

Single-Neuron Plasticity Models



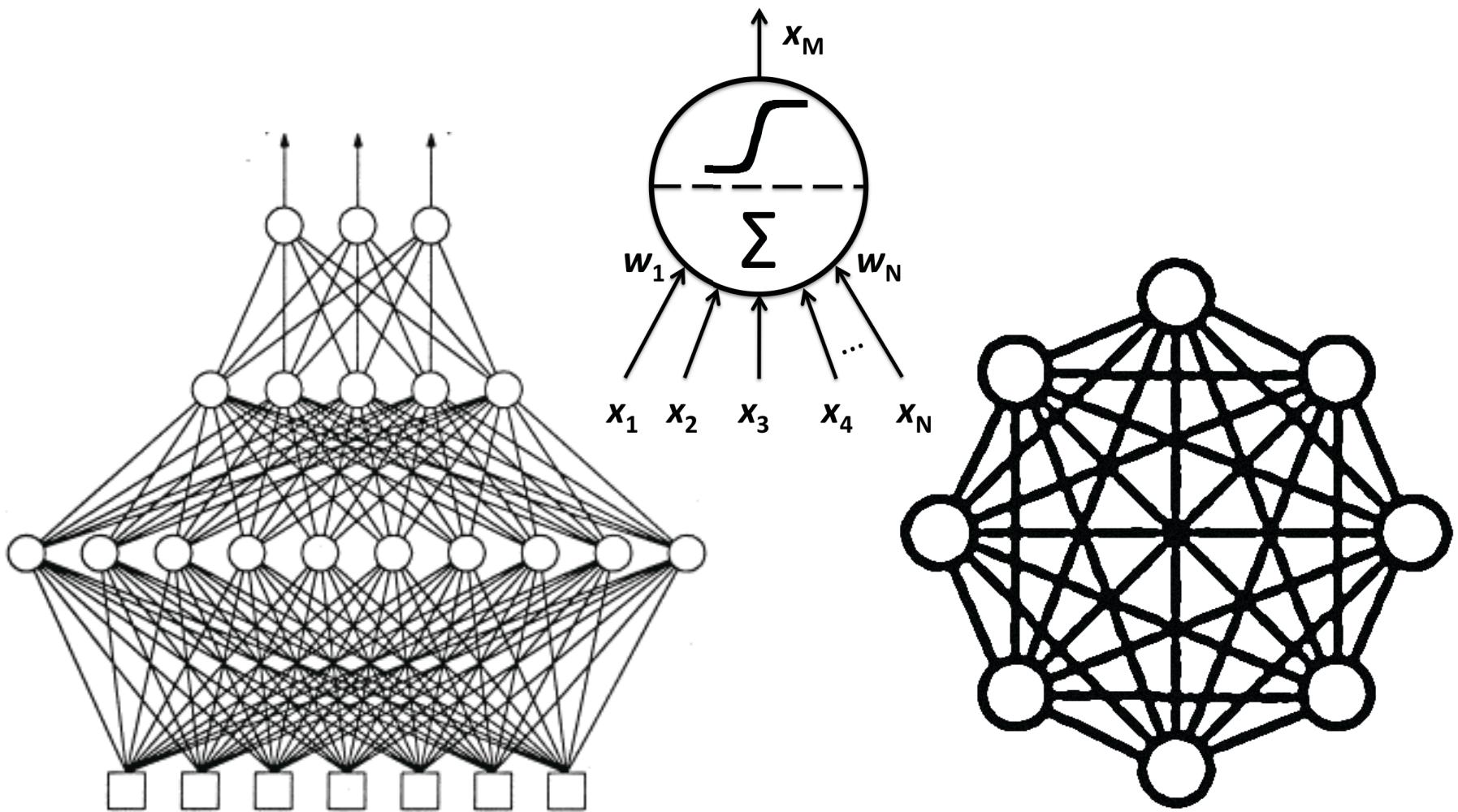
Rishikesh Narayanan

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July 8, 2016: Computational Approaches to Memory and Plasticity
National Centre for Biological Sciences, Bangalore

Phenomenological models for long-term synaptic plasticity

Synaptic learning from the Machine Learning literature: Phenomenological models for synaptic plasticity



Learning representations by back-propagating errors

NATURE VOL. 323 9 OCTOBER 1986

David E. Rumelhart*, Geoffrey E. Hinton†
& Ronald J. Williams*

Neural networks and physical systems with emergent collective computational abilities

(associative memory/parallel processing/categorization/content-addressable memory/fail-soft devices)

