**Conditional Random Fields for identification of Neuronal ensembles**

Luis Carrillo-Reid\*, Shuting Han\*, Tony Jebara, Rafael Yuste.

**Summary 150<150**

The state prediction of many variables with mutual dependencies is fundamental for the creation of models in varied applications including: natural language, computer vision, bioinformatics and the stock market. Such problems can be approached by structured prediction methods that combine graphical models and classification algorithms. Conditional random fields (CRFs) represent a widely used probabilistic method for structured prediction. However, CRFs application to infer the functional connectivity of biological neural networks remains unexplored. We used CRFs and graph theory in population calcium imaging from primary visual cortex (V1) of awake behaving mice to identify neuronal ensembles and predict visual stimuli. We show that our approach prediction performance exceeds existing methods for identification of cortical ensembles. Finally, by identifying the most significant neurons from artificial ensembles imprinted in vivo using two-photon optogenetics we demonstrate that our method provides a powerful tool for targeting individual neurons that can influence the overall network activity.

**Introduction 478**

The coordinated firing of neuronal populations is considered to be the substrate of sensory, behavioral and cognitive functions (refs). These coactive neuronal groups, defined as neuronal ensembles, are assumed to generate complex circuit functions that cannot be achieved by single neurons (refs). Recent advances in two-photon calcium imaging and two-photon optogenetics, have made possible the recording of simultaneous activity from large ensembles of neurons while manipulating population activity with single cell resolution in awake behaving animals (Carrillo-Reid 2016; Packer 2015, Rickgaguer 2015). However, how the functional connectivity in cortical microcircuits relate to their function has been difficult to elucidate because it requires the identification of physiologically relevant neurons that can be targeted during close-loop optogenetic experiments, allowing the manipulation of learned behavioral tasks.

Graph theory has been applied to model the structural and functional organization of the brain (Bullmore and Sporns, 2009). However, graphs are usually constructed with nodes representing brain regions (He et al., 2007), and edges representing information flow (Iturria-Medina et al., 2008). For functional analysis, many studies have constructed graphs with data from fMRI, EEG and electrode arrays, 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).

On the other hand, at the single cell level graphical models have been used to describe organizing principles of artificial neural networks, identifying neurons that could have a potential role orchestrating the overall network activity (Badhwar and Bagler, 2015; Iturria-Medina et al., 2008; Sporns, 2000; Towlson et al., 2013). Such graphs are usually associated with a restricted set of parameters that describe the weight and direction of edges obtained by pairwise correlations, therefore are incapable of characterizing cortical ensembles with emergent properties (refs) that could represent visual stimuli in a probabilistic way. Finally, although a few studies have applied graph theory to model network organization in calcium imaging data with single cell resolution in cultures or brain slices (Bonifazi et al., 2009; Gururangan et al., 2014; Yatsenko et al., 2015), it has not been applied to define the functional connectivity based on the joint probability distribution of neuronal ensembles in awake behaving animals.

Cortical ensembles in primary visual cortex consist of strongly interconnected neurons (refs), forming a network structure that can be naturally modeled with graph theory, where nodes and edges are biologically meaningful representing neurons and their connections respectively. We demonstrate that graph theory applied to CRFs allows the identification of cortical ensembles associated with different experimental conditions opening the possibility of targeting, with two-photon optogenetics, the most significant neurons from specific populations during physiological processes.

**Results**

**Identification of cortical ensembles from calcium imaging population data**

Cortical ensembles in primary visual cortex represent neuronal populations responding to specific features of visual stimuli (refs). The overall activity of multiple cells at a given time window can be understood as a multidimensional array of population vectors where vectors pointing to a similar space can be considered as a group (Figure 1C). We previously show that population vectors defining a group (i.e. a cortical ensemble) can be extracted from multidimensional arrays performing singular value decomposition (SVD) (Carrillo-Reid et al., 2015). Even though SVD can identify cortical ensembles reliably, it lacks from a fully characterized model that allows the systematic study of changes in functional connectivity during different experimental conditions (Figure 1. descriptive methods lack of model).

