2017 IEEE International Conference on Cyborg and Bionic Systems
October 17 - 19, 2017, Beijing, China

Dynamic micro-circuit analysis for calcium imaging data

Rong Chen, Senior Member, IEEE, Huaping Wang, Member, IEEE, Jiping He, Senior Member, IEEE, Da-Ting Lin

Abstract— **Micro-circuits are mesoscopic scale networks and play an important role in cognition, emotion, and learning. Analysis of micro-circuits provides a system-level understanding of the neurobiology of health and disease. We propose a computational framework for micro-circuit analysis. The proposed framework combines miniature cellular imaging and network modeling. We used the proposed framework to study micro-circuits of D1 and D2 medium spiny neurons in the dorsal striatum for saline and cocaine injection. We found that cocaine injection had reduced numbers of total-, cross-, and self-links, relative to saline injection. The proposed method enables us to develop a circuit-based approach to understand the brain.**

Keywords—micro-circuits, dynamics Bayesian network, graph theoretical analysis

I. INTRODUCTION

The analysis of circuit of interacting neurons has the potential to revolutionize neuroscience research and represents a real gap[1]. Increasing evidence supports nonrandom connectivity patterns exist between adjacent neurons during cognition and emotion[2]–[5]. Interactions among a set of neurons form a mesoscopic scale network (millimeter-to-micrometer resolution)[1]. Mesoscopic scale networks are micro-circuits. Micro-circuits are likely the substrate for cognitive processes underlying learning and memory. Analysis of micro-circuits measures intrinsic firing patterns and provides a system-level understanding of the neurobiology of health and disease.

Miniature cellular imaging[6]–[8] enables us to investigate micro-circuits during behaviors, for an understanding of network architecture of behavior, cognition, and emotion. Miniature cellular imaging records neuronal activity at cellular and sub-second levels of spatial and temporal resolution in freely moving animals. It is complementary to other brain recording techniques. First, compared with multi-electrode recording, miniature cellular imaging can probe all cells in the field of view[9]. Second, compared with magnetic resonance imaging or positron emission tomography that measures brain activity at the macroscopic scale with low temporal resolution, miniature cellular imaging provides high spatial and temporal resolution. Third, compared with non-miniature cellular imaging, miniature microscopes allow concurrent tracking of neural calcium activities of hundreds of neurons in superficial and deep brain areas of freely moving mice and rats.

We propose a computational framework for micro-circuit analysis called Advanced Computing for MIcro-Circuit Analysis (ACMICA). ACMICA combines miniature cellular imaging and network modeling. Miniature cellular imaging data analysis generally includes two steps: data preprocessing and modeling. Data preprocessing includes image registration, cell sorting, and spike detection. Several tools have been previously developed for data preprocessing[10], [11]. However, subsequent modeling methods are often based on simple statistical analysis methods such as correlation analysis. Such methods have limited capability to reveal interactions among neural dynamics. We hereby propose ACMICA to examine micro-circuits. ACMICA enables us to move toward a circuit-based approach to understand the brain, in which a behavior is understood to result from specific spatiotemporal patterns of circuit activity related to specific neuronal populations.

Rong Chen is with Beijing Advanced Innovation Center for Intelligent Robots and Systems, Beijing Institute of Technology, Beijing, China, and Department of Radiology, University of Maryland, Baltimore, MD, USA. Huaping Wang and Jiping He are with Beijing Advanced Innovation Center for Intelligent Robots and Systems, Beijing Institute of Technology, Beijing, China. Da-Ting Lin is with National Institute on Drug Abuse, National Institutes of Health (NIH), Baltimore, MD, USA. Corresponding author: Rong Chen, rong.chen.mail@gmail.com

II. METHODS

In a micro-circuit, nodes are neurons, and edges (links) represent interactions among neural dynamics. If a set of nodes, π_i, affects the activity of node i in a statistical sense, then there exists a link between node i and the nodes in π_i.

Figure 1 is the flowchart of ACMICA. ACMICA includes these components: preprocessing, association calculation, graph generation, graph descriptor calculation, and brain-behavior analysis. ACMICA uses a validated miniature cellular imaging data preprocessing pipeline[13] including image registration, cell sorting, and spike detection. Let P and T denote the number of neurons and the number of time

978-1-5386-3194-2/17/$31.00 © 2017 IEEE

points, respectively. The preprocessing step results in $\mathbf{x}_{1:T}$ and $\mathbf{s}_{1:T}$. For each subject, $\mathbf{x}_t$ is a P-dimensional vector representing calcium transients of all neurons at time t; and the sequence $\mathbf{x}_{1:T} = (\mathbf{x}_1, \ldots, \mathbf{x}_T)$ represents calcium transients for all time points. For neuron i, $s^i = 1$ indicates a calcium transient event, while $s^i = 0$ indicates no event. The collection of $\mathbf{s}_t$ is $\mathbf{s}_{1:T}$.

