**Identification of neuronal ensembles from primary visual cortex *in vivo* using probabilistic graphical models**

**Summary**

The coordinated firing of neuronal populations is considered to be the substrate of sensory, behavioral and cognitive functions. In particular, neuronal ensembles in primary visual cortex represent specific features of visual stimuli. However, how the functional connectivity in local microcircuits relate to their function has been difficult to elucidate *in vivo*. The development of recording and stimulation techniques with single cell precision has opened the possibility of testing the function and computation principles of cortical ensembles during physiological processes. To address these questions, it is necessary to identify online the most representative elements from a given neuronal ensemble. Here we used two-photon calcium imaging to record the responses to drifting gratings of layer 2/3 neurons in primary visual cortex of awake behaving mice, and then applied probabilistic graphical models to find the most representative neurons from each cortical ensemble. We demonstrate that the activity of the most representative neurons identified from each cortical ensemble is sufficient to predict a given visual stimulus. We anticipate that our approach will allow the design of close-loop two-photon optogenetic experiments with single cell resolution to test the physiological role of cortical ensembles during behavioral tasks.

**Introduction**

Many physiological and cognitive processes have been proposed to arise from the sequential activation of groups of neurons in a large population (Baeg et al., 2003; Buschman et al., 2012; Churchland et al., 2012; Harvey et al., 2012; Liu et al., 2012; Lorente de No, 1938; Mante et al., 2013). These co-activating neuronal groups, defined as neuronal ensembles, are assumed to generate complex circuit functions that cannot be achieved by single neurons. With recent advances in two-photon calcium imaging and optogenetic stimulation methods, it is now possible to record the simultaneous activity of large ensembles of neurons while manipulating neuronal group activity (Boyden et al., 2005; Chen et al., 2013). Although there is emerging causal evidence of neuronal ensembles encoding functions such as memory *in vivo* (Liu et al., 2012; Ramirez et al., 2013), much still remains to be explored about the computation principles of neuronal ensembles at single cell level *in vivo*. One major challenge of designing such close-loop optogenetic experiments lies in identifying constituent neurons in neuronal ensembles from population activity and using ensemble activity to predict neuronal network states.

Neuronal population consist of interconnected neurons, forming a network structure. Such network structures can be naturally modeled with graph theory, which defines a graph structure with nodes and connecting edges that are biologically meaningful. Graph theory has been applied to model both structural and functional organization of neuronal networks (Bullmore and Sporns, 2009). For structural analysis, graphs are usually constructed with nodes representing the functional units of the brain such as neurons or brain regions (He et al., 2007), and edges representing their connections. Such models have been used to reveal the organizing principles of neural networks, and to identify critical regions or neurons in the networks (Badhwar and Bagler, 2015; Iturria-Medina et al., 2008; Sporns, 2000; Towlson et al., 2013). For functional analysis, many studies have constructed graphs with data from fMRI, EEG and MEA, taking brain regions (Achard and Bullmore, 2007; Fair et al., 2008; Hagmann et al., 2008), voxels (Eguíluz et al., 2005; van den Heuvel et al., 2008; Zuo et al., 2012) or electrode position (Downes et al., 2012) as nodes, and activity associations such as cross correlation, mutual information and Granger causality as edges (Bullmore and Sporns, 2009; Fair et al., 2008; Khazaee et al., 2015; Micheloyannis et al., 2009; Wang et al., 2010). Such graphs are usually associated with a single set of parameters that describe the weight and direction of edges, therefore are incapable of fully characterizing the network states given observed firing pattern in a probabilistic way. Furthermore, although a few studies have applied graph theory to model functional network organizations in calcium imaging data with single cell resolution in slices (Bonifazi et al., 2009; Gururangan et al., 2014; Yatsenko et al., 2015), it has not been applied to identify representative neuronal ensemble cells in awake behaving animals.

