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Quantitative Models of Protein Dynamics in Synaptic Plasticity: Analysis of Spatial and Stochastic Effects

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ABSTRACT

Memory formation within neurons depends on complex protein signaling networks, which become dysregulated in neurological disorders such as Alzheimer's disease. To characterize therapeutic strategies for these disorders, we require a better understanding of the how the protein interactions are regulated. Conventionally, protein interactions are studied by experimental techniques and complemented by computational models. However, most models are deterministic, limiting their biophysical accuracy. First, deterministic models exclude the stochastic effects necessitated by the small protein concentrations often observed within neurons. Second, deterministic models exclude the effects of spatial localizations on neuronal protein binding and activation. Third, many different models exclude an explicit representation of competition for binding to the essential protein calmodulin when multiple calmodulin-binding proteins are known to simultaneously coordinate the regulation of synaptic plasticity. Therefore, here we present a highly detailed model that explicitly accounts for stochastic effects, spatial localizations, and competitive binding, using the open source software MCell. Using our model, we compare against previous models and experimental data to analyze how spatial and stochastic effects determine the dynamics observed. These conclusions will be drawn from the concentrations of various neuronal protein activations and chemical modifications. In the future, our model may be used as a tool to identify and characterize therapeutic targets for neurological disorders.

KEYWORDS

Synaptic plasticity, Calcium signalling, Dendritic spine