**CRF models predict external stimuli**

In order construct a fully characterized model from the observations, we used CRFs representing neurons and their functional connections as nodes and edges in a graph (Figure 2A). To obtain the probability estimation to observe different network states based on observed population vectors, we assume that the observed activity events from each neuron were generated by nodes in a graph structure, and that each node can have two values: ‘0’ corresponding to non-activity, and an ‘1’ corresponding to neuronal activity. In this way nodes interact with each other by connecting edges, which have four possible combinations ‘00’, ‘01’, ‘10’, and ‘11’, depending on the values of the two nodes on the edge. The two values associated with nodes and the four values 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 values on each node and edge. Using a part of the observation data, we obtained the model parameters and performed cross-validation on the withheld data. Therefore, the likelihood of the neuronal population exhibiting a specific activation pattern can be described by the normalized product of the corresponding nodes and edge potentials (Figure 2A).

To integrate the information of external stimulus with the observed data, we added a hidden node for each presented stimulus, and set it to ‘1’ when the corresponding stimulus was on, ‘0’ when the stimulus was off (Figure 2B). We then trained CRF models using the real data with hidden nodes. In this way, the nodes that are directly connected to the hidden nodes and the ones that are indirectly connected through one intermediate node are potentially involved in encoding the stimuli (Figure 2C).

CRFs model the conditional probability of network states given the observations. Therefore, by treating visual stimuli as nodes and comparing the output likelihood of observing each stimulus, such models are able to predict visual stimuli from observed data. For example, with two visual stimuli (horizontal and vertical drifting gratings), we computed the likelihood of and , corresponding to observing horizontal and vertical stimulus, separately. The relative likelihood, , corresponds nicely with presented stimuli (Figure 2D, 2F). Predictions made from thresholding the relative likelihood gives a mean accuracy of xxx (Figure 2G), with the precision xxx (Figure 2H) and recall xxx (Figure 2I).

**Emergent properties depicted from CRFs graphs**

To investigate if cortical ensembles identified by CRFs represent emergent network properties we compared CRFs graphs against graphs constructed from pairwise correlation values (CC graph) between neurons, using observed spikes similarly extended by stimulus-representing hidden nodes (Figure 3A) (Bonifazi et al., 2009; Downes et al., 2012; Sadovsky and MacLean, 2014; Zuo et al., 2012). CC and CRFs graphs show significantly different density (Figure 3B) as well as distribution of node degrees, local clustering coefficient and centrality (Figure 4C-E). Both also show nonrandom structures indicated by a heavy tail, compared with Erdos-Renyi random graphs, which preserve the number of nodes and edges (Figure 4C-E). Thus CRFs and CC graphs differ from each other (Figure 4), indicating that CRFs graphs capture emergent network properties (REF) that are not detected in CC graphs.

**Identification of significant neurons from CRFs ensembles using graph theory**

While most neurons interact with the hidden nodes through direct or one-step indirect connections, we wish to identify significant neurons among them that are most representative for each visual stimulus. As a type of Markov random field, the probability distribution of a CRF model can be factored as the product of clique potentials of maximal cliques, according to the Hammersley Clifford theorem:

where maximal cliques are complete subgraphs (fully interconnected subgraphs) that cannot be extended by adding more nodes (Figure 4A). Therefore, maximal cliques can be considered as functional units in a graph. We then examined the maximal cliques that contain at least one node that has a direct connection with the hidden nodes (Figure 4B). CC and CRF graphs show significantly different number and size of maximal cliques (Figure 4C, 4D), indicating that CRF graphs captures properties that cannot be found in CC graphs. The size of CRF maximal cliques is larger than that from Erdos-Renyi random graphs, indicating those structures cannot be considered as random. Therefore, maximal cliques can be considered as the most significant for a specific given condition.

Neuronal ensembles identified with CRFs and SVD consist of xxx% and xxx% cells of the total population, separately (Figure 5A, 5B), while they share xxx% cells (Figure 5C). In contrast, cells that are highly tuned to a specific orientation of visual stimuli (high OSI) consists of only xxx% of the total population and share only xxx% with CRFs ensembles (Supplementary Figure 5x) indicating that cortical ensembles are not purely orientation selective cells (Carrillo-Reid et al., 2015)

**Significant neurons from cortical ensembles are optimal for external stimuli prediction**

We then evaluated the identified significant neurons by their performance of predicting external visual stimuli presented to the mice. To make predictions with ensemble activity, we calculated the cosine similarity between population vectors observed in real data compared to population vectors defined by CRFs (Figure 1C). Similarity coefficients between CRFs population vectors and real data reproduces presented stimulus (Figure 5F), and is specific to the stimulus activation periods (Figure 5D). Prediction statistics show the CRFs defined ensembles have higher prediction accuracy, precision and recall than SVD method (Figure 5G-I), demonstrating that CRF models outperform existing ensemble identification approaches.