To obtain a graphical model that allows both identifying ensemble neurons and predicting external stimuli with observed ensemble activity in future experiment, a probabilistic graph model is required. One of the models that meets the criteria is a conditional random field (CRF) (Lafferty et al., 2001). CRFs model the conditional distribution *p*(**y**|**x**) for observed population activity **x** over all nodes and network state **y** with an associated graphical structure. A major advantage of CRFs is that they condition on the observation **x** without modeling it, therefore avoid making independence assumptions about **x,** which many other models including Hidden Markov Models rely on. Additionally, CRFs also avoid labeling bias problem exhibited by conditional Markov models such as maximum entropy Markov models (Lafferty et al., 2001). Therefore, CRFs have been successfully applied in diverse areas such as news and finance (Peng et al., 2011; Tang et al., n.d.), bioinformatics (Li et al., 2008; Liu et al., 2006; Sato and Sakakibara, 2005), computer vision (He et al., 2004; Sminchisescu et al., 2006) and natural language processing (Choi et al., 2005; Lafferty et al., 2001).

In this work, we developed a framework for identifying neuronal ensembles and predicting external stimulus using CRF models. We performed two-photon calcium imaging in the primary visual cortex (V1) of awake behaving mice while presenting them with drifting gratings of different orientations. We then built CRF models from inferred spike raster matrix of the neuronal population. By adding artificial nodes that encode each stimulus, we can identify ensembles whose prediction performance exceeds existing methods. Our method provides a tool for testing the physiological role of cortical ensembles during behavioral tasks by facilitating designing of close-loop two-photon optogenetic experiments with single cell resolution.

**Results**

**Ensemble activity of V1 neuronal population during visual stimuli**

To investigate the population activity of cortex, we performed two-photon calcium imaging in the primary visual cortex of awake mice that were allowed to run on a treadmill (Figure 1A). We recorded both spontaneous and visually evoked activity; for the latter, we presented the mice with horizontal and vertical drifting gratings on a black and white screen. To extract spike information from the imaging data, ROI detection and spike inference were performed for each recognized neuron (ref and details). Each complete experiment is then represented as a binary raster matrix, where row vectors represent activity time series from each identified neurons, and column vectors represent the population activity at each time points, which is defined as population vectors (citation) (Figure 1C).

Several methods have been proposed for identifying neuronal ensembles responding to specific conditions from population activity, while few applies to population calcium imaging (citation). To start with, we adopted the method previously developed in our group. Because identification of neuronal ensembles can be biased by neurons with high baseline activity, we first computed TF-IDF vectors from population vectors to decrease the weight of high activity neurons (citation). From the normalized TF-IDF matrix, we then calculated the similarity coefficients between all pairs of TF-IDF vector across experimental conditions, and kept significant entries determined by a threshold from similarity coefficients of shuffled data. Neuronal ensembles were subsequently identified by first performing singular value decomposition (SVD) on the similarity matrix, then finding cell indices in the singular vectors associated with singular values above a significance threshold (citation). In a representative dataset, we identified four ensemble groups using this method: two are associated with horizontal or vertical drifting grating stimulus, and two are associated with spontaneous activity (Figure 1E). Stimulus-associated ensembles are scattered in space while sharing a few common neurons (Figure 1D), and exhibited high evoked activity level when the corresponding stimulus was presented (Figure 1E).

**Discovering ensembles with a probabilistic graphical model**

Given the current methods of identifying neuronal ensembles, we wish to further quantitatively assess the overall ensemble activity in the neuronal population with a fully characterized model. A natural abstraction of an interconnected neuronal population is to represent the neuronal activity and their functional correlations as the nodes and connecting edges in a graph. To obtain the probability estimation of the population state based on observed population vector, we constructed a conditional random field (CRF) model (Figure 2A). This model assumes that the observed spikes from each neuron were generated by nodes in a graph structure, and that each node can be in two states: a 0 state which corresponds to a non-firing state, and an 1 state which corresponds to the firing state. Nodes interact with each other by connecting edges, which have four states 00, 01, 10, and 11, depending on the states of the two nodes on the edge. The two states associated with nodes and the four states associated with edges are characterized by a set of parameters called node potentials (ϕ0, ϕ1) and edge potentials (ϕ00, ϕ01, ϕ10, ϕ11) correspondingly (Figure 2A). These parameters reflect the likelihood of individual states on each node and edge. Model parameters were obtained by training using a part of the observation data, and cross-validation on the withheld data. Therefore, the likelihood of the neuronal population exhibiting a specific firing pattern can be described by the normalized product of corresponding node and edge potentials.

