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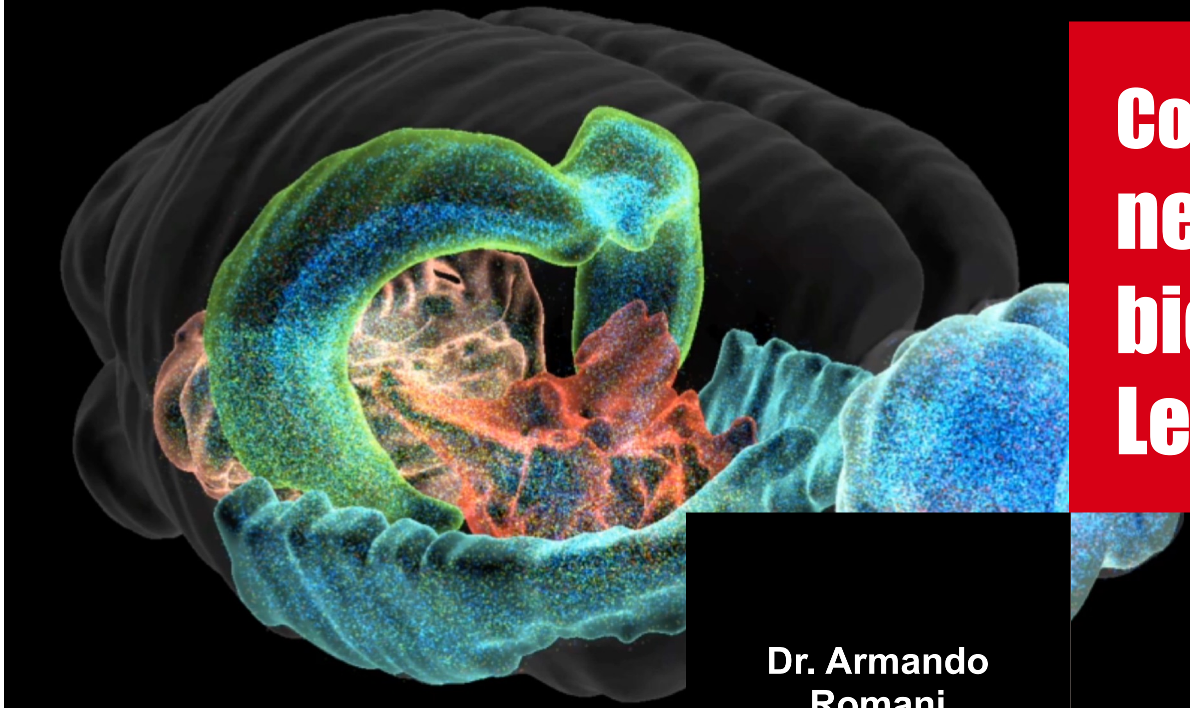


Computational neuroscience: biophysics - Lecture 9

Dr. Armando Romani

EPFL, 2024

- Blue Brain Project

Long-term plasticity

Lecture Overview

- Scope
- Approaches
- Applications

Lecture Overview

- **Scope**
- Approaches
- Applications

Synaptic plasticity

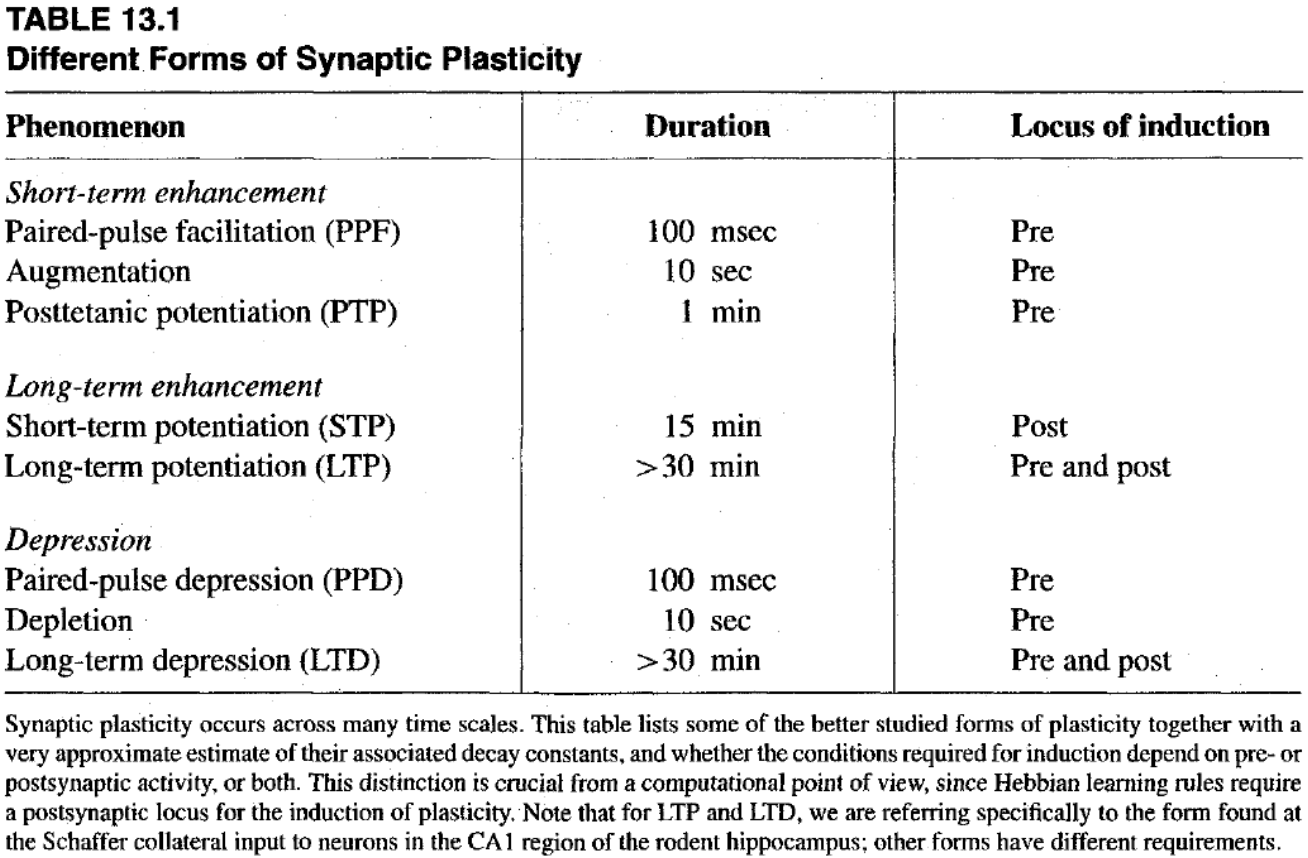


TABLE 13.1
Different Forms of Synaptic Plasticity

Phenomenon	Duration	Locus of induction
Short-term enhancement		
Paired-pulse facilitation (PPF)	100 msec	Pre
Augmentation	10 sec	Pre
Posttetanic potentiation (PTP)	1 min	Pre
Long-term enhancement		
Short-term potentiation (STP)	15 min	Post
Long-term potentiation (LTP)	>30 min	Pre and post
Depression		
Paired-pulse depression (PPD)	100 msec	Pre
Depletion	10 sec	Pre
Long-term depression (LTD)	>30 min	Pre and post

Synaptic plasticity occurs across many time scales. This table lists some of the better studied forms of plasticity together with a very approximate estimate of their associated decay constants, and whether the conditions required for induction depend on pre- or postsynaptic activity, or both. This distinction is crucial from a computational point of view, since Hebbian learning rules require a postsynaptic locus for the induction of plasticity. Note that for LTP and LTD, we are referring specifically to the form found at the Schaffer collateral input to neurons in the CA1 region of the rodent hippocampus; other forms have different requirements.

Koch, 2004

Synaptic plasticity

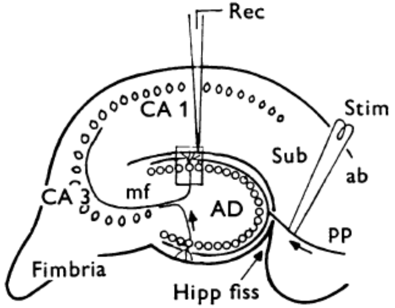
“When an axon of cell *A* is near enough to excite a cell *B* and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that *A*'s efficiency, as one of the cells firing *B*, is increased” (Hebb, 1949).

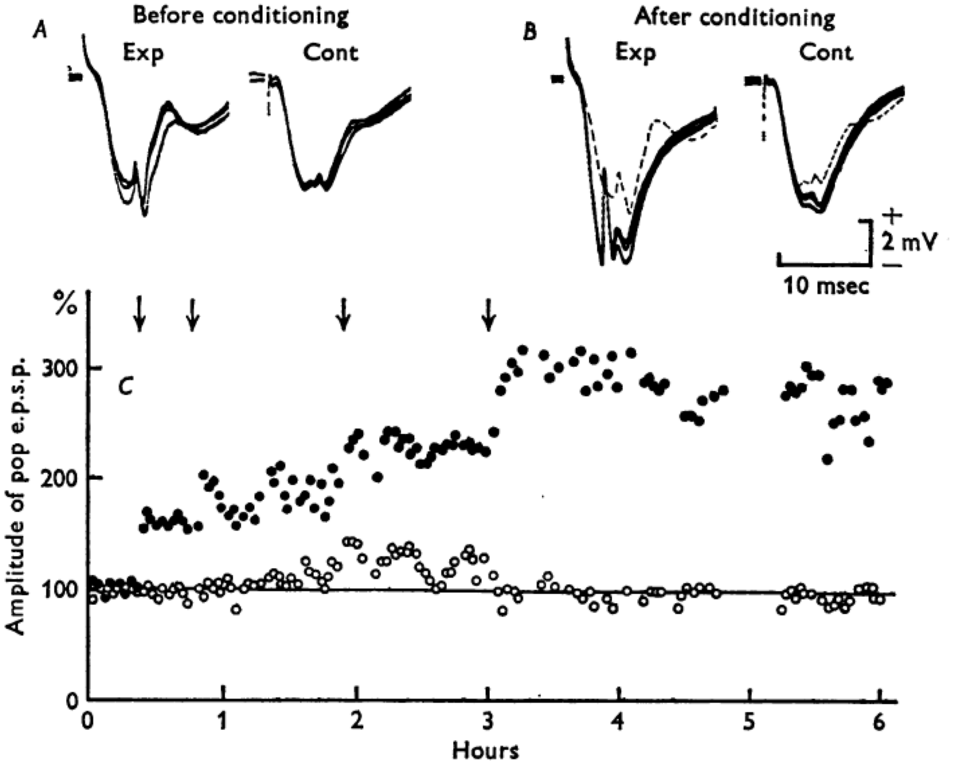
Cells that fire together wire together

Cells out of sync lose their link

Long-term potentiation (LTP)

- ‘Synaptic plasticity’ (Konorski, 1948)
- ‘Hebbian’ plasticity (Hebb, 1949)
- Post-tetanic potentiation (PTP)
- Higher stimulation (Lømo 1966)
- Long-term potentiation (Bliss and Lømo, 1970, 1973)

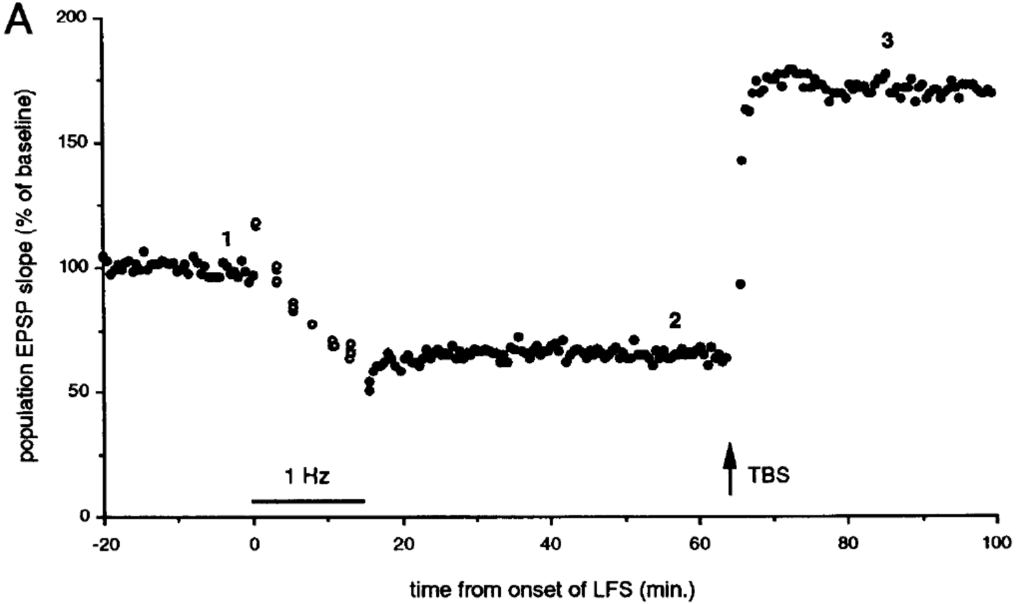




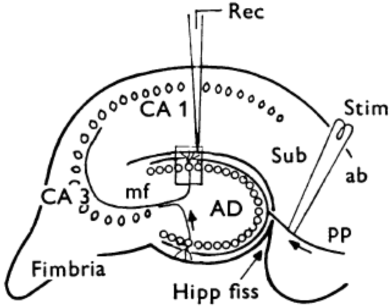
Bliss and Lømo, 1973

Long-term depression (LTD)

- Long-term depression (Dunwiddie and Lynch, 1978)
- Durable LTD (Dudek and Bear, 1992)
- Graded bidirectional synaptic modifiability (Dudek and Bear, 1993)

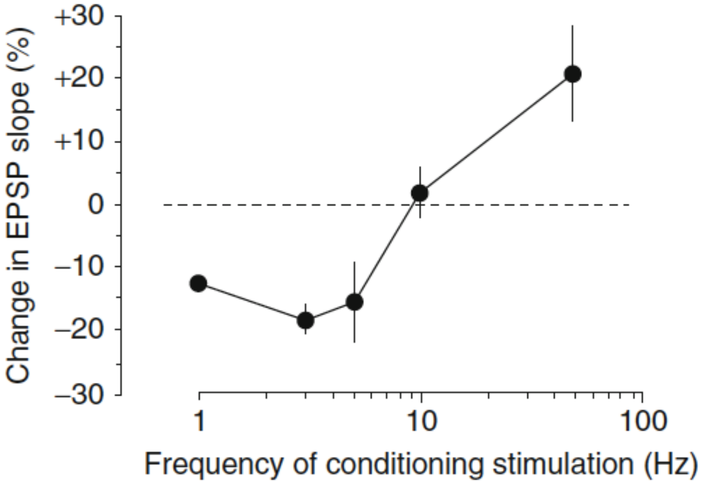


Dudek and Bear, 1993



Experimental protocols

- High-frequency stimulation (e.g. 100Hz for 1s) -> LTP
- Prolonged low-frequency stimulation (e.g. 900 stimuli at 1Hz) -> LTD
- Extracellular presynaptic stimulation at different frequencies



