sum_j \sum_m J_{ij}(t - t_j^m), \tag{1}$$

where t_j^m is the time of the mth spike of neuron j. The parameters of the model are $b_i(t)$, which represents the effects of the external covariates, and the kernels $J_{ij}(\tau)$, which represent the effect of a spike by neuron j on the spiking of neuron i a time τ later. Here, the effect of all the past spikes are assumed independent and are just added up. One could also assume more complicated dependences on previous spikes; for example, the effect of a pair of spikes might depend on their relative timing. This could be represented by adding a term like

$$\sum_{jk} \sum_{mn} K_{ijk}(t - t_j^m, t_j^m - t_k^n) \tag{2}$$

to $V_i(t)$ (it is still a GLM as long as $V_i(t)$ is a linear function of its parameters), but we will restrict our attention here to the simple form above.

Maximum-entropy models

Very frequently, one wants to estimate (or to 'model') a probability distribution for some variable in an unbiased way, that is, making no implicit assumptions beyond what is known from the data. In information theory, the entropy of a distribution, $-\sum_x p(x) \log p(x)$, where $p(x)$ is the probability that the variable takes the value x, quantifies the ignorance about the variable [48,49]. Thus, making no assumptions about the distribution corresponds to maximizing the entropy. If we know something about the statistics of the variable, the maximization has to be done subject to a corresponding constraint. As a simple example, suppose we know nothing about the distribution of some positive random variable except its mean. Then it turns out that maximizing the entropy of its distribution among all distributions with that mean (this is just a few lines of algebra), leads to the result that the distribution must be a decreasing exponential function (see, e.g. [14]). This is the principle behind max-ent models for neural data. Before constructing such a model, spike train data has to be binned in time. The data are then represented by a binary array $\{S_{it}\}$, where $S_{it} = 1$ if neuron i spikes in time bin t and $S_{it} = 0$ otherwise. From them, one computes the empirical spike rates and pair averages (spike coincidence rates) $\langle S_{it}\rangle_t$ and $\langle S_{it}S_{jt}\rangle_t$, where the subscript t means that the averages are over all the time bins. Of all models for the distribution $P[\{S_i\}]$ of spike patterns within a time bin, the one with the largest entropy is

$$P[\{S_i\}] = \frac{1}{Z}\exp(-E[\{S_i\}]) = \frac{1}{Z}\exp\left(\sum_i b_i S_i + \sum_{i<j} J_{ij} S_i S_j\right), \tag{3}$$

where Z is a normalisation constant chosen to ensure that the sum of $P[\{S_i\}]$ over all patterns $\{S_i\}$ is 1. Its parameters, b_i and J_{ij}, are then chosen so that the averages $\langle S_{it}\rangle$ and $\langle S_{it}S_{jt}\rangle$ over this distribution match the empirical ones from the data. Models like this appear frequently in statistical mechanics, where the function $E[\{S_i\}]$ is identified with the energy of the system.

If higher-order empirical statistics like 3-neuron coincidence rates $\langle S_{it}S_{jt}S_{kt}\rangle_t$ are available, one can generalize the model, adding terms in the argument of the exponential function proportional to $S_iS_jS_k$, etc. Usually the data are insufficient to permit accurate enough estimates of these statistics, so in practice this is seldom done. However, frequently one has reliable statistics on higher moments of the *average* (over neurons) of the firing rates, in which case one can include terms proportional to $(\sum_i S_i)^n$ in the energy. In the text we discuss an application of such a model [36•].

