Identification of Functional Information Subgraphs in Complex Networks

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We present a general information theoretic approach for identifying functional subgraphs in complex networks. We show that the uncertainty in a variable can be written as a sum of information quantities, where each term is generated by successively conditioning mutual informations on new measured variables in a way analogous to a discrete differential calculus. The analogy to a Taylor series suggests efficient optimization algorithms for determining the state of a target variable in terms of functional groups of other nodes. We apply this methodology to electrophysiological recordings of cortical neuronal networks grown *in vitro*. Each cell's firing is generally explained by the activity of a few neurons. We identify these neuronal subgraphs in terms of their redundant or synergetic character and reconstruct neuronal circuits that account for the state of target cells.

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Information plays a central role in conditioning structure and determining collective dynamics in many complex systems. For example, the ability to process and react to information certainly influences how neurons and synapses, or genes and proteins, interact in large numbers to generate the complexity of cognitive and biological processes. Despite their importance, however, systematic methodologies for identifying functional relations between units of successive complexity, involved in information processing and storage, are still largely missing.

Motivated by recent theoretical developments and experimental breakthroughs, new interest has arisen in applications of information theory to dynamical and statistical systems with many degrees of freedom [1]. Specifically, it has been shown that information quantities can identify and classify spatial [2] and temporal [3] correlations and reveal if a group of variables may be mutually redundant or synergetic [4,5]. In this way, an information theoretic treatment of groups of correlated degrees of freedom can reveal their functional roles as memory structures or those capable of processing information.

The application of these insights to identify functional connectivity structure is still just beginning [5] but should provide a useful complement to other established approaches [6] by directly relating observable dynamics or statistics to information structures. To date, the identification of functional relations between nodes of a complex network has relied on the statistics of *motifs*. These are specific (directed) subgraphs of k nodes that appear more abundantly than expected in randomized networks with the same number of nodes and degree of connectivity [6,7]. Although powerful for small subgraphs, this approach scales up poorly since the number of different subgraphs explodes combinatorially with increasing number of nodes k. Consequently, the extensive searches that are necessary for measuring motif frequencies become prohibitive beyond about $k \geq 5$. A general solution to this curse of dimensionality is to perform targeted searches guided by quantitative expectations for finding the most informative node combinations relative to an external signal or to other parts of the system.

Here, we present an approach based on the rigorous properties of information theory applied to the correlated statistical state of many variables. The uncertainty (Shannon entropy) in the state of any target variable can be expressed in terms of a cluster expansion of information quantities involving a successively larger number of variables. The sign and magnitude of each term in the expansion determines the functional connectivity among nodes to that order, specifically whether a set of nodes is functionally independent, redundant, or synergetic. Because the Shannon entropy is positive definite, this expansion gives a systematic approximation to the state of the target; the expansion can be truncated at any order to construct approximate nonexhaustive search algorithms, analogous to gradient methods in other optimization problems. We demonstrate the efficacy of this method through its application to spike time series of cortical neuronal networks grown *in vitro*.

Information is a relative quantity, quantifying the reduction in uncertainty of a variable's statistical state given knowledge of others with which it is correlated. The uncertainty in the state of X can be quantified by its Shannon entropy [8] $S(X) = -\sum_x p(x)\log_2 p(x)$, where $p(x)$ are the marginals for each state x of X. Note that $S(X) \geq 0$, where $S(X) = 0$ corresponds to precise knowledge of X and the probability distribution $p(x) = 1$ for some state x. Measuring correlated variables Y_i to X contributes to knowledge of its state and reduces its uncertainty; thus, $S(X) \geq S(X|\{Y\}_{k-1}) \geq S(X|\{Y\}_k)$, with $k \leq n$ for n total variables and where $S(X|Y)$ refers to the conditional entropy of X given Y [8]. We use the notation $\{Y\}_k$ to refer to the set $Y_1, \ldots, Y_k$. The difference between the entropy of X and its entropy given the joint state of a set $\{Y\}_k$ is the information in the set: $I(X;\{Y\}_k) = S(X) - S(X|\{Y\}_k) \geq I(X;\{Y\}_{k-1})$. These relations also specify the optimization

problem of minimizing the uncertainty in X given k measurements $\{Y\}_k$ within a larger (possibly infinite) set. Specifically, if a set exists at some order k so that $S(X|\{Y\}_k) = 0$, and therefore $I(X;\{Y\}_k) = S(X)$, then it fully determines the state of X, and no uncertainty remains. Each measurement can only reduce or leave unchanged $S(X)$, while information quantities are symmetric under permutation of the Y_i so that the maximal entropy reduction from any given set $\{Y\}_k$ is unique. The challenge resides in finding the measurement set of size k resulting in the smallest remaining uncertainty. The computational complexity of this search grows combinatorially with the number of arrangements of size k within n variables, which quickly becomes prohibitive. To evade this problem, we introduce the exact expansion

