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Assessing temporal and spatial evolution of clusters of functionally interdependent neurons using graph partitioning techniques

Karim G. Oweiss[1], *Member, IEEE*, Rong Jin[2], *Member, IEEE*, Feilong Chen[2]

Abstract—**This paper suggests a new approach for identifying clusters of neurons with correlated spiking activity in large-size neuronal ensembles recorded with high-density microelectrode arrays. The nonparametric approach relies on mapping the neuronal spike trains to a 'scale space' using a nested multiresolution projection. Similarity measures can be arbitrarily defined in the scale space independent of the fixed bin width classically used to assess neuronal correlation. This representation allows efficient graph partitioning techniques to be used to identify clusters of correlated firing within distinct behavioral contexts. We use a new probabilistic spectral clustering algorithm that simultaneously maximizes cluster aggregation based on similarity measures. The technique is able to efficiently identify functionally interdependent neurons regardless of the temporal scale from which rate functions are typically estimated. We report the clustering performance of the algorithm applied to a synthesized neurophysiological data set and compare it to known clustering techniques to illustrate the substantial gain in the performance.**

I. INTRODUCTION

Simultaneous recording of large-size neuronal ensembles with high-density microelectrode arrays (MEAs) is becoming a necessity in studying systems neuroscience [1]. Advances in microfabrication technology have greatly accelerated the integration of high-density microelectrode arrays on a single device [2]. In case of a stable recording with a relatively high Signal-to-Noise ratio (SNR), the neural yield can be in the order of 1.2 neurons/electrode [3]. With the number of electrode typically reaching a thousand in the near future, it is anticipated that thousands of cortical neurons can be simultaneously monitored.

Despite these advances, the identification of clusters of cortical neurons with correlated spiking activity from the observed spike trains becomes a formidable task. Neurons with correlated spike trains may reflect elements of a single neural circuit, or may reflect elements in different circuits receiving common input. Moreover, latency over which these elements may be correlated largely vary, ranging from highly synchronized activity to slow, lagged correlation that may be manifested later in the response.

Classical techniques, such as cross-intensity functions [4] and Joint Peri-Stimulus Histogram [5], are limited to the assessment of doublets or triplets of neurons. More recent methods depend on the selection of an appropriate bin width from which the histograms are computed [6]. These methods are limited by the variations of the measures of associations and the statistical significance tests, which produce different results for different assumptions and experimental conditions. It has been recently shown that bin width choice is among the significant causes of variability across trials because it causes many artifacts of joint firing correlation [7]. It is thus clear that existing techniques quickly erode in the face of large ensembles, or when nonstationarity in neural firing is encountered during bursts of neural activity, or due to neural plasticity during learning processes.

We propose a new unsupervised, nonparametric clustering approach for identifying clusters of functionally interdependent neurons from multiple single unit activity, independent of the time scale at which they are correlated. The advantage of the technique is that neurons in *local* circuits with relatively fast temporal synchrony, as well as neurons in *global* circuits with extended synaptic activation that may exhibit slower temporal dependency arising later in the response can be both mapped to a single cluster. In that regard, the technique is independent of projection methods or kernel choice. It also provides much larger flexibility for coping with variations of similar experiments across multiple trials.

II. THEORY

A. Mathematical Model

Suppose that P spike trains are recorded by an M electrode array within $T=[t_1,...,t_N]$. Each spike train is a discrete realization of a continuous time rate function $f_p(t)$. The spike trains are binned with bin width δT that accounts for the refractory period, so the neural discharge pattern during $N\delta T$ will be a binary vector of length N, forming a *digital* spike train for every neuron (can accommodate consecutive '1' bins). The spikes of each neuron will occupy some fraction N_p/N of these bins, where N_p denotes the number of bins where an event is present. This fraction approximates the firing probability of neuron p within T. If the bin width selected to estimate the firing probability is denoted by B, then the unknown function $f_p(t)$ can be approximated by counting the number of events within B. The mean is typically used to represent the activity of the neuron as

$$\mu(T)=E[N_p(T)]=\int_0^T f_p(\tau)d\tau=\sum_{n=1}^{N_B}\boldsymbol{f}_p[n].B \qquad (1)$$