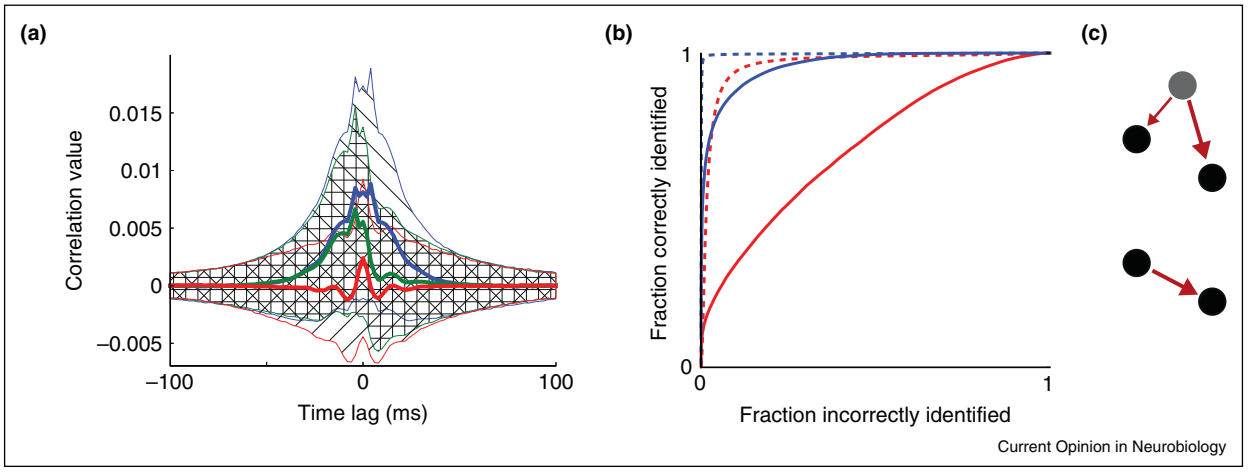
use these models to ask more and more interesting questions about the networks generating the data, as described in the following sections.

Effective models and functional connections

In both kinds of models, some of the parameters (the J_{ij}s) describe interactions between neurons within the terms of the fitted models and, thus, lend themselves to interpretation as some form of connectivity parameters in the network. These connections are 'effective' or 'functional' connection parameters: They describe how one neuron influences another *within the terms of a model*.[4] The use of the term 'functional connection' is not new. However, traditionally, functional connections have been identified directly from pairwise correlations. There is no model, just the data. And while interesting results can sometimes be found from direct inspection of the data, correlation measurements in a large, strongly interacting system can be misleading. In some multi-unit recording studies, statistically significant peaked pairwise correlations at short time lags are interpreted as functional or even synaptic connections [26–28]. However, it is quite possible that, even at short timescales, peaks in pairwise correlations are network effects involving many other neurons and external drives [23]. This effect is illustrated Figure 2, where pairwise cross-correlograms for connected and disconnected pairs in a cortical simulated network are shown. On average, for unidirectionally connected pairs there is a peak at positive time lag and for bidirectionally connected pairs there are two peaks, one at positive and one at negative lag. However, the fluctuations around this mean are large, so relying on the peak in the cross-correlagram to detect connections may lead to big errors. Furthermore, strongly peaked correlations can

[4] As opposed to the functional imaging literature where functional connections are taken to be the same as correlations, while effective connections are those inferred using more sophisticated approaches [25•], here we use functional and effective connections interchangeably, as something to be inferred from the data about the network.

Figure 2



(a) Cross-correlograms between pairs of unidirectionally connected (green), bidirectionally connected (blue) and disconnected (red) neurons for simulated cortical data. The solid curves shows means of cross-correlations over 1000 pairs of neurons, while the hatched areas show the standard deviations around these means. **(b)** The receiver operating characteristic (ROC) curves for the inferred excitatory (red) and inhibitory (blue) connectivity using both the kinetic Ising model (dashed line) as well as cross-correlations (solid line). For the cross-correlations analysis, an excitatory/inhibitory connection was assigned if the *z*-score at the peak on interval of [0, 6] ms was above/below a passing threshold (*z*-score = [−5, 10]/[−10, 5]). A data set of 66.5 min was recorded from a network [23] of 2000 spiking neurons of which 1000 were used in the reconstruction. The *z*-score was calculated with the background ([−50, 0] ms) mean and standard deviation for each pair. For the kinetic Ising model, the data were partitioned into 6ms bins and was fit using the exact mean field equations [24]. The excitatory/inhibitory connections were identified using a moving threshold from four standard deviations above/below the mean to four standard deviations below/above. **(c)** By considering only correlations between pairs of neurons (the black circles, top panel) that receive common input from a third one (gray circle, top panel), the cross-correlation analysis can incorrectly assign a connection between them and mistake the architecture in the top for that in the bottom. A GLM, however, is equipped to 'explain away' the correlation as coming from a common input, which could also be from the external covariates or even hidden neurons in addition to other recorded neurons.

