Modeling plasticity at a single neuron and network levels

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Overview

• Forms of synaptic plasticity
• Models of spike-timing-dependent synaptic plasticity:
  – phenomenological
  – optimal
  – biophysical
• Application of learning rules:
  – modeling brain in health and disease
  – neuronal robot control

Overview

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Synaptic plasticity

• Human brain consists of a trillion \(10^{12}\) neurons and a quadrillion \(10^{15}\) synapses
• Brain plasticity – the ability of the brain to modify itself and adapt to changing environment.
• Synaptic plasticity - modification of the synaptic strength triggered by the neuronal activity

Synaptic strength - weight

Presynaptically:
• Number of synaptic vesicles \(n\)
• Probability of neurotransmitter release \(p\)

Postsynaptically:
• Maximal conductance \(g\) associated with one synaptic vesicle

Synaptic weight:
\[ w = n p g \]

Forms of synaptic plasticity

• Short-term synaptic plasticity
  – Induction: presynaptic activity, 0.5 sec
  – Maintenance: 1 sec

• Long-term synaptic plasticity
  – Induction: correlated pre- and postsynaptic activity, 1-3 sec
  – Maintenance: several hours

• Long-term potentiation (LTP): Hebb’s rule
  – LTP is faster: ~1.3 min after the onset of the stimulation protocol

• Long-term depression (LTD): Stent’s rule
  – LTD is slower: ~3.1 min after the onset of the stimulation protocol

Hebb’s rule: LTP

When an axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it, some growth processes or metabolic change takes place in one or both cells so that A’s efficiency ... is increased.

Donald Hebb (1949)
Stent’s rule: LTD

When the presynaptic axon of cell A repeatedly and persistently fails to axcite the postsynaptic cell B while cell B is firing under the influence of other presynaptic axons, metabolic change takes place in one or both cells so that A’s efficiency ... is decreased.

Gunther Stent (1973)

Spike-timing-dependent plasticity (STDP)

• Spike-timing-dependent synaptic plasticity is a form of bidirectional change in synaptic strength that depends on the temporal order and temporal difference of the pre- and postsynaptic activity.

Induction and measuring synaptic modifications

1. Assessment: Presynaptic action potential evokes EPSP at a postsynaptic site

2. Induction: Pre- and postsynaptic neurons are activated simultaneously

3. Assessment: Presynaptic action potential evokes a stronger EPSP

Biophysics of Spike-timing dependent plasticity

• Pairing pre- and postsynaptic activity at 1-5Hz for 60-100sec

• Presynaptic site:
  – neurotransmitter release

• Postsynaptic site:
  – NMDAr, AMPAr channel activation
  – Somatic action potential, back-propagating spike
  – Voltage-gated calcium channel opening

Application of STDP in modelling: healthy brain

• Neuronal response shift earlier in time (Gerstner and Kistler, 2002)
• Formation of receptive fields in place cells (Gerstner and Kistler, 2002)
• Development of direction selectivity in the visual system (Honda, Urakubo, Tanaka, Kuroda, 2011)
• Temporal sequence learning (Izhikevich, 2007)
• Memory encoding and retrieval in hippocampus (Cutsuridis et al., 2010)

Neuronal response before learning

Neuron receives trains of 5 spikes.
Neuron fires after 4 synapses are activated.

\[
\Delta w(t) = \begin{cases} 
0, & \text{if } \Delta T < 0 \\
\tau_+ \Delta T, & \text{if } \Delta T > 0 \\
\tau_+ \Delta T - \tau_-, & \text{if } \Delta T \geq 0, T < 0 \\
\tau_+ \Delta T + \tau_-, & \text{if } \Delta T > 0, T < 0
\end{cases}
\]
Neuronal response after learning

The first synapses generate a response

\[
\Delta w = \begin{cases} 
+1, & T > 0 \\
-1, & T < 0 
\end{cases}
\]

Neuronal response shift earlier in time

Neuronal response before learning

Neuronal response after learning

Application of STDP models

Parkinson’s disease

- Parkinson’s disease – a neurogenerative disease characterized by tremors, rigidity, slowness of movement, stiffness.
- Electrical high frequency deep brain stimulation of the subthalamic nucleus is the effective surgical treatment for Parkinson’s disease.