We next investigated whether significant neurons from cortical ensembles identified by CRFs represent the optimal group of neurons for the prediction of presented visual stimuli. To do this, we randomly resized identified cortical ensembles adding or removing elements from the significant population (Figure 6 A-D) and examined the prediction performance. The similarity between population vectors of resampled ensembles has a maximum value when ensemble size is unchanged (Figure 6A). Furthermore, the most significant neurons from cortical ensembles achieve the best accuracy, precision and recall when predicting the presented visual stimuli, compared with resized ensembles (Figure 6B-D).

So far we have shown that the most significant neurons identified by CRFs represent the optimal population to predict external visual stimuli. This fact raises the question of whether CRFs ensembles are a specific non-random subgroup. To answer this question, we randomly sampled a subset of the total neuronal population, ranging from 10% to 90% of all neurons (Figure 6 E-H). We observed that prediction performance from random groups of neurons is significantly lower than CRFs ensemble performance (Figure 6 E-H), indicating that identified ensembles are non-random structures.

**CRFs as a tool for the targeted manipulation of cortical microcircuits**

A challenging issue regarding the design of closed-loop optogenetic experiments to manipulate behavioral tasks in awake animals is the identification of the dependencies between neurons that could be used to recall learned patterns. To investigate if our CRFs model based on population activity can predict changes in the functional connectivity of cortical microcircuits we compared the models generated by CRFs before and after two-photon population manipulation of a given set of neurons. It has been recently shown that the coordinated firing of an identified neuronal population imprints an artificial cortical ensemble (Carrillo-Reid et al., 2016). We demonstrate that the edge potential values are reorganized between photostimulated neurons but remained stable in non-photostimulated ones indicating that imprinted ensembles result from strengthening the functional connections of photostimulated neurons (FIG 7A conceptual). Interestingly the total number of edges depicted during ongoing activity remains the same suggesting that a new ensemble has been added to the network preserving an overall architecture. Finally, our approach also revealed the existence of highly connected neurons that are able to recall imprinted ensembles demonstrating that CRFs could be used to target specific members of ensembles that play a key role in the computational properties of cortical microcircuits (FIG 7B conceptual).

**Discussion**

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 with single cell resolution.

CRFs model the conditional distribution *p*(**y**|**x**) for observed population activity **x** over all nodes and network states **y** with an associated graphical structure. 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).

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).

To address these questions, it is necessary to identify online the most representative elements from a given neuronal ensemble. We demonstrate that the activity of the most representative neurons identified from each cortical ensemble is sufficient to predict a given visual stimulus.

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., 2005), hubs and modules (Bullmore and Sporns, 2009).

**Figure legends**

**Figure 1. Two-photon imaging of population activity in primary visual cortex in awake behaving mice**

(A) Illustration of the experimental setup. Mice were head fixed to a two-photon microscope, and were allowed to run on a treadmill. Visual stimuli of drifting gratings were presented on a screen to the monocular side of the mice. (B)A representative field of view with detected ROIs. Scale bar represents xxx. (C) Schematic of generating the dissimilarity matrix for finding neuronal ensembles. Binary spike vectors for each frame were normalized using TF-IDF, and the cosine distance between every pair of normalized vectors were calculated, which was further used as the input to SVD. (D) Example of visual ensemble activity identified using SVD. Red cells represent the ensemble of horizontal visual stimuli; blue cells represent the ensemble of vertical visual stimuli. (E) Activities of visual and spontaneous ensembles. Raster plot shows the extracted spikes during spontaneous activity or under visual stimuli. Mouse was shown with horizontal and vertical drifting gratings in an alternative fashion. Light red and blue vertical stripes indicate the time of horizontal and vertical stimuli, respectively. Red box highlights the activity of significant neurons for horizontal visual stimuli. Blue box highlights the activity of significant neurons for vertical visual stimuli. Black and purple box highlight significant neurons for spontaneous activity. Gray box shows the rest of the neurons. Scale bar represents 400 frames.