$$\begin{aligned} S(X|\{Y\}_k) - S(X) &= -I(X;\{Y\}_k) \\ &= \sum_i \frac{\Delta S(X)}{\Delta Y_i} + \sum_{i>j} \frac{\Delta^2 S(X)}{\Delta Y_i \Delta Y_j} + \ldots \\ &\quad + \frac{\Delta^k S(X)}{\Delta Y_1 \ldots \Delta Y_k}. \end{aligned} \tag{1}$$

The variational operators in Eq. (1) define the change in entropy resulting from a measurement as

$$\frac{\Delta S(X)}{\Delta Y_i} \equiv S(X|Y_i) - S(X) = -I(X;Y_i), \tag{2}$$

$$\frac{\Delta^2 S(X)}{\Delta Y_i \Delta Y_j} \equiv -\frac{\Delta I(X;Y_i)}{\Delta Y_j} = I(X;Y_i) - I(X;Y_i|Y_j), \tag{3}$$

and so on. Higher order variations follow automatically from the successive application of the first variation, resulting in a simple chain rule. Thus, variations to any order k are symmetrical under permutations of the Y_i. This expansion has two important properties. First, each term in the expansion at order k accounts for an irreducible set of correlations among a size-k group of Y_i nodes with the target X. Statistical independence among any of the Y_i results in a vanishing contribution to that order and terminates the expansion. For example, if all Y_i are mutually independent, all variations for $k > 1$ vanish identically and the information about X is given by $\sum_i I(X;Y_i)$, that is, the first order terms in Eq. (1). If the Y_i are correlated in pairs, but not in higher order multiplets, then only terms with $k \leq 2$ will be present, and so on. Thus, for a system where not all higher order correlations are realized, expression Eq. (1) allows the identification of correlated submultiplets and determines their mutual organization in specifying the state of X.

The second important property of this expansion is that the sign of each nonvanishing variation reveals the informational character of the corresponding multiplet. Specifically, negative indicates that the k-multiplet contributes to the state of X with more information than the sum of all its subgroups (synergy), while positive indicates the opposite (redundancy). We define a synergetic (redundant) core as a set $\{Y\}_k$ such that its variation and the variations of all its subgroups of two or more nodes are negative (positive). Explicit examples where the Y_i are inputs of a logical circuit and X is the output (e.g., an AND circuit) confirm that the sign of any variation of the Y_i identifies synergetic arrangements to any order. Likewise, arrangements where the same information is shared among some of the Y_i, as in a Markov chain, result in the sign of the variation indicating redundancy. Low order ($k \leq 3$) examples of these relations have been worked out recently [4,5], and their detailed generalization will appear elsewhere. Also, the order-by-order synergy or redundancy captured by each term in Eq. (1) generalizes the coefficient of redundancy $R_k^S(X,\{Y\}_k) \equiv \sum_{i=1}^k I(X;Y_i) - I(X;\{Y\}_k)$ proposed by Schneidman *et al.* Note that R_S^k gives the global information deficit (or excess if $R_k^S < 0$) of a set of size k, relative only to the sum of all binary contributions, but fails to isolate the nonindependence due to triplets and higher order interactions from that of the full set [9].

In this Letter, we use the expansion in Eq. (1) to define the problem of determining the set and decomposition of the Y_i in terms of functional information arrangements that best account for the stochastic behavior of a target X. Because the entropy $S(X|\{Y\}_k) \geq 0$ for all k, this defines a well posed optimization problem, with a single global minimum for each set of possible measurements.

