

8 Future Work

This thesis has demonstrated the usefulness of applying mathematical methodology and instilling physical insights into neurological systems. While neuroscience remains an active experimental research area, more theoretical work is needed to unify the experimental work and guide the design of further experiments. Based on the work that has been done in this thesis, we suggest the following four directions for further research.

8.1 Further investigate the cause and effect between amyloid fibrils and neuronal activities

The roles of amyloid fibrillation in the pathology of many neurodegenerative diseases remain controversial. The biggest question remains whether amyloid plaques are the actual cause of cellular malfunctions or just the effect of upstream homeostatic imbalance. Temporal order in which various symptoms occur is a valuable indicator to distinguish between causes and effects. There are evidences showing that the occurrence of abnormal functions in hippocampal neurons precede appearance of amyloid fibrils in time [9]. They reported transport deficits in axons result into the facilitated proteolytic processing of β -amyloid precursor protein and the subsequent accumulation of β -amyloid peptides. The other issues worth exploring are the function roles or the toxic effects of amyloid fibrils. Several mechanisms of how accumulated amyloid fibrils become toxic to neurons have been suggested. For instance, it has been proposed that amyloid fibrils physically disrupt tissue architecture such as microtubules and cytoskeleton [5, 7]. Also some researchers suggest the puncture of cell membranes leads to ion imbalance and the subsequence abnormality in signal transduction pathways [8]. As for the functional roles, amyloid fibrils have been suggested as a modulator of cholesterol balance [6] or an activation of melanin polymerization [2]. Research directions along these lines would be helpful in clarifying the causal relationship between accumulation of amyloid plaques and failure of neuronal functions.

8.2 Spatial modeling of synaptic plasticity

The morphology of neuronal network in central nervous systems appears to be one of the most complex living structures. Compared to the intensive modeling work that has been geared toward transient experimental data, many experiments exploring spatial responses in neuronal tissues remain unexplained. To establish the structure-based functionality of neurons, modeling such spatial responses is necessary. Building modules for different types of neurons based on their morphologies is a step toward the realization of small physiologically based neuronal network. NEURON is a set of simulation software suitable for neurobiologists to predict the electrophysiological responses based

on the specifications of morphological data [3]. Although it is partially based on cable theory, the user interface is inflexible in terms of modifying the underlying equations. Therefore, Matlab Simulink[®] (The MathWorks, Natick, MA) is an alternative simulation environment for computational neuroscientists to implement the spatiotemporal model with hierarchical structure. By comparison, it is easier to check and update the equation-based algorithm in Matlab Simulink[®].

8.3 Develop memory modules that incorporates gene expression

Some declarative long-term memory can last for months or years and be recalled at the onset of associated triggers. Although upstream signal transduction pathway is sufficient to elicit early stage of long term plasticity, synthesis of synaptic protein by translation of genes is a more likely way to leave permanent biomolecular memory traces. For instance, the binding between CREB (cAMP response element-binding) proteins and DNA is required in the consolidation of late phase long-term memories [4]. Theoretically, Hill equation is usually adopted to model the gene transcription activated by transcription factors [1]. Integration operation, compared to bistable theories, is more likely to be the true underlying algorithm by which synaptic plasticity can last robustly between neurons. Yet more experimental data beside graded long-term potentiation responses are necessary to test the statement. Experimentally, most of the current tests for long-term potentiation have run time of only a few hours which is too short compared to the time long-term memory can last. Therefore, experiments with longer time constants and detailed measurements of gene expression are critical in validating biophysical memory modules.

8.4 Apply biophysical models to neural network

What emerging properties and collective behaviors may arise from neural network consisting of individual neurons interconnected with one another remain an open question. The current basic elements used for constructing neural networks are oversimplified from a neurophysiological perspective. For instance, the spike timing dependent plasticity (STDP), one of the key underlying mechanisms of associative learning, is not reflected in generic neural network consisting of Hebbian synapses. Associative learning is a powerful ability for animals to generate new insights from collected information or experience. To imitate or even extend associative learning, the feature of STDP needs to be taken into account for the design of basic units in neural network. Other features missing from current neural network include the short-term and long-term synaptic plasticity as well as the firing of neurons.

Other intriguing questions include how neurons with different structure demonstrate distinct functionality and how the ensemble behavior may arise from heterogeneous neuronal network. There are more specific questions such as what response can be jointly demonstrated by a network of neurons connected by both depressing and facilitating synapses. In the meantime, what are the purposes of having synapses with these different attributes? Many of these questions are relevant to enhance our understanding on how learning and memory work yet they are not easy to answer. The

joint efforts from both the experimental work and theoretical modeling are required to put pieces of puzzles together before we can see the whole picture of our brains.

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