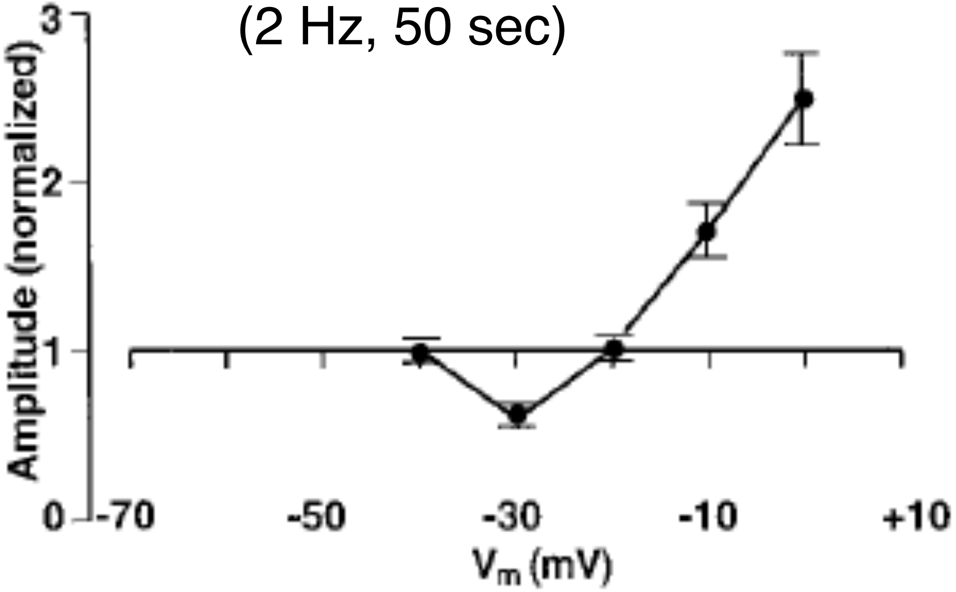
Fix stimulus duration

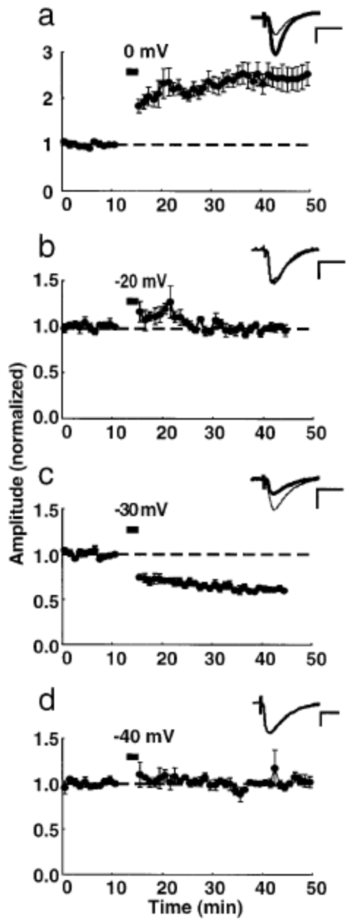
Clopath (2015)

Experimental protocols

Low-frequency stimulation + postsynaptic depolarization

(2 Hz, 50 sec)

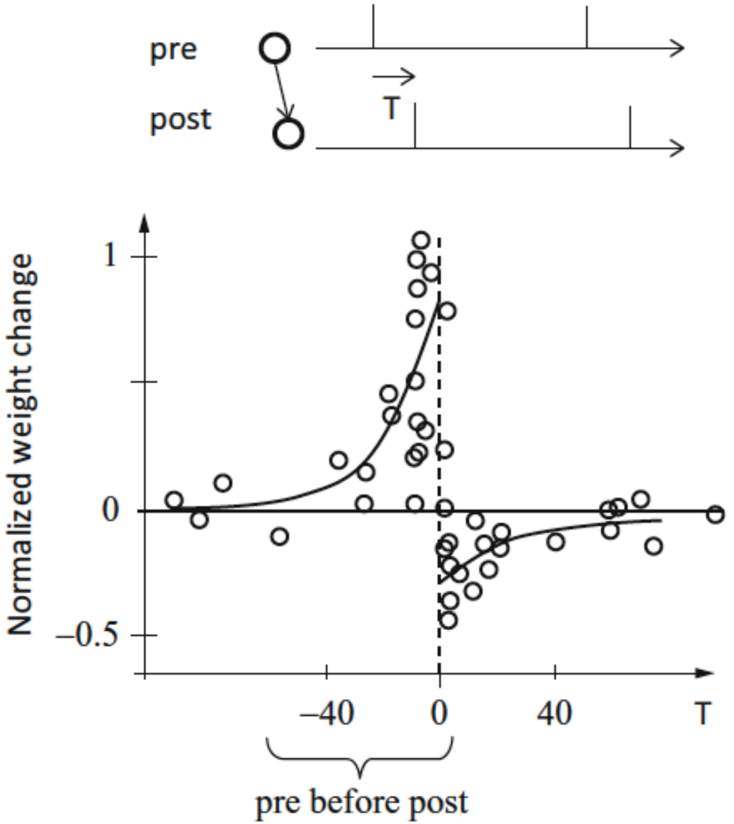




Ngezahayo et al., 2000

Experimental protocols

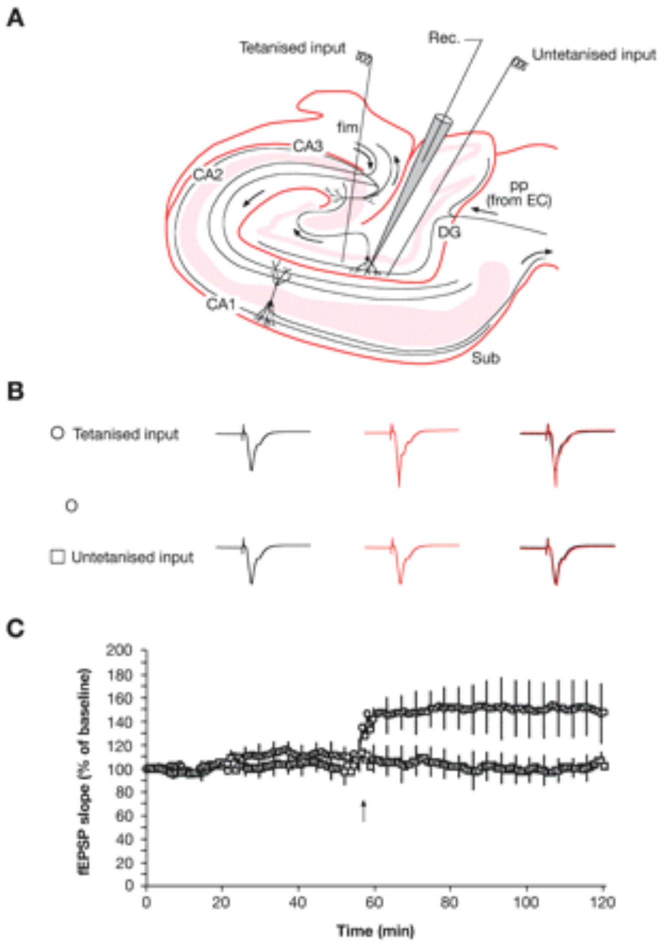
Spike-time dependent plasticity (STDP)



Clopath (2015)

Experimental protocols

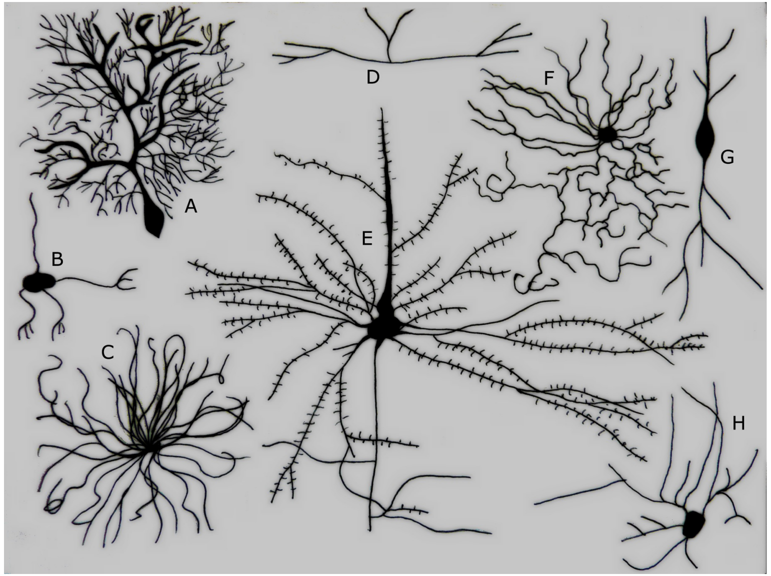
- Plasticity has similar mechanisms *in vivo* and *in vitro*
- Evidence for long-term plasticity in humans



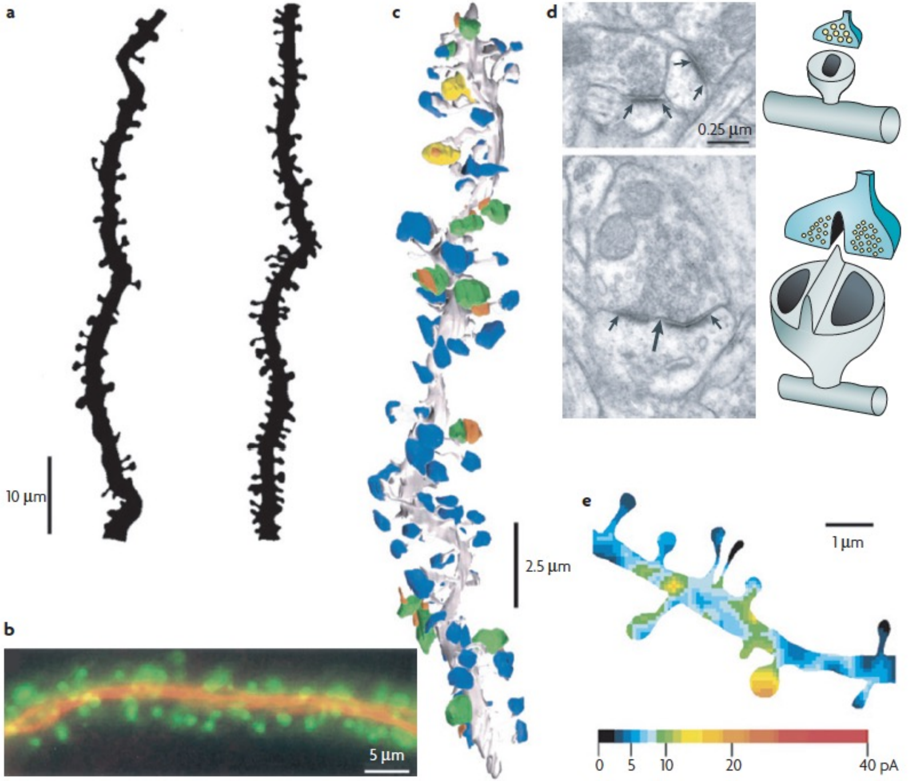
Cooke and Bliss, 2006

Dendritic spines

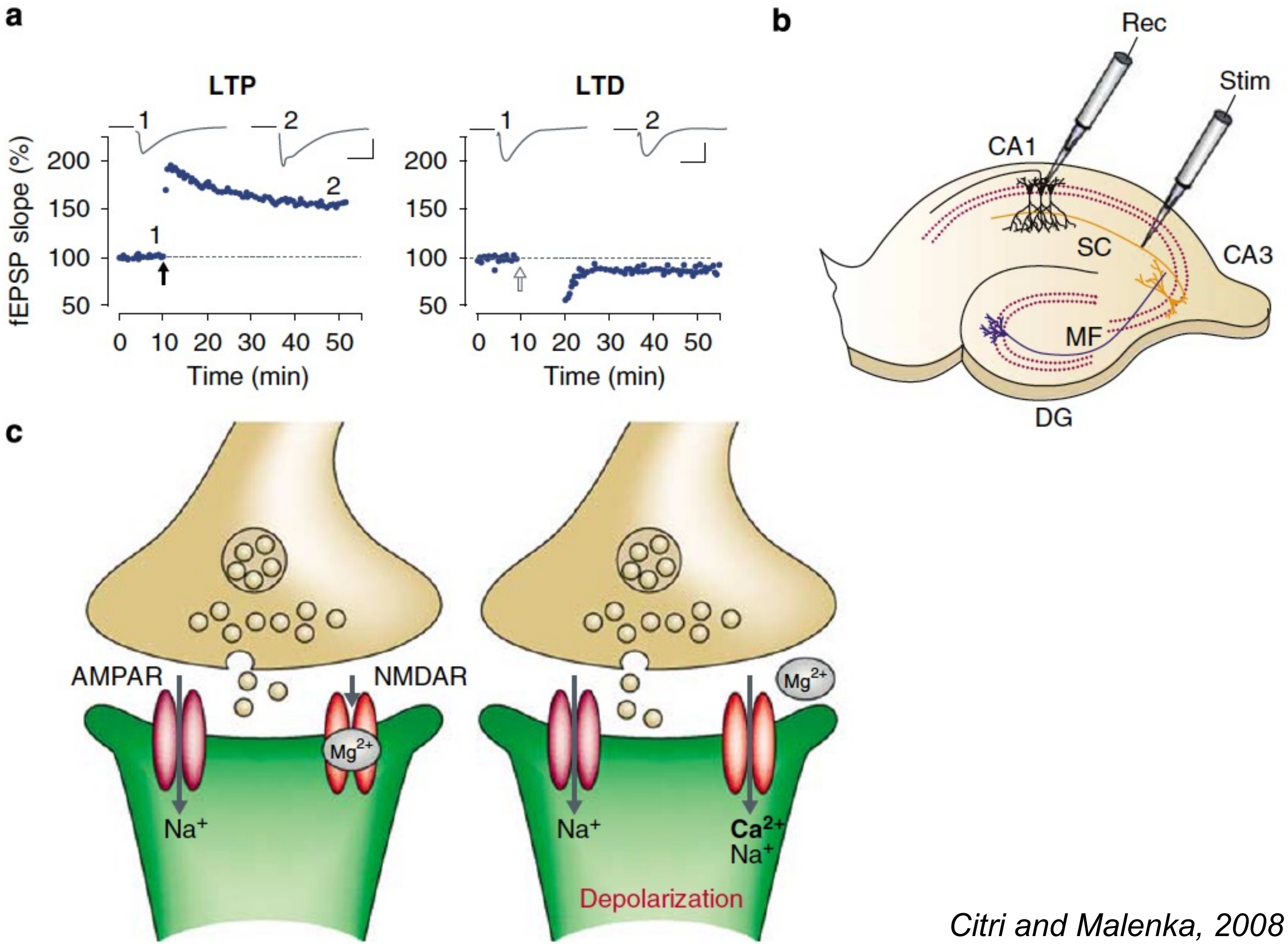
Neuron types
by Santiago Ramón y Cajal (1887)



Different Types of Neurons. A. Purkinje cell B. Granule cell C. Motor neuron D. Tripolar neuron E. Pyramidal Cell F. Chandelier cell G. Spindle neuron H. Stellate cell (Credit: Ferris Jabr; based on reconstructions and drawings by Cajal)



Spruston, 2008



Citri and Malenka, 2008

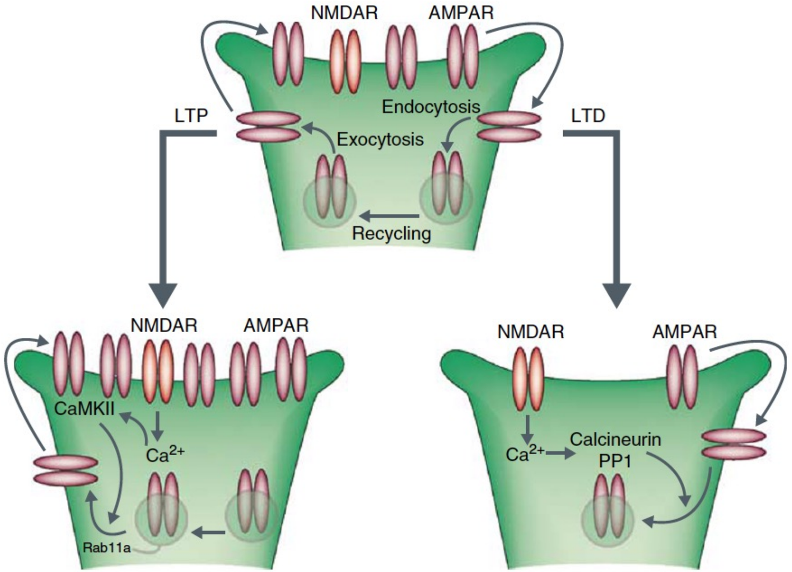
LTP

Induction

- It depends on NMDAR, increase in Ca^{2+}
- Calcium/calmodulin (CaM)-dependent protein kinase II (CaMKII) undergoes autophosphorylation

