Neuron Activity Extraction and Network Analysis on Mouse Brain Videos

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***Abstract*—Modern brain mapping techniques are producing increasingly large datasets of anatomical or functional connection patterns. Recently, it became possible to record detailed live imaging videos of mammal brain while the subject is engaging routine activity. We analyze a dataset of videos recorded from ten mice to describe how to detect neurons, extract neuron signals, map correlation of neuron signals to mice activity, detect the network topology of active neurons, and analyze network topology characteristics. We propose neuron position alignment to compensate the distortion and movement of cerebral cortex in live mouse brain and the background luminance compensation to extract and model neuron activity. To find out the network topology as an undirected graph model, a cross-correlation based method is proposed and used for analysis. Afterwards, we did preliminary analysis on network topologies. The significance of this paper is on how to extract neuron activities from live mouse brain imaging videos and a network analysis method to analyze topology that can potentially provide insight on how neurons are actively connected under stimulus, rather than analyzing static neural networks.**

I. Introduction

Brain neurons are excitable cells, which can receive both electrical and chemical stimulus and forward these signals to other neurons. Some medical scientists [1]–[3] utilized specific equipment, such as fMRI, to record the behaviors of neurons. However, fMRI requires several seconds of scanning to get an image, which makes it impossible to measure the live real-time simultaneous brain activities on the neuron level. Recent progresses in neural science using calcium imaging on microscopic whole-brain imaging [4] can record several frames per second on the live brain activities, and thus make it possible for researchers to study collective brain neuron activities towards specific stimulus, *e.g.*, measuring responsive neuron networks in the visual processing area while a mouse is seeing different patterns.

In a sequence of calcium-imaging videos that records live mouse brain neuron activities, each neuron varies between two states: lighting (active mode) and shading (inactive mode). To extract such neuron activity flashing signals, we first need to find out where the neurons are in the recorded videos. We propose a neuron position alignment method to compensate the distortion and movement of cerebral cortex in live mouse brain. To extract neuron signals under background variation, a luminance compensation is proposed to effectively eliminate the noise. Next, an neuron activity model is proposed to simulate a neuron firing status. By applying the proposed extraction algorithms, we can discover whether which neurons are active in each video frame. We assume that when neurons was stimulated, they become active for a while and then passes this stimulation to their connected relevant neurons. Afterward, these neurons become inactive again. We assume these flashing patterns of neurons were collected in the video sequences. Based on the literature, there are some common agreements about the flashing patterns of neurons that are applicable:

- First, the duration of active mode or inactive mode for each neuron is independent from others unless they are connected.
- Second, groups of neurons may work together for a certain purpose of brain. For example, when a person is seeing or thinking, some specific neurons are stimulated by the signal of "seeing" or "thinking" and a bunch of other neurons are triggered to work together.

In order to construct a specific network topology of brain neurons from a given flashing patterns of neurons, firstly, we can model the network as a set of neurons V, where $v_i \in V$ is the ith neuron with $i \in \{1, ..., n\}$ and $|V| = n$ is the number of neurons inside this set, in conjunction with a set of edges E between neuron pairs where $e_{ij} \in E$ represents the edge between ith and jth neurons, where $i, j \in \{1, ..., n\}$ and e_{ij} defines the weight of edge between node i and j. Therefore, the connectivities between all neuron pairs inside the brain form a specific network topology which can be described as a graph. By observing the flashing patterns of neurons, we propose a network model to analyze interaction between brain neurons. With network analysis, one of our goals is to find out the key neurons with Small World properties. These key neurons can then be used for future stimulation experiments that can potentially impact the memory or perception of mouse brain.

For the layout of this paper, Section II describes the proposed algorithm for signal extraction of brain neuron imaging. Network topology for mouse brain is explained in Section III. Verification of the proposed model and experimental results are presented in Section IV. Finally, Section V summarizes out work.

*Indicates equal contributions.

