Methods for simulating actin filament dynamics in MCell

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ABSTRACT

Learning is mediated by activity-dependent changes in synaptic strength that rely on Calcium-dependent signalling in the postsynaptic neuron. In the hippocampus, synapses are located on dendritic spines, small mushroom-like structures that grow from the dendrite. Dendritic spines form micro-compartments that are - to some extent - chemically isolated from the rest of the dendrite due to the long and narrow spine neck limiting diffusion in and out. The shape and the physical structure of a dendritic spine are determined by the actin filaments that form the cellular cytoskeleton. Long-term potentiation (LTP) of the synapse leads to remodelling of the polymeric actin cytoskeleton, which increases the size of the dendritic spine. This process is regulated by interactions between actin and other postsynaptic proteins [1]. Here, addressing the lack of spatiotemporal models that combine structure with biochemical signaling, we present a set of methods that allows the modelling of the biochemistry and spatial dynamics of actin filament dynamics using the spatial stochastic simulator MCell [2]. These methods allow us recapitulate the main events relevant for actin filament remodeling, including polymerisation, depolymerisation, branching and severing followed by filament displacement in space. They rely on the ability of MCell to model multi-state complex molecules [3] and on a system of virtual tags to label states of actin subunits. The complex molecule feature was utilised by defining an immobile three-dimensional matrix with 100^3 subunits, each belonging to one of the defined states. This provides a frame in which some of the subunits are occupied by actin monomers representing the cytoskeleton, while the rest are vacant. In response to biochemical reaction with freely diffusing modifier proteins the state of the subunits can be changed allowing the rearrangement of the filaments. In addition, with the help of the subunit tags, the monomers forming a single filament can change their location inside the immobile matrix *in corpore* by occupying previously vacant slots. In the future, the model could be extended by incorporating more elements from signaling pathways and modeling filament bundles present in non-stimulated synapses. As such, the model can provide insights into how the actin cytoskeleton interacts with postsynaptic proteins that mediate LTP. The model can be a valuable tool to investigate disease mechanisms as well as test therapeutic strategies for diseases where spine plasticity is implicated.

REFERENCES

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