Expression

- Early phase or E-LTP (30 – 60 min)
- Recycling endosomes contain AMPARs are mobilized via a process that requires the GTP-binding protein Rab11a
- New AMPARs are added in the postsynaptic density (PSD)

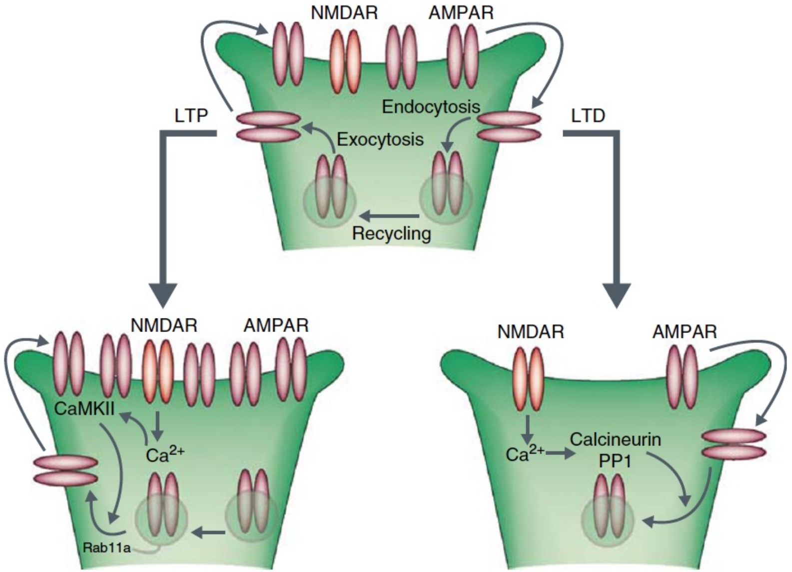


Citri and Malenka, 2008

LTP

Maintenance

- Late phase or L-LTP (> 1 – 2 hrs)
- Local dendritic synthesis (AMPAR, CAMKII…)
- Transcription on the nucleus



Citri and Malenka, 2008

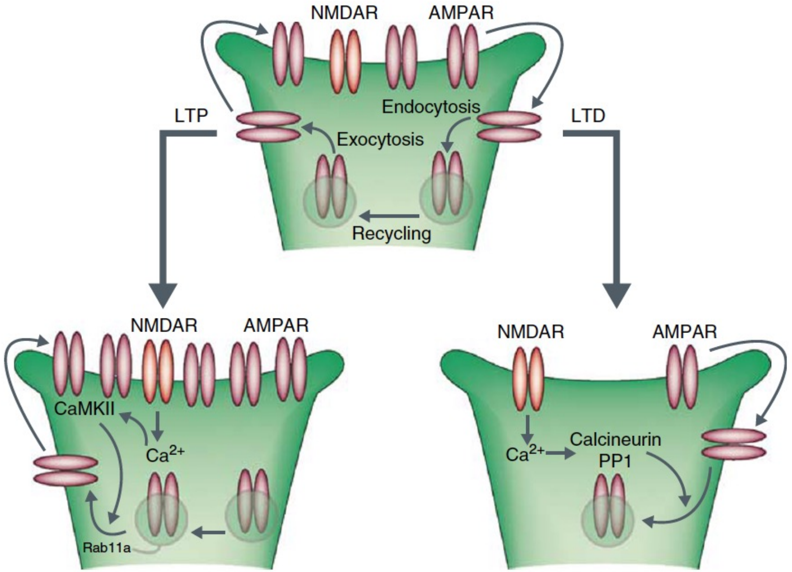
LTD

Induction

- It depends on NMDAR, modest increase in Ca^{2+}
- Calcium/calmodulin-dependent phosphatase calcineurin, protein phosphatase 1 (PP1)…

Expression

- Activity-dependent endocytosis of synaptic AMPARs



Citri and Malenka, 2008

Presynaptic LTP

Prototype: plasticity at Mossy fibers (DG-CA3)

Induction

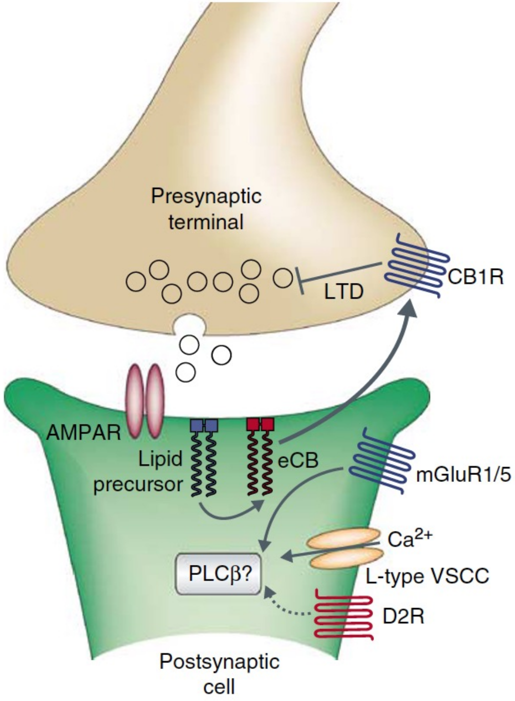
- increase in Ca^{2+} in presynaptic terminal, voltage-dependent calcium channels (VDCC)
- Calcium/calmodulin-dependent adenylyl cyclase
- increase in presynaptic cAMP and activation of Protein kinase A (PKA)

Expression

- Enhancement in transmitter release

Endocannabinoid-mediated LTD

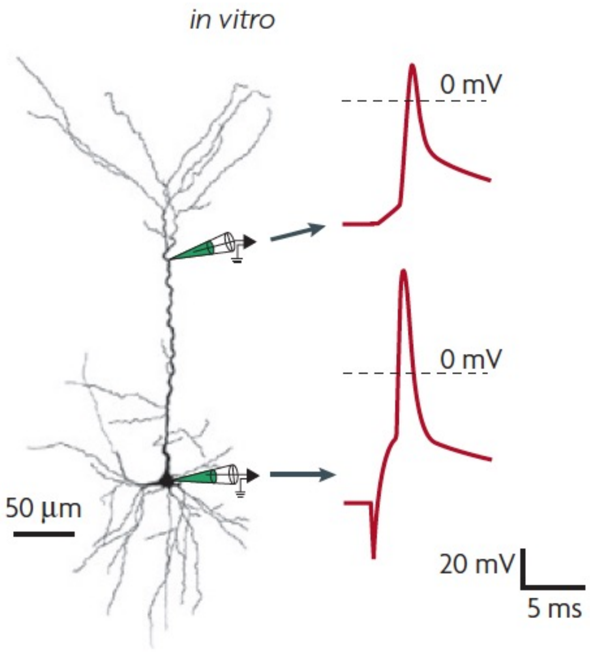
- Endogenous cannabinoids (neuromodulators)
- Retrograde messengers
- Strong depolarization and/or activation of G-protein-coupled receptors (e.g., mGluRs and muscarinic receptors)
- Activation of presynaptic CB1 receptors
- Inhibit transmitter release



Citri and Malenka, 2008

Backpropagating action potential (BPAP)

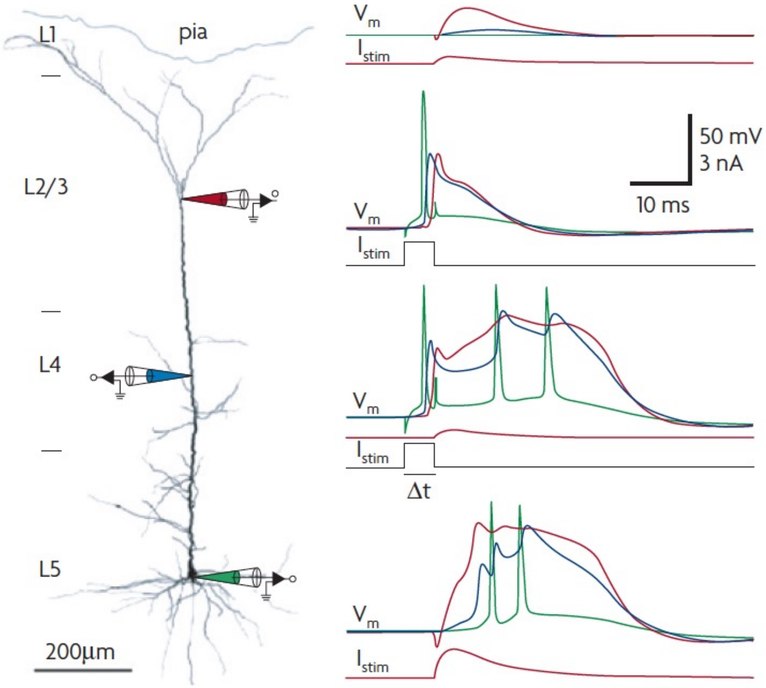
- An action potential (generated in soma or AIS) propagates backwards in the dendrites
- Ion channel composition affects how reliable the BPAP is transmitted
- BPAP can release the Mg^{2+}-block necessary to induce an NMDAR-mediated plasticity



Spruston, 2008

Dendritic spikes

- Na^+ spikes. Brief events
- Ca^{2+} spikes. Larger and broader events
- NMDA spikes. Due to release of Mg^{2+}. They remain where glutamate release occurs
- Backpropagation-activated Ca^{2+} spike (BAC spike). Synaptic stimulation + BPAP (figure)
- Dendritically initiated spikes are required for LTP or LTD induction in response to strong synaptic stimulation or during pairing of EPSPs with postsynaptic bursts



Spruston, 2008

Summary 1

- Long-term plasticity can be induced by several protocols
- There are several forms of plasticity in the brain
- Long-term plasticity includes phenomena at different spatial and temporal scales
- Hippocampal plasticity is the prototype of many forms of plasticity
- Plasticity has similar mechanisms *in vivo* and *in vitro*
- Evidence for long-term plasticity in humans
- Dendrites are highly non linear

Lecture Overview

- Scope
- **Approaches**
- Applications

Different approaches

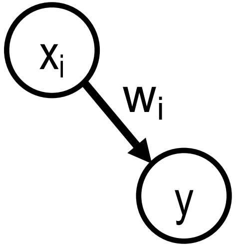
- There are a multitude of models
- Each model can reproduce a subset of experiments and is suitable to mimic certain forms of plasticity
- Models different from the variable that decides how the weights are updated
- Historically, the starting point is the Hebbian rule

Different approaches

- Rate based models
- Spike timing based models
- Voltage based
- Calcium based
- Subcellular models

Rate based models: Hebbian rule

$$\Delta w_i = \alpha x_i y,$$



a is learning rate. a=1 in the simplest expression of the Hebbian rule. In many models, a << 1 to guarantee a small change over time

A simple rule as above can lead to uncontrolled growth of weights.

A more general expression is:

$$\frac{dW_i}{dt} = f(x_i, y, W_i, other),$$

The rate of pre and postsynaptic firing measured over some time period, determines the sign and magnitude of synaptic plasticity

Rate based models: Linsker (1986)

$$\frac{dW_i}{dt} = \eta(x_i - x_0)(y - y_0),$$

x0 and y0 are the average activity

The weights can be augmented and reduced

Covariance of the two neurons

Rate based models: Oja’s rule (1982)

$$\Delta w_i = \alpha(x_i y - \boxed{y^2 w_i}),$$

Forgetting term

The squared output y^2 guarantees that the larger the output of the neuron becomes, the stronger is this balancing effect.

Rate based models: BCM rule (Bienenstock, Cooper, and Munro 1982)

$$\begin{aligned} \frac{dw_i}{dt} &= y(y - \theta_M)x_i - \epsilon w_i \\ \theta_M &= E^p[(y/y_o)] \end{aligned}$$

$-\epsilon w_i$ uniform weight decay

θ_M modification threshold

E[] average over all input patterns

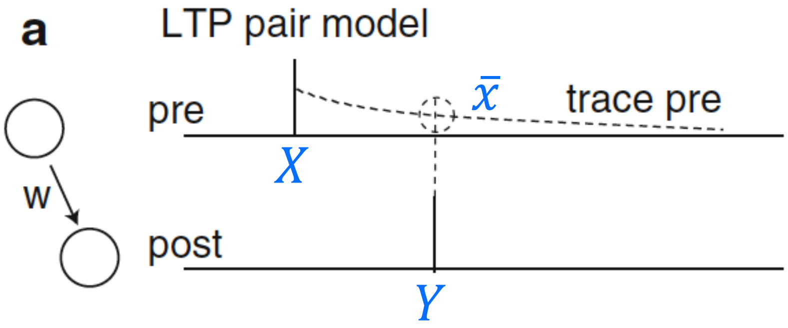
p exponent

y_0 constant

θ_M depends on the history of the cell

Lower rates of y leads to a decrease of w, higher rates to an increase of w

Spike timing based models



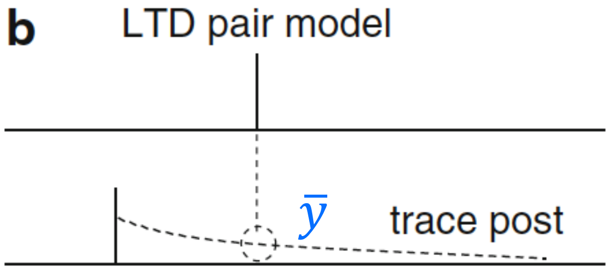
$$\frac{d}{dt} w_i^+ = +A_{\mathrm{LTP}}\left(w_i^+\right) Y(t) \bar{x}_i(t).$$

$$Y(t) = \sum{}_n \delta(t - t^n)$$

$$\tau_+ \frac{d}{dt} \bar{x}_i(t) = -\bar{x}_i(t) + X_i(t),$$

$$X_i(t) = \sum{}_n \delta(t - t_i^n)$$

xi could represent glutamate bound to postsynaptic receptors or the number of NMDA receptors activated



$$\frac{d}{dt} w_i^- = -A_{\mathrm{LTD}}\left(w_i^-\right) X_i(t) \bar{y}(t),$$

$$\tau_- \frac{d}{dt} \bar{y}(t) = -\bar{y}(t) + Y(t),$$

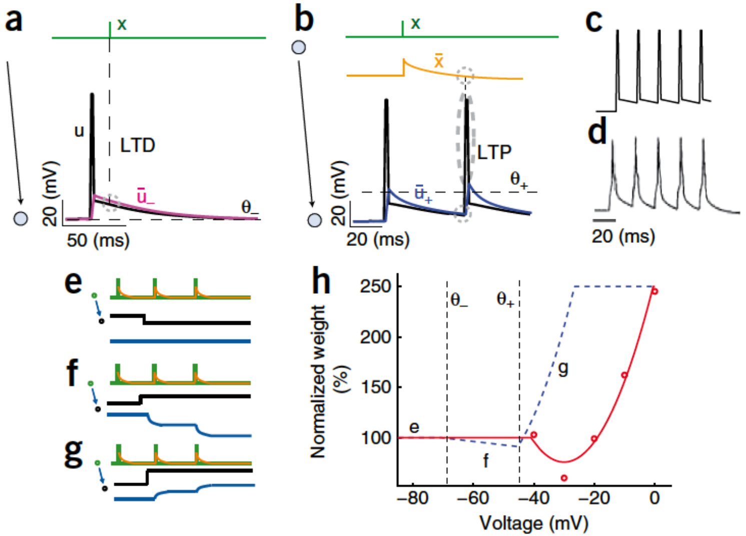
ȳ is an abstract variable which could reflect Ca, endocannabinoids, BPAP

Clopath (2015)

Voltage based models: Clopath et al., 2010

$$\frac{d}{dt}w_i^+ = A_{\mathrm{LTP}}\overbrace{\bar{x}_i}^{\text{pre}}\overbrace{(u-\theta_+)_+(\bar{u}_+-\theta_-)_+}^{\text{post}} \quad \text{if } w_i < w_{\max}$$

Here, A_{LTP} is a free amplitude parameter fitted to the data and $\bar{u}_+(t)$ is another low-pass-filtered version of $u(t)$ that is similar to $\bar{u}_-(t)$ but has a shorter time constant τ_+ of around 10 ms. Thus, positive weight changes can occur if the momentary voltage $u(t)$ surpasses a threshold θ_+ and, at the same time, the average value $\bar{u}_+(t)$ is above θ_-.