J. J. HOPFIELD

Proc. Natl. Acad. Sci. USA
Vol. 79, pp. 2554–2558, April 1982
Biophysics

The Self-Organizing Map

TEUVO KOHONEN, SENIOR MEMBER, IEEE

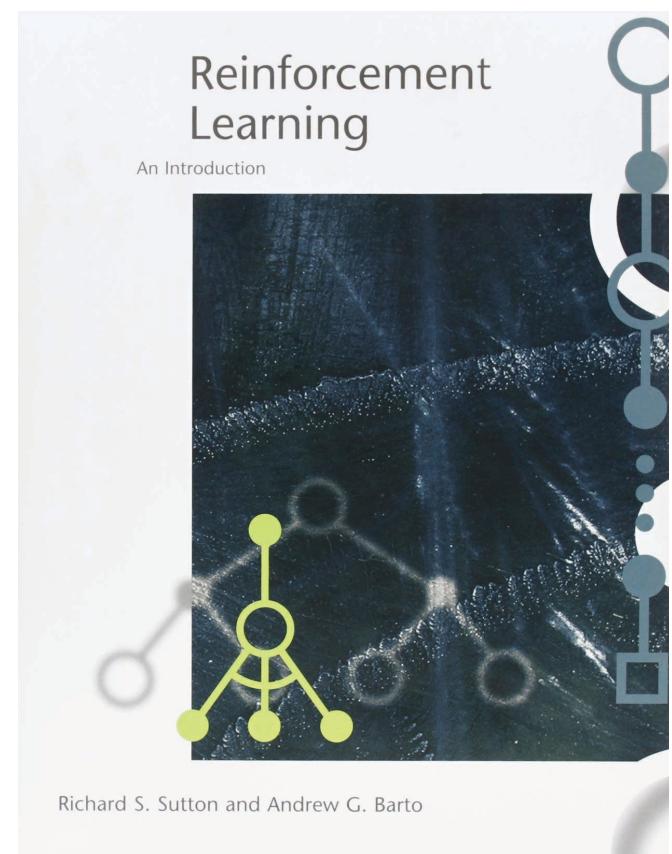
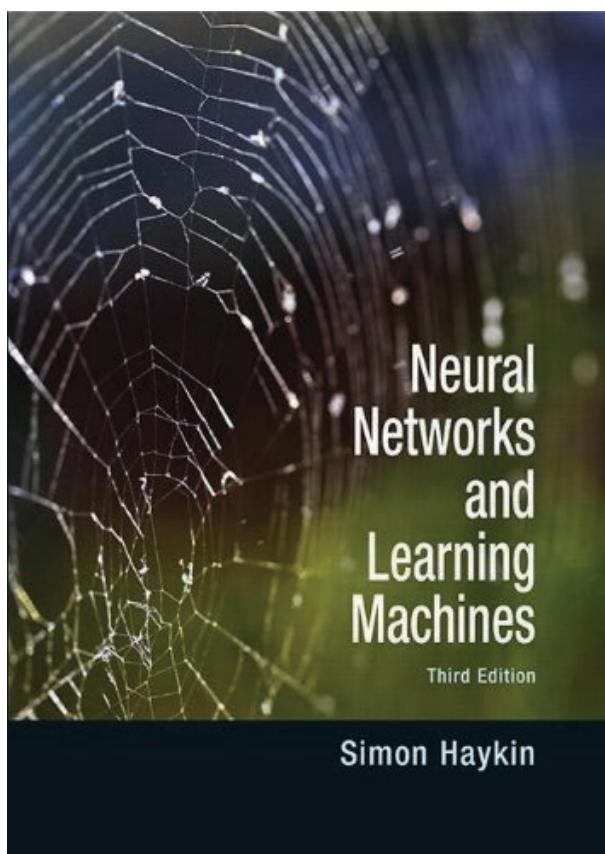
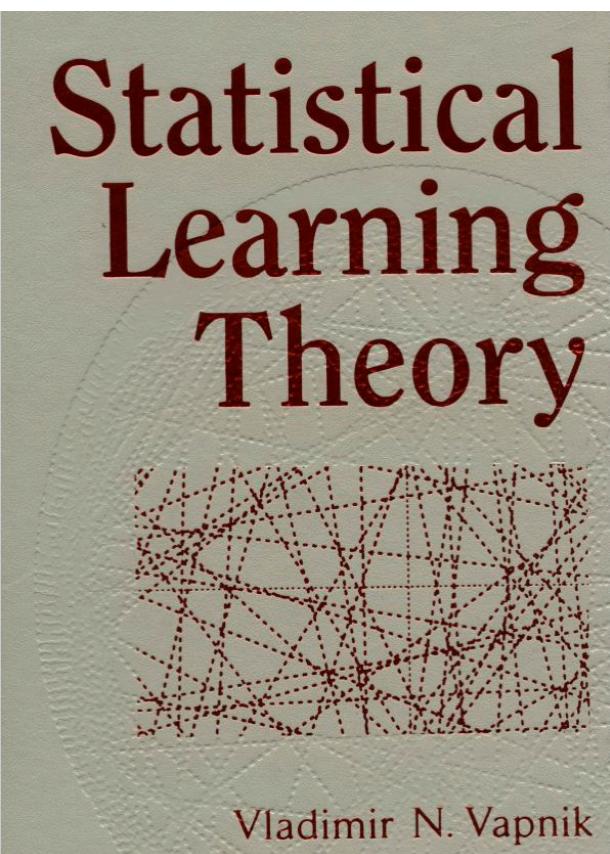
PROCEEDINGS OF THE IEEE, VOL. 78, NO. 9, SEPTEMBER 1990

