BMC Neuroscience

POSTER PRESENTATION Open Access

The effects of molecular crowding on LTD expression

Horace Deans[1], Daniel Sherwood[1], Fidel Santamaria[1,2*]

From Nineteenth Annual Computational Neuroscience Meeting: CNS*2010
San Antonio, TX, USA. 24-30 July 2010

Long term depression (LTD) in the parallel fiber-Purkinje cell synapse is a well characterized form of synaptic plasticity. The post-synaptic components of LTD are localized in dendritic spines. Spines contain volumes < 1 fL which traditionally have been thought to be well-mixed. Under such assumptions changes in concentration are quickly equilibrated. However, the presence of organelles, spine shape and macro-molecular density could make spines a more tortuous environment for molecules to diffuse and react. We studied the effects of large concentration of non-reacting macro-molecules in the expression of an LTD model.

We translated a recently published well-mixed differential equation model of LTD into a Monte Carlo simulation [1]. We used known diffusion coefficients from the literature or calculated them based on a globular approximation using their molecular weight and the Stokes-Einstein relation. The simulations were implemented in MCell [2] and ran on a large cluster (http://www.cbi.utsa.edu).

The simulation includes all the molecules involved in the phosphorylation of AMPA receptors (AMPAR) after $[Ca^{2+}]$ increase. The simulation includes translocation of molecules to the plasma membrane and diffusion in the cytosol and membrane. The simulation was instantiated in a box of 0.17 μm^3, the average volume of a Purkinje cell spine; the post-synaptic density (PSD) occupied one of the box faces. We ran each simulation for 150 seconds, with an increase in $[Ca^{2+}]$ at t = 15 sec. $[Ca^{2+}]$ increases range from 2-10 mM. The stimulus resulted in AMPAR accumulation in the PSD as a function of different levels of $[Ca^{2+}]$. LTD expression was determined by calculating the percentage drop in AMPAR at t = 150 sec compared from the initial condition. LTD under normal conditions showed a smooth expression of LTD as a function of the stimulus. Molecular crowding in the cytosol was implemented with 120 identical cubes randomly distributed inside the box. The cubes occupied 30 % of the intracellular volume. A classic approach to this problem would suggest that crowding would result in a shift to the right of the LTD curve due to a slowdown in the diffusion of molecules. However, instead, our results show that the sensitivity of LTD to $[Ca^{2+}]$ increases, consistent with non-classical theories of reaction and diffusion due to molecular crowding. LTD under molecular crowding conditions resembles the switch-like response reported in experiments [1]. Overall, our results show that there is a strong influence of molecular crowding in the activation of biochemical signals in spines.

Acknowledgements
NSF-0923339 and NSF-0934218

Author details
[1]Biology Department, University of Texas at San Antonio, San Antonio, TX 78249, USA. [2]Neurosciences Institute, University of Texas at San Antonio, San Antonio, TX 78249, USA.

Published: 20 July 2010

References

1. Tanaka K, Khiroug L, Santamaria F, Doi T, Ogasawara H, Ellis-Davies GC, Kawato M, Augustine GJ: **Ca2+ requirements for cerebellar long-term synaptic depression: role for a postsynaptic leaky integrator.** *Neuron* 2007, **54(5)**:787-800.
2. Stiles J, Bartol TM: **Monte Carlo methods for simulating realistic synaptic microphysiology using MCell.** *Computatinal neuroscience* CRCDe Schutter E. Boca Raton 2000.

doi:10.1186/1471-2202-11-S1-P6
Cite this article as: Deans *et al.*: The effects of molecular crowding on LTD expression. *BMC Neuroscience* 2010 **11**(Suppl 1):P6.

* Correspondence: fidel.santamaria@utsa.edu
[1]Biology Department, University of Texas at San Antonio, San Antonio, TX 78249, USA