

9 Conclusion

Quantitative models only explain experimental measurement but also suggest further design of experiments. There are substantial insights that can be gained the combination of theory and experiments in the field of memory formation. In this thesis, several physiology-based models have been built to elucidate the memory formation mechanisms and the kinetic process of amyloid fibrillation suspected as the cause of memory loss.

Amyloid fibrillation *in vitro* can be interpreted as a three-stage process. Amyloid proteins generally go through misfolding, nucleation, and elongation to become stable insoluble fibrils. Estimated by nonlinear least squares algorithms, the rate constants for nucleation were about ten million times smaller than those for fibril growth. These results, coupled with the positive feedback characteristics of the elongation process, account for the typical sigmoidal behavior during fibrillation. In addition, experiments with different proteins, various initial concentrations, seeding versus non-seeding, and several agitation rates were analyzed with respect to fibrillation using our new model. Moreover, according to *in vivo* findings, the existence of amyloid plaques in neurodegenerative patients is correlated with loss of ability to form short-term or long-term memory in the early stage of disease progression.

Models for short-term and long-term plasticity have been built, respectively with results matching experimental data well. The main reason for short-term depression is depletion of neurotransmitter vesicle while that for short-term facilitation is the enhanced transmitter release due to buildup of residual calcium. As for long-term plasticity, the calcium entrapment model we proposed outputs results that agree with graded long-term potentiation responses triggered by multiple trains of stimuli. In addition, the frequency dependent long term plasticity can be explained by the same model coupled with the calcium dependent protein kinase and phosphatase. This suggests the importance of postsynaptic calcium and the subsequent downstream signaling in sustaining the enhancement of synaptic conductance. Furthermore, in the late ninety's plasticity was found to depend not only on the frequency of stimuli but also on the relative spike timing between pre- and postsynaptic stimuli.

Ever since its discovery, spike timing dependent plasticity (STDP) has become a new experimental protocol for eliciting change in synaptic plasticity. Yet there was few theoretical work that can well clarify its underlying mechanism until we set up a unifying model that can cover quite a variety of STDP responses. Most of the responses can be interpreted as the results of a two-step process. First, the activation of NMDA receptor-gated calcium ion channels requires both release of glutamate from presynapse and postsynaptic membrane depolarization. The relative timing between these two signals determines the amount of calcium ion flowing into postsynapse. Second, the level of postsynaptic calcium in turn determines the synaptic conductance through calcium

signaling. Again, the importance of calcium ions in synaptic plasticity and thus memory formation is indicated.

The toxic effects and functional roles of A β fibrillation in human brains remain controversial. With the knowledge gained from modeling long term synaptic plasticity, we realize that calcium signaling and AMPA receptors are key factors regulating memory formation. Therefore, we support the hypothesis that the oligomeric form of amyloid derivatives perforates neuron membranes and disturbs the intracellular calcium balance. Change in the amount of calcium entrapped in neurons in turn influences the synaptic strength by altering the total number of AMPA receptors available for synaptic signal transmission. The abnormal variation in synaptic strength as well as neuronal activities can have significant impact on the triggering immune systems and determining cell fate. Further work to clarify the casual effects among amyloid fibrillation, disease symptoms, and physiological reaction pathways is an important step toward better understanding in the fundamental causes of memory loss and the pathology of neurodegenerative diseases.