Each submission should be accompanied by a cover letter, which should contain a brief explanation of what was previously known, the conceptual advance provided by the findings, and the significance of the findings to a broad readership. A cover letter may contain suggestions for appropriate reviewers and up to three requests for reviewer exclusions. The cover letter is confidential to the editor and will not be seen by reviewers.

We submit our manuscript “Conditional random fields for single cell targeting of cortical ensembles” as a NeuroResource for your consideration.

In this paper, we developed a method to identify single neuron targets during specific physiological processes for optogenetic manipulations. Using probabilistic graphical models, we built functional models of cortical neurons from two-photon calcium imaging *in vivo*. With these models, we demonstrated that we are able to find neuronal ensembles corresponding to specific stimuli, and to identify the important cells within the ensemble that are capable of changing the ensemble activity. Moreover, our method can capture network reconfigurations induced by two-photon optogenetic stimulation. We demonstrated that our method is stable across different datasets acquired with varying experimental conditions, and our codebase will be made publicly available upon publication.

Our method is novel and significant for a broad scientific community because it provides a tool for manipulating the network activity via single important neurons, as well as quantifying the resulting functional changes of the network. During sensory, behavioral and cognitive processes, the importance of coordinated firing of neuronal populations have been implied in previous research (Harvey et al., 2012). However, the role of specific groups of neurons in these functions have been difficult to elucidate since it requires the identification of single cell targets. Our approach contributes to the designing of single cell optogenetic manipulation in closed loop experiments. This will allow us to investigate the role of a specific subpopulation of neurons during different behavioral events. In clinical research, electrical stimulation of visual cortex has been used for decades as an attempt to provide useful visual sensations to patients that have lost the functionality of their eyes (Brindley and Lewin, 1968). A challenging issue regarding this method is the use of devices with a large number of electrodes (Shepherd et al., 2013). We demonstrated that the identification of neurons with pattern completion capability could be used to reduce the number of active points that require stimulation. Targeting single neurons offers the possibility to alter behavior or treat pathological disorders at microcircuit level with single cell resolution.

As reviewers we recommend Ed Bullmore, Olaf Sporns, Danielle Bassett,