A Neural Substrate of Prediction and Reward

Wolfram Schultz, Peter Dayan, P. Read Montague*

SCIENCE • VOL. 275 • 14 MARCH 1997

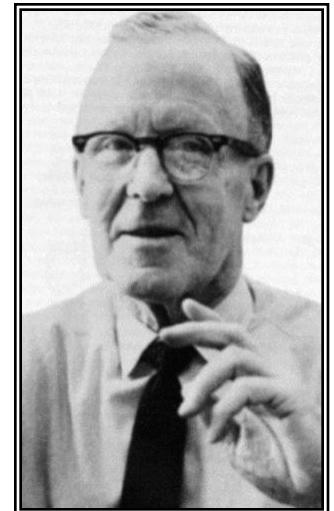
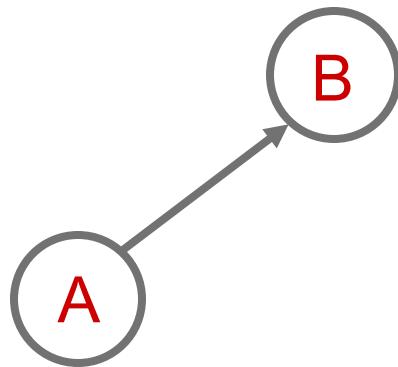
Synaptic learning from the Machine Learning literature: Phenomenological models for synaptic plasticity



Physiologically-relevant phenomenological models for long-term synaptic plasticity

Hebb's rule and long term potentiation (LTP)

“When an axon of cell A is near enough to excite a cell B and repeatedly and 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, increases.”



“Cells that fire together wire together”

**Experimental evidence:
LTP**

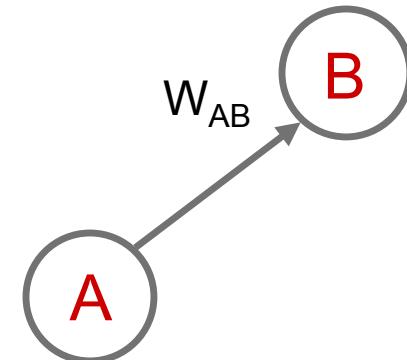
Bliss and Lomo, 1973

Long term depression (LTD)

If positive correlations (as postulated by Hebb) lead to potentiation, what do negative correlations mean? Depression??

Covariance rule: $\Delta w_{AB} = k \cdot f_A f_B$

Sejnowski, J. Math. Biol., 1977



- Postsynaptic activity greater than ***threshold*** \Rightarrow potentiation
- Postsynaptic activity lesser than ***threshold*** \Rightarrow depression

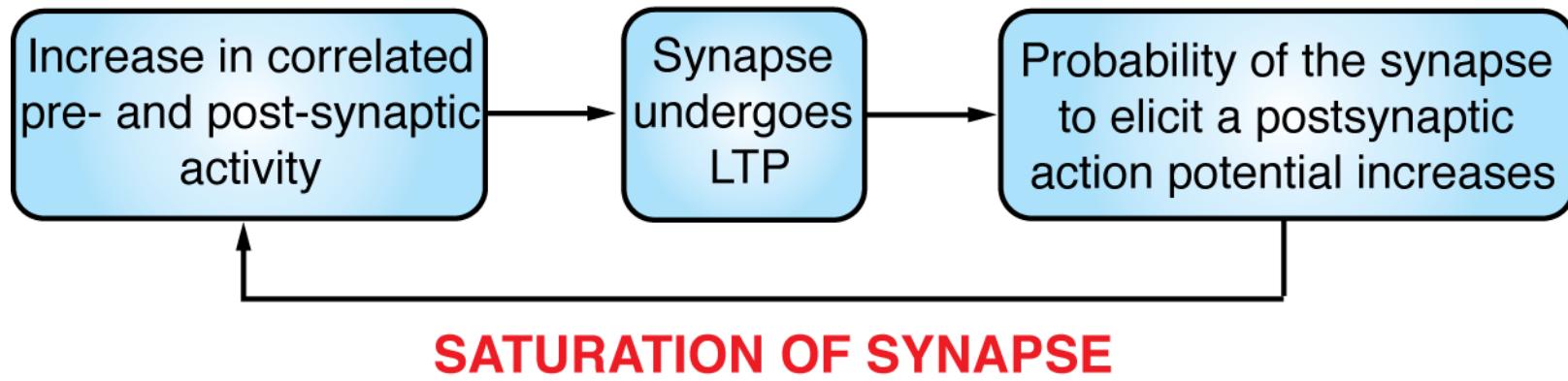
Cooper et al., Biological cybernetics, 1979