To illustrate this methodology, we apply it to temporal action potential activity from murine frontal cortex neuronal cultures grown *in vitro* on noninvasive microelectrode arrays (MEAs) [10]. Figure 1(a) shows an example network growing on an MEA and Fig. 1(b) typical time series data. Details of MEA fabrication and culture preparation are described elsewhere [5,11]. These experimental platforms have become model systems for studying living neuronal networks in controlled environments. Recent progress includes studies of dynamical patterns of collec-

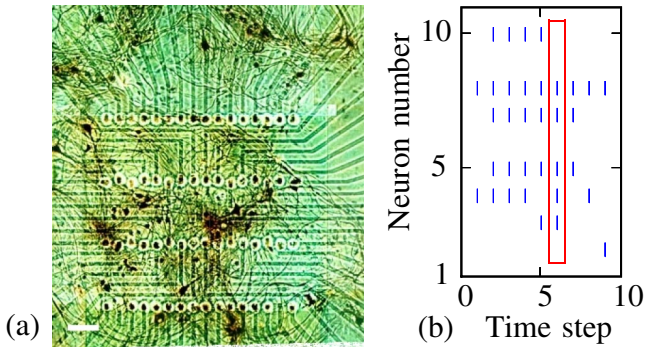

FIG. 1 (color online). (a) Neuronal culture over a microelectrode array (white circles; bar = 40 μm). (b) Detail of a spike time series. The box shows network state 011101100 (bottom to top).

tive activity [12–15], connectivity structure [5], network growth and development [14], and even learning and activity pattern modification [16] via external stimulation. Results presented here refer to 62 cells of a mature (42 days *in vitro*) cortical network. We analyze a 5 h recording (2.3×10^6 spikes) of network activity. We verified that this is long enough for accurate probability estimation [17], while avoiding issues of nonstationarity. We sample the analog field potentials at each electrode at 44 kHz and use standard data acquisition software to determine time stamps for action potentials of individual neurons [11]. To analyze patterns of neuronal activity, we construct binary states [Fig. 1(b)] for each neuron's time series using temporal bins of $\tau = 10$ ms; 1 is recorded if a neuron fires within a bin and 0 otherwise. Results are insensitive to changes in τ within a few ms, with $\tau = 10$–20 ms being a good range [18]. Probability distributions for states of k neurons are estimated via frequencies and provide the basis for calculating information theoretic quantities. Probabilities are considered significant if substantially larger than from a null model with randomized spiking at observed rates for each neuron. Nearly all of the network activity occurs as global coordinated spiking events, known as network bursts or avalanches [14,15,19]. For these reasons, estimation of probabilities become possible within our samples, for a large number of neurons (15–20), with negligible error in mutual informations. Most results below refer to this regime. Slightly larger errors of 10–20% are observed for some target neurons (not shown), relative to groups of 20–30 cells, but become again smaller for larger groups due to the highly coordinated nature of cortical activity.

Figure 2 shows the relative entropy reduction of a target neuron, due to successive measurements of other neurons. Different lines correspond to searches for the optimal sequence of measurements at different orders of approximation in the expansion in Eq. (1). A search to exact order means that all $I(X;\{Y\}_k)$ are considered, given the previous $\{Y\}_{k-1}$, and the set $\{Y\}_k$ with greatest information gain is chosen. Most neurons show an initial large drop in entropy due to the measurement of only a few other cells in the network (typically ≤ 5) and a subsequent slower information gain as more cells are measured.

Figure 2 (inset) shows the histogram of the ratio of final to initial entropy for all 62 neurons. Final entropy refers to the fraction of a neuron's initial entropy left unaccounted for once all other neurons are measured. Remarkably, the stochastic patterns of most cells can be nearly fully predicted by the activity of others, even if most degrees of freedom in the actual network remain unobserved (we estimate that only about 5–10% of all neurons are measured). To better understand the informational nature of arrangements of neurons, we show in Fig. 3(a) R_k^S for each of the measured cells in the network. By this measure, most cell groups are globally redundant (red) relative to their

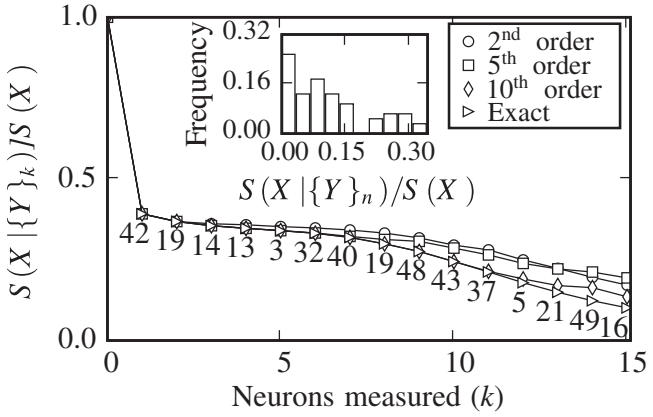

FIG. 2. Joint entropy of neuron 46 and a set of other neurons of size k. The next neuron measured is chosen by maximizing the variation to various orders; the neuron numbers appear for the exact curve. Inset: Histogram of entropy fraction for each neuron remaining after all possible measurements.

