From symmetric building blocks to neural synchronization in the connectome

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Introduction

The nematode C. elegans is a tractable model organism with a fully mapped synaptic connectome. It displays stereotyped behavior, with specific gaits of locomotion. In our previous work, performing whole brain Ca2+ recordings, we showed that motor programs are represented by globally coordinated brain dynamics with large groups of synchronized neuronal ensembles [1].

Functions of living networked systems are controlled by the structure of interconnections between the network components. Therefore, understanding how function emerges from structure can be based on graph theory analysis. Uncovering these structures that lead to cluster synchronizations from incomplete or naturally mutated connectivities is an important analytical problem previously covered in our findings [2,3,4] with the creation of important tools for the symmetry analysis of connectomes. Accordingly, we recently showed that connectivity features such as left-right bilateral symmetry as well similarities in input connectivity can predict functional interactions between neurons [5]

In our approach symmetry features uncovered in our previous study [6] are called permutation symmetries and form the automorphism group of the graph; a collection of neurons that when swapped preserve the connectivity matrix of the network (Fig. 1.D). Additionally the connectivity matrix of the connectome is used to partition neurons into groups with “minimum balanced coloring” where connections from one group into a neuron of another group depends only on the pair of groups, but not on the individual pair of neurons chosen. Graph theory indicates that these quantities predict the cluster synchronization of dynamics among groups of neurons observed experimentally.

In this project, we aim to develop a novel theoretical analysis toolbox that identifies various forms of symmetries in the neuronal network. Our central hypothesis is that these symmetries are important for synchronizing neuronal population activity. To test this hypothesis, we compare the symmetries of the connectome with nervous system wide functional connectivity matrices following subsequent experimental network perturbations.

Hypothesis

Symmetry features govern neuronal population activity

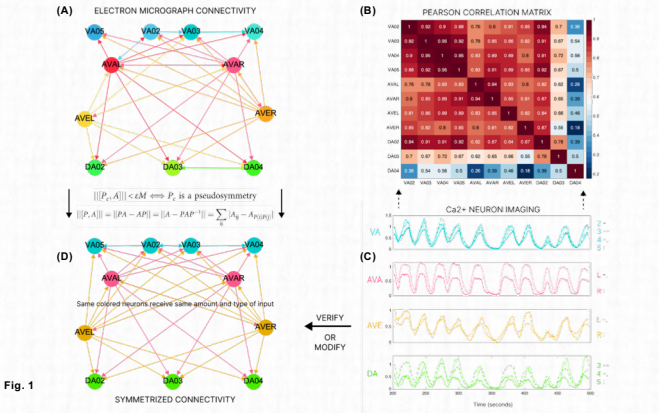

Fig. 1

An incomplete connectivity (Fig. 1.A) is transformed into a symmetrized version through identification of pseudo-symmetries (Fig. 1.D) and verified against experimental data (Fig. 1.C) for the identification of cluster synchronizations.

Our hypothesis has firm grounding as symmetries have already been shown to be in relation to cluster synchronizations in biological (gene) networks from our previous uncovering [8].

Corroborating synchronization & neural structures

We start by finding the minimum balanced coloring of a processed and symmetrized network by initially coloring all nodes and arrows the same. Next, we recolor all nodes that have the same amount of colored input with a new and same color including their outgoing arrows, this sequence is repeated until no re-colorings are needed. We apply this method through the algorithm proposed by Kamei & Cock [9] and implement it through the code developed in Leifer et al. [10]. These synchronizations are corroborated through various Ca2+ imaging experiments varying from wild type worms, chemical synapses or gap junction hindered worms in combination with neural ablations. Any detected synchronizations from the experiments not in alignment with the minimum color balancing of a reconstructed network are used to guide the necessary modifications of the neural structures in order to make these two compatible.

User Friendly App and ODE models

We have built a user friendly MatLab application (Fig. 2.B) [11] in which one can simulate neural activity of the forward and backward networks with or without inter-connectivity. The state of each neuron is dynamically evolved through equations of the form of equation 1. which are in-degree dependent and give rise to the expected minimal color balancing analyzed in our reconstructed networks.

$$\dot{V}_i = \mathbf{f}(V_i) + \sum_{j=1}^{n} \tilde{A}_{ji}\, \mathbf{g}(V_i, V_j) + I_i^{ext}, \quad i = 1, \ldots n \qquad \textbf{Eq.1}$$

$$LoS_{ij} = \frac{1}{T} \sum_{t=time\ step}^{T} \exp - \frac{(V_i - V_j)^2}{2\sigma^2}. \qquad \textbf{Eq.2}$$

Additionally in our app one can specify the type of networks used (electron micrograph connectivity , left-right symmetrized, fully symmetrized), the type of weights used for the connectivity (binary or integer) and the ability to randomly alter these, initial distribution of voltages, type of model used for the chemical synapses interactions, strength of the gap junctions and chemical synapses interactions and more. Even more one is able to specify which neurons receive a static input current, the amplitude and frequency of an undulatory input and a Gaussian random walk input. The app also calculates the level of synchronicity (LoS) as per equation 2 for the each of the two networks for the last second of simulation time.