( )+ indicates rectification, that is, any value *<0* does not lead to a change

$$\tau_x \frac{d}{dt}\bar{x}_i(t) = -\bar{x}_i(t) + X_i(t)$$

$$\frac{d}{dt}w_i^- = -A_{\mathrm{LTD}}(\bar{\bar{u}})X_i(t)(\bar{u}_- - \theta_-)_+ \text{ if } w_i > w_{\min}$$

$$\tau_- \frac{d}{dt}\bar{u}_-(t) = -\bar{u}_-(t) + u(t)$$

$$\frac{d}{dt}w_i = -A_{\mathrm{LTD}}(\bar{\bar{u}})X_i(\bar{u}_- - \theta_-)_+ + A_{\mathrm{LTP}}\bar{x}_i(u-\theta_+)_+(\bar{u}_+ - \theta_-)_+ \quad \text{hard bounds } w_{\min} \le w_i \le w_{\max}$$

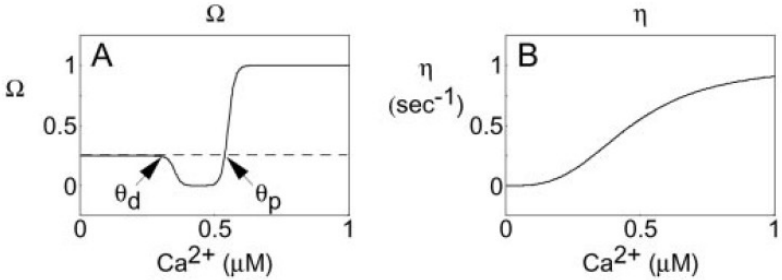
Voltage based models

- The voltage based models can potentially integrate the non linearity of the dendrites (e.g. BPAP, dendritic spikes)
- They are closer to the biophysics
- They are more general and can explain more experiments

Calcium based models: Shouval et al., 2002

$$\dot{W}_j = \eta\Omega([Ca]_j),$$

where W_j represents the synaptic strength of synapse j, η is the learning rate, and the calcium level at synapse j is denoted by $[Ca]_j$. When the calcium level is below a lower threshold θ_d, no modification occurs. If $\theta_d < [Ca]_j < \theta_p$, W_j is depressed, and for $[Ca]_j > \theta_p$, the synaptic strength is potentiated (Fig. 1*A*).



$$\dot{W}_j = \eta(\Omega([Ca]_j) - \lambda W_j),$$

where λ represents a decay constant.

$$\dot{W}_j = \eta([Ca]_j)(\Omega([Ca]_j) - W_j).$$

The learning rate η is inversely proportional to the learning time constant τ. In Eq. **3**, we set $\lambda = 1$ without loss of generality.

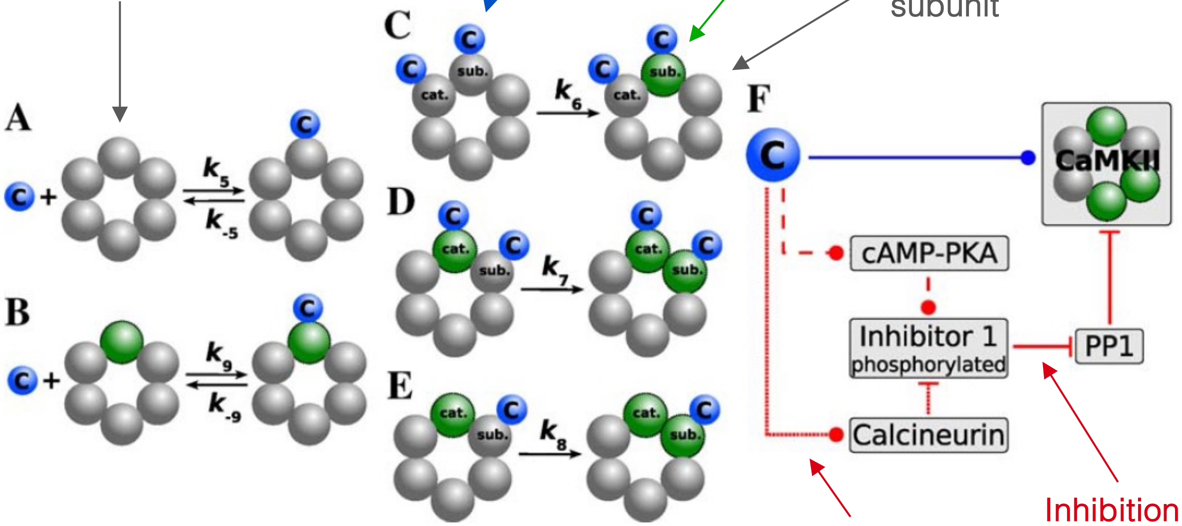
Calcium based models: Shouval et al., 2002

- Calcium influx from NMDAR
- The model can be expanded with voltage-dependent Ca^{2+} channels and release from intercellular stores
- Bidirectional synaptic plasticity
- Pairing Presynaptic Stimulation with Postsynaptic Voltage Clamp
- Varying the Rate of Presynaptic Stimulation
- Varying Spike Timing (STDP)

Subcellular models: Groupner and Brunel, 2007

- Two stable states of the CaMKII phosphorylation level exist at resting intracellular calcium concentration, and high calcium transients can switch the system from the weakly phosphorylated (DOWN) to the highly phosphorylated (UP) state of the CaMKII (similar to a LTP event). We show here that increased CaMKII dephosphorylation activity at intermediate Ca^{2+} concentrations can lead to switching from the UP to the DOWN state (similar to a LTD event).
- It includes model postsynaptic calcium and postsynaptic membrane potential dynamics induced by presynaptic and postsynaptic spikes
- The model reproduces STDP and presynaptic stimulation protocols

Subcellular models: Groupner and Brunel, 2007



CaMKII

Ca^{2+}-calmodulin complex

Phosphorylated subunit

Dephosphorylated subunit

Stimulation

Inhibition

Subcellular models

Manninen et al. (2010) reviewed 117 models which are biophysical and have postsynaptic mechanisms

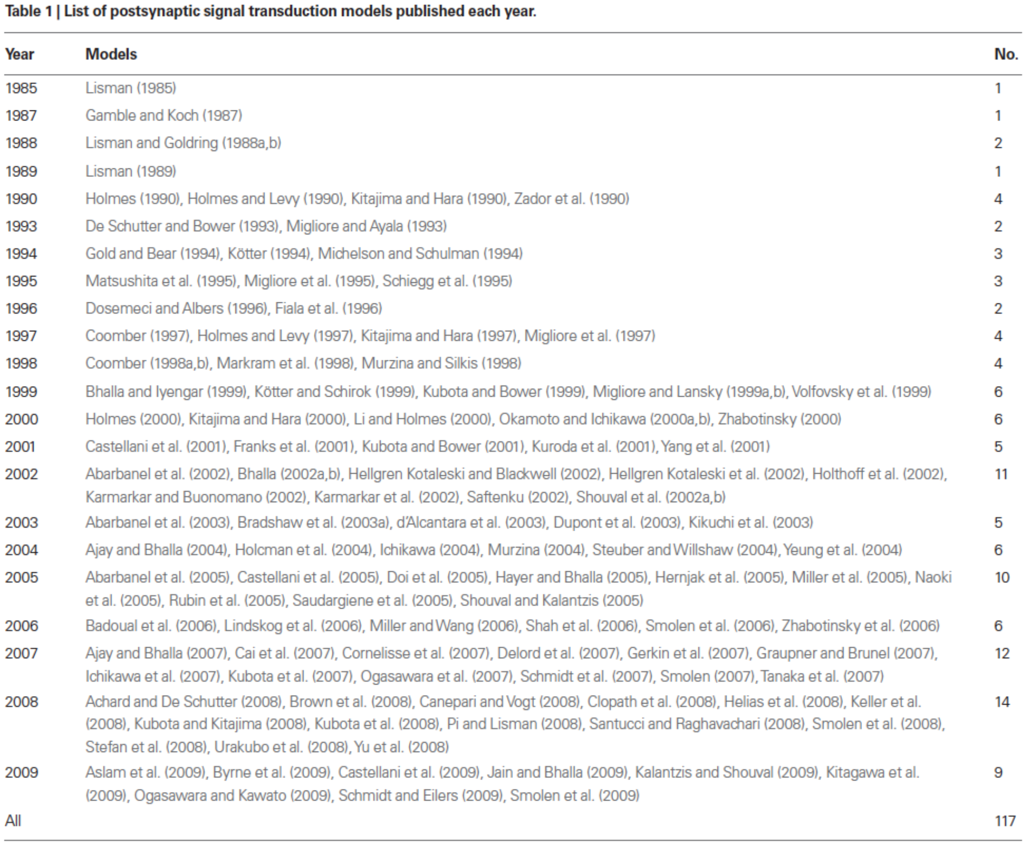


Table 1 | List of postsynaptic signal transduction models published each year.

Year	Models	No.
1985	Lisman (1985)	1
1987	Gamble and Koch (1987)	1
1988	Lisman and Goldring (1988a,b)	2
1989	Lisman (1989)	1
1990	Holmes (1990), Holmes and Levy (1990), Kitajima and Hara (1990), Zador et al. (1990)	4
1993	De Schutter and Bower (1993), Migliore and Ayala (1993)	2
1994	Gold and Bear (1994), Kötter (1994), Michelson and Schulman (1994)	3
1995	Matsushita et al. (1995), Migliore et al. (1995), Schiegg et al. (1995)	3
1996	Dosemeci and Albers (1996), Fiala et al. (1996)	2
1997	Coomber (1997), Holmes and Levy (1997), Kitajima and Hara (1997), Migliore et al. (1997)	4
1998	Coomber (1998a,b), Markram et al. (1998), Murzina and Silkis (1998)	4
1999	Bhalla and Iyengar (1999), Kötter and Schirok (1999), Kubota and Bower (1999), Migliore and Lansky (1999a,b), Volfovsky et al. (1999)	6
2000	Holmes (2000), Kitajima and Hara (2000), Li and Holmes (2000), Okamoto and Ichikawa (2000a,b), Zhabotinsky (2000)	6
2001	Castellani et al. (2001), Franks et al. (2001), Kubota and Bower (2001), Kuroda et al. (2001), Yang et al. (2001)	5
2002	Abarbanel et al. (2002), Bhalla (2002a,b), Hellgren Kotaleski and Blackwell (2002), Hellgren Kotaleski et al. (2002), Holthoff et al. (2002), Karmarkar and Buonomano (2002), Karmarkar et al. (2002), Saftenku (2002), Shouval et al. (2002a,b)	11
2003	Abarbanel et al. (2003), Bradshaw et al. (2003a), d'Alcantara et al. (2003), Dupont et al. (2003), Kikuchi et al. (2003)	5
2004	Ajay and Bhalla (2004), Holcman et al. (2004), Ichikawa (2004), Murzina (2004), Steuber and Willshaw (2004), Yeung et al. (2004)	6
2005	Abarbanel et al. (2005), Castellani et al. (2005), Doi et al. (2005), Hayer and Bhalla (2005), Hernjak et al. (2005), Miller et al. (2005), Naoki et al. (2005), Rubin et al. (2005), Saudargiene et al. (2005), Shouval and Kalantzis (2005)	10
2006	Badoual et al. (2006), Lindskog et al. (2006), Miller and Wang (2006), Shah et al. (2006), Smolen et al. (2006), Zhabotinsky et al. (2006)	6
2007	Ajay and Bhalla (2007), Cai et al. (2007), Cornelisse et al. (2007), Delord et al. (2007), Gerkin et al. (2007), Graupner and Brunel (2007), Ichikawa et al. (2007), Kubota et al. (2007), Ogasawara et al. (2007), Schmidt et al. (2007), Smolen (2007), Tanaka et al. (2007)	12
2008	Achard and De Schutter (2008), Brown et al. (2008), Canepari and Vogt (2008), Clopath et al. (2008), Helias et al. (2008), Keller et al. (2008), Kubota and Kitajima (2008), Kubota et al. (2008), Pi and Lisman (2008), Santucci and Raghavachari (2008), Smolen et al. (2008), Stefan et al. (2008), Urakubo et al. (2008), Yu et al. (2008)	14
2009	Aslam et al. (2009), Byrne et al. (2009), Castellani et al. (2009), Jain and Bhalla (2009), Kalantzis and Shouval (2009), Kitagawa et al. (2009), Ogasawara and Kawato (2009), Schmidt and Eilers (2009), Smolen et al. (2009)	9
All		117

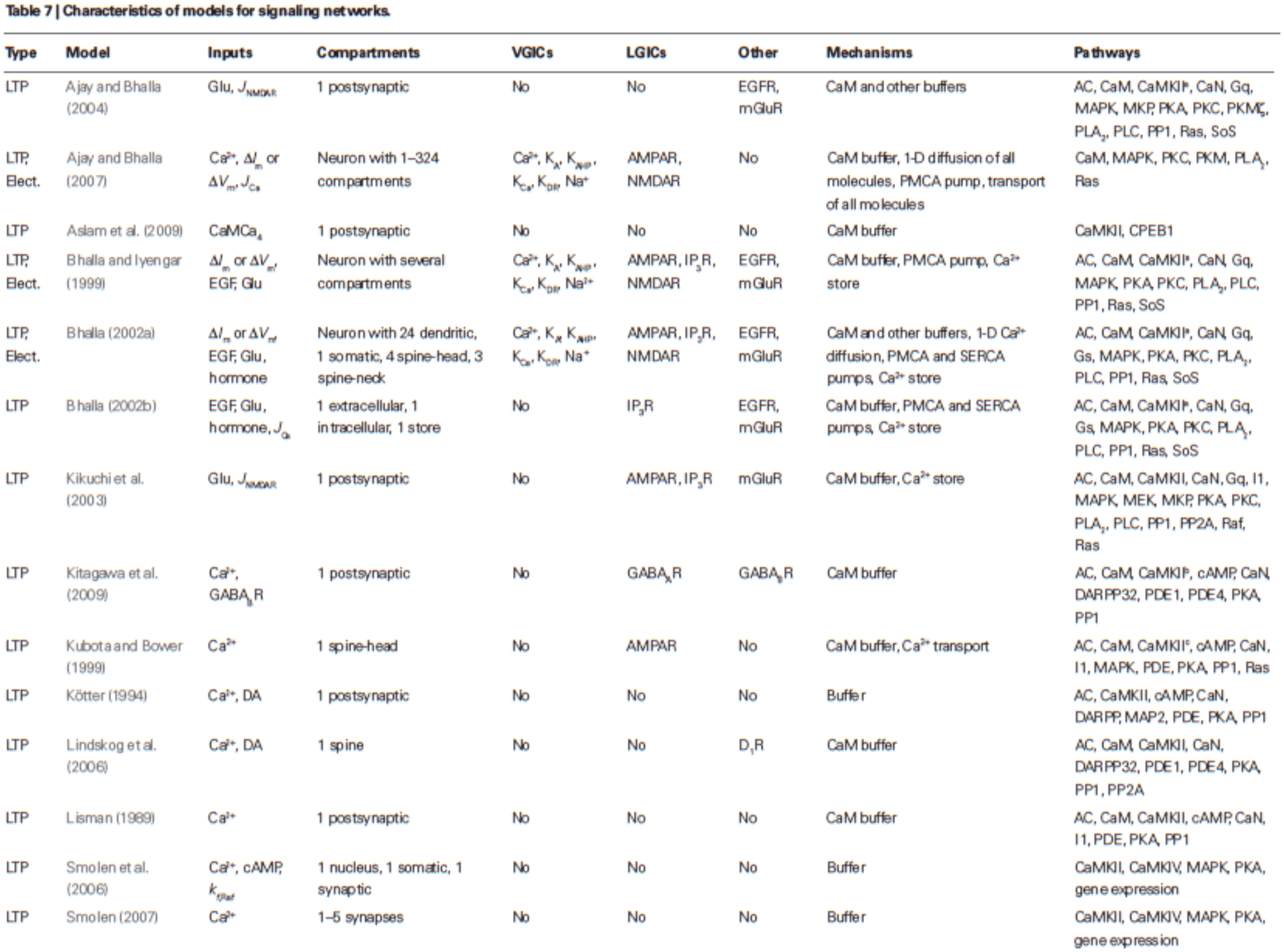


Table 7 | Characteristics of models for signaling networks.

