Neural Networks 24 (2011) 943–949

Contents lists available at SciVerse ScienceDirect

Neural Networks

journal homepage: www.elsevier.com/locate/neunet

2011 Special Issue

Multiscale interactions between chemical and electric signaling in LTP induction, LTP reversal and dendritic excitability

Upinder S. Bhalla *

National Centre for Biological Sciences, TIFR, Bellary Road, Bangalore 560065, India

ARTICLE INFO

Keywords:
Multiscale model
Synaptic plasticity
Long-term potentiation
Homeostasis
Receptor trafficking
MAPK

ABSTRACT

Synaptic plasticity leads to long-term changes in excitability, whereas cellular homeostasis maintains excitability. Both these processes involve interactions between molecular events, electrical events, and network activity. Here I explore these intersections with a multilevel model that embeds molecular events following synaptic calcium influx into a multicompartmental electrical model of a CA1 hippocampal neuron. I model synaptic plasticity using a two-state (bistable) molecular switch that controls glutamate receptor insertion into the post-synaptic density. I also model dendritic activation of the MAPK signaling pathway, which in turn phosphorylates and inactivates A-type potassium channels. I find that LTP-inducing stimuli turn on individual spines and raise dendritic excitability. This increases the amount of calcium that enters due to synaptic input triggered by network activity. As a result, LTD is now induced in some synapses. Overall, this suggests a mechanism for cellular homeostasis where strengthening of some synapses eventually balances out through weakening of a possibly overlapping set of other synapses. Even in this very narrow slice of cellular events, interesting system properties arise at the interface between multiple scales of cellular function.

Synaptic plasticity and homeostasis in neuronal excitability both involve interactions across multiple scales of neuronal function. Each of these phenomena depend in a tightly coupled way on network activity, electrical signaling, and biochemical signaling (Ajay & Bhalla, 2007; Marder & Goaillard, 2006; Turrigiano, 2008). There are many feedback loops in this process. First, temporal and spatial patterns of synaptic input arrive from other cells in the network, and the cell activity itself feeds back into the network. Second, these inputs and the cell's own electrical properties trigger second messenger events, especially through calcium influx. These signals set off cascades that modify the expression, location, and properties of ion channels, thus altering electrical properties of the cell. For example, plasticity-inducing stimuli activate the mitogen-activated protein kinase (MAPK) in hippocampal neuronal dendrites, which phosphorylates potassium channels and alters excitability (Watanabe, Hoffman, Migliore, & Johnston, 2002). Further levels of interactions include broadcast neurotransmitters and metabotropic receptor-mediated signals that couple network activity to chemical signaling, and alteration in morphology and connectivity mediated by signaling events. Many experimental and modeling studies have looked at each of these interactions, but technical difficulties and paucity of supporting data have restricted the number of studies that explicitly span multiple scales of signaling (Ajay & Bhalla, 2007; Coggan et al., 2005; Oliveira et al., 2010). The current study specifically explores multiscale interactions in synaptic plasticity.

Many models of synaptic plasticity assume that it arises from bistable chemical switches, that are triggered by synaptic activity and calcium influx (Aslam, Kubota, Wells, & Shouval, 2009; Hayer & Bhalla, 2005; Kuroda, Schweighofer, & Kawato, 2001; Lisman, 1985; Miller, Zhabotinsky, Lisman, & Wang, 2005). These proposed switches then alter receptor insertion or phosphorylation, leading to changes in synaptic conductance. Switches act in a fundamentally non-homeostatic manner: they are designed to perpetuate long-term changes in cellular excitability. In contrast, neuronal activity homeostasis works toward restoring cellular excitability to a set point which is characteristic of a given neuronal class (Ibata, Sun, & Turrigiano, 2008; Liu, Golowasch, Marder, & Abbott, 1998; Turrigiano, 2008). Since both these classes of models rely on calcium influx as a key signal, it is interesting to explore how they might coexist.

1.1. Model construction

I constructed a multiscale model of a hippocampal CA1 pyramidal neuron. This neuronal model was based loosely on a model by (Traub, Wong, Miles, & Michelson, 1991) and GENESIS implementations of the same model (Bower & Beeman, 1995). I modeled a small section of the lateral dendrite in particular detail, using smaller spatial subdivisions for the compartments and

* Tel.: +91 80 23666130; fax: +91 80 23636662.
E-mail address: bhalla@ncbs.res.in.

0893-6080/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neunet.2011.05.001

Abbreviations

MAPK:	Mitogen-activated protein kinase
PKA:	Protein kinase a
CaN:	Calcineurin
LTP:	Long-term potentiation
LTD:	Long-term depression
AMPA:	α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
AMPAR:	AMPA receptor
NMDA:	N-methyl D-aspartate
NMDAR:	NMDA receptor
MOOSE:	Multiscale object-oriented simulation environment
PSD:	Post-synaptic density
K_A:	A-type potassium channel
mV:	Membrane potential

including three dendritic spines. In this small segment of dendrite I embedded diffusively coupled models of MAPK signaling. I also implemented signaling models for AMPAR trafficking, that were embedded in the dendritic spines. The signaling models and spines were implemented only in this small dendritic segment to reduce computational load. All models were implemented in MOOSE (Ray & Bhalla, 2008), using a module designed to automatically merge in single-compartment signaling models into the spatial and diffusive context of the electrical model morphology.