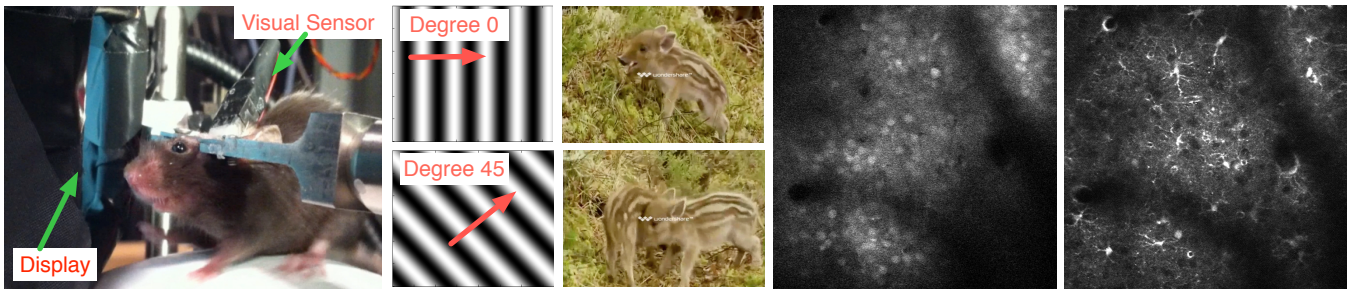

Figure 1. Experiment setting of brain neuron imaging. The mouse is under various visual stimulus and its neuron status is recored with calcium images and fluorescence images.

II. Neuron Signal Extraction and Analysis from Live Brain Videos

Figure 1 shows the experimental setting of mouse brain imaging. A mouse is settled up on a white sphere where it is able to spontaneously move as shown in Figure 1(a). There is a display screen in front of the mouse to play visual stimulus like the grating videos in Figure 1(b) or nature videos in Figure 1(c). Two sensing methods, were used – calcium imaging [5] and 2-photon microscopy [6], to record the activity of brain neurons with calcium images and fluorescence images, respectively. Calcium images shown in Figure 1(d) are able to record the density of calcium ion within brain neurons and tissue cells. Fluorescence images shown in Figure 1(e) record the distribution of tissue cells, which are used as a reference in filtering tissue cells in calcium images. In this section, we propose methods to extract neuron activity and detect firing neurons via captured videos.

A. Neuron Position Alignment

In calcium imaging, neuron activity is recorded as luminance variation among consecutive images. Activity of each brain neuron can be analyzed by the luminance variation on temporal distribution. However, due to the experiments with live mouse, captured images are usually vibrating from mouse movement that makes neuron position misaligned on the consecutive frames. In the lab experiments, the misalignment of neuron position mainly comes from mouse's physical movement during image capturing. Although the sensor is fixed on mouse head, there is still some vibration when mouse spontaneously moves. To deal with the misalignment, we propose a global neuron plane to record and annotate all observed neurons as shown in Figure 2. Each captured image is projected on global neuron plane by perspective motion model to compensate sensor translation, rotation, titling and panning. The parameters of projective transform can be calculated by minimizing the cost function E,

$$E = \sum_{i \in N} |e(i)|^2 = \sum_{i \in N} |I(x_c, y_c) - I'(x'_c, y'_c)|^2, \quad (1)$$

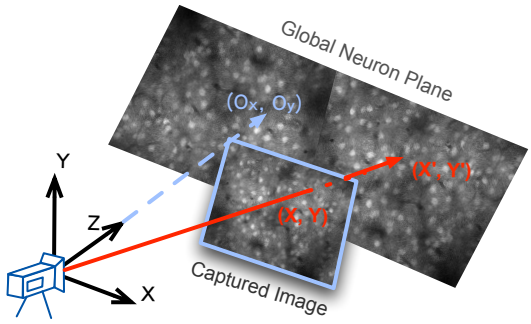

Figure 2. Projecting the captured images to global neuron plane for neuron position alignment.

