1
Introduction

1.1 MOTIVATION

Brain is one of the most complex biological systems which serves as an information processing organ controlling the behavior of the animal [E.R. Kandel, Schwartz, and Jessel, 2000]. No single neuron in isolation can direct high-level functions, but when organized in the form of a network the nervous system generates an array of cognitive, sensory and motor functions [Bressler and Menon, 2010; Gazzaniga, 2004]. Collectively the intricately linked web of neurons is responsible for emergence of cognition and consciousness [Park and Friston, 2013]. Hence, going beyond reductionist approaches, holistic investigations of structure and function of brain as a networked system is critical for gaining insights into its architecture, evolution and control [Sporns, 2011].

Nervous systems have evolved to acquire various forms, from a primitive collection of cells to sophisticated information processing organs [Kaas, 2006]. Among multicellular organisms with simplest nervous systems (Figure 1.1), Poriferans like sponges have cellular level organization devoid of interconnections. Hydra, a Coelenterate, on the other hand, have tissue level organization comprising of interconnected specialized cells (neurons). Signaling over these neurons specifies control and coordination of the animal. The nervous systems of higher phyla, such as Platyhelminthes and Nematodes, have increased complexity of neuronal interconnections. With increase in structural complexity, the functional repertoire of the animal behavior also gets richer [Bear, Connors, and Paradiso, 2007; Khundrakpam et al., 2013; Sporns, Chialvo, Kaiser, and Hilgetag, 2004]. This evolutionary trend has led to the emergence of highly complex structures such as mammalian brains.

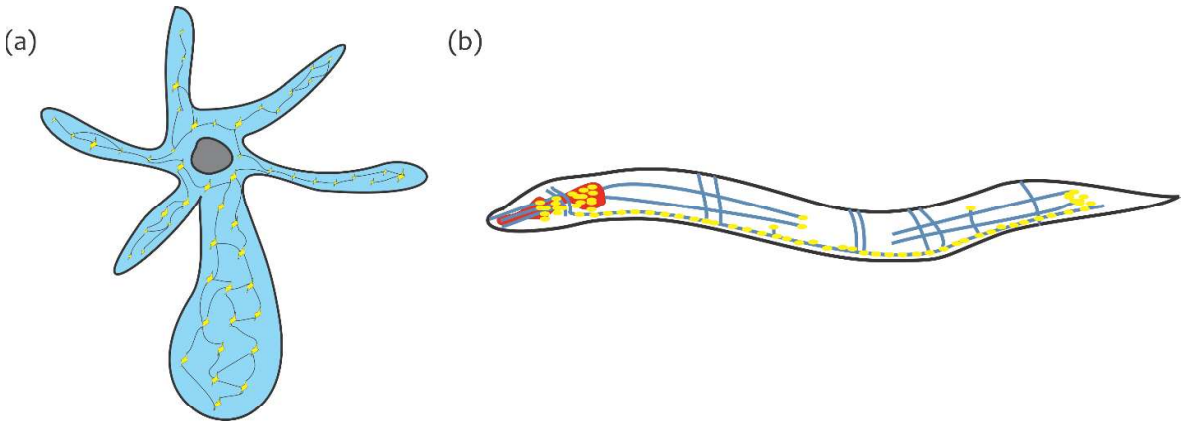

Figure 1.1 : Evolution in structural complexity of nervous systems. (a) In primitive organisms such as a Hydra (a coelenterate), neurons are connected in an unorganized manner. (b) In nematodes such as *C. elegans*, the nervous system is more nuanced with specialized structures like nerve cords and ganglions.

Brain function and control have been studied with divergent perspectives to consider structural details or by focusing on molecular specifics. The notion that brain can be fully explained in terms of physiological processes of cells is as ill-conceived as the complementary view that higher-level functions can be understood without making reference to its biological substrates. Brain is a complex interconnected system of neurons with emergent behavior that is

greater than the sum of individual function of neurons. This calls for integrative methods that account for details at different levels.

Brain could be seen as a meta-system comprising of hierarchy of sub-systems (Figure 1.2). At the highest level, it could be seen as an entity made of sub-components such as brain regions or neurons. At this level it is modeled as a network of interconnected brain regions or that of neurons interlinked through synapses. At another level, nervous systems could be modeled by focusing on details of synaptic connections (receptors, ion channels). Further down, one could consider specifics of genes and molecules (expression patterns, cell-specific molecules) while building models of nervous system.

