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Summary

Brain research has been driven by inquiry for principles of brain structure organization and its control mechanisms. Brain is a complex system comprising of large number neurons that interact with each other giving rise to its functions. Hence, going beyond reductionist approaches, holistic study of structure and function of brain as a networked system is expected to yield insights into its architecture, evolution and control. Investigating brain as a complex network of neuronal connections provides better understanding of emergent properties and integrative functions such as behavior and memory. With this view, we asked questions addressing brain structure organization, its control and network correlates of neuropathology. What are the constraints under which the neuronal wiring evolves to acquire its motif characterization and global connectome organization? What are the genotypic and phenotypic underpinnings of its control? How to utilize functional brain network models to extract key features characterizing a neuropathology? Towards answering these questions we implemented systems-level models of brain, rooted in empirical data of neuronal connectivity and functional activity.

For investigating questions related to constraints and control in a neuronal network, we studied nervous system of *C. elegans*. Neuronal wiring diagram of *C. elegans*, the only complete connectome available till date, presents an incredible opportunity to learn basic governing principles that drive structure and function of its neuronal architecture. Despite its apparent simplicity, the nervous system of this worm forms an important underlying framework that specifies complex phenotypic features associated to sensation, movement, conditioning and memory. The *C. elegans* neuronal network (CeNN) is known to be characterized with small world nature and saturation of feedforward neuronal motifs, features that are of potential functional relevance.

Rooted in the notion of network controllability and driver nodes, we probed the nature of control in CeNN. We identified 'driver neurons' in this network and studied their 'phenoframe' and 'genoframe' that encode for phenotypic and genotypic features, respectively. The driver neurons are primarily motor neurons located in the ventral nerve cord and contribute to biological reproduction of the animal. Identification and characterization of driver neurons adds a new dimension for investigation of control mechanisms in CeNN. These results point to relevance of driver neurons in specifying behaviour of the organism.

Beyond identification and characterization of driver neurons of CeNN, we created network models of CeNN to scrutinize role of features that confer controllability, small world nature and prevalence of feedforward motifs. These models were aimed to unravel contribution of neuronal rewiring, connectivity, spatial organization and distance constraint towards structural organization of CeNN. The simple 1-dimensional ring model indicated critical threshold in response to synaptic rewiring for exhibiting saturation of feedforward motifs, increased neuronal clustering and short path-length, but could not account for number of driver neurons. Using empirically observed distance constraint in the neuronal network as a guiding principle, we created a 'distance constrained synaptic plasticity model' that simultaneously explained all of these features. Importantly, this model was also able to encode the identity of specific driver neurons matching with those observed empirically with high accuracy (77%). Thus, the model highlights optimum long distance synaptic connections as a key feature specifying control of the network.

Synaptic plasticity can alter the neural wiring pattern, potentially affecting brain function. We studied response of controllability to increase and decrease in feedforward motifs due to synaptic plasticity by implementing a motif tuning algorithm. Interestingly, we observed that 'number of driver neurons' shows an asymmetric sigmoidal response indicating robust control mechanism for increase in feedforward motifs and a fragile behavior on the other hand. Our simulations of synaptic rewiring further suggest that while distance constrained synaptic rewiring would lead to robust control response, random rewiring will disrupt the control mechanism. We therefore conclude that distance constrained connectivity is a critical feature for evolving functional structural organization as well as to maintain the same under inevitable synaptic rewiring.

Real world networks display emergent phenomena arising out of interplay of positive and negative relationships among its constituent nodes. The functionality of networks is often due to the balance they achieve in the presence of competing relationships. Beyond studying systems level properties such as, network traversal, transitivity (clustering), modularity, we studied the structural balance in *C. elegans* neuronal network. We divided this graph to study topological properties of the excitatory (positive) and inhibitory (negative) subgraphs. We found that, while the negative subgraph is akin to a random network, the positive component has higher clustering, closer to the original network. By the notion of Cartwright-Harary theorem, this neuronal network is unbalanced. We propose quantification of structural balance to enumerate the 'frustration' in a network with the balance index, which quantifies the extent of balance in the network. Given the relevance of structural balance in the presence of conflicting relationships, our results suggest importance of excitatory synapses vis-à-vis inhibitory synapses in this neuronal system.

For investigating questions related to network biomarkers of neuropathology, going beyond the structural investigations of CeNN, we constructed human functional brain network models using fMRI data. Neurological disorders such as schizophrenia are known to have basis in abnormal functional activities, which could be captured in terms of network markers. Brain Functional Networks (BFNs), graph theoretical models of brain activity data, provide a systems perspective of complex functional connectivity within the brain. We created weighted and binary BFN models of schizophrenia patients as well as healthy subjects. By investigating 45 topological features of BFNs and their higher order combinations, we found that network features embodying modularity, betweenness, assortativity and edge density emerge as key markers of schizophrenia. These topological markers indicate to mechanisms of functional activity underlying disease phenotype, and could be used for designing algorithms for clinical diagnosis of schizophrenia as well as its early detection.

Thus, through systems biological investigations of brain networks, we have addressed questions related to brain structure organization, mechanisms of its control and network correlates of schizophrenia. Studied in the context of neuronal connectivity of *C. elegans*, the former two questions led to genotypic and phenotypic characterization of driver neurons, and highlighted the importance of distance constrained synaptic connections in shaping the neuronal organization of this worm. Study of functional connectivity of human brain networks, conducted in response to the third question, led to identification of network markers that characterize the disease. These studies highlight the importance of systems-level models of brain networks and provide insights into their structure and function.

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