where $I(x_c, y_c)$ is the luminance value of pixel (x_c, y_c) in the capture frame, $I'(x'_c, y'_c)$ is the luminance value of the corresponding position (x'_c, y'_c) in the global neuron plane, and N is the set of pixels on the overlap region. The minimization process is implemented by use of gradient iterative minimization algorithm as shown below.

$$\mathbf{M_d} = \mathbf{M_{d-1}} + \mathbf{A}^{-1}\mathbf{B}, \quad (2)$$

$$A_{k,j} = \sum_{i \in N} \frac{\partial e(i)}{\partial m_k} \frac{\partial e(i)}{\partial m_j}, B_k = \sum_{i \in N} -e(i) \frac{\partial e(i)}{\partial m_k}, \quad (3)$$

where $\mathbf{M_d}$ is the transformation matrix at the d-th iteration, $\mathbf{A}$ is an 8×8 matrix for perspective transform, B is an eight-tuple vector, $\partial e(i)$ is the differential of pixel difference in (1), and m_k and m_j are the transformation parameters from m_1 to m_8. The iterative process is repeated until the improvement of each parameter converges, or the number of iteration is larger than the maximum number of iteration.

B. Background Luminance Compensation

Sometimes, the background luminance of captured images would dramatically enhance and then decline in a few frames. The enhancement of background luminance would also make neuron imaging brighter that may become a false positive in neuron activity analysis. From the experiments, it

seems that the background luminance variation comes from mouse movement that changes the focal depth of capturing sensor.

Here, a background luminance compensation is proposed to compensate the luminance change of neuron imaging. We assume the background luminance increasing/decreasing can be modeled as an overall luminance scaling on original pixel values. Therefore, by scaling the background luminance of each imaging frame to a constant, the background variation among consecutive frames can be compensated.

Because the non-neuron regions occupy large area of captured image, as shown in Figure 1(d), we can assume the peak index P of luminance histogram would be the background luminance, which can be calculated by (4).

$$P = \arg \max_{0 \le i \le 255} h(i), \tag{4}$$

where $h(i)$ is the luminance histogram of neuron imaging, and i is the luminance index.

$$h'(i) = h(i) f(D, P) \tag{5}$$

For each captured image, the luminance change is compensated by linearly scaling the histogram $h(i)$ to $h'(i)$ by $f(D, P)$, which is a linear function for aligning the peak histogram index P to the target constant D. The compensated luminance can reduce the false alarm in neuron firing detection.

C. Neuron Detection

With neuron position alignment and background luminance compensation, the global neuron plane shown in Figure 2 composes all observing neurons. Before analyzing neuron context like position, size, shape, and activity, a Bilateral filter [7] is applied for noise reduction. From literature [8], we know each neuron may have multiple synapses connecting to other neurons that a neuron shape can be visually similar to a circle.

For circle detection on neuron imaging, the first step is to employ edge filter to extract binary map $Edge(x_i, y_i)$, where x_i and y_i are the image coordinates on global neuron plane. Then we extend Hough transform [9], an algorithm used to detect straight line on a plane, to detect circles on $Edge(x_i, y_i)$. The accumulator plane of Hough transform would have to be replaced with an three-dimension accumulator volume: one for circle center $\underline{x}$, one for circle center $\underline{y}$, and the other for the circle radius $\underline{r}$. The equation can be formulated below,

$$\underline{r}^2 = (x_i - \underline{x})^2 + (y_i - \underline{y})^2, \forall Edge(x_i, y_i) = true. \tag{6}$$

The circles are detected by the peak distributions of $E(x_i, y_i)$ on $\underline{x}/\underline{y}/\underline{r}$ parameter spaces. The parameter spaces of $\underline{x}/\underline{y}/\underline{r}$ are limited to specific regions to increase the detection accuracy and decrease the computation time. Finally, a region is recognized as a neuron if the accumulator volume higher than a threshold. A higher threshold setting only preserves the shapes like perfect circles, and a lower threshold setting preserves the shapes including ellipse or polygon. Note that the detection results on global neuron plane should be exclusive of the detection results on fluorescence images as shown in Figure 1(e), which are tissue cells but neurons. The texture on fluorescence images are tissue cells that can be used as the mask to eliminate the false positive of detected neurons from calcium images.