be the result of various common external inputs whose effects cannot be quantitatively taken into account in correlation analyses. To understand such effects, one needs models, like those we describe here, where the whole recorded population is taken into account, external covariates can be included in a controlled way, and statistical significance can be evaluated systematically. Assuming the correct level of sparsity, even the simplest possible model of this type (the kinetic Ising model) could correctly identify 94% of the inhibitory connections and 62% of the excitatory ones in a model cortical network (Figure 2b). By contrast, using the cross-correlation analysis only 68% and 22% of the inhibitory and excitatory connections, respectively, could be correctly identified.

The relation between the functional connections inferred using multi-unit recordings and the actual synaptic connectivity pattern is a nontrivial one. Two recent simulation studies on biologically realistic cortical models show that the functional connections inferred using simple statistical models may be used for network reconstruction, that is, to identify connected versus disconnected pairs [15,16•]. How these results extend to real neuronal networks remains to be seen and requires applying the methods to multi-unit neuronal recordings where the actual synaptic contacts are known. In any case, regardless of the relationship between the functional connections and synaptic connectivity patterns, some features of these inferred connections may be robust to various changes in the model and the data, thus signaling crucial features of the neuronal systems that generated the observed spike trains.

Using a kinetic Ising model (a simplified GLM with limited temporal memory), Dunn *et al.* [29•] showed that inferred functional connections between grid cells exhibit a systematic dependence on 'phase', that is, the relative positions of their grids: Cells with nearby phases have positive functional connection strengths, while those further apart have negative ones. This feature is stable even when confounding factors that can cause correlations, for example, overlap of the firing fields, theta oscillations, and head directional input, are taken into account. Since attractor models of grid cells [30–33] rely heavily on this type of effective connectivity, this work provides support for the idea of attractor dynamics in the grid cell assembly.

In another study, using *in vivo* spike-triggered stimulation, Rebesco *et al.* [34] induced plastic changes in rat forelimb sensorimotor cortex. These changes were

reflected in altered functional connectivity in the GLMs that they fit to the data before and after the induced changes. Furthermore, these changes depended on the timing of the spikes. This study thus goes beyond typical pairwise stimulation studies, monitoring plasticity and its dependence on the spike timing at the network level.

Beyond functional connections

In addition to inferring functional connections, statistical models can be used to investigate a number of other aspects of networks. For example, they allow us to quantify the importance of various external factors in shaping the neuronal activity. The power of this approach, compared to mechanistic or normative models of neural information processing, is illustrated nicely in a recent paper by Park *et al.* [35••]. Applying the framework of GLMs to multi-unit recordings from lateral intraparietal area (LIP), these authors show that the responses of neurons there encode not only accumulation of evidence in a decision making task, but also a number of task-related signals.

Max-ent models afford another avenue for probing and characterizing networks, because they are equivalent to the Ising model used extensively to describe cooperative systems in physics. One can then apply the formalism of statistical mechanics and ask about their thermodynamic properties. Pursuing this approach, Tkacik *et al.* [36•], building on previous work by Mora and Bialek [37], fit a max-ent model to data from 160 retinal ganglion cells in a salamander retina. They calculated, for the resulting model, the entropy $S(E)$, the logarithm of the number of firing patterns at energy E, with a simple, striking result: $S(E) = E$. This purely linear dependence is highly unusual and interesting. In normal equilibrium physical systems, $S(E)$ is curved upwards ($d^2S/dE^2 > 0$) except for special combinations of values of their parameters. These are 'critical points', where, in equilibrium statistical physics, correlations between the nodes in the system are singularly strong. Thus, these authors identified the recorded network as in a 'critical' state. Marsili and Mastromatteo [38] have argued that such critical states can be a general consequence of the inference procedure in the sense that inference from any informative dataset will, with high probability, lead to critical models.

