Dendritic Excitability and Synaptic Plasticity

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Dendritic Excitability and Synaptic Plasticity

1. Synaptic Plasticity

2. Regulation of Electrical Properties of Dendrites

3. How Do Dendritic Properties Affect Synaptic Plasticity?
1. Synaptic Plasticity
1.A) Hebbian Plasticity

Donald O. Hebb [Hebb 1949] postulated that
if the presynaptic cell A is repeatedly taking part in activating the postsynaptic
cell B, along with a set of other presynaptic neurons, then the strength of the
synaptic connection between A and B should be increased.

- a temporal or causal order is implied
- cell A needs to act in cooperation with other presynaptic cells
- Hebbian plasticity is unstable
- treats all synapses equal
1.B) Long-Term Potentiation (LTP)

[Bliss and Lomo, J Physiol 73]

EPSPs evoked by electrical stimulation in the dentate gyrus of the rat hippocampus increased in amplitude after high-frequency stimulation (LTP).
Properties of LTP

- To a first approximation, LTP is input specific.

- Typically, LTP depends on N-methyl-D-asparate (NMDA) receptor-mediated $\text{Ca}^{2+}$ influx.

- LTP leads to a reduced threshold for postsynaptic spiking (EPSP-spike potentiation).

- LTP exhibits cooperativity (see later).

- LTP is by definition long-lasting.
1.C) Long-Term Depression (LTD)

**Heterosynaptic LTD:**

Attempting to induce LTP by high-frequency stimulation of one pathway produced LTD of other, inactive pathways in hippocampus [Lynch, Phys Rev 77].

This was before postulated by Gunther Stent [PNAS 73].

**Homosynaptic LTD:**

Prolonged low-frequency stimulations (LFS, 900 pulses at 1-4Hz) resulted in LTD in hippocampus and cortex.
1.D) Spike timing-dependent plasticity (STDP)

Long-term plasticity depends critically on the millisecond timing of pre- and postsynaptic spikes (in neocortex L4, L2/3, L5, hippocampus, striatum, etc.)

STDP exhibits several of the hallmark features of LTP such as

- NMDA receptor dependence
- cooperativity
- frequency dependence
- intrinsic instability
STDP: Abundant Diversity of Rules and Phenomena

- The width of the LTD timing window varies with brain region.
- Inverted and other timing windows exist.
- STDP depends on frequency
- Timing-dependent LTP at L5 synapses requires a threshold postsynaptic depolarization which can be provided either by high-frequency temporal summation or by low-frequency spatial summation.
- and more…

Diversity within cells:

- Excitatory inputs of different origins converging onto neighboring dendritic locations in amygdala have different forms of plasticity.
- Connections originating from the same somatosensory cortical L2/3 pyramidal neuron have distinct plasticity rules depending on the interneuronal type they target.
- STDP windows depend on dendritic location.
1.F) The role of NMDA receptors and postsynaptic Ca

NMDA receptors can act as a detector for coincident pre- and postsynaptic activity.

- Both LTP and LTD depend on elevations in intracellular Ca$^{2+}$ concentration.
  - Brief and strong elevations lead to LTP.
  - Smaller, more prolonged Ca$^{2+}$ transients induce LTD.
- However, also voltage-dependent Ca$^{2+}$ channels play a role in long-term plasticity.
NMDA receptors and Cooperativity

[McNeughton et al., Brain Res 78]

High-frequency stimulation of a weak path produced LTP only when in synchrony with a stronger pathway (cooperativity).

Possible mechanisms:

- Weak inputs may not depolarize NMDA receptors sufficiently.
- The need for postsynaptic somatic spiking.
2. Regulation of Electrical Properties of Dendrites
2.A) Dendritic signalling: Backpropagating Action Potentials (bAPs)

Somatic action potentials can backpropagate into the dendritic tree [Stuart and Sakmann, Nature 94].

Passive propagation leads to massive attenuation of the bAP, so active channels are crucial.

Most important: \textbf{Na$^+$ channels}.

Diversity in the reliability depending on neuron type.
Dendritic signalling: Backpropagating Action Potentials (bAPs)

Backpropagation depends critically on
- dendritic morphology
- location and availability of different ionic conductances
- local dendritic potential
  - depolarisation enhances backpropagation
  - hyperpolarisation or synaptic inhibition can reduce it.

Backpropagation is more robust \textit{in vivo} in L2/3, L5, CA1 pyramids [Helmchen et al., Nat Neurosci 99, Water and Helmchen, J Neurosci 06]
2.B) Dendritic signalling: Local dendritic spikes

Voltage-gated ion-channels provide a positive feedback mechanism. With sufficient depolarization, dendritic spikes are triggered.