D. Neuron Activity

After extracting neuron position and shape, the neuron activity can be analyzed with the luminance variation in temporal domain. From our observation, the luminance distribution of each neuron has different peak value and different mean value. It is difficult and inapplicable to set an absolute thread for all neurons in firing detection. How to model the neuron activity and detect firing neurons become a challenge.

Here, we propose an equation to model neuron activity by both considering absolute luminance value and relative luminance change on temporal distribution. The equation of neuron activity is modeled below.

$$N_t^i = P^i(L_t^i) + \omega L_t^i, \forall i \in N, t \in T, \tag{7}$$

where N_t^i is the neuron activity of neuron i at time index t, L_t is the absolute luminance value of the neuron, $P^i(L_t^i)$ is the term to model luminance change on temporal distribution, ω is a factor to balance both terms, N is total neuron number on global neuron plane, and T is the observation time window.

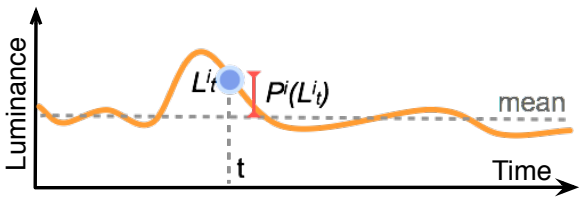

Figure 3. Neuron activity in time domain.

As shown in Figure 3, $P^i(L_t^i)$ can model the difference between current luminance value and the mean luminance value of neuron i. In other words, the same absolute difference would be recognized as higher neuron activity when a neuron has relative stable luminance change on temporal domain. The proposed neuron activity models both absolute luminance and the luminance change on temporal distribution for each neuron. For firing detection, we manually label hundreds of firing neurons and use SVM classifier to train the model for firing detection. A neuron activity would be recognized as firing by SVM classifier.

III. Network Topology for Mouse Brain

The neuron activity data are represented by the brightness of each neuron in each frame to capture the mouse brain neuron network topology. To apply techniques from network analysis we must first define the nodes and edges of an appropriate network. In the literature, there are two major kinds of networks that are reasonable to characterize brain neuron network: directed and undirected graph. To model the brain neuron network as an undirected graph, a method based on cross-correlation (CC) between each neuron pairs is proposed. When considering directed graph model, the causality between neurons can be represented by directionality and use causal Bayesian network to capture causality relationships between neurons.

To determine whether there is a binary edge between two neurons, we define an edge to exist between two nodes if their activeness data sequences are sufficiently coupled. There exist many measures to determine the coupling between two time series of data [10]. Here we modify the cross-correlation [11] and propose a linear coupling method specifically for mouse brain neuron. In signal processing, cross-correlation is a measure of similarity of two waveforms as a function of a time-lag applied to one of them. To find out whether two neurons have connection in signal transmission process, we will first calculate cross-correlation between each neuron pairs then stored them in a matrix $\mathbf{CX}$. Considering both the size of mouse brain neuron the speed of signal transmission in brain neuron and our video frame length, we find out that the middle three entries of cross-correlation sequence are the most representable ones to determine whether there is connection between those neurons. Entry $\mathbf{CX_{ij}}$ denotes the mean of middle three entries of the calculated sequences between activeness data sequences of neuron i and j. Based on matrix $\mathbf{CX}$, we set an undirected binary edge between two neurons when their cross-correlation metric is above a threshold T, which is showed as follows:

$$T = \frac{1}{N}\sum_{j} \mathbf{CX}(i,j) + \alpha \times std\left(\mathbf{CX}(i)\right) \qquad (8)$$

where *std* is the standard deviation and α is a coefficient to adjust the threshold. Because the mouse brain neurons can be represented as a 3D real world model, the difference of distances between neurons and camera may cause difference of neuron brightness. The utilization of standard deviation is aimed to avoid the influence coming from depth of each neuron.