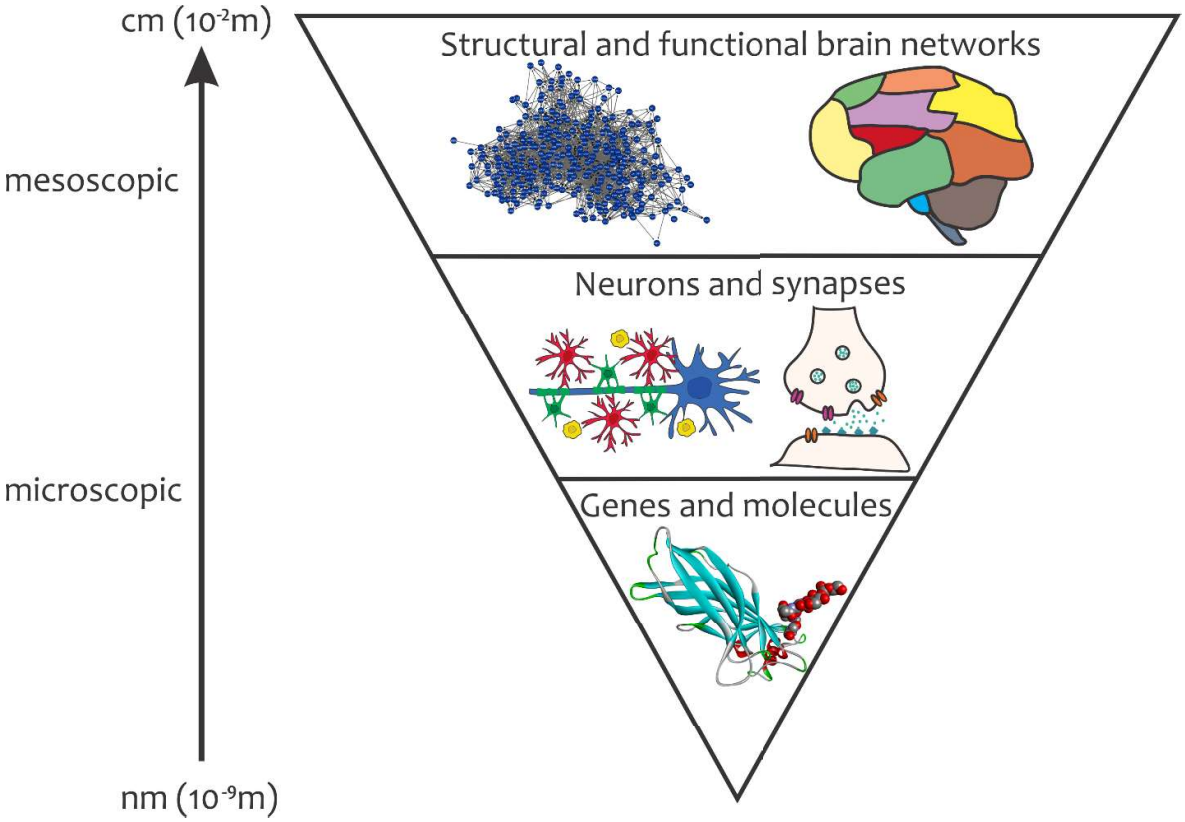

Figure 1.2 : Nervous systems seen as a meta-system comprising of different layer of sub-systems. Systems biological investigations conducted as part of this thesis invoke these towards answering questions addressing structure, function and control of brain networks.

Graph theory provides an abstract framework for modeling interconnected mechanisms spanning brain regions, neurons, synaptic connections and genetic mechanisms. Integrative studies that meaningfully incorporate these elements, effectively modeling brain function as an outcome of networks, are expected to provide interesting insights into principles governing brain structure, function and control [Rubinov and Sporns, 2010; Sporns, 2011]. The emergent patterns of functional activity on these networks are known to play an important role in behavior and are found to be impaired in neuropathological disorders [Hammond, Bergman, and Brown, 2007; Norman, Polyn, Detre, and Haxby, 2006; Salinas and Sejnowski, 2001]. Knowing this, understanding how the functional dynamics alters control and mediates pathology remains an elusive challenge.