Type	Model	Inputs	Compartments	VGICs	LGICs	Other	Mechanisms	Pathways
LTP	Ajay and Bhalla (2004)	Glu, J_{NMDAR}	1 postsynaptic	No	No	EGFR, mGluR	CaM and other buffers	AC, CaM, CaMKII^{p}, CaN, Gq, MAPK, MKP, PKA, PKC, PKMζ, PLA_2, PLC, PP1, Ras, SoS
LTP, Elect.	Ajay and Bhalla (2007)	Ca^{2+}, ΔI_m or ΔV_m, J_{Ca}	Neuron with 1–324 compartments	Ca^{2+}, K_A, K_{AHP}, K_{Ca}, K_{DR}, Na^+	AMPAR, NMDAR	No	CaM buffer, 1-D diffusion of all molecules, PMCA pump, transport of all molecules	CaM, MAPK, PKC, PKM, PLA_2, Ras
LTP	Aslam et al. (2009)	$CaMCa_4$	1 postsynaptic	No	No	No	CaM buffer	CaMKII, CPEB1
LTP, Elect.	Bhalla and Iyengar (1999)	ΔI_m or ΔV_m, EGF, Glu	Neuron with several compartments	Ca^{2+}, K_A, K_{AHP}, K_{Ca}, K_{DR}, Na^{2+}	AMPAR, IP_3R, NMDAR	EGFR, mGluR	CaM buffer, PMCA pump, Ca^{2+} store	AC, CaM, CaMKII^{p}, CaN, Gq, MAPK, PKA, PKC, PLA_2, PLC, PP1, Ras, SoS
LTP, Elect.	Bhalla (2002a)	ΔI_m or ΔV_m, EGF, Glu, hormone	Neuron with 24 dendritic, 1 somatic, 4 spine-head, 3 spine-neck	Ca^{2+}, K_A, K_{AHP}, K_{Ca}, K_{DR}, Na^+	AMPAR, IP_3R, NMDAR	EGFR, mGluR	CaM and other buffers, 1-D Ca^{2+} diffusion, PMCA and SERCA pumps, Ca^{2+} store	AC, CaM, CaMKII^{p}, CaN, Gq, Gs, MAPK, PKA, PKC, PLA_2, PLC, PP1, Ras, SoS
LTP	Bhalla (2002b)	EGF, Glu, hormone, J_{Ca}	1 extracellular, 1 intracellular, 1 store	No	IP_3R	EGFR, mGluR	CaM buffer, PMCA and SERCA pumps, Ca^{2+} store	AC, CaM, CaMKII^{p}, CaN, Gq, Gs, MAPK, PKA, PKC, PLA_2, PLC, PP1, Ras, SoS
LTP	Kikuchi et al. (2003)	Glu, J_{NMDAR}	1 postsynaptic	No	AMPAR, IP_3R	mGluR	CaM buffer, Ca^{2+} store	AC, CaM, CaMKII, CaN, Gq, I1, MAPK, MEK, MKP, PKA, PKC, PLA_2, PLC, PP1, PP2A, Raf, Ras
LTP	Kitagawa et al. (2009)	Ca^{2+}, $GABA_BR$	1 postsynaptic	No	$GABA_AR$	$GABA_BR$	CaM buffer	AC, CaM, CaMKII^{p}, cAMP, CaN, DARPP32, PDE1, PDE4, PKA, PP1
LTP	Kubota and Bower (1999)	Ca^{2+}	1 spine-head	No	AMPAR	No	CaM buffer, Ca^{2+} transport	AC, CaM, CaMKII^{c}, cAMP, CaN, I1, MAPK, PDE, PKA, PP1, Ras
LTP	Kötter (1994)	Ca^{2+}, DA	1 postsynaptic	No	No	No	Buffer	AC, CaMKII, cAMP, CaN, DARPP, MAP2, PDE, PKA, PP1
LTP	Lindskog et al. (2006)	Ca^{2+}, DA	1 spine	No	No	D_1R	CaM buffer	AC, CaM, CaMKII, CaN, DARPP32, PDE1, PDE4, PKA, PP1, PP2A
LTP	Lisman (1989)	Ca^{2+}	1 postsynaptic	No	No	No	CaM buffer	AC, CaM, CaMKII, cAMP, CaN, I1, PDE, PKA, PP1
LTP	Smolen et al. (2006)	Ca^{2+}, cAMP, k_{fRaf}	1 nucleus, 1 somatic, 1 synaptic	No	No	No	Buffer	CaMKII, CaMKIV, MAPK, PKA, gene expression
LTP	Smolen (2007)	Ca^{2+}	1–5 synapses	No	No	No	Buffer	CaMKII, CaMKIV, MAPK, PKA, gene expression

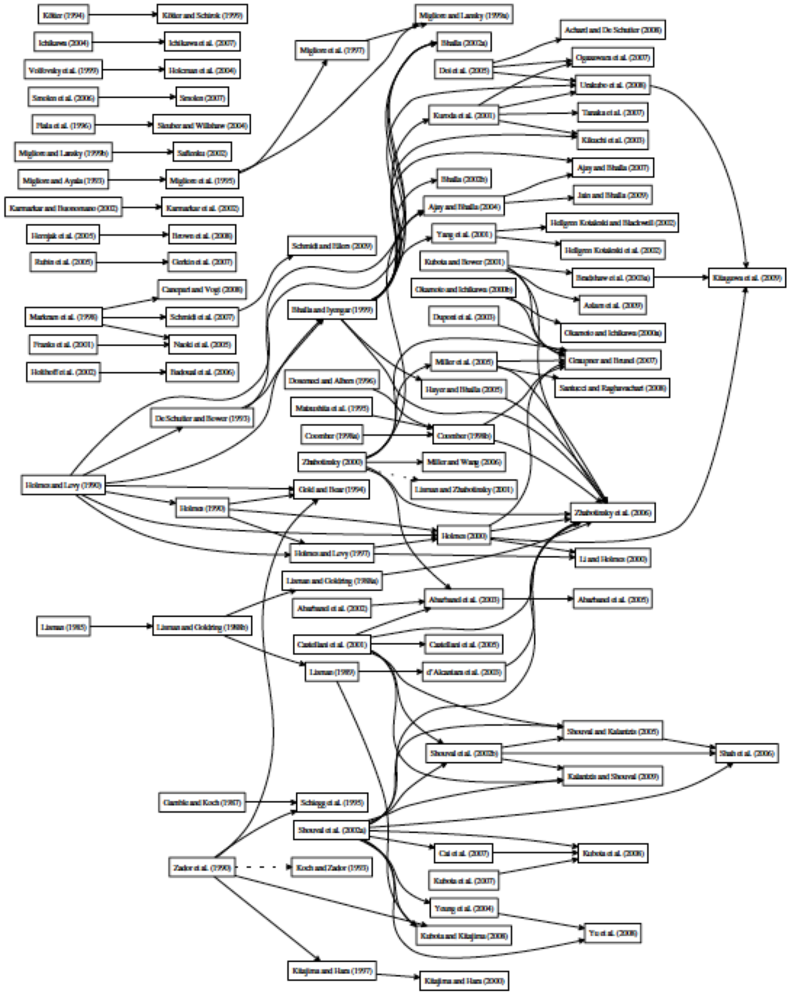


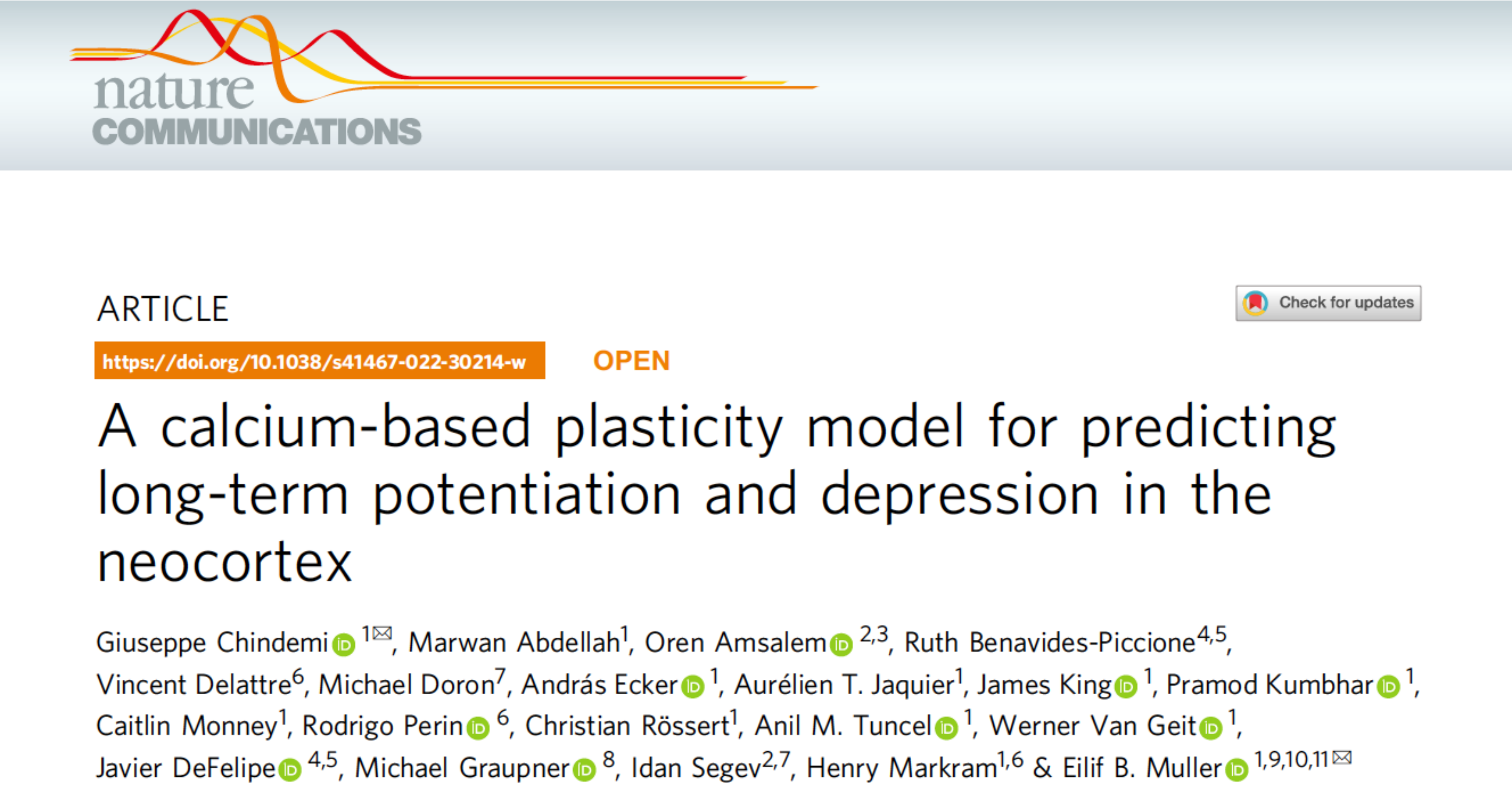
FIGURE 2 | Evolution of postsynaptic signal transduction models from 1985 to 2009. The starting point of an arrow represents the model which is used by the latter model indicated as the arrowhead. A dotted line in the arrow means that the two studies use exactly the same model (the latter study is not presented in **Tables 1–9**).

Summary 2

- There are multiple forms of plasticity and plasticity is a complex phenomenon
- This can explain the multitude of existing models
- Calcium is the fundamental element that triggers plasticity
- In principle, all the models could work with large networks of multi-compartmental models of single neurons
- Calcium based models are the most suitable since they are close to the biophysics of the synapses but remain relatively simple compared to the subcellular models

Lecture Overview

- Scope
- Approaches
- **Applications**



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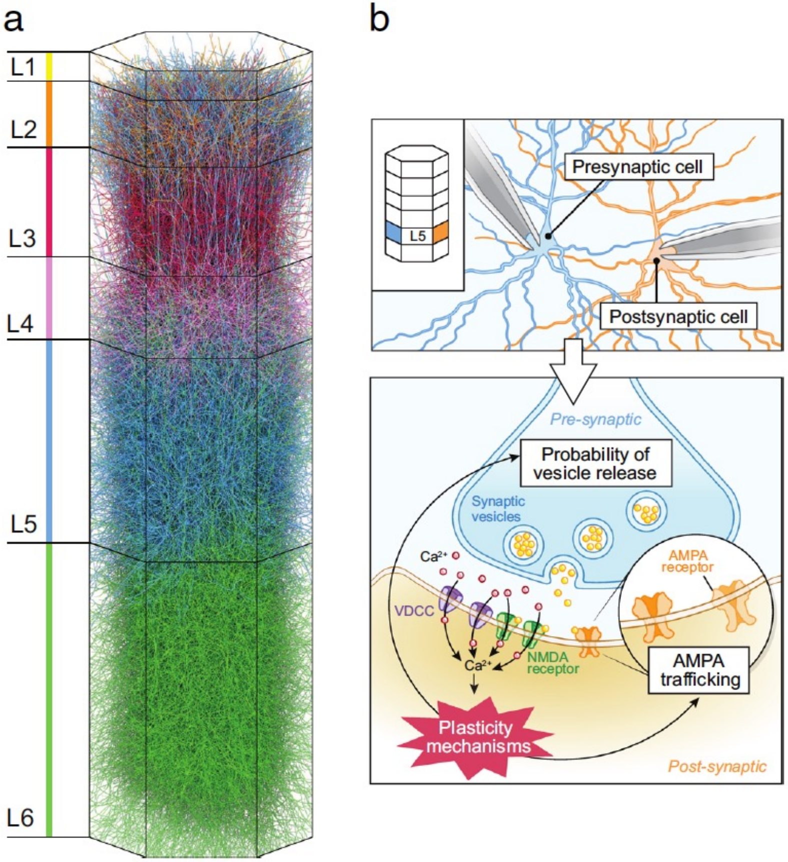
A calcium-based plasticity model for predicting long-term potentiation and depression in the neocortex