Experimental evidence: LTD

Lynch et al., 1977;
Dudek and Bear, 1992

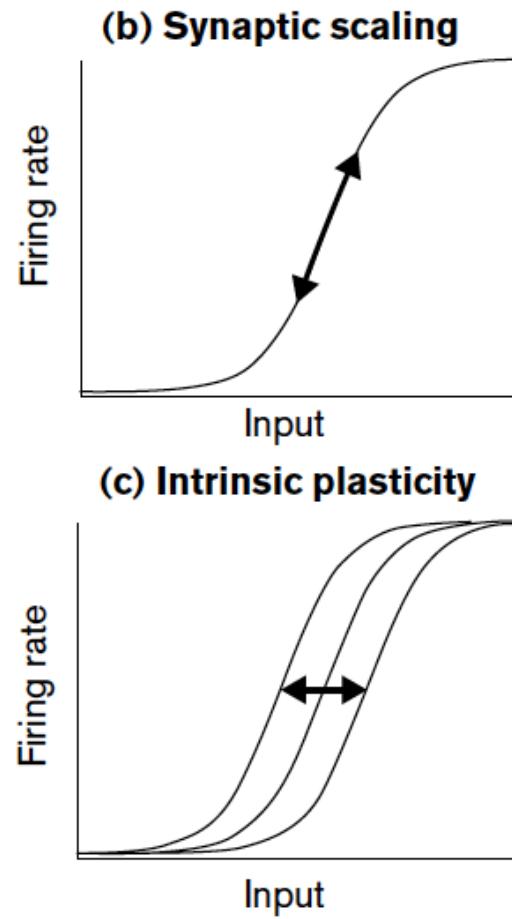
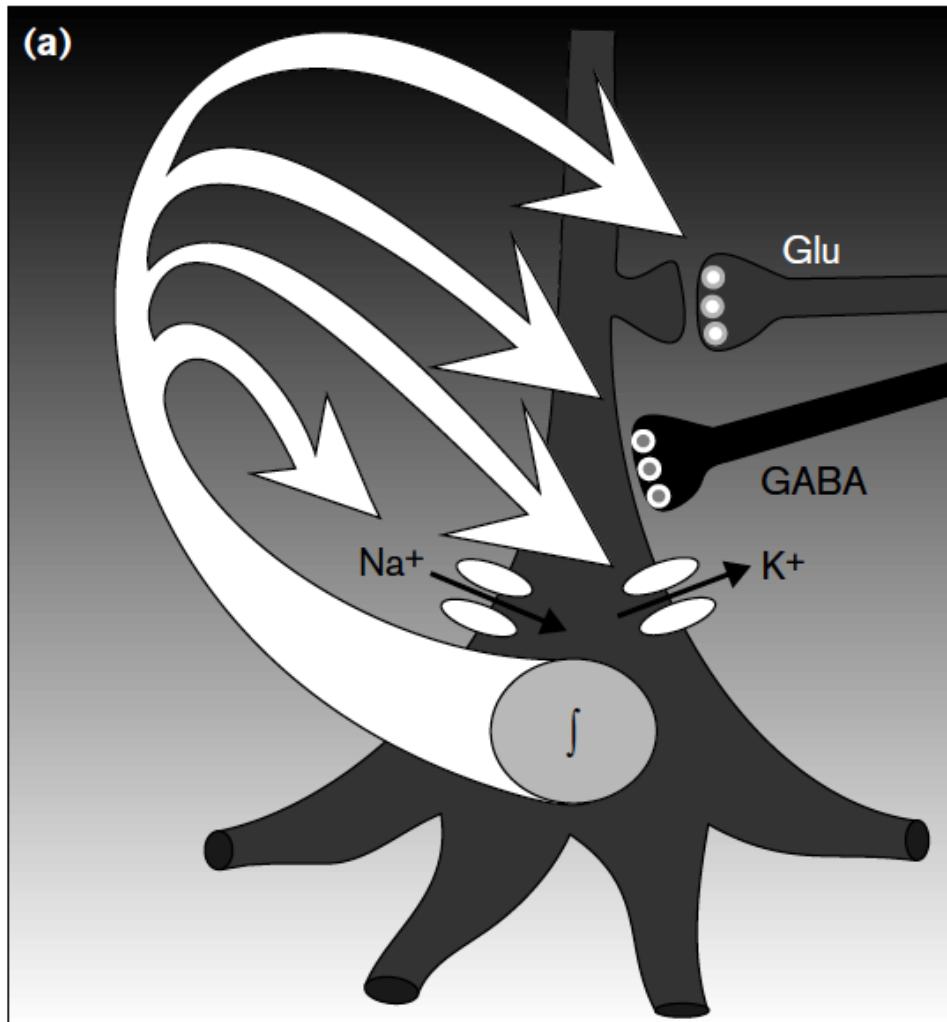
Lack of stability in Hebbian plasticity

Hebbian plasticity is a positive feedback mechanism



Similar thing holds good for LTD — synapses are set to zero

Two possible ways to achieve stability



Also see other Turrigiano reviews. e.g., Annu. Rev. Neurosci. 2011 Current Opinion in Neurobiology