To identify neurons that are positively correlated with each presented stimulus during a complete experiment, we added one stimulus-associated node for each stimulus in the population vectors, and set it to 1 when the corresponding stimulus was on, 0 when the stimulus was off. Correlation between neuron nodes and stimulus nodes is reflected by ϕ11 in the edge potential term, which quantifies the likelihood of individual neuron firing only during specific stimulus. Therefore, all the nodes that have positive ϕ11 terms with each of the stimulus-associated nodes were then defined as the ensemble for that corresponding stimulus (Figure 2C). This method identifies a subset of neurons as stimulus-associated neurons, or ensembles, for each presented visual stimulus, separately (Figure 2D).

**Clique and community properties of constructed graphical models**

Brain network shows both structural and functional modularization, in both macro-scale and micro-scale (Achard et al., 2006; Bonifazi et al., 2009; Hagmann et al., 2008; He et al., 2007; Shimono and Beggs, 2015; Sporns et al., 2007; Stetter et al., 2012; Zuo et al., 2012). Network modularization is often characterized by local structures with high inter-connectivity, where a group of neurons show dense physical or functional connections. Such structures can be described with concepts defined in different spatial scales such as cliques, communities (Palla et al., 2005b), hubs and modules (Bullmore and Sporns, 2009). To characterize the neuronal group properties of constructed graphs in the population, we examined *k*-clique and *k*-clique community structures (Palla et al., 2005a). As defined in previous literature, a *k*-clique describes a fully interconnected subgraph (a complete subgraph) consisting of *k* nodes (Figure 3A). A *k*-clique community is defined as a subgraph consisting of a collection of *k*-cliques that shares at least *k*-1 common nodes with their adjacent neighbors (Figure 3B). Thus, *k*-cliques and *k*-clique communities represent the subgroups of neuron that might serve as functional cores under specific experimental conditions.

CRF graphs constructed from population calcium imaging data in V1 have more *k*-cliques and *k*-clique communities for *k* = 2, 3, 4 compared with Erdos-Renyi random graphs, which preserve the number of nodes and edges (Figure 3C and 3D). As *k* further increases, the number of *k*-cliques and *k*-cliques communities decreases (Figure 3C and 3D), and no *k*-cliques were found with *k* ≥ 6 in all experiments (Figure 3C). We then empirically chose *k* = 3 for all the following analysis. 3-clique communities in CRF graphs also possess more constituent nodes than Erdos-Renyi random graphs (Figure 3E). These results together indicate that CRF graphs have non-random structures.

A straightforward but widely used method for constructing graphs from population neuronal recording is to first calculate the pairwise correlation values of nodes, which can be neurons, voxels, or brain regions, then define edges based on a correlation value threshold (Bonifazi et al., 2009; Downes et al., 2012; Sadovsky and MacLean, 2014; Zuo et al., 2012). Therefore, we also constructed a correlation-based graph (CC graph) using the spike data (Figure 4A). We first compared the properties of the resulting graphs from CC and CRF models. CC and CRF graphs show significantly different distribution of node degrees and global clustering coefficient, while both also show nonrandom structures (Figure 4C and 4D). Then, we measured the following community properties, as defined previously: community degree *d*com, which is the sum of node degrees in the community; community size *s*com, which is the number of nodes in the community; community overlap *s*ov, which is the overlap size between two communities; and community membership *m*, which is the number of communities a node belongs to (Palla et al., 2005b). The result shows that CRF and CC graphs have nonrandom community structures, but they differ from each other (Figure 4B, 4E-F), indicating that CRF graphs capture network properties that are not detected in CC graphs.

Cells that are shared by multiple communities can be considered as representative for the specific given condition, since they are also shared by multiple cliques, therefore are highly connected. Similarly, cells with high centrality values are also highly connected in the graph. Therefore, we defined neuronal ensembles using community membership for both CRF and CC graphs (CRFcomm and CCcomm) by determining a community membership threshold from shuffled data. We also defined neuronal ensembles using centrality for CRF and CC graphs (CRFcent and CCcent) in a similar way by threshold from shuffled data. Including finding neuronal ensembles by adding stimulus-associated nodes in CRF graphs (CRFstim) and the SVD method developed in previous work, we are now equipped with six different methods of identifying neuronal ensembles in population calcium imaging data.