Conductances underlying dendritic spikes in neocortical pyramidal neurons:
- Proximal dendrites: Na$^+$ channels
- Distal dendrites: Voltage-dependent Ca$^{2+}$ channels
- Basal dendrites: NMDA receptors
Ca$^{2+}$ and NMDA spikes

Oblique dendrites

CA1

NMDA spike, basal dendr.

L5
Ca$^{2+}$ bursts and BAC firing

BAC firing:
2.C) Modulation of dendritic channels

**Synaptic input:**
- Synaptic input can activate or deactivate dendritic channels.
- Propagation of dendritic spikes from distal apical dendrites to the soma are enabled by more proximal synaptic input.

**Neuromodulation:**
- Dopamine can increase (in basal ganglia) or decrease (in hippocampus) Na\(^+\) currents.
- Acetylcholine (ACh) and Norepinephrine can increase the amplitude of bAPs.
  - Spikes in oblique apical dendrites of hippocampal pyramids are highly plastic and subject to neuromodulation [Losonczy et al., Makara et al.]
- Serotonin hyperpolarizes dendrites, thus limiting backpropagation.
Plasticity of dendritic channels

LTP:
Following theta-burst pairing in CA1, LTP can lead to local changes in dendritic excitability. [Frick et al., Nat Neurosci 2004].

STDP of dendritic excitability:
- STDP pairing with
  - pre-before-post (10ms) leads to increased presynaptic excitability [Ganguly et al., Nat Neurosci 04].
  - post-before-pre (10ms) leads to decreased presynaptic excitability [Li et al., Neuron 04].
- Bidirectional changes (probably local) in dendritic integration following STDP in CA1 pyramids [Campanac and Debanne, J. Physiol 08].
3. How Do Dendritic Properties Affect Synaptic Plasticity?
3.A) Backpropagating Action Potentials as Triggers for Plasticity

The bAP will often fail to invade the distal dendrites of pyramidal neurons.
In CA1:
- Na\(^+\) channels that support backpropagation are there
- However, K\(^+\) (I\(_A\)) channels hinder backpropagation

- Synaptic input can briefly inactivate I\(_A\) channels and rescue AP backpropagation (a plasticity gating mechanism).

In fact, dendritic depolarization can convert distal LTD to LTP [Sjöström and Häusser, Neuron 2006].
3.B) Dendritic depolarization can convert distal LTD to LTP

[Sjöström and Häusser, Neuron 2006] L5 pyramidal neuron:

Backpropagating action potentials are boosted by dendritic depolarization.

Dendritic depolarization switches LTD to LTP at distal synapses
Dendritic depolarization can convert distal LTD to LTP

[Sjöström and Häusser, Neuron 2006] L5 pyramidal neuron: Local gating of plasticity

Note: boosting of bAPs can also be locally restricted to individual branches [Magee et al., Annu Rev Phys 98]
3.C) Ca\textsuperscript{2+} Bursts and Distal Regenerative Events in Plasticity

Above a critical frequency (~100Hz), bAPs are significantly amplified due to distal dendritic regenerative events.

**Plasticity** [Letzkus et al, J Neurosci 06]:
- EPSP 10ms before the burst leads to LTD
- opposite temporal order leads to LTP

Relation to BAC firing?
3.C) Ca$^{2+}$ Bursts and Distal Regenerative Events in Plasticity

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3.D) Synaptic Plasticity:
Somatic APs vs. Dendritic Spikes

Are somatic APs typically involved in plasticity in vivo, or are local dendritic spikes the dominating factor?

- In CA1 neurons, APs are not necessary for LTP induction of distal synapses [Golding et al., Nature 02].
- No LTP was evoked below the threshold for distal dendritic spikes.
Rapid Synaptic Plasticity and Local Dendritic Spikes

Local NMDA-like dendritic spikes in the absence of somatic APs result in rapid LTD induction in L5 neurons [Holthoff et al, J Phys 04].

A rapid form of LTP in CA1 neurons also depends critically on local spikes [Remy and Spruston, PNAS 07].
Conclusions

- Synaptic input drives the cell and activates voltage gated ion channels.
- Synaptic plasticity is triggered, but depends on biophysical properties and context in the different compartments of the cell.
- The biophysical properties of dendrites, however, are in turn also regulated by the ongoing activity triggered by these same plastic synapses.

The net result is a loop of reciprocal dependencies that determines the computations performed by an individual cell.