Turrigiano and Nelson, CONB, 2000

Scaling synapses

Two opposing plasticity mechanisms pulling a single synapse

Ithai Rabinowitch^{1,2} and Idan Segev¹

Homeostatic synaptic plasticity: $\tau_H \cdot \frac{dG_{\text{syn},i}}{dt} = \frac{V_{\text{trg}} - V_{\text{soma}}}{\kappa} \cdot G_{\text{syn},i}$

The Role of Constraints in Hebbian Learning

Kenneth D. Miller *

Division of Biology, Caltech 216-76, Pasadena, CA 91125 USA

David J. C. MacKay†

Computation and Neural Systems, Caltech 139-74, Pasadena CA 91125 USA

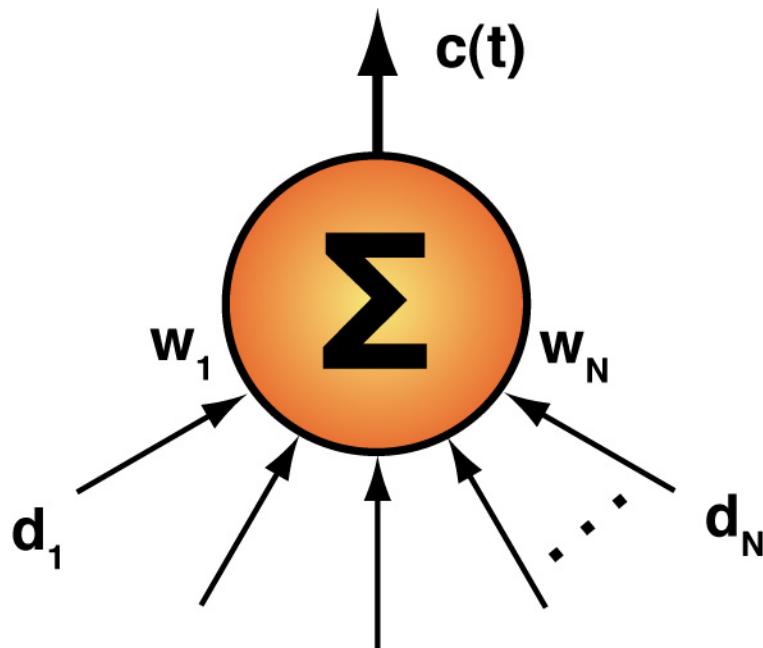
$$\frac{d}{dt}\mathbf{w}(t) = \mathbf{C}\mathbf{w}(t) - \gamma(\mathbf{w})\mathbf{w}(t) \quad (\text{Multiplicative Constraint})$$

$$\frac{d}{dt}\mathbf{w}(t) = \mathbf{C}\mathbf{w}(t) - \epsilon(\mathbf{w})\mathbf{n} \quad (\text{Subtractive Constraint})$$

\mathbf{n} is a vector of constants

Synaptic plasticity is a zero-sum game! Used in visual cortical development models.