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K. G. Oweiss is with the ECE Dept., R. Jin and F. Chen are with the CSE Dept., Michigan State University, East Lansing, MI 48824 USA (Phone: 517-432-8137; fax: 517-353-1980; e-mail: koweiss@msu.edu).

where $N_p(T)$ is the number of arrivals in $(0,T]$, $\boldsymbol{f}_p = \left[f_p[1]\, f_p[2] \ldots f_p[N_B]\right]^T$ denotes the sampled $f_p(t)$, and N_B denotes the total number of bins of length B in the interval $(0,T]$. It is further assumed that each of the P neurons may belong to any of K clusters. Each cluster represents neuronal elements that exhibit all types of short and long range temporal interdependency. We also assume that clusters may overlap. In other words, a neuron can be recruited in more than one cluster with a certain degree of membership. This implies that a neuron can belong to a short rapid synchronized population as well as a slow asynchronous population in response to both *local* and *global* inhibition/excitation from other populations.

B. Scale space representation

To obtain a multiscale representation of the spike trains, the spike train $\boldsymbol{s}_p$ of neuron *p* is binned at windows of length $B/2^j$, where j is the time scale index. This operation is conveniently achieved by a wavelet transformation using the Haar basis [8]. At level *j*, this is expressed as

$$\boldsymbol{s}_p^j = \mathrm{W}^{(j)}\, \boldsymbol{s}_p \qquad (2)$$

For *P* neurons in the total population, a $P \times N$ data matrix $\boldsymbol{S}$ is obtained by stacking the spike trains $\boldsymbol{s}_p$ along the rows of $\boldsymbol{S}$. The *J*-dimensional scale space representation of $\boldsymbol{S}$ is obtained similarly by stacking the spike trains $\boldsymbol{s}_p^j$ along the rows of $\boldsymbol{S}_j$, for $j = 0,1,\ldots,J$. Let $\boldsymbol{F}_k$, $k = 1,\ldots,K$, denote an underlying unknown "base" rate functions of the K clusters that are independent. Then, for neuron *p*, its firing rate function can be expressed as

$$\boldsymbol{f}_p = \sum_{k=1}^{K} a_{pk} \boldsymbol{F}_k \qquad (3)$$

where a_{pk} ψdescribes the degree of membership of neuron *p*ψ to cluster *k*. Thus

$$\boldsymbol{s}_p^j = \sum_{k=1}^{K} a_{pk} \boldsymbol{F}_k^j \delta T + \mathrm{W}^{(j)}\, \boldsymbol{z}_p \qquad (4)$$

where $\boldsymbol{z}_p$ represents the estimation error incurred in the approximation of the true rate function $f_p(t)$ in (1), and $\boldsymbol{F}_k^j$ represents the kth cluster base rate function estimated at time scale *j*.

C. Similarity measures

To quantify *similarity* between distinct neuronal discharges, the sample cross correlation between neurons p_1 and p_2 can be computed at time scale *j* as

$$\boldsymbol{c}_{p_1 p_2}^j = \tfrac{1}{N} \boldsymbol{s}_{p_1}^{j\,T} \boldsymbol{s}_{p_2}^j = \tfrac{1}{N} \sum_{n=1}^{N} \boldsymbol{s}_{p_1}^j[n] \boldsymbol{s}_{p_2}^j[n] \qquad (5)$$