The approach of Tkacik *et al.* [36•] does not aim at explaining the source of these correlations, but this question is in any case an interesting and important one. The property $S(E) = E$ can be shown to imply Zipf's law for the observed spike patterns: If they are ordered by their frequencies in the data, the frequency is inversely proportional to rank. Focusing on this feature of the data, two recent studies, Schwab *et al.* [39•] and Aitchison *et al.* [40•], argue that in the equilibrium models, Zipf's law can be explained by the presence of correlated external input to neurons and not internal couplings. Although, from a purely algebraic point of view, an equilibrium max-ent model with couplings can be mapped to one without couplings but with probabilistic external inputs, the number of parameters required for describing the external input that gives rise to the Zipf's law can be lower than that of the connectivity. In another recent study, Tyrcha *et al.* [41•] compared the likelihood of the data recorded from retinal ganglion cells under a max-ent model with that under a kinetic Ising model subject to time-varying external fields. They found that, when corrected for the number of parameters, the kinetic model with external input outperformed the max-ent one in explaining the data and also exhibited the Zipf's law.

What to do next: the dark side of the network

A less developed yet very important feature of statistical approaches to studying cells assemblies is that they can allow inclusion of hidden parts of the network in statistical data analysis. Even with the most advanced population recording techniques, a significant fraction of neurons in an assembly of interest will not be recorded, and functional connections inferred using a given recorded population might have been different if the model could have taken into account some of the unrecorded neurons. For instance, one might have inferred a strong connectivity between some pair of cells, when really they just shared appropriately timed common input from unrecorded neurons. Furthermore, the model may be unable to characterize the neuronal response under new conditions, due to the fact that the hidden part of the network is not taken into account.

Kulkarni and Paninski [42] formulated an approach to this problem in which all the information from hidden causes was encoded in the form of a multivariate Gaussian process whose parameters were inferred by maximizing the likelihood of the data. Analyzing data from the retinal ganglion cells this way, they and their collaborators [43] found that the common input included in this way can describe the data at least as well as a model without the common input but with internal connectivity between neurons. In other work, a max-ent model was fit to data from a subset of the nodes in a simulated balanced network of Hodgkin-Huxley neurons. It was shown that the main qualitative effect of the hidden nodes was to change the magnitude of the inferred couplings, but not their overall structure [44]. To a large extent, this result stems from the mean-field structure of the balanced network, in which the effect of adding extra units is to effectively change all the correlations between cells in a largely similar way. Consequently, this result may not hold, for example, in an architecture where a hidden node acts as a hub in the network.

Recently, a number of studies have tried to address the problem of hidden nodes explicitly using the framework of the Kinetic Ising model. Two of them have addressed

the question of inferring connections in networks with hidden nodes using mean field methods [45,46], while another one has focused on the properties of Bayes optimal inference of hidden states in such networks [47••]. A number of interesting theoretical issues are open with this problem, including the exactness of mean-field approaches and from a more practical side, how to include priors over the structure of the hidden part. These methods have not yet been applied to neural data sets, but we believe such applications may lead to interesting results and insights into the dynamics of cell assemblies.

Conflict of interest statement

Nothing declared.

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Algorithms for learning the parameters of statistical models with hidden nodes usually take the form of expectation-maximization, where at the expectation step, one tries to infer the state of hidden variables, after which one maximizes the likelihood given the inferred states. Both steps are usually done approximately, and the question of bounds over such approximations is of great theoretical importance. The authors of this paper use the replica method to find the error of the Bayes optimal predictor of the hidden nodes in a partially observed kinetic Ising model (see Refs [42,43]), providing a crucial step towards optimal learning and inference in models with hidden nodes. General and quantitative analyses of this type are of great importance for better understanding of statistical models with hidden variables

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