Based on the proposed model above, we can further generate an undirected graph to represent a mouse brain neuron network topology and create Conditional Bayesian Networks. Because of the limitation of the paper length, this part of analysis is not reported in this paper.

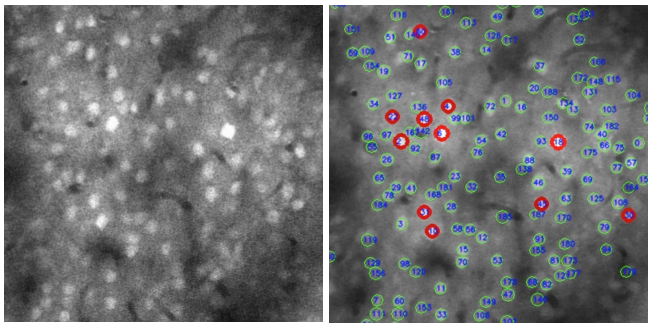

Figure 4. Left: image frame of calcium imaging. Right: the detected neurons are labeled with red circle as firing status and green circle as normal(non-firing) status.

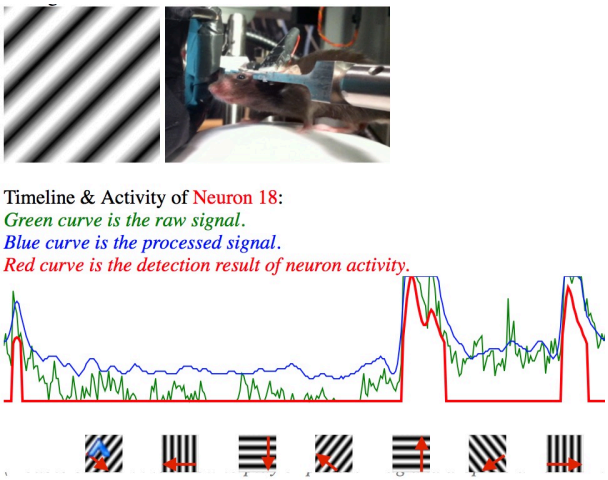

Figure 5. Neuron activity analysis under different visual stimulus. The grating patterns along the x-axis show the category of visual stimulus in time series.

IV. Experiments and Observations

A. Signal Extraction and Neuron Activity Analysis

Figure 4 shows the processing results of neuron detection and firing status analysis. The detected neurons on calcium imaging are labeled with red circle for firing status and green circle for normal(non-firing) status. We made a demo webpage[1] to visulize the processing results of neuron extraction and neuron graph networks under different visual stimulus. As shown in Figure 5, by clicking a neuron circle, the user interface(UI) will show its raw luminance distribution on time domain with green curve, processing result after background compensation with blue curve, and the detected neuron activity with red curve. Note that the grating patterns along the x-axis show the category of visual stimulus in time series, each visual stimulus lasting 5-second long and a 5-second white screen between two successive stimulus.

The results show that the proposed neuron position alignment can effectively compensate the camera vibration from

[1] http://systemg.research.ibm.com/cn-brainviz.html

mouse movement and the distortion of brain cerebral cortex. Next, the proposed background luminance compensation can adequately reduce background noise and enhance neuron visibility that provides a more accurate input for neuron activity analysis. The experiments also demonstrate the proposed neuron activity algorithm can effectively detect the firing status. With these analytics of neuron activity, we further conduct graph analysis for neuron network.

B. Network Analysis: Small-worldness of Brain Network

We calculate small-worldness for the networks generated by our proposed network analysis approach for brain neurons on the following purposes:

- Evaluate our proposed algorithm by checking whether the generated network structures are small-world network.
- Analyze the brain neuron network properties upon different visual stimulations.