Knowledge of structural organization is crucial for creating better models of brain as an integrated system and can provide fundamental insights into brain structure organization. Data of brain structural connectivity as well as functional connectivity is becoming increasingly available, facilitating their systems-level investigations. *C. elegans* neuronal network (CeNN) is

one of the most complete and accurate map of neuronal connectivity available till date, and has been updated over last few decades [Choe, McCormcik, and Koh, 2004; Hall and Russell, 1991; White, Horvitz, Sulston, and Brenner, 1985]. While data of structural connectivity in higher organisms has been elusive, functional network models of human brain can be constructed via invasive and non-invasive techniques such as electro electroencephalogram (EEG), Magneto encephalography (MEG), Positron emission tomography (PET) and Functional magnetic resonance imaging (fMRI).

1.2 OBJECTIVES

With these premises, in this thesis, we investigated structural connectivity of brain networks in *C. elegans* and functional connectivity of human brain networks. Investigating brain as a complex network is expected to provide better understanding of emergent properties. We asked questions addressing brain structure organization and control in CeNN using neuronal structural connectivity, and seeking for network correlates of neuropathology using functional connectivity in human brain.

- What are the constraints under which the neuronal wiring of CeNN has evolved to acquire its motif characterization and global connectome organization?
- What are the genotypic and phenotypic underpinnings of control in CeNN?
- What is the role of inhibitory and excitatory synapses in structural balance of CeNN?
- What are the markers of functional brain networks in human that characterise Schizophrenia?

1.3 CONTRIBUTION

By applying the concept of structural controllability, we investigated CeNN to identify its driver neurons and to study its 'phenoframe' and 'genoframe' that encode for phenotypic and genotypic features, respectively. Beyond identification and characterization of driver neurons, we created models of CeNN to scrutinize the role of structural features that confer controllability, small world nature and prevalence of feedforward motifs. We also show that nature of control in CeNN has an asymmetric sigmoidal response, robust to increase in feedforward motifs and fragile for their depletion. Our implementation of 'structural balance' in CeNN revealed the importance of inhibitory synapses in conferring balance, in the presence of competing excitatory and inhibitory relations. Going beyond the structural investigations of CeNN, we constructed human functional brain network models using fMRI data. By investigating topological features of weighted and binary brain functional network models of schizophrenia patients as well as healthy subjects we identified graph theoretical markers of neuropathology. In summary, our systems-biological investigations provide interesting insights into structure, function and control of brain networks.

1.4 THESIS ORGANIZATION

Thus, in this thesis we take an integrative view of brain to create network models using structural connectivity data (*C. elegans* neuronal network) and functional activity data (human brain) to address questions related to their structure, control and topological markers of neuropathology.

The organization of the thesis is as follows:-

- **Chapter 2**: We highlight important concepts relevant to the thesis, and present a survey of literature around the objectives dealt with in this thesis.
- **Chapter 3**: In this chapter we present description of materials and methods utilised for the analysis of structural and functional brain networks.

- **Chapter 4**: We present our studies of controllability in CeNN, and phenotypic as well as genotypic characterization of 'driver neurons'. (Badhwar and Bagler, PLoS One, 2015)
- **Chapter 5**: In this chapter we present a distance constrained synaptic plasticity model that accounts for controllability and motif saturation in CeNN. (Badhwar and Bagler, Physica A, 2017)
- **Chapter 6**: Here, we present our investigations of robustness of CeNN in the presence of synaptic plasticity. (Badhwar and Bagler, International Joint Conference on Rough Sets, Lecture Notes in Computer Science, Springer, 2017)
- **Chapter 7**: We present application of the concept of 'structural balance' in CeNN and importance of inhibitory neurons in specifying balance. (Badhwar and Bagler, NetSci-International Conference on Network Science, Network Neuroscience 2017)
- **Chapter 8**: Beyond investigations of neuronal network of *C. elegans*, we describe our studies aimed at construction and classification of brain functional networks in resting state fMRI between healthy individuals and schizophrenic patients (Singh, Badhwar and Bagler, International Conference on Signal Processing and Communication, IEEE Xplore, 2016).
- **Chapter 9**: Summary

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