Desynchronization of neural populations

- Parkinson’s disease is characterized by abnormally strong, pathological neuronal synchronization
- Synaptic coupling is strong and has to be unlearned

Unlearning strong synaptic coupling via STDP

- Network of Hodgkin–Huxley neurons and STDP learning rule
- Stimulation causes an unlearning of pathological synchronization
  - Weak or strong stimulation does not have a long-lasting effect
  - Intermediate strength stimulation suppresses synaptic coupling and leads to a long-lasting desynchronization

Models of Spike-timing Dependent Plasticity

- Phenomenological – encode data and intuitions about synaptic plasticity.
- Optimal – use some optimality criterion to deduce the rules of synaptic modifications.
- Biophysical – biophysically realistic, usually based on calcium dynamics, involve detailed biochemical reactions to explain synaptic plasticity.
Phenomenological models

- Black box approach
- No explicit modelling of biophysical processes
- Used in networks – memory formation, neuronal selectivity

\[ T = T_{pre} - T_{post} \]

\[ \Delta \theta = \begin{cases} A^+ \theta^+, & T > 0 \\ A^- \theta^-, & T < 0 \end{cases} \]

(Abbott and Song, 1999; Gerstner et al, 1996; Pfister and Gerstner, 2006; Kempter et al, 1999; Kistler et al, 2000; Song et al, 2000; van Rossum, 2000)

Optimal models

- Derive the optimal STDP function for a given task:
  - Maximal information transfer in network of spiking neurons – use information theory to obtain STDP curve (Bell and Parra, 2003; Toyoizumi et al, 2005)
  - Optimal filter function - STDP shape represents the filter to remove the noise from the signal and increase the influence of its significant components; (Dayan et al, 2004)
  - Optimal firing time of the postsynaptic neuron – maximization of the probability of firing at the defined times leads to the STDP function (Pfister et al, 2004)

Biophysical models

- White box approach
- Based on Ca\(^{2+}\) dynamics in spine of a postsynaptic neuron
- Used to model synaptic plasticity at a single synapse, local microcircuit

Calcium dynamics in spines

- NMDA channels
- Ca\(^{2+}\) pumps
- Voltage gated Ca\(^{2+}\) channels
- Ca\(^{2+}\) buffers
- Ca\(^{2+}\) diffusion


Calcium concentration

Calcium current through voltage-gated calcium channels:

\[ I_{Ca,VGCC} = \bar{g}_{Ca} I_m h(V - E_{Ca}) \]

Calcium current through NMDA receptor-gated channels:

\[ I_{Ca,NMDA} = 0.1 \bar{g}_{NMDA}(V - E_{NMDA}) \]

Calcium concentration:

\[ \frac{d[Ca^{2+}]}{dt} = -I_{Ca} \frac{[Ca^{2+}]}{2F_0} + \frac{[Ca^{2+}]}{\tau_D} \]

Decay due to pumping, buffering, diffusion

Ca\(^{2+}\) transients

STDP stimulation protocol

Amplitude and time course of Ca\(^{2+}\) transient depend on the temporal order and temporal difference of pre- and postsynaptic activity.
Biophysical models
Calcium control hypothesis

- Weight change is determined by $[\text{Ca}^{2+}]$ levels:
  - low $[\text{Ca}^{2+}]$ levels – no changes
  - intermediate $[\text{Ca}^{2+}]$ levels between $\theta_d$ and $\theta_p$ – LTD
  - high $[\text{Ca}^{2+}]$ levels above $\theta_p$ – LTP

Biophysical models
Calcium control hypothesis

- Weight change is proportional to the threshold function $\Omega([\text{Ca}])$:
  \[ \Delta w \propto \eta \Omega([\text{Ca}]) \]
- Plasticity outcomes:
  - short positive $T$ – LTP
  - short negative and large positive $T$ – LTD

Biochemical mechanisms of
Spike-timing dependent plasticity

- Correlated activity of pre- and postsynaptic neurons
- Glutamate release
- Activation of NMDAr-gated channels
- Increase in calcium concentration in a spine

Biophysical models
LTP and LTD enzyme competition

LTD enzyme $P$

$$\frac{m + \text{Ca}^{2+}}{K_a} m^* \xrightarrow{h + \text{Glu}} P^*_m$$

Long-term depression

Phosphatases

Dephosphorylation of AMPA receptors

LTP enzyme $K$

$$K + 4\text{Ca}^{2+} \xrightarrow{K_a} K^*$$

Reflects activity of $\text{Ca}^{2+}$/calmodulin-dependent protein kinase II, activated by $\text{Ca}^{2+}$