**Figure 2. Conditional random field model predicts visual stimulus**

e (B) Illustration of hidden nodes in a CRF model. In this case, two hidden nodes (squares) were added for the horizontal (red) and vertical (blue) visual stimuli, separately. Nodes that are directly connected to the two hidden nodes are also highlighted in the corresponding color. (C) An example of graphs constructed with hidden nodes. Nodes that are either directly connected to the hidden nodes or indirectly connected to the hidden nodes through one intermediate nodes are highlighted. Connecting edges between them are also highlighted. Square on the upper left corner corresponds to horizontal stimulus (red); square on the lower left corner corresponds to vertical stimulus (blue). (D) Example of relative log-likelihood calculated by the CRF model. Black trace shows . Gray dashed line represents 0. Light red and blue vertical stripes indicate the time of horizontal and vertical stimuli, respectively. (E) Prediction raster plot from the example in (D). Top panel shows the prediction for horizontal stimulus; bottom panel shows the prediction for vertical stimulus. (F) Relative log-likelihood during horizontal and vertical stimuli. Red box represents the distribution of relative log-likelihood during horizontal stimulus; blue box represents the vertical stimulus. Gray region represents the threshold of 3 times baseline standard deviation level. (G-I) Accuracy (G), precision (H) and recall (I) of prediction.

**Figure 3. Graph properties of CRF models and correlation-based models**

(A) An examples of graphs constructed with CRF model and with pairwise correlations (CC). In the latter case, pairwise Pearson correlations between frames were calculated, and the threshold is determined by 5% significance level of correlation values of shuffled data. Here node size is proportional to the node degree, and the edge color represents the synchrony edge potential (ф11+ ф00- ф01- ф10). (B) Graph density of CRF and CC models. (C-E) The complementary cumulative distribution of node degrees (C), local clustering coefficients (D), and eigenvector centrality (E) in CC and CRF model. Both models show more dispersed distributions than random models, while the properties of CRF model differ from CC model.

**Figure 4. Maximal clique properties of CRF models and correlation-based models**

(A) Illustration of 3, 4 and 5-cliques with corresponding adjacency matrices. (B) An example of maximal cliques that contain at least one node directly connected with the hidden nodes. The top panel highlights all the maximal cliques for horizontal stimulus; the bottom panel highlights all the maximal cliques for vertical stimulus. (C) The number of maximal cliques in CC and CRF models. (D) The complementary cumulative distribution of maximal clique sizes.

**Figure 5. Predicting visual stimuli with identified significant neurons**

(A) Examples of significant neurons identified using SVD with TF-IDF normalization and CRF models. Red and blue circles represent the ensemble cells of horizontal and vertical visual stimuli, respectively; nodes filled with red and has blue edges represents significant neurons shared between the two visual stimuli. (B) Percentage of significant neurons with SVD and CRF models. (C) Percentage of shared neurons identified by SVD and CRF models. Percentage is calculated by number of cells belong to both models divided by the sum of number of unique cells in two models. (D) Raster plot of by significant neurons from two models. Black bars in the raster plot indicate the predicted stimulus-on frames. Light red and blue vertical stripes indicate the time of horizontal and vertical stimuli, respectively. (E) Examples of raw calcium traces from significant neurons in CRF model during visual stimuli. (F) Cosine similarities of frames with stimuli that match or not match the model. (G-I) Accuracy (G), precision (H) and recall (I) of predictions from different models.

**Figure 6. Ensembles are composed of groups of neurons that are specific to the stimulus**

(A) Examples of identified ensemble cells, 10% subsample of ensemble cells, randomly sampled cells of 20% ensemble cell number, and randomly sample cells of 90% ensemble cell number. Their corresponding prediction raster plot and frame cosine similarities are shown on the right. (B) Mean cosine similarity of randomly down-sampled or up-sampled ensemble groups, in frames with matching or non-matching stimulus. (C-D) Accuracy (C), precision (D) and recall (E) of predictions from randomly down-sampled or up-sampled ensemble groups. (F) Mean cosine similarity of randomly sampled cells, in frames with matching or non-matching stimulus. (G-I) Accuracy (G), precision (H) and recall (I) of predictions from randomly down-sampled or up-sampled ensemble groups.