**Ensemble activity predicts external stimuli**

Next, we compared the neuronal ensembles identified by different methods. Neuronal ensembles identified with both CRFstim and SVD consist of around 30% cells of the total population (Figure 5x), while they share around 40% cells (Figure 5x). Community ensembles (CRFcomm and CCcomm) and centrality ensembles (CRFcent and CCcent) differ their sizes with CRFstim ensembles, and show less overlay with CRFstim ensembles (Figure 5x). In contrast, cells that are highly tuned to a specific orientation of visual stimuli (high OSI) consists of x% of the total population and share only around 30% with CRFstim ensembles (Figure 5x). This indicates that neuronal ensembles are not purely orientation selective cells, which is consistent with our previous result (Carrillo-Reid et al., 2015).

We then evaluated the identified ensembles by their performance of predicting external visual stimuli presented to the mice. To make predictions with ensemble activity, we take an all-on state of the ensemble vector as the stimulus-on state, and calculated the cosine similarity between ensemble activity vectors and the ensemble all-on vector. The similarity values are then binarized to be a raster prediction according to the noise level. Similarity between CRFstim ensemble activity vectors and the all-on vector reproduces presented stimulus (Figure 5x), and is specific to the stimulus-on periods (Figure 5x). Prediction statistics show the CRFstim ensembles have higher prediction accuracy, precision and recall than the rest of the methods (Figure 5x), proving that this graph theory based model outperforms existing ensemble identification approaches.

**Ensembles are optimal neuronal group that encode specific stimuli**

CRFstim method consistently identifies a subset of neurons in the population as representative neuronal ensembles for the presented visual stimuli. This fact raises the question of whether CRFstim ensembles are a specific non-random subgroup that encode the external stimuli. To answer this question, we randomly sampled a subset of the total neuronal population, ranging from 10% to 90% of all neurons. Similarity values between population vectors of randomly sampled neuronal group activity and an all-on vector show no difference between stimulus-on and stimulus-off period for all sizes of random groups (Figure 6F). This results in chance level prediction performances that is much lower than the original CRFstim ensemble performance (Figure 6G-I), indicating that ensembles are non-random structures.

We next investigated whether CRFstim ensembles are sufficient and necessary for encoding the stimuli. To do this, we randomly downsampled and upsampled the CRFstim ensembles (Figure 6A, top panels) and examined the prediction performance as above. Similarity between population vectors of resampled ensemble and ensemble all-on vector is most well distinguished between stimulus-on and stimulus-off periods when ensemble size is unchanged (Figure 6B). Furthermore, intact ensembles achieve the best accuracy, precision and recall when predicting the presented visual stimuli, compared with downsampled and upsampled ensembles (Figure 6C-E). All the above results indicate that stimulus-specific CRFstim ensembles are a non-random subgroup of cells that are both sufficient and necessary for encoding external stimuli.

**Discussion**

**Experimental Procedures**

**Two-photon *in vivo* calcium imaging**

***Surgical Procedures***

***Two-photon imaging***

***Visual stimulation***

***Data Processing***

**Data Analysis**

***Conditional Random Fields***

We construct a conditional random field (CRF) with the observed population activity where , and the target hidden network state , where , for *M* samples (time points). For each sample, the conditional probability can be expressed as:

where *φ* is a vector of sufficient statistics of the distribution, *θ* is a vector of parameters, and *Z* is the partition function:

The conditional probability can be factorized over a graph structure , where *V* is the collection of nodes representing observation variables and target variables, and *E* is the collection of edges representing the independencies.

A conditional random field is an undirected graphical model *G = (V, E)* conditioned on the observation variables ***X*** (Wallach, 2004). Each vertex *v* ϵ *V* in *G* is associated with a target variable **Y***v* in **Y**, which obeys Markov property with respect to *G*. A conditional random field models the conditional distribution p(**Y**|**X**) without explicitly modeling the distribution of **X** or putting any assumptions on **X**, therefore has been successful in many applications [ref].

A conditional random field can be parameterized by a set of node potentials *φ*(**Y***i*) and edge potentials *φ*(**Y***i*, **Y***j*) defined on the graph. These potential functions take the values of the target variable and project them into the response space, and are associated with the conditional independencies in the graph. The probability of a specific system state ***y*** given the observation ***x*** can then be written as:

where

and are usually compactly defined as log-linear functions: *φ*(**Y***i*, **Y***j*).

two steps: structural learning and parameter learning; allows cycles; challenges and solutions for cyclic graphs

***Correlation-based Graphs***

***Shuffling Methods***

***Cliques and Communities***

***Graph properties***

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