The definition of small world is that: most nodes are not neighbors of one another, but most nodes can be reached from every other by a small number of hops or steps. Most studies examining functional brain networks reported various degrees of small-world organization. It is commonly thought that such an organization reflects an optimal balance of functional integration and segregation. For a given graph g, the small-worldness **SW** of g is defined as:

$$\mathbf{SW} = \frac{\gamma_g^{\Delta}}{\lambda_g}, \tag{9}$$

where $\gamma_g^{\Delta} = \mathbf{C}_g^{\Delta}/\mathbf{C}_{random}^{\Delta}$ and $\lambda_g = \mathbf{L}_g/\mathbf{L}_{random}$. The suffixes g stands for the graph g and $random$ stands for a randomly generated graph consisted of the same number of nodes and edges as the graph g. The **C** represents for the clustering coefficient of the suffixed graph and **L** is the mean of shortest path lengths of the suffixed graph. According to the definition in [13], if the estimated $\mathbf{SW} > 1$, then the graph g meets the requirement of being a small world. Note that since (9) involves a random term, we calculate the **SW** for 100 times and take the average of them as the valid small-worldness value.

Table I
THE SW VALUES FOR ANESTHETIZED-GRATING NEURON NETWORK FOR 8 ANGLES OF VIEW WITH DIFFERENT PARAMETER SETTINGS

Angles →	0°	45°	90°	135°	180°	225°	270°	315°
CC, $\alpha = 1$	329.99	74.72	60.12	188.89	136.28	267.72	15.69	139.02
CC, $\alpha = 1.5$	157.90	124.54	77.16	209.33	173.94	250.81	19.74	263.32
CC, $\alpha = 2$	349.67	372.22	151.74	339.59	430.94	140.43	28.84	291.30

Our experiment data consists of video sequences that record the status of brain neurons with 4 frames per second. Among these videos, mice acted in two different states: awake and anesthetized. There are 4 mice in anesthetized state and 6 in awake state. In awake state, mice were vivacious to perform as active living things that were able to see, eat, run, and think through their brains. On the other hand, anesthetized mice were injected with anesthetic so that they are almost unconscious. Moreover, for each mouse in those two states, videos have been collected when they were watching three different categories of videos: grating videos from 8 different angles of views from 0 to 315 degree as shown in Figure 1; nature videos like the ones in "Discovery" and no video, which we notate as spontaneous video.

Given the 10 mice in two different states and three video categories, we have 30 datasets drew from videos. We implemented the undirected-graph analyzing algorithm for each datasets, and for the Cross-Correlation (CC) based algorithm, we conduct it with three different thresholds: we set α in equation (8) as 1, 1.5 and 2. The results have been classified into 6 categories based on the status of the mice and the patterns they

Table II
THE SW VALUES FOR ANESTHETIZED-NATURE NEURON NETWORK FOR 5 SUB-FRAME SETS WITH DIFFERENT PARAMETER SETTINGS

sub-frame # →	1	2	3	4	5
CC, $\alpha = 1$	154.50	157.76	89.32	109.12	29.37
CC, $\alpha = 1.5$	157.48	158.24	99.73	129.67	30.65
CC, $\alpha = 2$	168.07	228.72	103.34	242.84	41.79

Table III
THE SW VALUES FOR ANESTHETIZED-SPONTANEOUS NEURON NETWORK FOR 5 SUB-FRAME SETS WITH DIFFERENT PARAMETER SETTINGS

sub-frame #→	1	2	3	4	5
CC, $\alpha = 1$	51.48	175.34	61.88	152.04	48.49
CC, $\alpha = 1.5$	103.46	171.96	77.53	133.49	57.39
CC, $\alpha = 2$	150.94	380.59	109.45	109.34	75.98