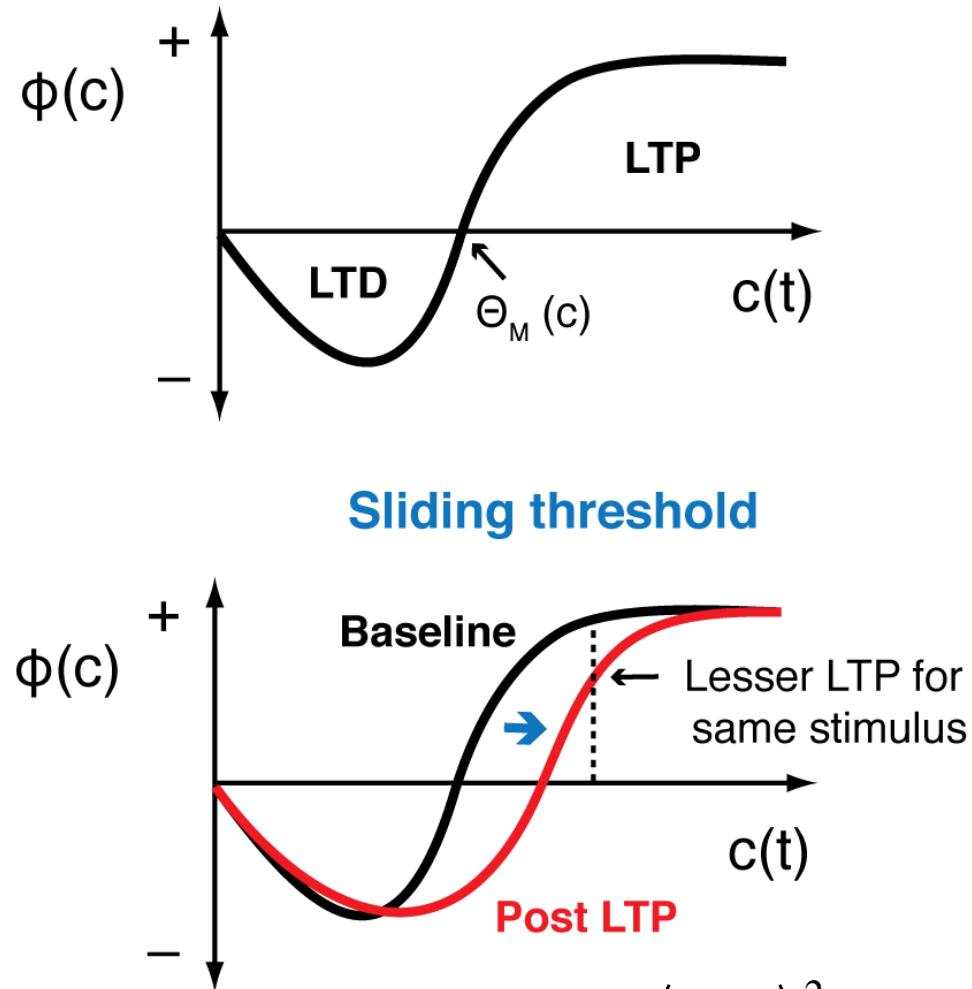
The BCM framework: Sliding threshold



$$c(t) = \sum_j w_j(t) d_j(t)$$

Plasticity rule

$$\dot{w}_j(t) = \phi(c(t)) d_j(t) - \varepsilon w_j(t)$$

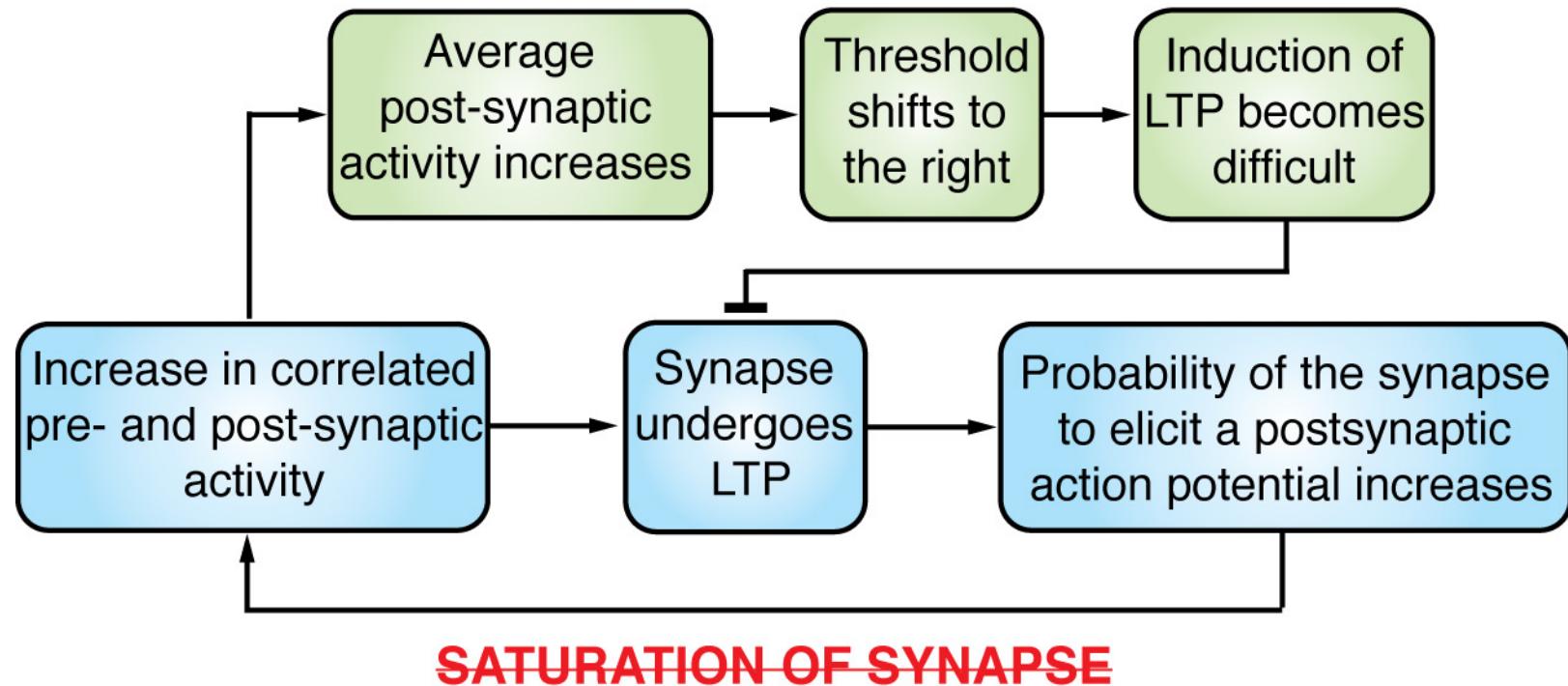


$$\Theta_M = \langle c(t) \rangle^2$$

Bienenstock et al., JNS, 1982

BCM rule and stability

How does the BCM rule work?