Giuseppe Chindemi[1]✉, Marwan Abdellah[1], Oren Amsalem[2,3], Ruth Benavides-Piccione[4,5], Vincent Delattre[6], Michael Doron[7], András Ecker[1], Aurélien T. Jaquier[1], James King[1], Pramod Kumbhar[1], Caitlin Monney[1], Rodrigo Perin[6], Christian Rössert[1], Anil M. Tuncel[1], Werner Van Geit[1], Javier DeFelipe[4,5], Michael Graupner[8], Idan Segev[2,7], Henry Markram[1,6] & Eilif B. Muller[1,9,10,11]✉

Chindemi et al., 2022

- SSCx microcircuit (Markram et al., 2015)
- Connections between L5_TTPCs
- Excitatory synapses are made principally on dendritic spines
- Calcium-based model
- Calcium enters via VDCC and NMDAR



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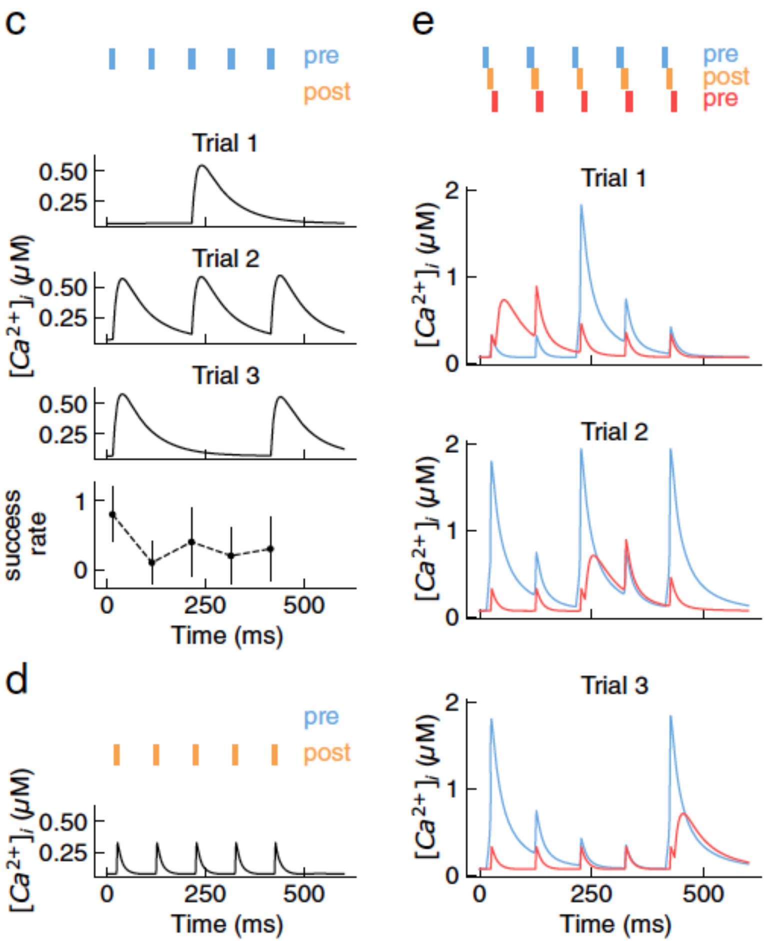
- Ca^{2+} decays exponentially after the input
- Pre events open NMDARs
- Post events open VDCCs
- The interplay produce the non linearity seen in STDP
- Pre-post causes larger calcium transient
- Post-pre causes smaller transient



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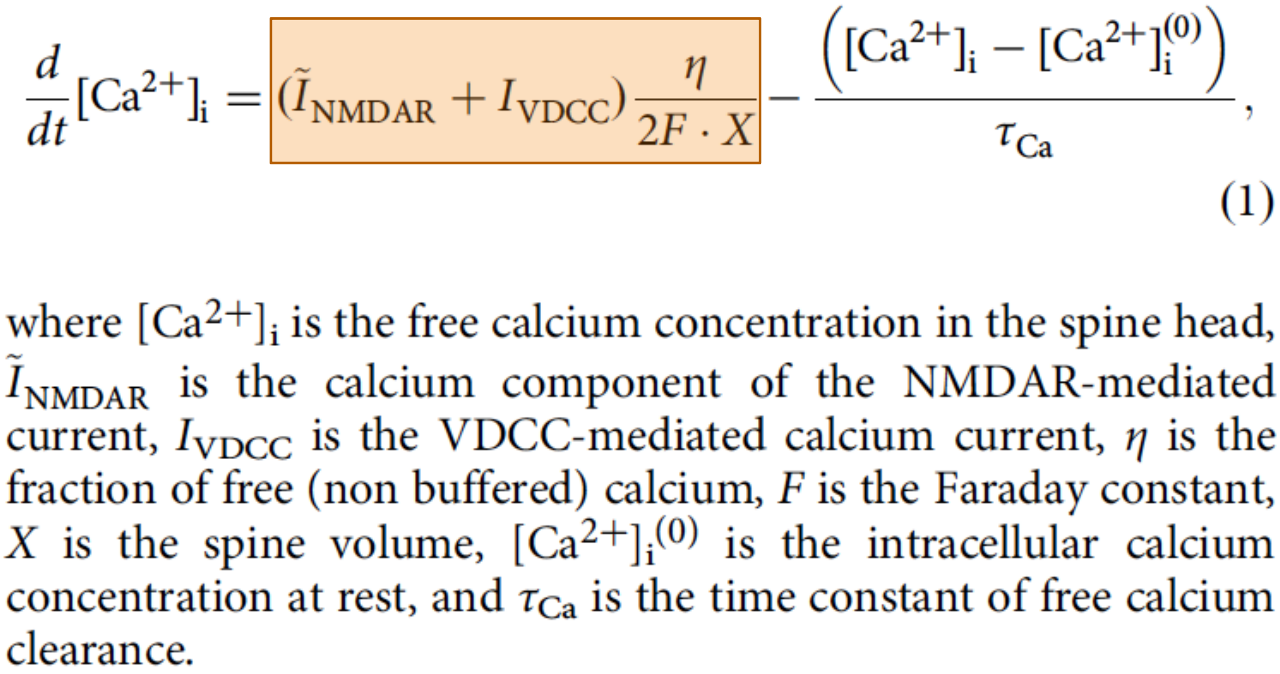
Δ of free $[\mathrm{Ca}^{2+}]_\mathrm{i}$



$$\frac{d}{dt}[\mathrm{Ca}^{2+}]_\mathrm{i} = \boxed{(\tilde{I}_\mathrm{NMDAR} + I_\mathrm{VDCC})\frac{\eta}{2F \cdot X}} - \frac{\left([\mathrm{Ca}^{2+}]_\mathrm{i} - [\mathrm{Ca}^{2+}]_\mathrm{i}^{(0)}\right)}{\tau_\mathrm{Ca}}, \tag{1}$$

where $[\mathrm{Ca}^{2+}]_\mathrm{i}$ is the free calcium concentration in the spine head, $\tilde{I}_\mathrm{NMDAR}$ is the calcium component of the NMDAR-mediated current, I_VDCC is the VDCC-mediated calcium current, η is the fraction of free (non buffered) calcium, F is the Faraday constant, X is the spine volume, $[\mathrm{Ca}^{2+}]_\mathrm{i}^{(0)}$ is the intracellular calcium concentration at rest, and τ_Ca is the time constant of free calcium clearance.

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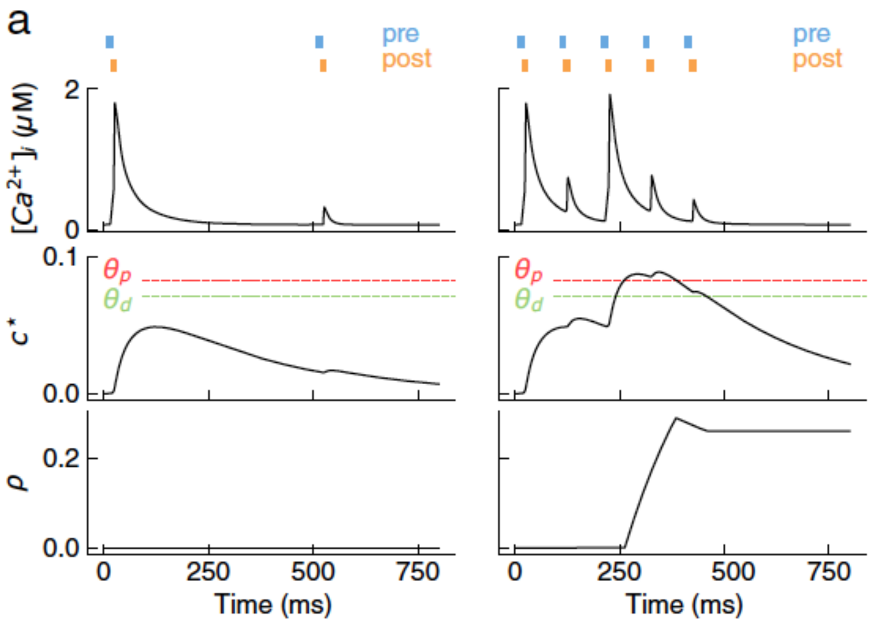
- Introduced a longer calcium integration time constants to explain plasticity (c*)
- It could arise from the interplay of fast and a slow buffers in the spine head, involving for example calmodulin
- To model persistent changes, the “synaptic efficacy”, ρ, is driven by the integrated calcium concentration, and exhibiting bistable dynamics



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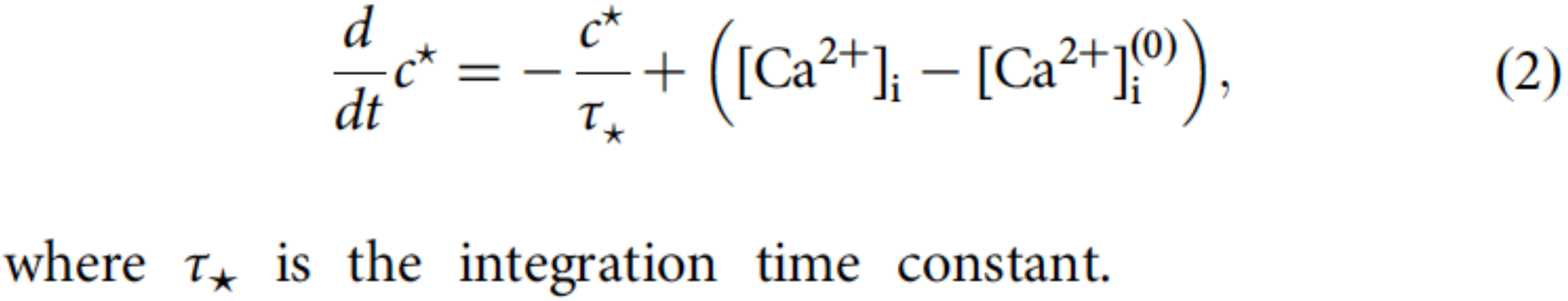

$$\frac{d}{dt}c^{\star} = -\frac{c^{\star}}{\tau_{\star}} + \left([\mathrm{Ca}^{2+}]_{\mathrm{i}} - [\mathrm{Ca}^{2+}]_{\mathrm{i}}^{(0)}\right), \tag{2}$$

where $\tau_{\star}$ is the integration time constant.

At t=0, c*=0

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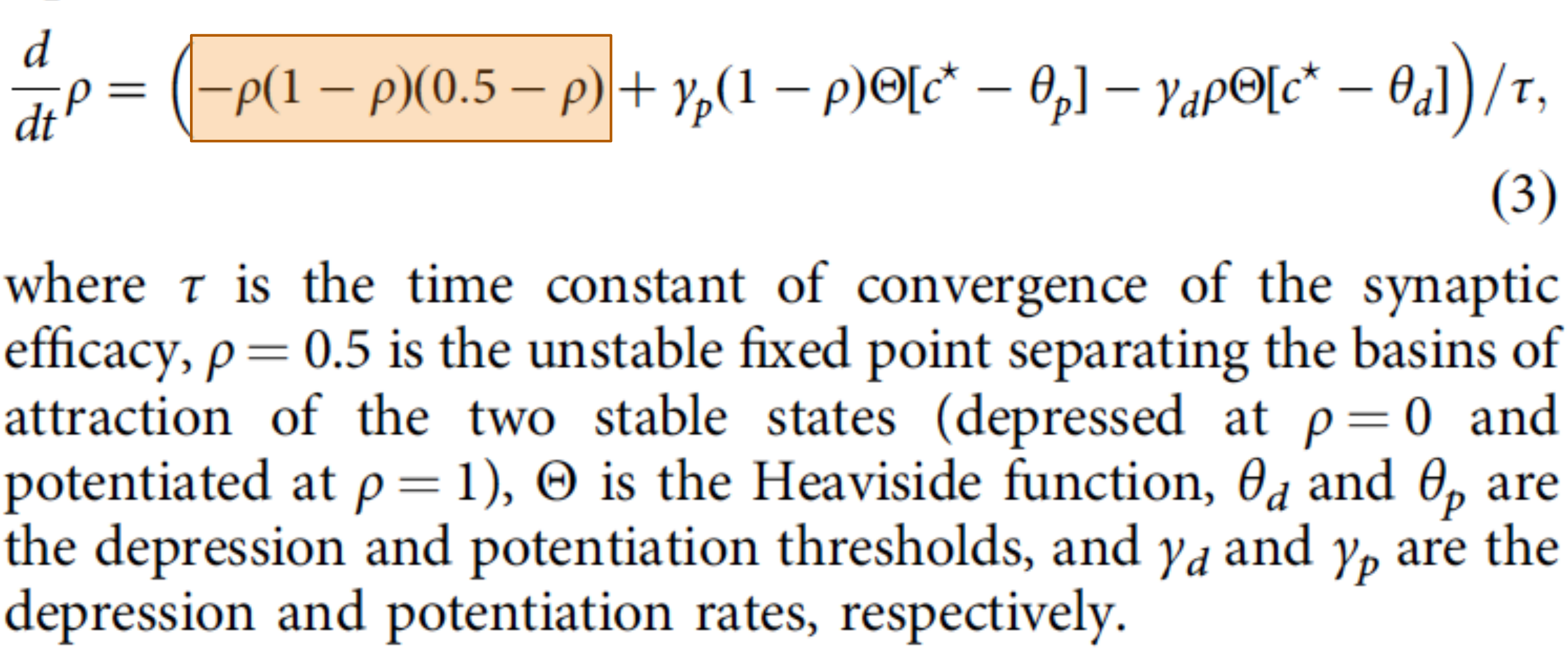
Dynamics of the synaptic efficacy
in the absence of pre- and postsynaptic activity
Two stable state: 0 and 1



$$\frac{d}{dt}\rho = \Big(-\rho(1-\rho)(0.5-\rho) + \gamma_p(1-\rho)\Theta[c^\star - \theta_p] - \gamma_d\rho\Theta[c^\star - \theta_d]\Big)/\tau, \tag{3}$$

where τ is the time constant of convergence of the synaptic efficacy, $\rho = 0.5$ is the unstable fixed point separating the basins of attraction of the two stable states (depressed at $\rho = 0$ and potentiated at $\rho = 1$), Θ is the Heaviside function, θ_d and θ_p are the depression and potentiation thresholds, and γ_d and γ_p are the depression and potentiation rates, respectively.

