BMC Neuroscience

Poster presentation

Open Access

Results from a novel Cellular Dynamics Simulator reveal a quantitative mechanism for Ca^{2+}-CaM activation in dendritic spines

Yoshihisa Kubota*, Michael J Byrne and M Neal Waxham

Address: Department of Neurobiology and Anatomy, University of Texas Medical School, 6431 Fannin, Houston, TX 77030, USA

Email: Yoshihisa Kubota* - Yoshihisa.Kubota@uth.tmc.edu

* Corresponding author

from Seventeenth Annual Computational Neuroscience Meeting: CNS*2008
Portland, OR, USA. 19–24 July 2008

Published: 11 July 2008

BMC Neuroscience 2008, **9**(Suppl 1):P107 doi:10.1186/1471-2202-9-S1-P107

This abstract is available from: http://www.biomedcentral.com/1471-2202/9/S1/P107

Particle-based Monte-Carlo simulations are an important tool for the analysis of microscopic molecular physiology. One of the major challenges in the field is how to accurately simulate molecular diffusion, interaction, and multi-protein complex assembly in the cellular environment. Here we present a novel event-driven simulation scheme (Cellular Dynamics Simulator, CDS) that can address how volume exclusion and molecular crowding impact signaling cascades in small subcellular compartments such as dendritic spines. We contend that the exact molecular collision detection scheme used in this simulator is essential to understand the spatio-temporal pattern of Ca^{2+}-CaM activation during synaptic stimulations.

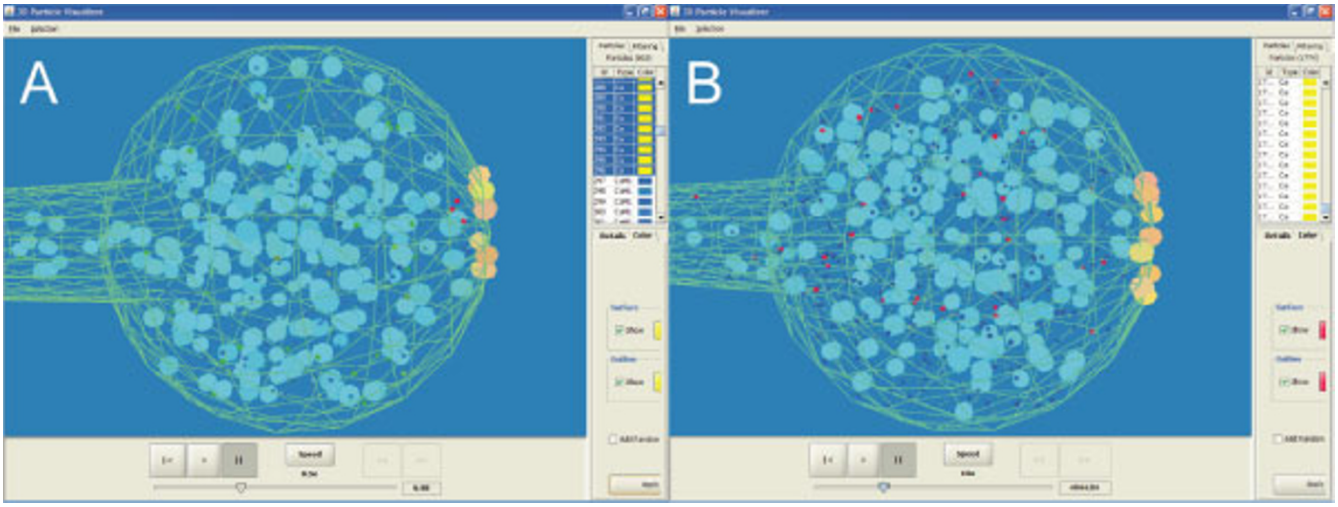

Figure 1
Ca^{2+}-CaM Activation domain. (A) A snapshot of a simulation showing that CaM molecules become fully Ca^{2+} saturated only within close proximity of ion channels with low Ca^{2+} injection rates. The probability of CaM entering into a fully Ca^{2+} saturated state depends sharply on the distance of CaM molecules from the source of Ca^{2+} entry. (B) A snapshot of a simulation having a higher Ca^{2+} injection rate. The CaM molecules become fully Ca^{2+} saturated throughout the entire spine. The red spots in the figures indicate fully Ca^{2+} saturated CaM molecules while dark blue are partially Ca^{2+}-saturated CaM. The light brown particles represent Ca^{2+} channels. The small yellow particles are Ca^{2+} ions.

Combining this novel simulator and a detailed kinetic model of Ca^{2+}-CaM-CaMKII interactions, we investigate how the rate of Ca^{2+} injection and the spatial localization of Ca^{2+} channels impact the spatio-temporal patterns of Ca^{2+}/CaM and CaMKII activations in a simplified dendritic spine. The activation of CaM requires a rapid and successive binding of Ca^{2+} ions. For this successive binding to happen, the CaM molecule must collide into the second Ca^{2+} ion before the first one dissociates from it. Thus, at a relatively low Ca^{2+} injection rate (0.01 ~0.1Ca^{2+} ions per microsecond per ion channel), the number and the location of Ca^{2+} channels have a major impact on the spatio-temporal pattern of CaM activation. In fact, at these rates even if ten ion channels are open simultaneously, only a small number of CaM molecules become fully saturated and the Ca^{2+} saturation takes place only in close proximity to the Ca^{2+} channels (Figure 1A). On the other hand, at higher Ca^{2+} injection rates (1 ~10 Ca^{2+} ions per microsecond) with the same number of ion channels present, the Ca^{2+} saturation of CaM takes place throughout the spine volume (Figure. 1B). Thus, depending on the type and/or number of ion channels, the spine Ca^{2+} signaling system operates in different modes: one produces a highly localized nano-domain of Ca^{2+}/CaM activation while the other produces a global and homogenous Ca^{2+}/CaM activation.