**References**

Achard, S., Bullmore, E., 2007. Efficiency and Cost of Economical Brain Functional Networks. PLoS Comput. Biol. 3, e17. doi:10.1371/journal.pcbi.0030017

Achard, S., Salvador, R., Whitcher, B., Suckling, J., Bullmore, E., 2006. A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. J. Neurosci. 26, 63–72. doi:10.1523/JNEUROSCI.3874-05.2006

Badhwar, R., Bagler, G., 2015. Control of Neuronal Network in Caenorhabditis elegans. PLoS One 10, e0139204. doi:10.1371/journal.pone.0139204

Bonifazi, P., Goldin, M., Picardo, M.A., Jorquera, I., Cattani, A., Bianconi, G., Represa, A., Ben-Ari, Y., Cossart, R., 2009. GABAergic hub neurons orchestrate synchrony in developing hippocampal networks. Science 326, 1419–24. doi:10.1126/science.1175509

Bullmore, E., Sporns, O., 2009. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat. Rev. Neurosci. Neurosci. 10, 186–98. doi:10.1038/nrn2575

Carrillo-Reid, L., Miller, J.-E.K., Hamm, J.P., Jackson, J., Yuste, R., 2015. Endogenous sequential cortical activity evoked by visual stimuli. J. Neurosci. 35, 8813–28. doi:10.1523/JNEUROSCI.5214-14.2015

Choi, Y., Cardie, C., Riloff, E., Patwardhan, S., 2005. Identifying sources of opinions with conditional random fields and extraction patterns. Proc. Conf. Hum. Lang. Technol. Empir. Methods Nat. Lang. Process. HLT 05 355–362. doi:10.3115/1220575.1220620

Downes, J.H., Hammond, M.W., Xydas, D., Spencer, M.C., Becerra, V.M., Warwick, K., Whalley, B.J., Nasuto, S.J., 2012. Emergence of a small-world functional network in cultured neurons. PLoS Comput. Biol. 8, e1002522. doi:10.1371/journal.pcbi.1002522

Eguíluz, V.M., Chialvo, D.R., Cecchi, G.A., Baliki, M., Apkarian, A.V., 2005. Scale-free brain functional networks. Phys. Rev. Lett. 94, 018102. doi:10.1103/PhysRevLett.94.018102

Fair, D.A., Cohen, A.L., Dosenbach, N.U.F., Church, J.A., Miezin, F.M., Barch, D.M., Raichle, M.E., Petersen, S.E., Schlaggar, B.L., 2008. The maturing architecture of the brain’s default network. Proc. Natl. Acad. Sci. U. S. A. 105, 4028–32. doi:10.1073/pnas.0800376105

Gururangan, S.S., Sadovsky, A.J., MacLean, J.N., 2014. Analysis of graph invariants in functional neocortical circuitry reveals generalized features common to three areas of sensory cortex. PLoS Comput. Biol. 10, e1003710. doi:10.1371/journal.pcbi.1003710

Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C.J., Wedeen, V.J., Sporns, O., 2008. Mapping the structural core of human cerebral cortex. PLoS Biol. 6, e159. doi:10.1371/journal.pbio.0060159

He, X., Zemel, R.S., Carreira-Perpinan, M.A., 2004. Multiscale conditional random fields for image labeling. Proc. 2004 IEEE Comput. Soc. Conf. Comput. Vis. Pattern Recognit. 2, 695 –702. doi:10.1109/CVPR.2004.1315232

He, Y., Chen, Z.J., Evans, A.C., 2007. Small-world anatomical networks in the human brain revealed by cortical thickness from MRI. Cereb. Cortex 17, 2407–19. doi:10.1093/cercor/bhl149

Iturria-Medina, Y., Sotero, R.C., Canales-Rodríguez, E.J., Alemán-Gómez, Y., Melie-García, L., 2008. Studying the human brain anatomical network via diffusion-weighted MRI and Graph Theory. Neuroimage 40, 1064–76. doi:10.1016/j.neuroimage.2007.10.060

Khazaee, A., Ebrahimzadeh, A., Babajani-Feremi, A., 2015. Identifying patients with Alzheimer’s disease using resting-state fMRI and graph theory. Clin. Neurophysiol. 126, 2132–41. doi:10.1016/j.clinph.2015.02.060

Lafferty, J., McCallum, A., Pereira, F.C.N., 2001. Conditional random fields: Probabilistic models for segmenting and labeling sequence data. ICML ’01 Proc. Eighteenth Int. Conf. Mach. Learn. 8, 282–289. doi:10.1038/nprot.2006.61

Li, C.-T., Yuan, Y., Wilson, R., 2008. An unsupervised conditional random fields approach for clustering gene expression time series. Bioinformatics 24, 2467–73. doi:10.1093/bioinformatics/btn375