Binary synapse model

- Synaptic changes are all-or-none switch-like events
- Two stable states of synaptic transmission efficacy at resting calcium levels:
  - DOWN, low synaptic strength
  - UP, high synaptic strength
- Transitions:
  - UP-DOWN: LTD
  - DOWN-UP: LTP

Ca$^{2+}$/calmodulin (CaM)-dependent protein kinase CaMKII

- CaMKII holoenzyme consists of 6 subunits.
- Each subunit can be in:
  - active, phosphorylated state;
  - not active, dephosphorylated state.
- CaMKII can be stable in two states at resting calcium:
  - weakly phosphorylated state - DOWN
  - highly phosphorylated state - UP
- CaMKII switch in a binary synapse:
  - Transition UP-DOWN: LTD
  - Transition DOWN-UP: LTP
Bistable synapse model based on CaMKII activation network

- Ca^{2+}/calmodulin activates CaMKII
- PP1 inhibits, dephosphorylates CaMKII
  - PP1 influence is increased by calcineurin activation
  - PP1 influence is reduced by cyclic-AMP and PKA activation

Biochemical networks of synaptic plasticity: more details

- Model of CaMKII regulation, mGlu receptor and NMDA receptor activation

Multiple forms of STDP

- STDP depends on:
  - Stimulation protocol
    - Pattern of post activity (single spike, burst)
    - Frequency of pairings
    - Duration of stimulation
  - Properties of neuron
    - Dendritic plasticity
    - Dendritic synapse location
  - Neuron type
  - Brain region

STDP timing windows

Diversity of STDP curves

- Numbers of postsynaptic spikes and duration of the stimulation qualitatively change the STDP curve.
NEURON demo
Modeling learning in hippocampus

- NEURON simulator
- STDP model: synaptic efficacy variables $\rho_{UP}$, $\rho_{DOWN}$
- Associative learning in a CA1 microcircuit

Models of LTP and LTD: review

- Postsynaptic signal transduction models for long-term potentiation and depression
- 117 models analyzed
- Models of molecular mechanisms underlying synaptic plasticity are classified:
  - Direction: LTP/LTD
  - Complexity: single pathways/simplified processes/signaling networks
  - Method: deterministic/stochastic method
  - Cell type

Neuromodulation of STDP

- STDP depends on:
  - pre- and postsynaptic activity
  - a “third factor” — neuromodulators dopamine, acetylcholine, etc
- Neuromodulators open the STDP gate:
  - necessary for plasticity induction or
  - change the shape of the STDP
- Time and spatial scale:
  - Correlated pre-post activity, STDP — local and fast, ms
  - Neuromodulation — global and slow, 3-5 sec

Dopamine pathways

- Dopamine is involved in:
  - reward-motivated behavior
  - pleasure
  - motor control
- Dopamine signal mimics reward prediction error (reinforcement learning theory)

Dopamine controls STDP in hippocampal neurons

- Dopamine changes the shape of the STDP window.
  - LTP window is wider
  - LTD converts into LTP
- Dopamine reduces the number of spike pairs required to induce LTP from 60 to 10.

How do molecules affect behaviour?

Dopamine is involved in:
- reward-motivated behavior
- pleasure
- motor control
- Dopamine signal mimics reward prediction error (reinforcement learning theory)
Application of STDP-like learning rule in robotics

RunBot - a biped walking robot – learns to walk on a terrain

Collision sensors

Vision sensors

Robot learns to navigate without collisions

RunBot – a biped walking robot – learns to walk on a terrain

Differential Hebbian learning:
\[ \frac{dw}{dt} = \mu R_{\text{vision}} y' \]

STDP-like weight change

Final remarks

- Phenomenological models apply the STDP function and analyze the computational principles and its functional consequences in networks.
- Optimal models derive optimal STDP function for a given task – optimal firing time, maximal information transfer between neurons, optimal filter function.
- Biophysical models explain STDP using the principles of ion channel dynamics and intracellular processes. Usually contains a large parameter space.

Final remarks

- Neuromodulation gates STDP and provides link from correlation-based synaptic plasticity rules to behaviorally based learning.
- Link between the cellular processes and behaviour is hard to establish. Robotics offer one of the possibilities to analyze the functional consequences of the learning rules.
- Models contribute to understanding of brain functioning in health and disease.

Final remarks

- Modeling synaptic plasticity:
  - from molecules (nm) to a system level (m);
  - from fast electrical events (ms) to slow chemical processes (min, hours);
  - from unsupervised learning to reinforcement learning (reward-based).

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