

The Summer Undergraduate Research Fellowship (SURF) Symposium  
6 August 2015  
Purdue University, West Lafayette, Indiana, USA

## Competitive Tuning of Calmodulin Target Protein Activation Drives E-LTP Induction in CA1 Hippocampal Neurons

Daniel R. Romano and Tamara Kinzer-Ursem  
Department of Biomedical Engineering, Purdue University

### ABSTRACT

A number of neurological disorders are caused by disruptions in dynamic neuronal connections called synapses. Normally, electrical activity between neurons activates protein cascades that cause long-lasting, localized changes in the structure and molecular composition of synapses. These changes either increase or decrease the strength of synaptic connections, leading to long-term-potential (LTP) or long-term-depression (LTD), respectively. The protein cascades responsible for this synaptic plasticity are initiated in a stimulus-dependent manner by the  $\text{Ca}^{2+}$  sensor calmodulin (CaM). Ultimately, it is disruptions within these signaling pathways that cause disease. Traditionally, these protein networks are studied in the laboratory, but limitations in existing experimental technology have created demand for computational models capable of predicting molecular phenomena. These predictions can then guide focused experimental investigations. Although CaM binds and regulates over 100 different target proteins, the competitive dynamics of these proteins and their effect on LTP induction have not been investigated. Using a system of ordinary differential equations to model competition between four neuronal CaM target proteins, we found that the stimulus-dependence of target protein activation is tuned by competition and that this competitive tuning is unique to each protein. We therefore conclude that competition-free models fail to capture the true stimulus-dependence of  $\text{Ca}^{2+}$ /calmodulin-dependent protein kinase II (CaMKII) and protein phosphatase 2B (PP2B/calcineurin/CaN) activation. Furthermore, these results suggest that competitive tuning drives early LTP (E-LTP) induction in CA1 hippocampal neurons and is an important dynamic process underlying learning and memory. Therapeutics that re-tune CaM-dependent proteins through competition may be useful in treating neurological disorders.

### KEYWORDS

Long Term Potentiation, Calmodulin, Calcium Signaling, Competition, Computational Model