Liu, X., Ramirez, S., Pang, P.T., Puryear, C.B., Govindarajan, A., Deisseroth, K., Tonegawa, S., 2012. Optogenetic stimulation of a hippocampal engram activates fear memory recall. Nature 484, 381–385. doi:10.1038/nature11028

Liu, Y., Carbonell, J., Weigele, P., Gopalakrishnan, V., 2006. Protein fold recognition using segmentation conditional random fields (SCRFs). J. Comput. Biol. 13, 394–406. doi:10.1089/cmb.2006.13.394

Micheloyannis, S., Vourkas, M., Tsirka, V., Karakonstantaki, E., Kanatsouli, K., Stam, C.J., 2009. The influence of ageing on complex brain networks: a graph theoretical analysis. Hum. Brain Mapp. 30, 200–8. doi:10.1002/hbm.20492

Palla, G., Palla, G., Derényi, I., Derényi, I., Farkas, I., Farkas, I., Vicsek, T., Vicsek, T., 2005. Uncovering the overlapping community structure of complex networks in nature and society. Nature 435, 814–8. doi:10.1038/nature03607

Peng, H.-K., Zhu, J., Piao, D., Yan, R., Zhang, Y., 2011. Retweet Modeling Using Conditional Random Fields, in: 2011 IEEE 11th International Conference on Data Mining Workshops. IEEE, pp. 336–343. doi:10.1109/ICDMW.2011.146

Ramirez, S., Liu, X., Lin, P.-A., Suh, J., Pignatelli, M., Redondo, R.L., Ryan, T.J., Tonegawa, S., 2013. Creating a false memory in the hippocampus. Sci. (New York, NY) 341, 387–391. doi:10.1126/science.1239073

Ravikumar, P., Wainwright, M.J., Lafferty, J.D., 2010. High-dimensional Ising model selection using ℓ1-regularized logistic regression. Ann. Stat. 38, 1287–1319.

Sadovsky, A.J., MacLean, J.N., 2014. Mouse visual neocortex supports multiple stereotyped patterns of microcircuit activity. J. Neurosci. 34, 7769–77. doi:10.1523/JNEUROSCI.0169-14.2014

Sato, K., Sakakibara, Y., 2005. RNA secondary structural alignment with conditional random fields. Bioinformatics 21, ii237–ii242. doi:10.1093/bioinformatics/bti1139

Shimono, M., Beggs, J.M., 2015. Functional Clusters, Hubs, and Communities in the Cortical Microconnectome. Cereb. Cortex 25, 3743–57. doi:10.1093/cercor/bhu252

Sminchisescu, C., Kanaujia, A., Metaxas, D., 2006. Conditional models for contextual human motion recognition. Comput. Vis. Image Underst. 104, 210–220. doi:10.1016/j.cviu.2006.07.014

Sporns, O., 2000. Theoretical Neuroanatomy: Relating Anatomical and Functional Connectivity in Graphs and Cortical Connection Matrices. Cereb. Cortex 10, 127–141. doi:10.1093/cercor/10.2.127

Sporns, O., Honey, C.J., K??tter, R., 2007. Identification and classification of hubs in brain networks. PLoS One 2, e1049. doi:10.1371/journal.pone.0001049

Stetter, O., Battaglia, D., Soriano, J., Geisel, T., 2012. Model-free reconstruction of excitatory neuronal connectivity from calcium imaging signals. PLoS Comput. Biol. 8, e1002653. doi:10.1371/journal.pcbi.1002653

Tang, K., Gubert, H., Tonge, R., Wang, A., Wu, L., Campbell, D., Kedzie, C., Wang, L., Russell, A., Kimball, A., Kambadur, A., Mann, G., Pacifico, S., Hodson, J., Yao, D.D., Mckeown, K., Jebara, T., n.d. Learning a Graphical Model of Bloomberg Financial and News Data 1–3.

Tang, K., Ruozzi, N., Belanger, D., Jebara, T., 2016. Bethe Learning of Graphical Models via MAP Decoding. Artif. Intell. Stat.

