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Modeling spontaneous and evoked glutamate release of NMDA receptors

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Introduction

Spontaneous synaptic fusion is a feature in all synapses. These random release events have been extremely instrumental in the analysis of unitary properties of neurotransmission. Here, we detail some modeling studies for the kinetic scheme of NMDA receptors in a synapse that was published in [1]. In a synapse, spontaneous and action-potential-driven neurotransmitter release is assumed to activate the same set of postsynaptic receptors. However, new experiments using MK-801, a well characterized use-dependent blocker of NMDA receptors shows NMDA-receptor-mediated spontaneous miniature EPSCs (NMDA-mEPSCs) and NMDA-receptor-mediated evoked EPSCs (NMDA-eEPSCs) responded with very different characters [1]. Modeling glutamate diffusion and NMDA receptor activation revealed that postsynaptic densities larger than ≈0.2 μm^2 can accommodate two populations of NMDA receptors with primarily nonoverlapping responsiveness. Collectively, these results support the premise that spontaneous and evoked neurotransmissions activate distinct sets of NMDA receptors and signal independently to the postsynaptic side.

Results

This model can recapitulate several key features (including the asymmetry in the extent of cross talk detected after MK-801 block of NMDA-mEPSCs vs NMDA-eEPSCs) with the assumption that within a 0.36 μm^2 PSD, a release event near the center (e.g., the vicinity of R6) represents evoked neurotransmission, whereas a fusion event at the periphery of the PSD (e.g., near R16) corresponds to spontaneous release. Moreover, in the Figure, this model indicates that experimental findings [1] are in line with the commonly accepted parameters governing glutamate diffusion in synapses (Xu-Friedman and Regehr [2]; Popescu et al., 2004 [3]). According to this model, medium to large (>0.2 μm^2 area) synapses can easily accommodate independent signaling via spontaneous and evoked release with some geometric constraints.

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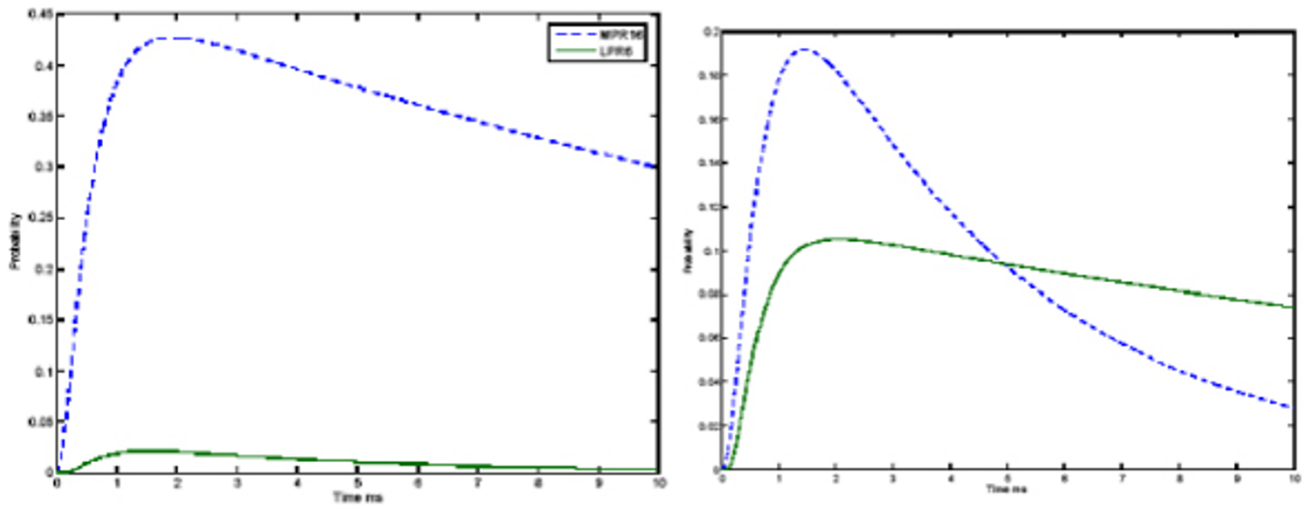

Figure 1
The time courses of probability openings at R16 and R6 when a glutamate vesicle is released at the edge (near R16, left panel) and near the center (R6, right panel). Blue curves (dotted) correspond to the NMDA receptors that are directly opposed to release site, and green ones are at locations away from release site.