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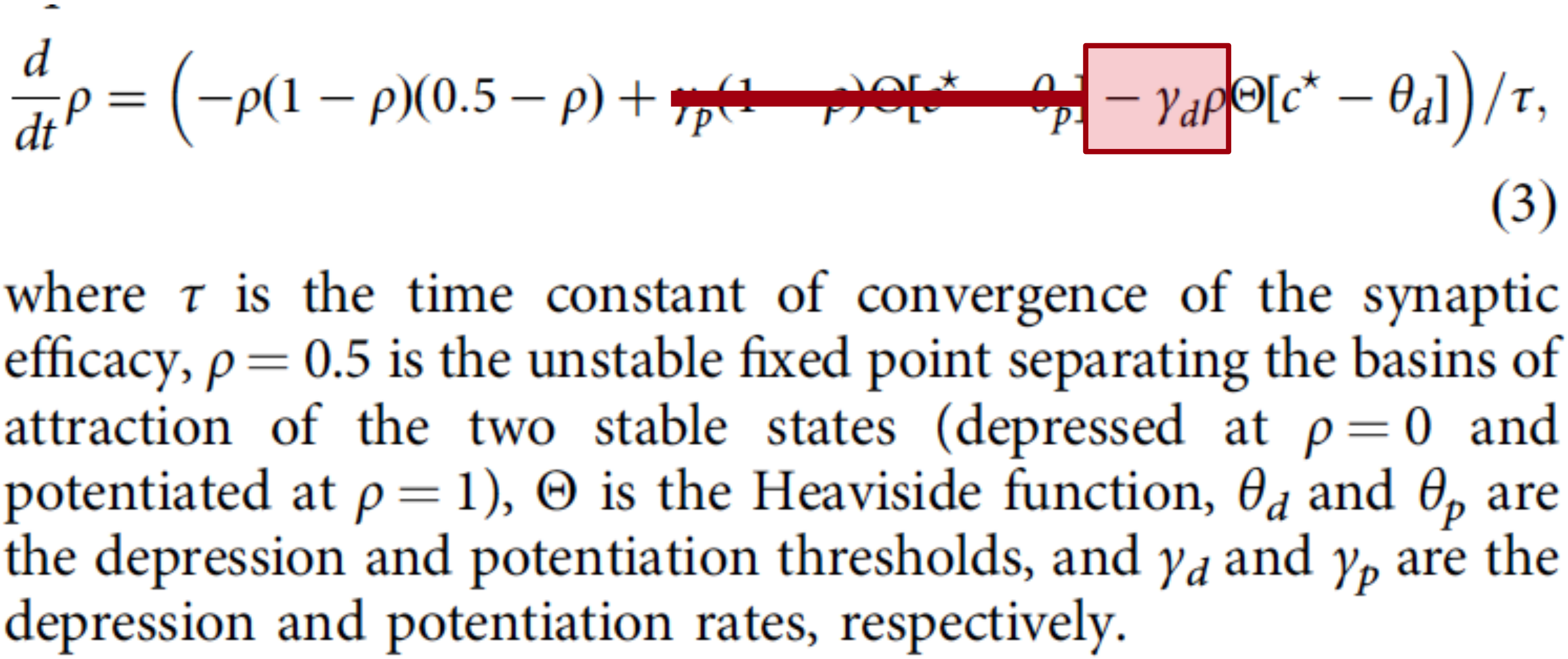
theta_d < c* < theta_p



$$\frac{d}{dt}\rho = \left(-\rho(1-\rho)(0.5-\rho) + \cancel{\gamma_p(1-\rho)\Theta[c^\star - \theta_p]} \boxed{-\gamma_d\rho}\Theta[c^\star - \theta_d]\right)/\tau, \tag{3}$$

where τ is the time constant of convergence of the synaptic efficacy, $\rho = 0.5$ is the unstable fixed point separating the basins of attraction of the two stable states (depressed at $\rho = 0$ and potentiated at $\rho = 1$), Θ is the Heaviside function, θ_d and θ_p are the depression and potentiation thresholds, and γ_d and γ_p are the depression and potentiation rates, respectively.

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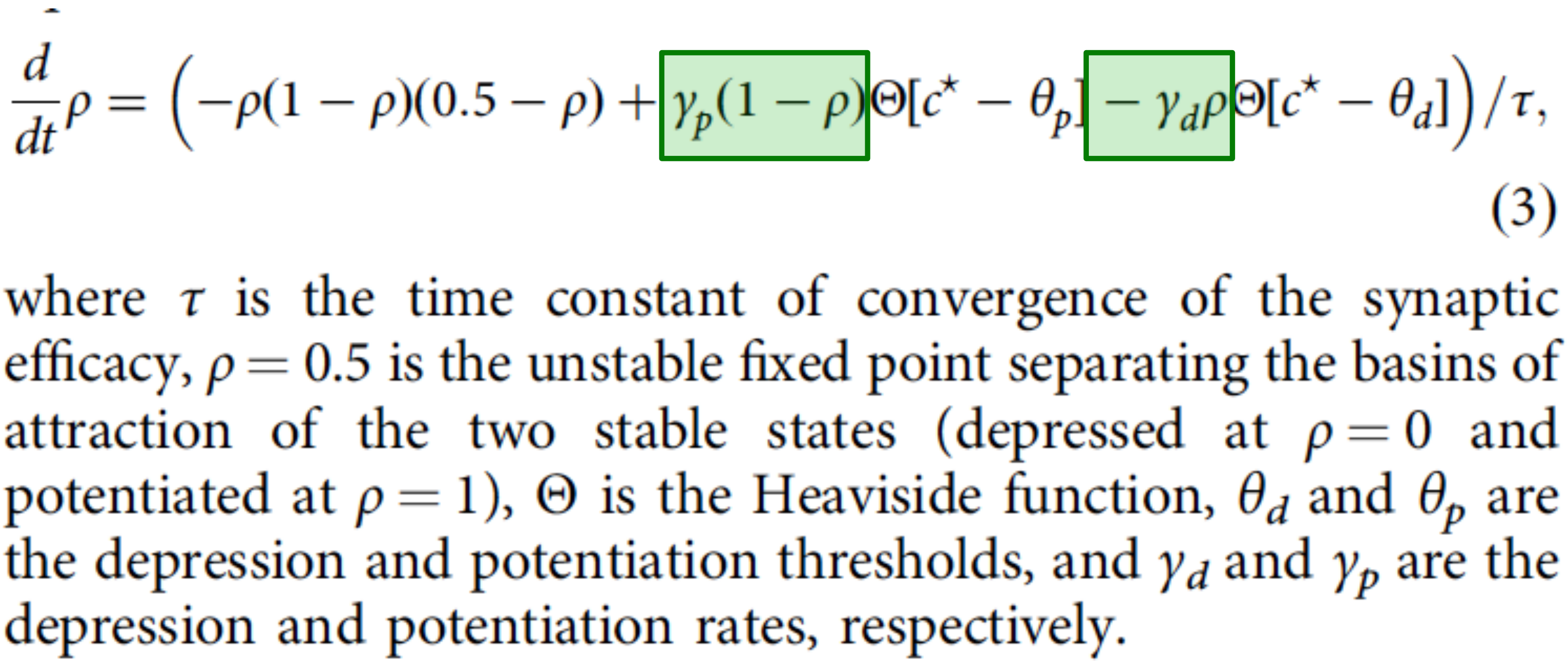
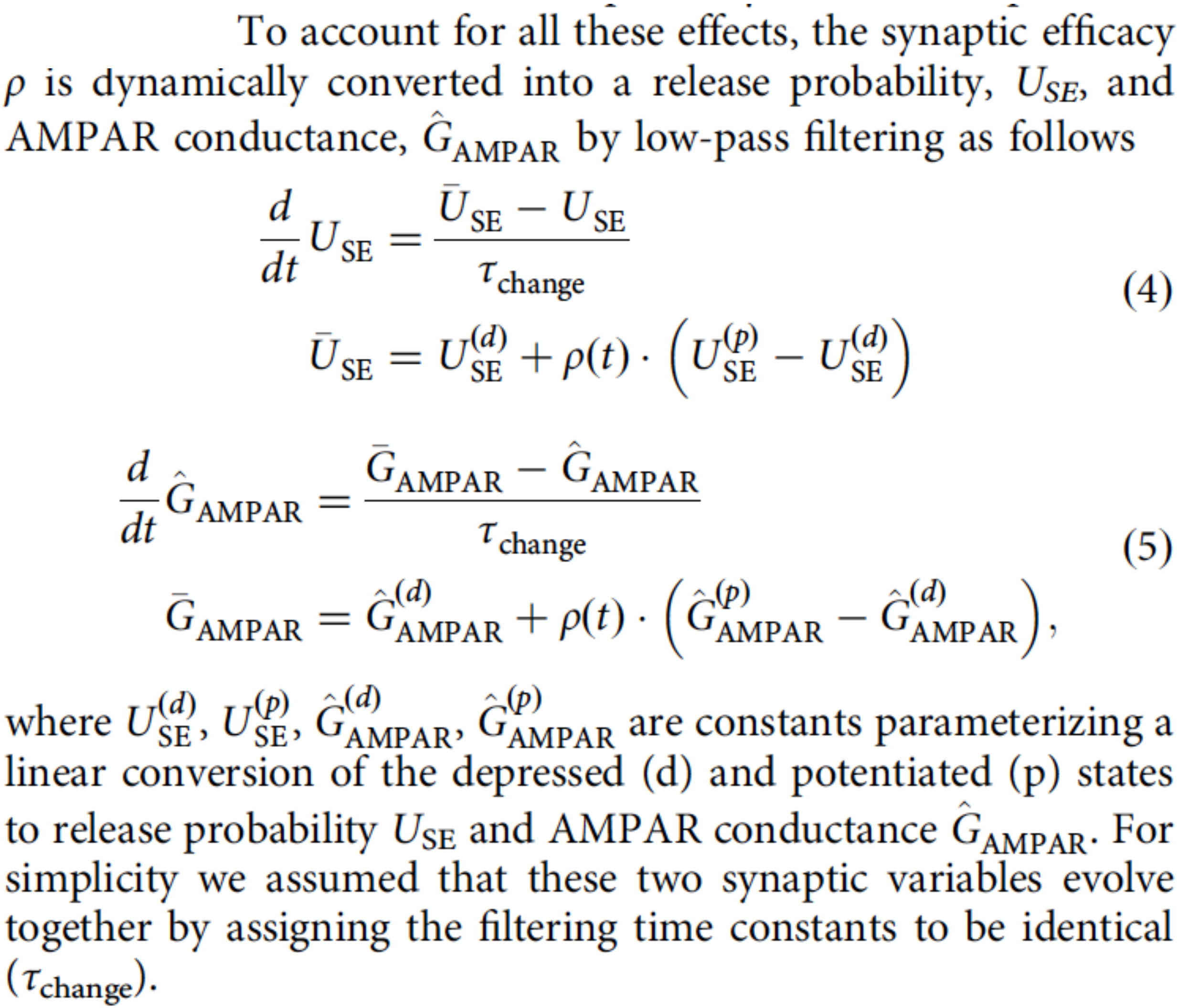
c* > theta_p



$$\frac{d}{dt}\rho = \left(-\rho(1-\rho)(0.5-\rho) + \boxed{\gamma_p(1-\rho)}\Theta[c^\star - \theta_p]\boxed{-\gamma_d\rho}\Theta[c^\star - \theta_d]\right)/\tau, \tag{3}$$

where τ is the time constant of convergence of the synaptic efficacy, $\rho = 0.5$ is the unstable fixed point separating the basins of attraction of the two stable states (depressed at $\rho = 0$ and potentiated at $\rho = 1$), Θ is the Heaviside function, θ_d and θ_p are the depression and potentiation thresholds, and γ_d and γ_p are the depression and potentiation rates, respectively.



To account for all these effects, the synaptic efficacy ρ is dynamically converted into a release probability, U_{SE}, and AMPAR conductance, $\hat{G}_{\text{AMPAR}}$ by low-pass filtering as follows

$$\frac{d}{dt}U_{\text{SE}} = \frac{\bar{U}_{\text{SE}} - U_{\text{SE}}}{\tau_{\text{change}}}$$
$$\bar{U}_{\text{SE}} = U_{\text{SE}}^{(d)} + \rho(t)\cdot\left(U_{\text{SE}}^{(p)} - U_{\text{SE}}^{(d)}\right) \qquad (4)$$

$$\frac{d}{dt}\hat{G}_{\text{AMPAR}} = \frac{\bar{G}_{\text{AMPAR}} - \hat{G}_{\text{AMPAR}}}{\tau_{\text{change}}}$$
$$\bar{G}_{\text{AMPAR}} = \hat{G}_{\text{AMPAR}}^{(d)} + \rho(t)\cdot\left(\hat{G}_{\text{AMPAR}}^{(p)} - \hat{G}_{\text{AMPAR}}^{(d)}\right), \qquad (5)$$

where $U_{\text{SE}}^{(d)}$, $U_{\text{SE}}^{(p)}$, $\hat{G}_{\text{AMPAR}}^{(d)}$, $\hat{G}_{\text{AMPAR}}^{(p)}$ are constants parameterizing a linear conversion of the depressed (d) and potentiated (p) states to release probability U_{SE} and AMPAR conductance $\hat{G}_{\text{AMPAR}}$. For simplicity we assumed that these two synaptic variables evolve together by assigning the filtering time constants to be identical (τ_{change}).

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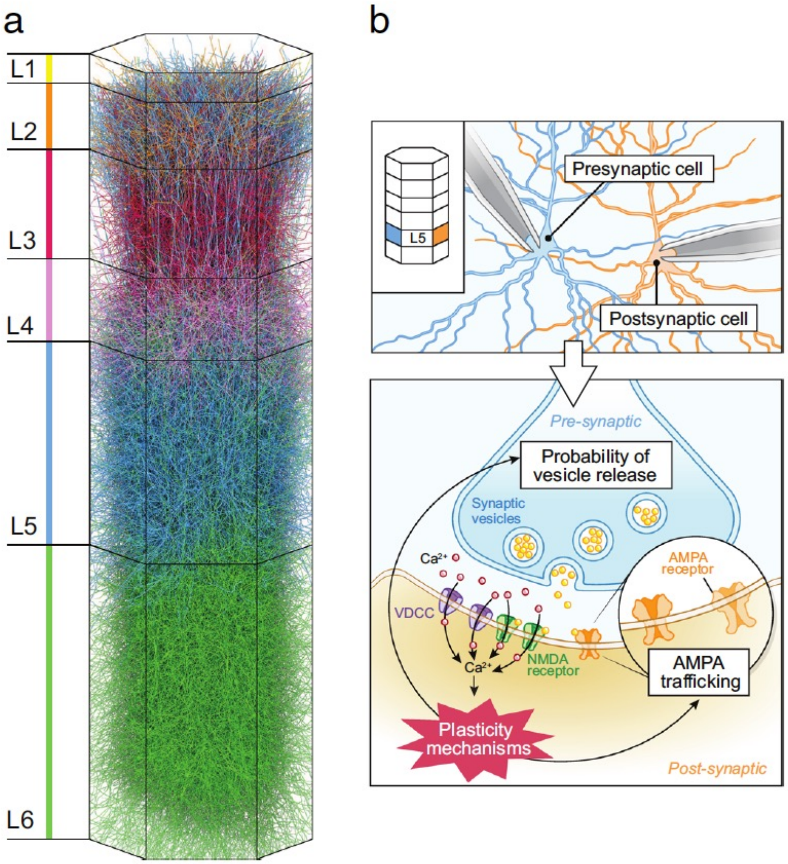
- The model uses a postsynaptic mechanism to change presynaptic release probability
- This could be interpreted as having a retrograde messanger (e.g. endocannabinoids)
- Change of (presynaptic) release probability and (postsynaptic) AMPAR conductance have the same time course
- The relative contribution of the two mechanisms may be adjusted using a different set of parameters



