Application of the principle of symmetry to neural circuitry: From building blocks to neural synchronization in the connectome

PI: Hernan Makse | Levich Institute and Physics Department - The City College of New York | **CO-PI: Manuel Zimmer** | IMP - University of Vienna | **Grant#:** R01 EB028157

Abstract: This BRAIN Initiative for Theories, Models and Methods Project (R01) seeks to develop a software tool that would enable neuroscience end-users to identify and analyze the most important building blocks of the brain across neural circuits of connectomes and explore their relationship with function. The broad, long-term objective of this grant is to advance a new theoretical approach to identify synchronized building blocks of neural circuits based on group theory and its application to understand the permutation symmetries of these circuits. Based on the developed theoretical framework we validate our theory by probing brain dynamics at single-cell resolution and in real-time, i.e., sub-second scale, in C. elegans, which is a system with a fully mapped synapse-resolution connectome.

Our analytical tool: We have developed a network theoretical toolbox to extract the symmetries of the connectome. The symmetries are graph automorphisms or symmetry permutations, i.e., specific similarities in the connectivity patterns of the connectome, that predict synchronization of neural populations. The theory successfully predicted functional building blocks in the C. elegans connectome, like circuits governing locomotion (see: Ref [1,2,3]).

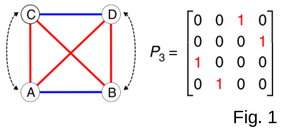
Questions to answer: Our central hypothesis to test is if the symmetries in connectivity underly the synchronization of neuronal population activity, and therefore, can be used to discover functional units within complex connectome data. Our graph theoretical toolbox will classify the symmetries of all connectomes thereby identifying neural circuits that potentially form functional building blocks. Using our symmetry finder, we aim at predicting which neurons synchronize their activity and then to further test and investigate these structure-function relations by (I) measuring neuronal activity and (II) manipulating the underlying circuits experimentally.

We are calling all connectomes: We would be happy to analyze your connectome and dynamical data. Connectomes could include larval zebrafish, larval annelid Platynereis, partial reconstructions of the drosophila adult and larval brain (e.g., visual system or mushroom body) or partial reconstructions of rodent brains. Dynamical data: Alongside these anatomical data, we look for dynamical single-cell resolution neuronal activity data that can be acquired from these models, e.g., population wide calcium imaging data and multi-unit electrophysiological recordings.

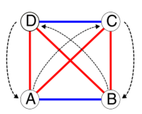
Permutation Symmetries: A permutation symmetry is an operation that conserves the connectivity structure of a graph. Take for example the graph in fig. 1 with 24 possible permutation of its nodes, yet only 8 (2 shown) are permutation symmetries (of the D8 group); the exchange of A and D would not result in a permutation symmetry.

(1) $||[P_\varepsilon, A]|| < \varepsilon M \iff P_\varepsilon$ is a pseudosymmetry

(2) $||[P, A]|| = ||PA - AP|| = ||A - PAP^{-1}|| = \sum_{ij} |A_{ij} - A_{P(i)P(j)}|$



$P_3 = \begin{bmatrix} 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \end{bmatrix}$



$P_4 = \begin{bmatrix} 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 \end{bmatrix}$

Fig. 1

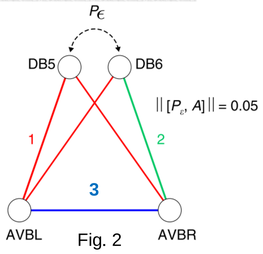


Fig. 2

Connectome variability: There is natural variability between the connectome connections across different C. elegans with previous studies having revealed a 25% variability on average. This quantity aids in the exploration of certain permutation of neurons within the worm's neural system which when applied to the connectome of this creature should not produce a variability higher than 25% measured by the equations above. Measures of pseudo-symmetries can be seen in table 1.