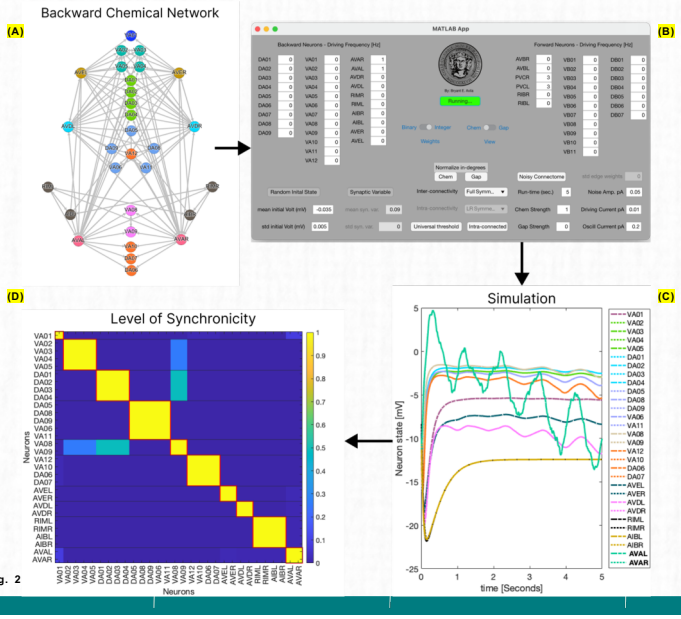

Fig. 2

Experimental setup and recordings

Currently, we are able to record the totality of the C.elegans nervous system activity while having an overlapping precise color map (NeuroPal) of the neuronal identities. (3.A)Microfluidic chip (top, based on Schrödel et al., 2013 [12]) and transmitted light image of a C.elegans adult hermaphrodite (bottom). We immobilize young adult worms in a microfluidic chip and record neuronal activity for 10-18mins, 3Hz. Neuronal activity is inferred from calcium fluctuations (GCaMP) in the neurons, since calcium influx is a proxy for synaptic transmission. (3.B1) Pan-neuronal nuclear GCaMP6f expression. GCaMP is quantitative calcium indicator; meaning that upon calcium entry into the cell, GCaMP fluorescence rapidly increases, but upon calcium extrusion, it also rapidly decreases. (3.B2) NeuroPal [13] Z-stack used for precise neuronal identification. NeuroPaL is a stereotyped nuclear multicolor map of neuronal landmarks that allows robust neuronal identification between different individual worms. (3.C) Neuronal activity heatmap (based on Kato et al 2015 [1]) . Our current pipeline allows us to extract neuronal activity with single cell resolution.

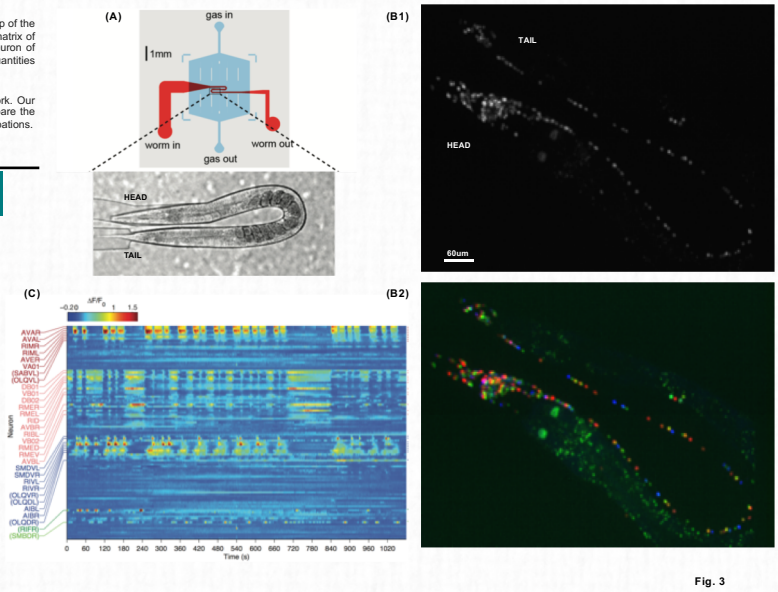

Fig. 3

Results and analysis

To evaluate functional interactions between neuronal pairs, we plot the average correlations across our datasets. (Fig. 4)Average person correlation heatmap of 4 recordings. Neurons hierarchically sorted. The major clusters represent known neurons involved either in forward or backward locomotion [14]

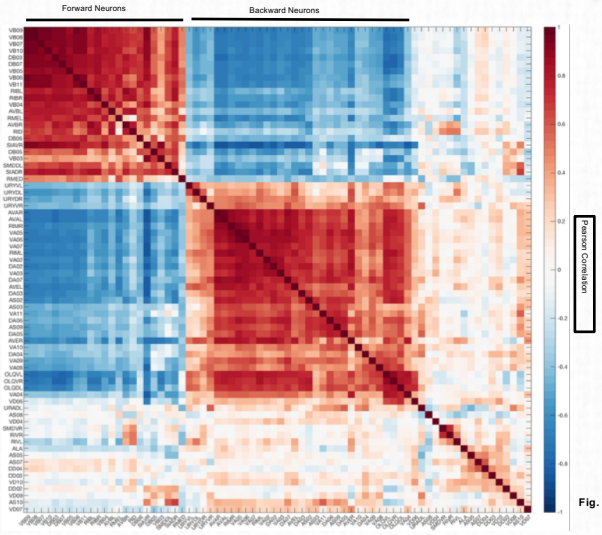

Fig. 4

Future Perspectives

Our next step would be to disrupt network symmetries by ablating target neurons that participate in such groups, and evaluate if the previous neuronal activity synchronization is abolished or preserved.

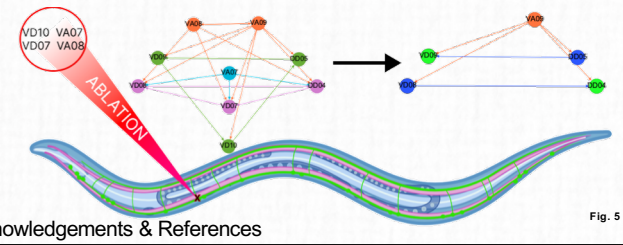

Fig. 5

Acknowledgements & References

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