decomposition in terms of purely binary correlations to other cells. About a third of the cells, though, show substantial synergy (blue) that persists despite many sequential measurements. Figure 3(b) shows the distribution of each term in the expansion in Eq. (1) to order k. We include all multiplets up to order $k = 2$, and thereafter use a random sample of 36 000 multiplets. Recall that the value and sign of each term in the expansion indicates redundancy or synergy relative to the sum of *all* submultiplets of lower order. Globally redundant multiplets often result in terms with alternating signs to lower orders, while a smaller number of multiplets corresponding to synergetic arrangements have negative contributions at every order. Since a negative variation indicates the *relative* redundancy of the set to its subsets, the individual variations alternate signs with order. To determine whether a set is purely redundant, its variation and all the variations of its subsets must be positive.

Figure 4(a) shows the frequency of synergetic and redundant cores, while Fig. 4(b) shows the reconstruction of

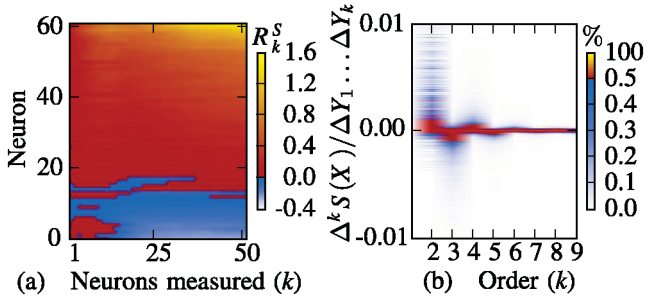

FIG. 3 (color). (a) Sorted global information deficit or excess of a multiplet, relative to the sum of the pairwise mutual informations: R_k^S. (b) Values of each term in the expansion in Eq. (1) vs k for 36 000 randomly sampled variable combinations. White to blue: 0–0.5%; red to yellow: 0.5–100%.

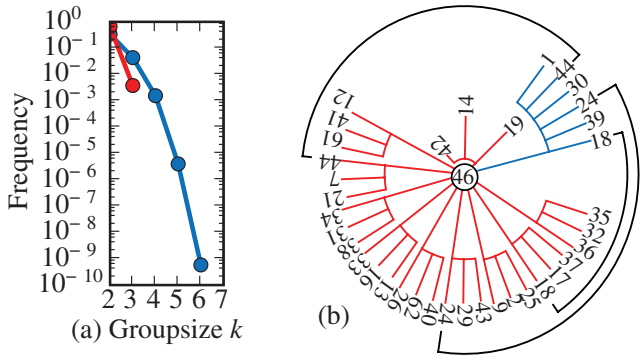

FIG. 4 (color). (a) Frequency of redundant (red) and synergetic (blue) cores versus size k. (b) Purely redundant (red) and purely synergetic (blue) circuits relative to neuron 46. Neurons and groups with the most information about 46 are closest to the center; c.f. Fig. 2. Arcs identify neurons that participate in multiple functional groups.

circuits from functional subgraphs which account for the activity of target neuron 46 of Fig. 2. Evidently, the target neuron is part of both redundant and synergetic functional multiplets, with the former being substantially more abundant. The most informative neuron is labeled 42, but its information about the target is shared to a large extent with neurons 14 and 19. The target neuron is also part of a synergetic circuit with other neurons, several of which are part of smaller mutually redundant subgraphs. Some of these can, at least partially, be interchanged with other neurons carrying the same information, resulting globally in an interconnected ensemble where specific synergetic functional relationships are embedded on robust redundant cell arrangements.

In summary, we present a new information theoretic approach to constructing functional subgraphs in complex networks where nodes display observable stochastic dynamics. By performing targeted searches guided by expected information gain from new measurements, we avoid some of the combinatorial issues involved in the search for motifs in complex networks. We apply this approach to action potential time series from cortical networks and find that the activity of most neurons is to a large extent determined by the observation of other cells. This finding is remarkable because only a small portion (5–10%) of cells are accessible to measurement, indicating that large amounts of redundancy characterize neural network dynamics in these cultures. Despite these observations, an important fraction of a neuron's entropy and detailed firing patterns is contained in multiple cell arrangements of varying size. These findings agree well with recent neuronal network reconstructions in terms of binary correlations [20] and small multiplets [5], but also provide a new view of the functional contribution of higher order correlations. The identification of functional connectivity subgraphs in living neuronal cultures is critical for designing future experiments that promote computational tasks within neural networks and should find applications generally in other complex systems.

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