1.2. Numerical methods

All calculations were done in MOOSE. The compartmental electrical model of the neuron was solved using the implicit Crank–Nicolson method (Hines, 1984) with a timestep of 50 μsec. The system of ordinary differential equations (ODEs) arising from the biochemical equations were solved using an adaptive timestep fifth-order Runge–Kutta–Fehlberg method using the GNU Scientific Library, GSL (Galassi et al., 2009). Bistability in the biochemical systems was inferred by solving the ODE system for stable states using the GSL multiroot solver functions and the GSL linear algebra package. For some calculations this failed due to numerical issues with singular matrices. In these cases the stable states were estimated by numerically integrating the ODE system till near steady state. In either case, the initial conditions were varied to see if the system converged to just one or two stable states, and the presence of two states was taken as evidence for bistability. Diffusion calculations were done by partitioning the diffusive volume into a one-dimensional series of compartments and representing diffusion processes as additional flux reactions between compartments (Ajay & Bhalla, 2007). This generated a larger ODE system which was solved as before, using the GSL Runge–Kutta–Fehlberg functions.

1.3. Electrical model

There were three primary differences between the current model and the original (Traub et al., 1991) 1. the addition of two small lateral dendrites off the apical dendrite, which were designed to facilitate the modeling of dendritic signaling. 2. a small descending gradient of Na and K channels introduced in all dendrites so as to give rise to decremental back-propagating action potentials (Yuan, Adams, Swank, Sweatt, & Johnston, 2002). 3. the introduction of ligand-gated channels for glutamate, AMPAR and NMDAR, located in each dendritic compartment and on the spine heads. The electrical model included 33 compartments (Fig. 1A). Three dendritic spines were each modeled as a narrow (0.1 μm) neck compartment and a 0.5 μm diameter head compartment. The model included voltage-gated sodium and calcium channels and non-diffusing calcium dynamics with calcium pump. Potassium channels included the delayed rectifier, an afterhyperpolarizing K channel, a calcium-dependent potassium channel and an A-type K channel. Model parameters are detailed in the supplementary material.

The AMPAR and NMDAR conductances in the model were parameterized against three activity readouts:

- EPSPs resulting from single synaptic input should be about 0.5 mV at the soma.
- Cell-wide synaptic input should elicit a somatic spike
- Cell-wide tetanic input should give about 10 times as much peak calcium influx in a spine, as single synaptic input to the same spine.

The cell model parameters were robust by each of these measures. As expected from cable theory, the EPSP had an almost linear dependence on the receptor conductances. The somatic spike criterion was also easily met with a reasonable (50–100) number of simultaneous synaptic inputs. The calcium influx in the spine had a somewhat more complex dependence on the receptor channel conductances. I scanned a 5-fold range for the AMPAR and found that the tetanic response increased in a sublinear manner, whereas the single pulse response increased supralinearly with the receptor conductance. Thus the ratio of the two calcium responses (tetanic:single pulse) declined with increasing AMPAR. I also scanned a 5-fold range of NMDAR conductances, and found that both the single pulse and tetanic responses increased sublinearly, and the ratio of the two was not much affected by conductance changes.

The parameter sensitivity to voltage-gated ion channel distributions was also examined in the process of developing the final model. For example, the Na and K_DR distributions in the apical and lateral dendrites, varied over a 20% range (K_DR) and 2$\times$ range (Na). There was relatively little effect on somatic responses, but these changes did cause effects on dendritic spiking which was necessary to elicit the above Ca^{2+} influx effects.

The response of the cell to current injection is indicated in Fig. 1B. Fig. 1C and D show the voltage and calcium response to six kinds of synaptic input, respectively. The synaptic stimuli were on spine 1, spine 2, cell-wide, spine 1 + cell-wide, spine 2 + cell-wide and finally a 100 Hz tetanus for 1 s on spine 1 + cell-wide. All these responses were in line with the physiology and previously developed models. The calcium level in the spine was set to be somewhat high, specially during tetanus, because it was designated as representing the post-synaptic density microdomain which has high local calcium levels. For the same reason, the time-course for the spine calcium pump was made faster (4 ms) than the dendrite (13 ms).

1.4. MAPK model

The MAPK model was derived from (Ajay & Bhalla, 2007). This was a very reduced model, containing 18 molecular species, 6 reactions, and 13 enzymes (Fig. 2B) as compared to approx 60 molecular species in the original model. Nevertheless the reduced model exhibited bistability, and switched from the inactive to the active stable state following a 1 s, 1 uM pulse of Ca^{2+} (Fig. 2C). The target of the active, phosphorylated form of MAPK (P-MAPK) is the K_A channel. When P-MAPK switches on, it phosphorylates K_A. As discussed in Section 2.1, the phosphorylated form of K_A is non-conducting in the model.

As the MAPK model was highly reduced compared to the original model, the main effort in its parameterization was to replicate the fundamental property of bistable responses. This