Dynamic range of the synapses retained by the negative feedback mechanism induced by the modification threshold

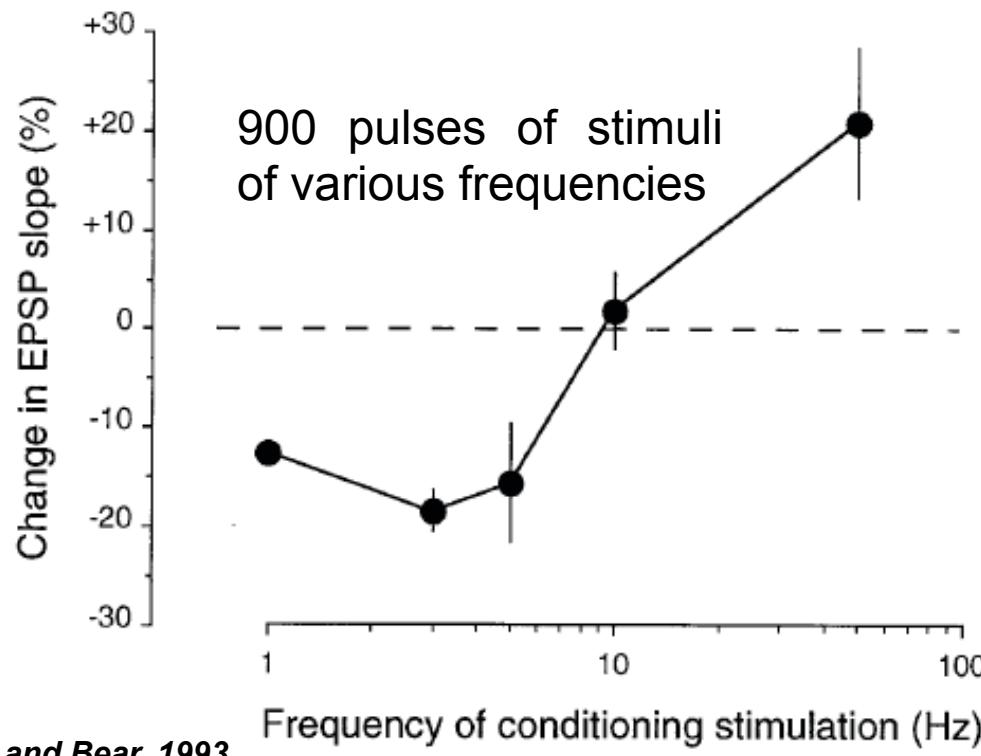
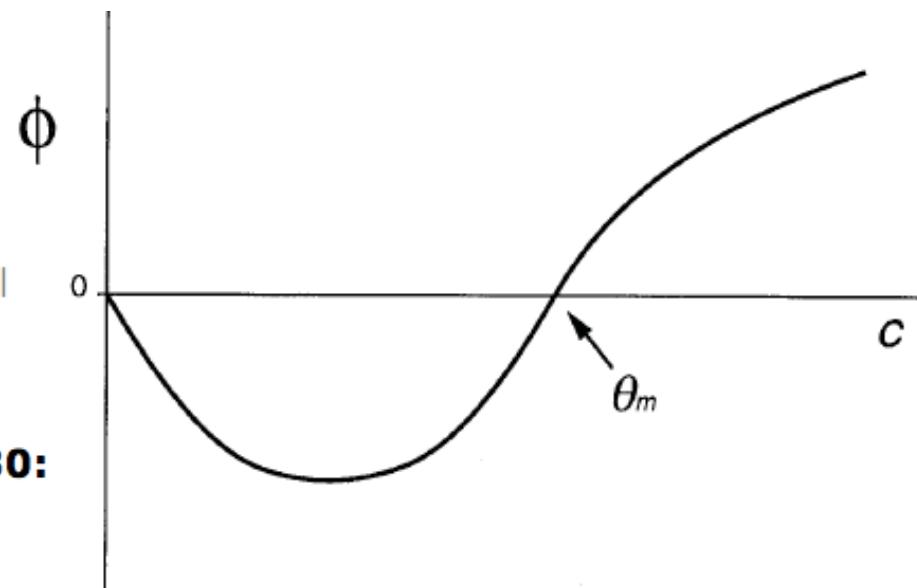
Experiment vs. Theory

Nature Reviews Neuroscience 13, 798-810 (November 2012) |
doi:10.1038/nrn3353

OPINION

The BCM theory of synapse modification at 30: interaction of theory with experiment

Leon N Cooper¹ & Mark F. Bear² [About the authors](#)