Pseudo Symmetry: Where Pε is the permutation operator applied on the adjacency matrix A representing the connectome, M is the addition of all weighted connections and ε is called the uncertainty constant which has a value of 0.25 for this creature's connectome. An example of this procedure can be observed above in figure 2.

	ε (%)	Subgroup	*p*-value
Pseudosymmetry-Forward gap-junction			
(RIBL, RIBR)	0.0%	$\mathbf{C_2}$	0.001
(VB3, VB7)	5.3%	$\mathbf{C_2}$	0.02
(VB8, VB9)	9.6 %	$\mathbf{C_2}$	0.004
(AVBL, AVBR)	24.5%	$\mathbf{C_2}$	0.0007
(DB5, DB6, DB7, VB10, VB11)	5.5 %	$\mathbf{S_5}$	0.0002
(DB1, VB2, DB2, VB5, DB3, VB4, VB1, VB6)	23.4%	$\mathbf{D_1}$	0.00001
Pseudosymmetry-Backward gap-junction			
(AIBL, AIBR, RIML, RIMR)	1.5%	$\mathbf{D_1}$	0.00001
(DA8, DA9, DA2, VA1, DA1, DA4)	6.9%	$\mathbf{D_6}$	$<10^{-6}$
(AVEL, AVER)	1.5%	$\mathbf{C_2}$	0.005
(VA4, VA5)	3.8%	$\mathbf{C_2}$	0.005
(VA2, VA3, VA6, VA7, VA8, VA9, VA10, VA11, VA12, DA3, DA6, DA7)	13.8%	$\mathbf{S_{12}}$	$<10^{-6}$

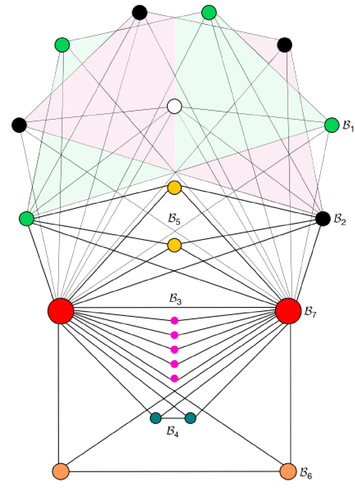
	ε (%)	Subgroup	*p*-value
Pseudosymmetry-Forward chemical synapse			
(VB3, VB4, VB5, VB10, VB11, DB2, DB4, DB6, DB7, DB8)	3.8%	$\mathbf{S_{10}}$	0.014
(VB6, VB7, VB8, VB9)	3.8%	$\mathbf{D_1}$	0.0012
(PVCL, PVCR)	3.8%	$\mathbf{C_2}$	0.0006
(AVBL, AVBR, RIBL, RIBR)	7.6%	$\mathbf{D_1}$	$<10^{-6}$
Pseudosymmetry-Backward chemical synapse			
(VA2, VA3, VA4, VA5)	4.5%	$\mathbf{D_1}$	0.002
(VA8, VA9)	0.8%	$\mathbf{C_2}$	9×10^{-5}
(DA5, DA8, DA9, VA6, VA11)	10.8%	$\mathbf{S_5}$	$<10^{-6}$
(AVAL, AVAR)	21.5%	$\mathbf{C_2}$	4×10^{-6}
(AVEL, AVER)	15.5%	$\mathbf{C_2}$	8×10^{-5}
(AVDL, AVDR)	24.5%	$\mathbf{C_2}$	0.004
(DA1, DA2, DA3, DA4)	2.3%	$\mathbf{S_4}$	4×10^{-6}
(VA10, DA6, DA7)	3.8%	$\mathbf{S_3}$	0.002

Table 1

When a specific permutation is applied to the C. elegans connectome and the left side of equation 1 equals zero it is said that these neurons have a perfect permutation symmetry; if the left side is not equal to zero but less than the right side, it is said that these neurons have a pseudo-permutation symmetry.

