Abstract

Neuroscience has been driven by inquiry for principles of brain structure organization and its control mechanisms. Brain is a complex system comprising of large number of neurons that interact with each other giving rise to its functions. Hence, going beyond reductionist approaches, systems biological investigations using graph theoretical models of brain mechanisms is expected to provide better understanding of emergent properties of brain. With this view, in this thesis, we asked questions addressing brain structure organization, its control and network correlates of neuropathology. We modeled the neuronal connectivity of *C. elegans* as a network to characterise its graph theoretical properties. Using structural controllability analysis, we identified its 'driver neurons' and characterised them for their phenotypic and genotypic properties. The driver neurons were found to be primarily motor neurons located in the ventral nerve cord and contributing to biological reproduction of the animal. Using empirically observed distance constraint in the neuronal network as a guiding principle, we created a 'distance constrained synaptic plasticity model' that simultaneously explained small-world nature, saturation of feedforward neuronal motifs as well as number of driver neurons. Importantly, our model was able to accurately encode the identity of specific driver neurons matching with those observed empirically. By implementing a motif tuning algorithm, we observed that 'number of driver neurons' shows an asymmetric sigmoidal response, indicating robust control for saturation of feedforward motifs and a fragile behavior for their depletion. We further modeled the interplay of excitatory and inhibitory synapses for the study of structural balance in this neuronal system, to highlight the contribution of inhibitory synapses. Beyond investigating structural brain network in *C. elegans*, we constructed human functional brain network models to probe network correlates of schizophrenia. 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. Our studies highlight the importance of systems-level models of brain networks and provide insights into their structure, function and control.

...