We use a Dynamic Bayesian Network (DBN) to represent interactions among neural dynamics. A DBN is an extension of Bayesian network to model temporal processes. DBNs can characterize system dynamics, handle noisy data, to describe locally interacting processes, and to support causal inference[12]. A DBN is defined as a pair, $(B_1, B_{\rightarrow})$, where B_1 is a Bayesian network defining the baseline probability distribution; and $B_{\rightarrow}$ defines the transition probability $P(\mathbf{s}_{t+1} \mid \mathbf{s}_t)$. That is, $B_{\rightarrow}$ is a two-slice temporal Bayesian network (2TBN).

Network construction infers the graph based on $\mathbf{s}_{1:T}$. It has two steps: association calculation and graph generation. In association calculation, the state of node i at time point t is determined by the states of its parent set before t, and independent of the states of any other nodes. We use π_i to denote the parent set of node i. π_i is a subset of $\mathbf{S}_{t-1}$. For example, if S^A_{t-1} and S^B_{t-1} determines S^C_t, then $\pi_C = (S^A_{t-1}, S^B_{t-1})$. The association between a node and a set of other nodes is measured by the Bayesian Dirichelet score[14]. For each node, we use the algorithm in [12] to search for a set of nodes which maximizes the Bayesian Dirichelet score. This set of nodes is π_i. Based on π_i, we can generate a graph G. G describes the interactions among neural dynamics.

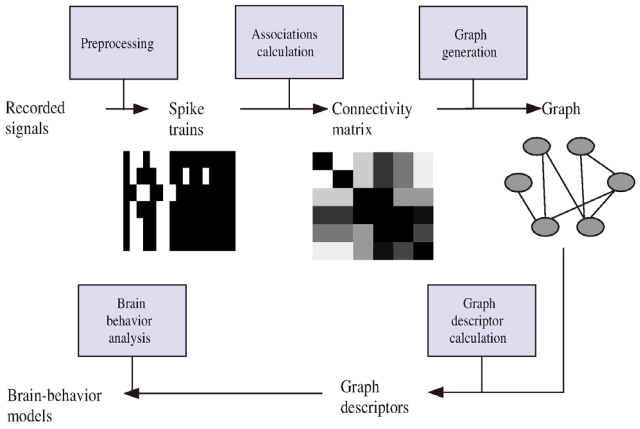

Figure 1 Flowchart of ACMICA

In graph descriptor calculation, we calculate a set of graph descriptors to characterize graph complexity. Graph descriptors are quantitative metrics to represent micro-circuit characteristics. Graph descriptors are numerical graph invariants that quantitatively characterize the topology or the information-theoretic aspect of the underlying network.

The last step is brain-behavior analysis to model associations among graph descriptors and behavior variables. We generate a micro-circuit for each experimental condition. Then we calculate graph descriptors. We compare graph descriptors across different conditions.

III. RESULTS

In this experiment, we examined micro-circuits of D1 and D2 medium spiny neurons (MSNs) in the dorsal striatum. We re-analyzed the MSN data described in [13]. Dr. Da-Ting Lin at National Institute on Drug Abuse acquired this dataset[13]. In this dataset, Cre-dependent AAV-GCaMP6 was injected into D1-Cre and D2-Cre mice to selectively label D1- or D2-MSN in the dorsal striatum. Subsequently, a gradient index (GRIN) lens was implanted into the dorsal striatum, and a calcium imaging device was mounted above the GRIN lens.

For a mouse, six sessions of MSN (D1 or D2) neural activity data for about 200 neurons in the dorsal striatum were acquired. There were two conditions in the experiment: saline injection and cocaine injection. Let C denote this behavior variable. For each condition (saline or cocaine injection), three sessions of 5-minute imaging for calcium signal were conducted; and there was a 5-minute rest between two consecutive sessions. In each session, 3000 images were acquired. There were 18000 images in total for saline or cocaine injection. The above procedure was repeated for five days.

Using ACMICA, we constructed a micro-circuit for each condition and day. There were five days and two conditions (saline or cocaine injection). Therefore, we generated 10 networks for each mouse.

Figure 2 is the generated networks for a D1-MSN at day 1. The left panel is the network for saline injection and the right panel is for cocaine injection.

We classified the detected links as self-link or cross-link. A

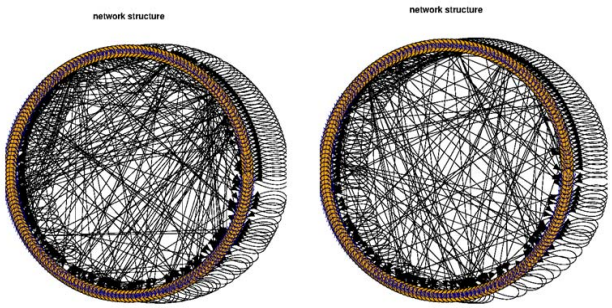

Figure 2 Micro-circuits for saline (left panel) and cocaine injection (right panel).

self-link is a link representing that the state of a neuron at time