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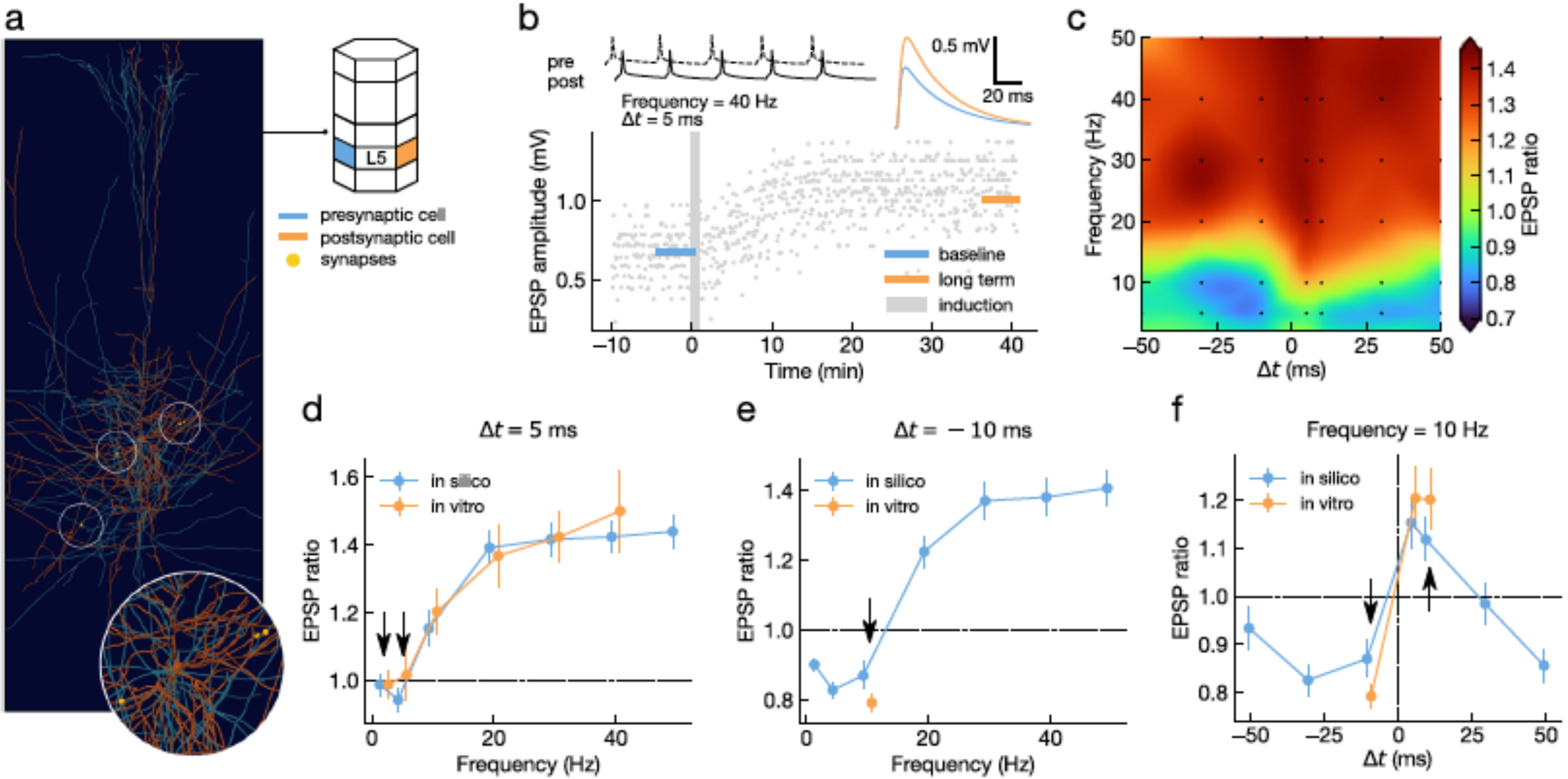

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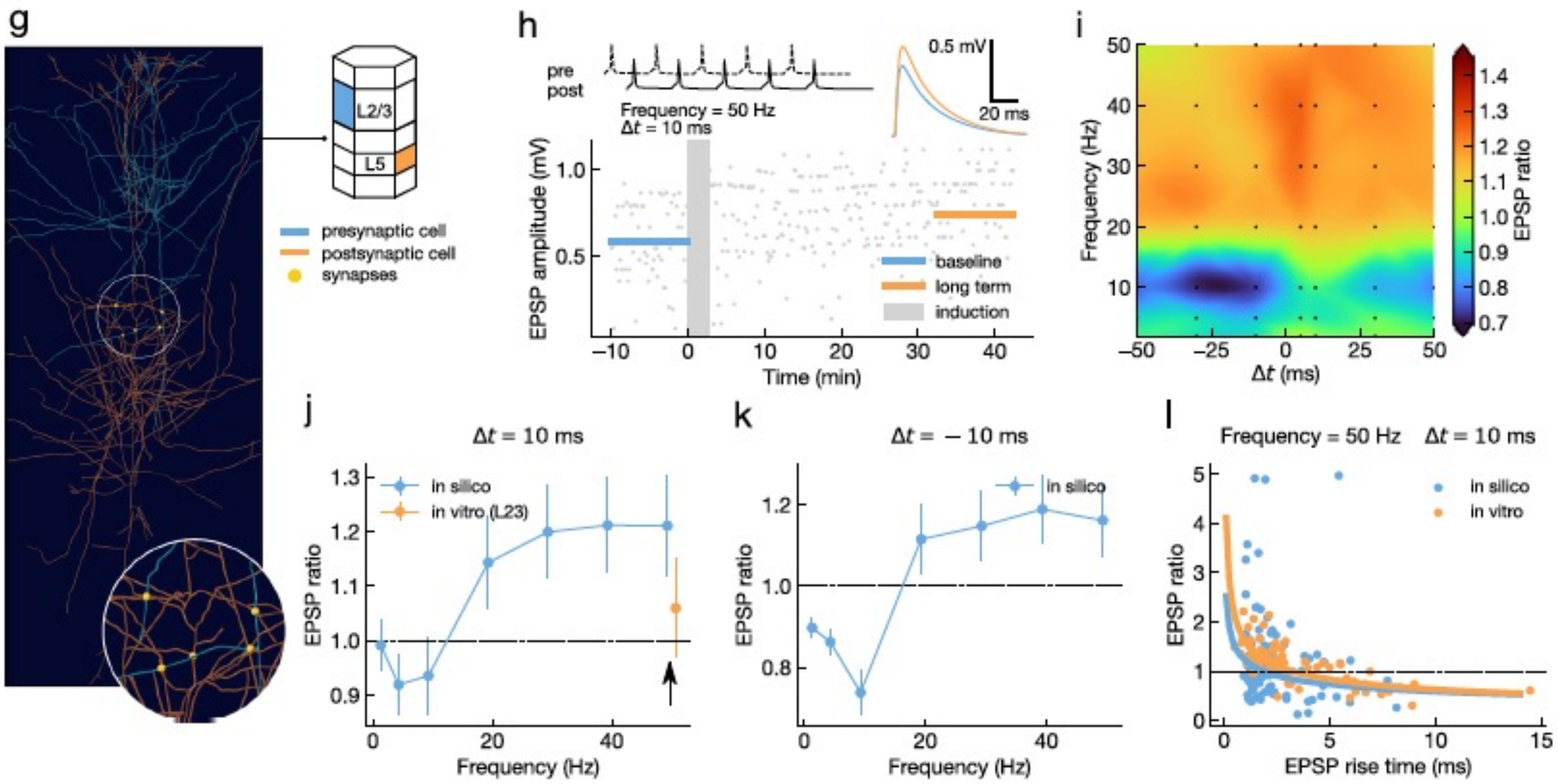

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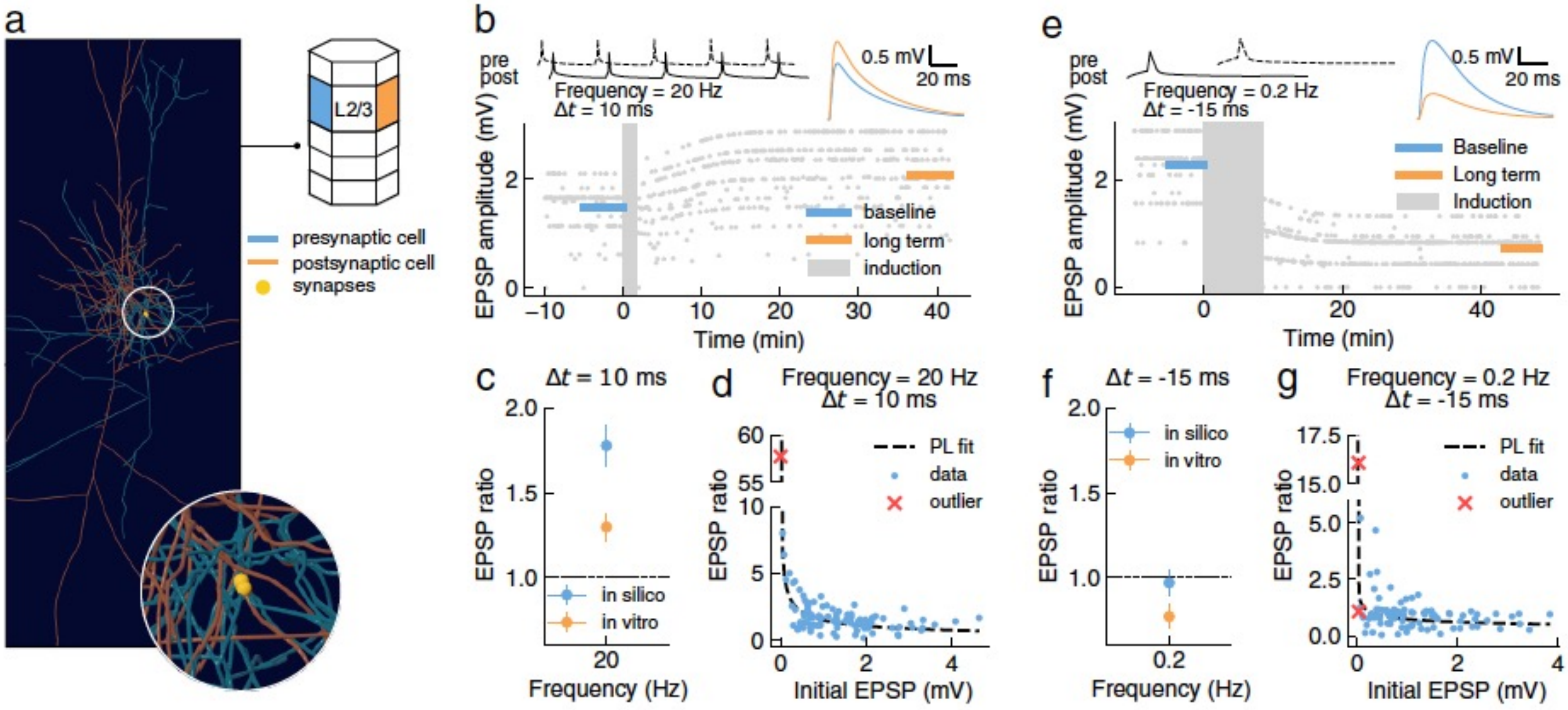

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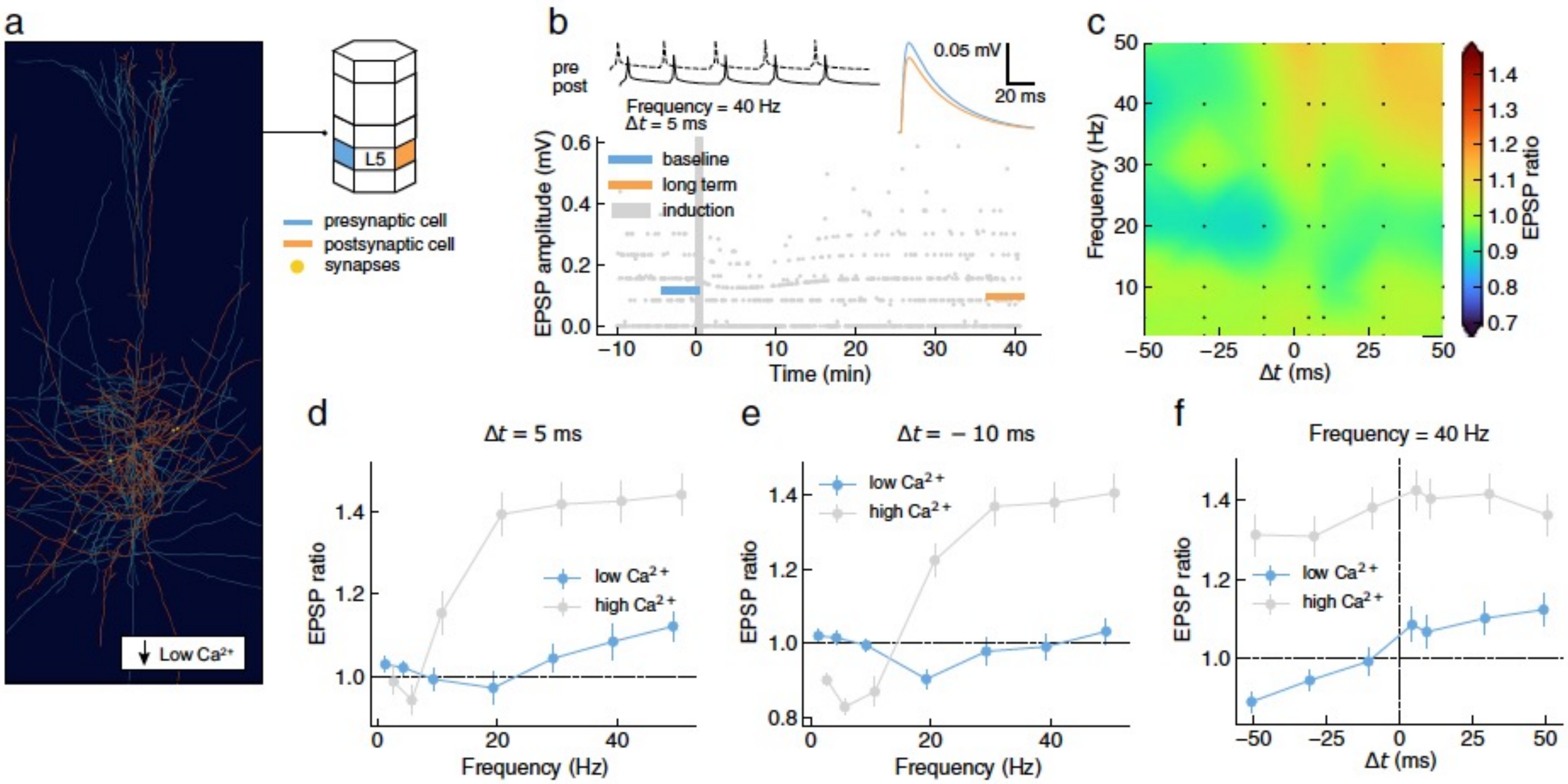

Summary 3

- Chindemi’s model preserves some biophysical details
- Variables that chance with different time constants represent the different cascade of events acting at different scales
- The model is suitable for biophysically-detailed neuronal networks
- The simulation cost is still relatively high considering the fitting and the simulations of several minutes typical of long-term plasticity experiments
- The same model can be generalized to other connections
- The different behaviors of other connections arise from the differences in the pathways and do not require model reparameterization

Lecture Summary

- Different experimental protocols, different mechanisms and a multitude of models
- Despite this complexity, some ideas are recurrent (e.g., Hebbian rules, bistable variables, depression and potentiation thresholds…)
- Calcium based models are a preferred choice to work with biophysical network models
- The use of these models is still relatively limited due to the computational cost

What you have learnt

- Different types of long-term plasticity, experimental methods, molecular mechanisms
- Different types of modeling approaches
- General understanding of the different equations. No need to memorize the details.