The complete correlation matrix at time scale *j*, $C^{(j)} \in \Re^{P \times P}$ can be formed using (5) for all $p_1, p_2 \in \{1,\ldots,P\}$. It can be shown [9] that

$$E[\boldsymbol{c}_{p_1 p_2}^j] = \begin{cases} \sum_{k=1}^{K} a_{p_1 k} a_{p_2 k} e_k^j & \forall\, p_1, p_2 \in \{k\} \\ 0 & \textit{otherwise} \end{cases} \qquad (6)$$

where $e_k^j = \frac{1}{N} \boldsymbol{F}_k^{j\,T} \boldsymbol{F}_k^j\, (\delta T)^2$ represents the ℓ_2-norm (energy) of $\boldsymbol{F}_k^j$. This means that the temporal evolution of the cluster can be computed using (6) at different observation intervals. Moreover, spatial evolution of the clusters can be dynamically tracked by labeling the neurons with the electrode index on which they were recorded. From (6), it is also clear that pairwise correlation among two neurons p_1 and p_2 belonging to the same cluster will always be a function of $a_{p_1 k}$ and $a_{p_2 k}$, the degree of membership of the neurons in cluster *k*.

D. Graph representation

The graph representation of the spike trains enables recently established graph partitioning theory and data mining techniques to be applied [10]. Each neuron is represented as a point object and connects to other neurons with a *vertex* that depends on the similarity measure. This measure between any given pair of neurons p_1 and p_2 consists of a user defined statistic $w_{p_1 p_2}$. For example, when Pearson correlation in (5) is used, the resulting measure expresses the correlation of the firing rates between the two neurons at time scale *j*. This may indicate the strength of their synaptic connectivity. On the other hand, if mutual information is used, the resulting measure expresses the information that both neurons are receiving from a common input.

Clustering neurons can be subsequently undertaken using a probabilistic spectral clustering algorithm that simultaneously maximizes cluster aggregation based on the similarity measures as well as cluster segregation based on dissimilarity measures [10]. We use *soft* memberships to reduce the computational complexity in which a_{pk} represents the *probability* for the pth neuron to be in the kth cluster. A maximum cut problem is solved to find the set of probabilities $\{a_{pk}\}$ that maximizes the following objective function:

$$l = \sum_{k=1}^{K} \frac{\sum_{p_1=1}^{P} \sum_{p_2=1}^{P} a_{p_1 k} a_{p_2 k} w_{p_1, p_2}}{\sum_{p_1=1}^{P} \sum_{p_2=1}^{P} a_{p_1 k} w_{p_1, p_2}} \qquad (7)$$

The final cluster memberships are derived from $\{a_{pk}\}$ by assigning each object to the cluster with the largest probability, i.e., $k_p^* = \underset{k \in [1,\dots,K]}{\arg\max}\, a_{pk}$.

In practice, correlations across multiple time scales can be fused such that the nonzero entries in the pairwise correlation can be obtained by simultaneously diagonalizing the $P \times P$ correlation matrices $C^{(j)}$, $j = 0,1,\dots,J$. To see this, we form a block diagonal matrix $R \in \Re^{(P \times J)\times(P \times J)}$ that has the j^{th} $P \times P$ block as $C^{(j)}$. Then, the matrix R is diagonalized using Singular Value Decomposition (SVD) as

$$R = \begin{bmatrix} C^{(0)} & & & \\ & C^{(1)} & & \\ & & \ddots & \\ & & & C^{(J)} \end{bmatrix} = \sum_{q=1}^{P \times J} \lambda_q \boldsymbol{u}_q \boldsymbol{u}_q^T \tag{8}$$

where $\lambda_q^j / \boldsymbol{u}_q^j$ denote the eigenvalue/eigenvector pair associated with the q^{th} dominant mode of the augmented correlation R. We set the distance/dissimilarity between the two neurons $w_{p_1 p_2}$ in (7) to be $R[p_1, p_2]$ from (8).

