Title: Calcium electro-chemical dynamics support nonsynaptic plasticity in a multiscale model of a pyramidal neuron

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We use multiscale modeling (MSM) to study the interaction of fast electrical dynamics with slow intracellular molecular dynamics in the neuronal dendritic tree. MSM enables us to study how these interactions endow neurons with the capability to hold short-term memories without altering synaptic efficacy (nonsynaptic plasticity). This process depends on interactions between synaptic events and intracellular calcium (Ca2+) dynamics. Nonsynaptic plasticity also depends on intracellular compartments that store Ca2+: since Ca2+ triggers destructive processes, neurons regulate cytosolic Ca2+ concentration via buffers and sequestration into mitochondria or endoplasmic reticulum (ER). To initiate nonsynaptic plasticity, synaptic stimuli first open voltage-gated ion channels (eg L-type calcium channels, NMDA receptors), admitting Ca2+, which is then sequestered within the ER, priming the ER. We hypothesized that ER priming would allow a later stimulus to cause larger Ca2+ efflux from ER stores. In this way, electrical and chemical signaling would allow a neuron to store a dynamical trace of prior stimuli. To test our hypothesis, we developed a reaction-diffusion/electrical model of a hippocampal pyramidal neuron in NEURON (www.neuron.yale.edu) . The model neuron consisted of 1100 compartments with a distribution of ion channels: multiple K+ channels, Na+ channels, several variants of voltage-gated Ca2+ channels, and AMPA/NMDA receptors. Temporal scales in the model ranged from order of milliseconds to order of seconds; spatial scales ranged from nanometers (molecules) up to hundreds of microns (dendritic tree). Intracellular compartments were split up into cytosol and ER, continuously throughout the neuron. Intracellular species included diffusible inositol triphosphate (IP3), Ca2+, and Ca2+ buffers. Reaction mechanisms included ER IP3 receptors (IP3Rs), ER Ca2+ leak (ER to cytosol), ER pump (cytosol to ER), ER ryanodine receptors (RYR), Ca2+ buffering, IP3 degradation, and plasma membrane Ca2+ extrusion. We also modeled metabotropic glutamate receptors (mGLUR) via a signaling cascade, that started with glutamate binding and ended in the production of IP3. IP3 then bound to IP3Rs, which combined with Ca2+, caused the ER to expel Ca2+ into the cytosol. Nonsynaptic plasticity emerged from electro-chemical interactions and ER priming: NMDA/AMPA activation caused Ca2+ influx from extracellular sources and intracellular sequestration within a nearby portion of ER. Subsequent synaptic stimulation of mGLURs caused production of IP3, and triggered heightened Ca2+ release from ER stores. We explored whether the Ca2+ dynamics allowed the neuron to respond preferentially to stimulation patterns that were similar to those previously presented. We found that both the pattern of spatiotemporal stimuli and recall prompts had a profound effect on the ability of the neuron to recall previous patterns. Our modeling demonstrates that the interaction between electrical and chemical signaling at multiple spatial and temporal scales may allow neurons to store memory traces of prior synaptic activation patterns, which would have consequences for nervous system information processing in vivo.