Symmetrization of the connectome:
Fortunately, these circuits are small enough that one can even introduce connections by hand to produce a perfect permutation symmetry of neurons. When this method is applied to the neuron circuits of the forward and backward locomotion for both the gap junction and chemical synapses versions of the (unweighted) connectome idealized circuits are obtained. See figures 3, 4 and 5.

Forward gap-junction circuit



$F_{gap} = [C_2 \times C_2] \times [S_5 \times D_1 \times [C_2 \times C_2]$

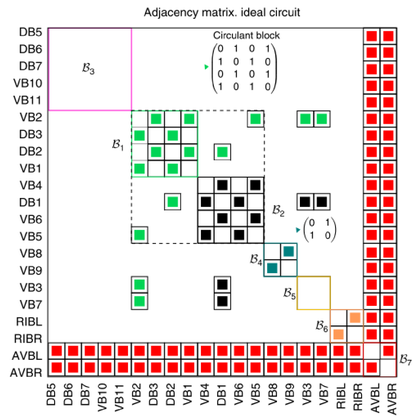


Fig. 3

Circuits are composed of imprimitive blocks:
Each permutation only affects the neurons within its group therefore it can be observed that after idealizing these networks these are composed of imprimitive blocks (a set of neurons that are mapped to others in the same set, domain of a normal subgroup, e.g., green nodes in fig. 3).

Imprimitive blocks are all circulant in nature and act as frequency filters:
The most exciting finding after idealization of these 4 locomotion networks (3 shown) is that the imprimitive blocks are composed of only circulant matrices. A circular matrix is a square matrix in which each row is rotated one position relative to the preceding row. Furthermore, there are 3 types of circulant matrices that appear in signal processing terms in these networks, low-pass (circ(1,1)) and high-pass (circ(0,1)) filters as well as translational invariant filter (circ(0,1,0,1)).

Backward chemical synaptic circuit

$B_{ch} = [C_2] \times [C_2 \times C_2] \times [S_5 \times S_4 \times S_3 \times C_2 \times D_1]$

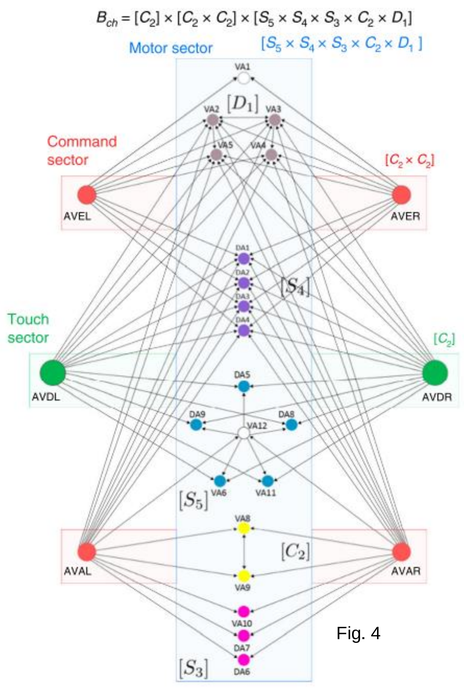


Fig. 4

Forward chemical synaptic circuit

$F_{ch} = [C_2] \times [D_1] \times [S_{10} \times D_1]$

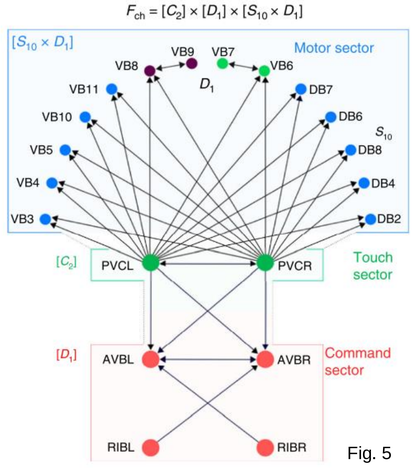


Fig. 5

Partitioning of C. elegans locomotion circuits into synchronous sets of nodes:
These idealized networks show further symmetries under isomorphic partitioning. This means nodes in a graph are colored (categorized) the same if they have the same number of input connections preceding from the same set of nodes. Same colored neurons should synchronize under the context that they receive the same information and if the internal dynamics of the neurons are the same. The algorithm used to partition the graph in fig. 4 was based on Cardon and Crochemore (see Ref [4]) on the unweighted version of the idealized network.