E. Nonlinear functional interdependency

Functionally interdependent neurons can exhibit a mixture of linearly and nonlinearly related populations. When the functional relationship is nonlinear, the ℓ_2-norm e_k^j in (6) is no longer a good measure of separability, and should be replaced by the nonlinear kernel function Ψ. In fact, this transformation permits using the well-established results of *Kernel-based* PCA [11]. Instead of computing a dot product between a pair of spike trains, the correlation is based on the nonlinear kernel function Ψ, which is used to compute the correlation matrix entries as

$$\boldsymbol{c}_{p_1 p_2}^j = \Psi(\boldsymbol{s}_{p_1}^j, \boldsymbol{s}_{p_2}^j) \tag{9}$$

It is noteworthy that any positive semi-definite function that satisfies Mercer's condition can be used as kernel function. Therefore, the nonlinear extension to the algorithm is straightforward.

III. METHODS

To test the performance of the technique, we simulated a population of 120 neurons using freely available software [12]. The software tool simulates biological neural networks with a considerably large number of neurons using synthetic neurons from a library of pre-built neuronal models. Noise controls can be used to control the variation of each neuron type from a baseline cell model. These controls mimic the statistical distribution of axonal lengths and synaptic weights within a given cluster. For example, if a large mean and standard deviation are used in a given cluster, this would imply that the network is largely distributed, with a mix of strongly and weakly connected, adjacent and spatially distant neurons. The type of connectivity can also be set between clusters to choose excitatory, inhibitory or random connections from neurons of one cluster to those of another.

We simulated 4 different clusters of functionally interdependent neurons with 30 neurons in each cluster as illustrated in Figure 1. In each cluster, a distinct pre-built neuronal model was selected; for each model, the parameters to be set include *firing threshold*, *resting potential* and *post-spike potential*, *noise mean*, *noise standard deviation*. Table I shows the values of these parameters for the four clusters.

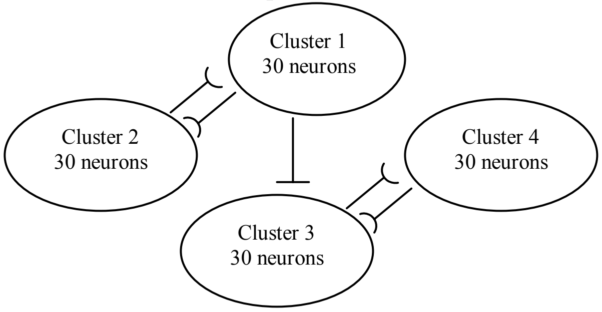

Figure 1: 120 neuronal population divided into 4 clusters. Clusters 1 and 2 connections are excitatory, so as clusters 3 & 4. Clusters 1 and 3 connections are inhibitory.

TABLE I
PARAMETERS FOR NEURON MODELS OF THE 4 CLUSTERS

	Firing threshold	Resting potential	Postspike potential	Noise mean	Noise std
Cluster 1	-50	-46	-65	8.78	4.35
Cluster 2	-50	-46	-65	18.049	7.033
Cluster 3	-48	-43	-43	5.854	9.39
Cluster 4	-51	-43	-43	5.854	9.39

The parameters for cluster 1 and 2 were set to be similar, so are those for cluster 3 and 4, such that the two pairs will behave similarly. The noise parameters were varied to synthesize a variety of within-cluster distributions. For example, noise parameters were set to small values for cluster 1. This means that the neurons belonging to these two clusters behave *similarly*. In contrast, the noise parameters for cluster 2 were set to a much larger value, so as to induce more *stochastic* behavior in the neuronal firing. The network editor of the software allows selecting the type of connectivity. Clusters 1 and 2, cluster 3 and cluster 4 were bi-directionally linked. In particular, slow variations of resting potential was shown to be of crucial important in characterizing cross correlations between spike trains since it can yield artefactually fast cross-correlations. Figure 2 illustrates a snapshot of the 120 spike trains obtained as a 4-band structure (neurons 1-30 are from cluster 1, 31-60 from cluster 2, etc.). In particular, neurons in clusters 3-4 tend to be more synchronized, while neurons in clusters 1-2 tend to be more stochastic.

IV. RESULTS

We compared the performance of the proposed algorithm to that of the *k*-means, and the Expectation-Maximization (EM) algorithm as a function of the number of clusters.