Table IV
THE SW VALUES FOR AWAKE-GRATING NEURON NETWORK FOR 8 ANGLES OF VIEW WITH DIFFERENT PARAMETER SETTINGS

Angles →	0°	45°	90°	135°	180°	225°	270°	315°
CC, $\alpha = 1$	9.26	12.03	31.26	15.68	14.12	12.63	11.18	37.42
CC, $\alpha = 1.5$	15.26	29.42	65.80	28.45	36.79	16.88	25.54	77.59
CC, $\alpha = 2$	22.55	49.66	93.27	49.73	53.48	44.84	53.10	68.24

Table V
THE SW VALUES FOR AWAKE-NATURE NEURON NETWORK FOR 5 SUB-FRAME SETS WITH DIFFERENT PARAMETER SETTINGS

sub-frame #→	1	2	3	4	5
CC, $\alpha = 1$	6.90	7.18	18.13	6.91	9.62
CC, $\alpha = 1.5$	11.51	10.92	8.56	11.96	7.82
CC, $\alpha = 2$	25.12	16.68	16.70	29.91	11.42

Table VI
THE SW VALUES FOR AWAKE-SPONTANEOUS NEURON NETWORK FOR 5 SUB-FRAME SETS WITH DIFFERENT PARAMETER SETTINGS

sub-frame #→	1	2	3	4	5
CC, $\alpha = 1$	68.02	67.32	41.65	16.61	24.67
CC, $\alpha = 1.5$	81.90	174.60	53.90	28.85	35.82
CC, $\alpha = 2$	97.88	244.11	68.61	48.94	64.53

were watching: *Anesthetized-Grating, Anesthetized-Nature, Anesthetized-Spontaneous, Awake-Grating, Awake-Nature, Awake-Spontaneous.*

Table I-VI show the SW values for the neuron networks of the above 6 categories for different angles and sub-frames with different parameter settings. When the visual input of mice is grating, we conducted our algorithm on video frames of each angles of view; for nature and spontaneous data, to balance the length of time slots between different video categories, we separate the video frame to 5 subsets and each has 480 frames. Meanwhile, for each category, the SW metrics are calculated by averaging the metrics of mice in the same category.

We observed these two characteristics from the experiments:

1. Anesthetized mice' brains are more likely to be small-world networks. For instance, in Table II, when $\alpha = 1$, the average SW value of the 5 sub-frame sets is 97.84, which is almost $10\times$ higher than the average SW value (9.748) that is obtained from the same experiment setting but with awake mice in Table V. We can observe similar patterns when the mice are shown with videos that have contents, i.e. grating and natural videos in Table I, II, IV and V. Based on the definition of Small-worldness, we know that higher SW value refers to larger number of different small groups are well connected. Since when the mouse is anesthetized, the functional segregation will be random, so that there will be limited number of huge functional clusters. But for awake mice, since they can actively response to the outside stimulations, some small and random groups will be assigned for similar processing function and grouped into a larger functional segregation, which will result in smaller SW value.

2. For both anesthetized and awake mice, when they were watching spontaneous videos, their small-world property have no significant difference, which can be explained by the randomness of spontaneous videos. For example, when $\alpha = 2$, the average SW value of the 5 sub-frame sets is 165.26 in Table III, while the one in Table VI is 104.82. Since the mouse was shown nothing, intuitively we could assume that the response caused by this image pattern is random so that in both anesthetized and awake states, the mouse brain neurons may have very similar topology, which can be partially reflected by the SW value.

V. Conclusion

In this paper, we proposed a methodology to extract neuron activities from calcium imaging videos. We also proposed a network model in undirected network to analyze interactions between brain neurons of various states of mice that were watching different visual patterns. At this moment of time, this video imaging technology is intrusive. So, it cannot be applied to human beings yet. However, the video and network graph analysis technology proposed in this paper can be a good indication on how to create multimodality signal analysis tools (on video and on network graphs) to analyze such live brain videos for future neural science applications.

VI. Acknowledgment

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