Brain wide calcium imaging in C. elegans by Zimmer Group – Vienna Biocenter

Kato, Zimmer, et al. Cell (2015)

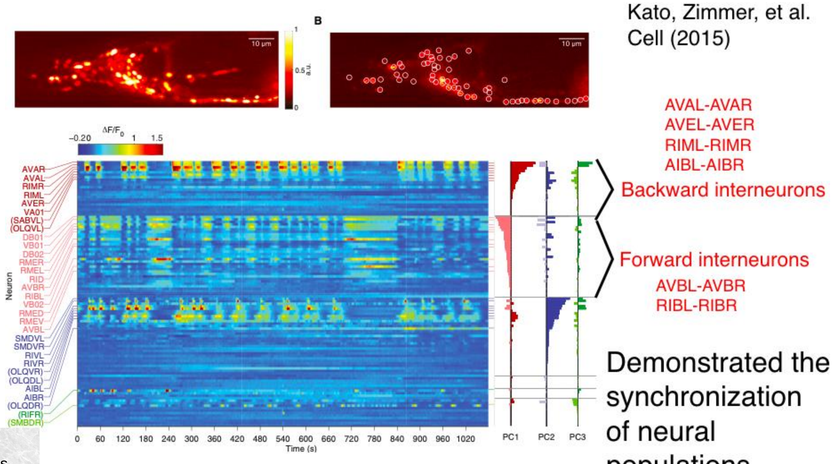


Fig. 6

Demonstrated the synchronization of neural populations in locomotion

Recorded data shows synchronization: Indirect voltage recordings through calcium imaging of multiple neurons within a C. elegans show correlations in the image above. It is clear the neurons belonging to the forward network correlate with each other as well as the neurons in the backwards network do with each other, yet there is clear anti correlation between these two systems (see: Ref [5,6]) A snapshot of this can also be seen below. The coloring of the network also plays a key role in enforcing these correlations among same-colored neurons through synchronization but does not necessarily indicate strong correlations between neurons of different colors.

Anti-correlation between Forward and Backward neurons

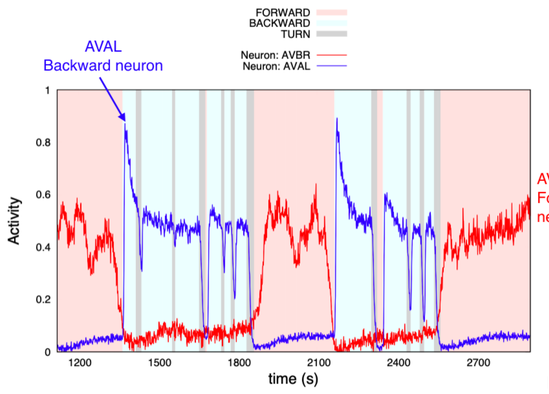


Fig. 7

References:
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[3] Circuits with broken fibration symmetries perform core logic computations in biological networks. Ian Leifer, Flaviano Morone, Saulo D. S. Reis, José S. Andrade Jr., Mariano Sigman, Hernán A. Makse
[4]Partitioning a graph in O(¦A¦log2¦V¦), A. Cardon, M. Crochemore, Theoretical Computer Science, Volume 19, Issue 1, 1982, Pages 85-98, ISSN 0304-3975,
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[6]Global Brain Dynamics Embed the Motor Command Sequence of Caenorhabditis elegans Kato, S., Kaplan, HS., Schrödel, T., Skora, S., Lindsay, TH., Yemini, E., Lockery, S., Zimmer, M. (2015). Cell. 163(3):656-69