Towlson, E.K., Vértes, P.E., Ahnert, S.E., Schafer, W.R., Bullmore, E.T., 2013. The rich club of the C. elegans neuronal connectome. J. Neurosci. 33, 6380–7. doi:10.1523/JNEUROSCI.3784-12.2013

van den Heuvel, M.P., Stam, C.J., Boersma, M., Hulshoff Pol, H.E., 2008. Small-world and scale-free organization of voxel-based resting-state functional connectivity in the human brain. Neuroimage 43, 528–39. doi:10.1016/j.neuroimage.2008.08.010

Wang, J., Zuo, X., He, Y., 2010. Graph-based network analysis of resting-state functional MRI. Front Syst Neurosci 4, 16. doi:10.3389/fnsys.2010.00016

Yatsenko, D., Josić, K., Ecker, A.S., Froudarakis, E., Cotton, R.J., Tolias, A.S., 2015. Improved estimation and interpretation of correlations in neural circuits. PLoS Comput. Biol. 11, e1004083. doi:10.1371/journal.pcbi.1004083

Yu, S., Huang, D., Singer, W., Nikolic, D., 2008. A small world of neuronal synchrony. Cereb. Cortex 18, 2891–901. doi:10.1093/cercor/bhn047

Zuo, X.-N., Ehmke, R., Mennes, M., Imperati, D., Castellanos, F.X., Sporns, O., Milham, M.P., 2012. Network centrality in the human functional connectome. Cereb. Cortex 22, 1862–75. doi:10.1093/cercor/bhr269

**Experimental Procedures**

***Conditional Random Fields***

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

where is a vector of sufficient statistics of the distribution, is a vector of parameters, and is the partition function:

The conditional probability can be factored over a graph structure , where is the collection of nodes representing observation variables and target variables, and is the collection of subsets of . The conditional dependencies can be then written as

This model is a generalized version of Ising models, which have been previously applied to model neuronal networks (Yu et al., 2008). The log-likelihood of each observation can be then written as:

Given the inferred binary spikes from raw imaging data, we construct a CRF model by two steps: (1) structure learning, and (2) parameter learning. For structure learning, we learnt a graph structure using l1-regularized logistic regression and performed structure elimination by thresholding the edge potentials (Ravikumar et al., 2010). Based on the learnt structure, we use the Bethe approximation to approximate the partition function, and iterative Frank-Wolfe methods to perform parameter estimation by maximizing the log-likelihood of the observations with a quadratic regularizer (Tang et al., 2016):

Cross-validation was done to find the best model parameters via model likelihood.

***Shuffling Methods***

We performed shuffling of binary data while preserving the activity level for each cell and each frame. To do this, we randomly selected two cells and two time points where they show different activity (‘0’ and ‘1’), and exchange the activity pairs across them. This procedure was repeated for a large number (2n, where n is the number of total spikes) to complete one shuffling. For each dataset, shuffling was done for 100 times unless noted otherwise.

***Correlation-based Graphs***

To construct correlation-based graphs, we first calculated the Pearson correlation coefficients between the binary spike vectors of each pair of cells. Then, we generated correlation threshold by calculating Pearson correlation coefficients of shuffled data, fitting the coefficients to a normal distribution, and finding the 95% CDF level.

***Maximal Cliques***

Finding maximal cliques using exhaustive search methods is computationally unrealistic with a relatively large number of vertices. To find maximal cliques in an adjacency matrix efficiently, we used the Bron-Kerbosch algorithm. This algorithm recursively detects all the maximal cliques in a given graph . The algorithm starts with three sets: an empty set with currently growing maximal clique, a set with all prospective vertices connected to all vertices in , and a set with nodes that have been processed. In each call of the algorithm, a pivot vertex with the largest node degree is chosen. Since for each vertex , either the vertex or its non neighbors but not both will be in a clique, each is tested as candidate component for by recursively calling the algorithm with and restricted to the neighbors of . The algorithm then moves from to , and reports as a maximal clique when both and are empty.

***Graph properties***

Given the adjacency matrix where if node is linked to node , we investigated the following graph properties: graph density, node degrees, local clustering coefficients, and eigenvector centrality. Graph density is calculated as the number of existing edges divided by the number of total possible edges:

where *NV* is the number of vertices in the graph. Node degree is defined for node as the number of edges connected to the it:

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Local clustering coefficient is defined for each node as the fraction edges connected to it over the total number of possible edges between the node's neighbors (nodes that have a direct connection with it). Eigenvector centrality is defined on the relative centrality score matrix , where

This can be written in the form of eigenvector equation:

Solving the above equation gives a set of eigenvalues and associated eigenvectors. The entry of the eigenvector associated with the largest gives the eigenvector centrality for node .

***Prediction with cosine similarity***

significant neurons