Table II lists the clustering errors achieved. It is clear that the proposed technique outperforms the other techniques irrespective of the choice of the number of clusters. We also compared the performance for the specific cases of 2 and 3 clusters. Table III and IV lists the results for all combinations of pairs and triplets of clusters were given to the algorithm. Figure 3 illustrates that minimum clustering error is achieved at the correct number of clusters for different number of principal components in (8).

TABLE II

PERFORMANCE COMPARISON VS. K-MEANS AND EM

	k-means	EM	SPEC	WASPEC
2 clusters	53.3	50.0	31.6	0
3 cluster	47.7	33.3	31.1	0
4 clusters	54.17	43.3	38.3	23.3

∗ SPEC= proposed algorithm without scale space representation

∗ WASPEC= proposed algorithm with scale space representation

TABLE III

PERFORMANCE COMPARISON FOR DOUBLETS OF CLUSTERS

2 clusters	***k*-means 44.4±12**	**EM 50.28±0.6**	**SPEC 12.78±20**	**WASPEC 1.3±3.4**
(1,2)	56.6	50.0	45	0
(1,3)	36.6	50.0	0	0
(1,4)	33.3	50.0	0	0
(2,3)	35.0	50.0	0	0
(2,4)	43.3	50.0	0	0
(3,4)	61.6	51.6	31.6	8.3

TABLE IV

PERFORMANCE COMPARISON FOR TRIPLETS OF CLUSTERS

3 clusters	***k*-means 50.8±5.5**	**EM 35.8±4.2**	**SPEC 25.56±4.1**	**WASPEC 4.4±5.2**
(1, 2, 3)	46.6	33.3	31.1	0
(1, 2 ,4)	45.5	33.3	25.5	0
(1, 3, 4)	54.4	34.4	24.4	7.7
(2, 3, 4)	56.6	42.2	21.1	9.9

V. CONCLUSION

A new technique for analyzing multiple spike trains in large-size neuronal ensembles is presented. The technique relies on identifying a similarity measure between neurons based on a scale space representation that captures "causal" dynamics of neuronal firing. A graph representation is subsequently obtained in which spectral clustering is used to maximize cluster compactness (within-cluster correlation) and minimizes across-cluster correlation. The approach results in an improved performance over other algorithms resolving neuronal interactions, even when the incorrect number of clusters is given. Minimum clustering error is further attained at the correct number of clusters. The technique can be further applied to neurons within each cluster to increase the accuracy and identify sub-clusters. It can be easily generalized using other similarity measures or nonlinear relationships depending on the application at hand.

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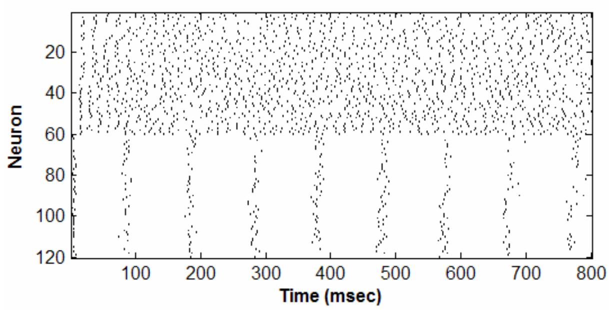

Figure 2: 120 synthetic spike trains illustrating 4 clusters of functionally interdependent neurons with various firing properties.

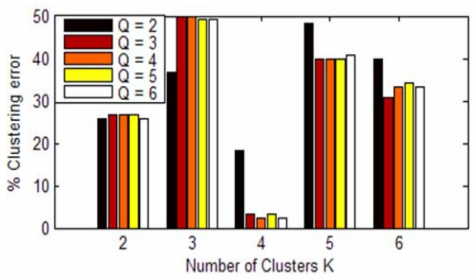

Figure 3: Clustering error metric as a function of the number of principal components Q used in the WASPEC algorithm. The error surface reaches a minimum when the correct number of clusters is reached.