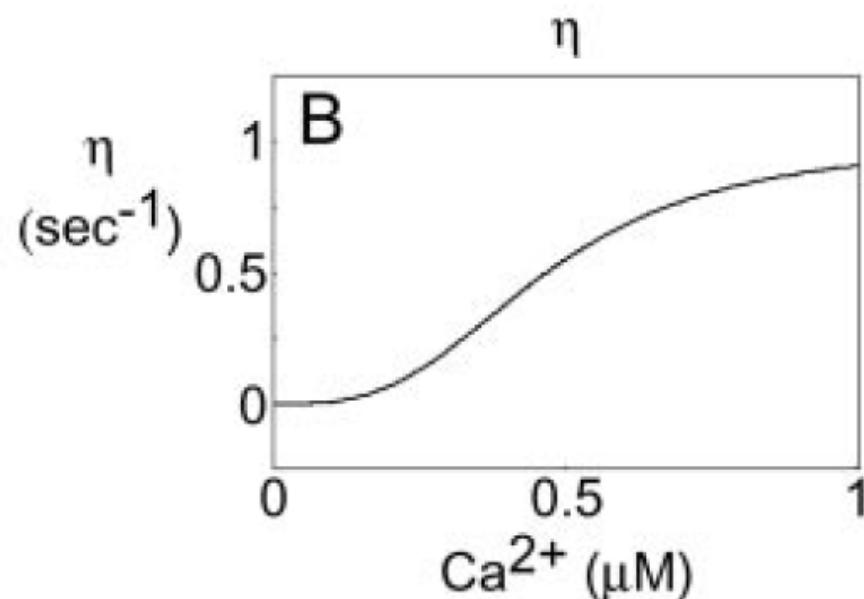
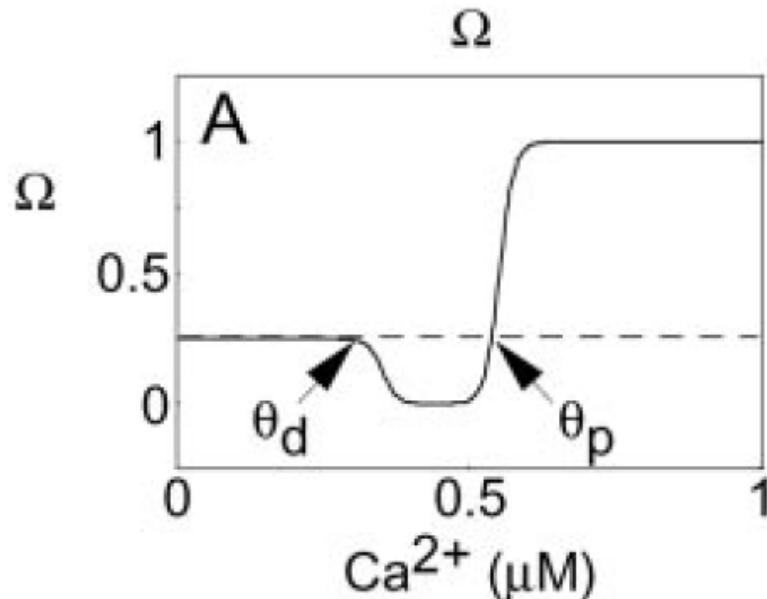
Bringing calcium into the BCM picture

A unified model of NMDA receptor-dependent bidirectional synaptic plasticity

Harel Z. Shouval^{*†}, Mark F. Bear^{*‡§}, and Leon N Cooper^{*†¶}

PNAS | August 6, 2002 | vol. 99 | no. 16 | 10831–10836

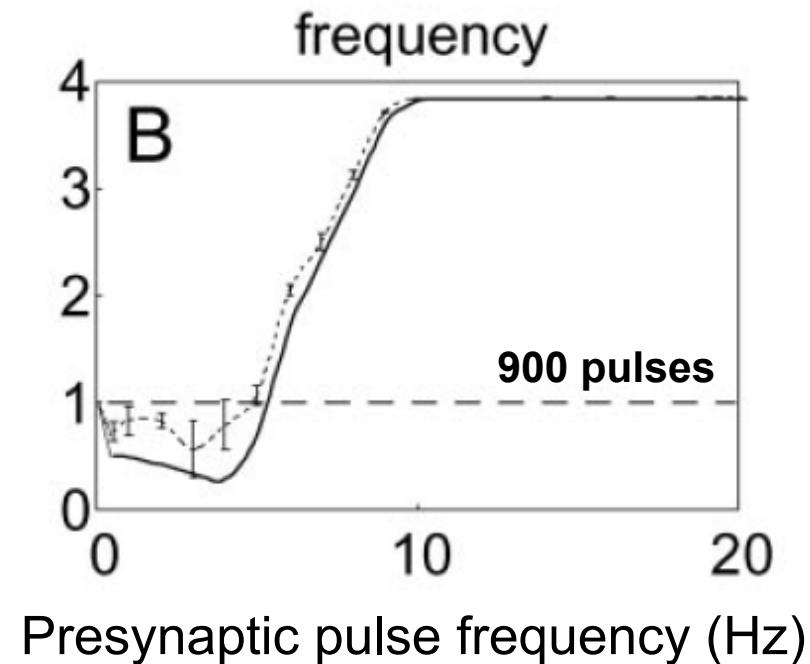
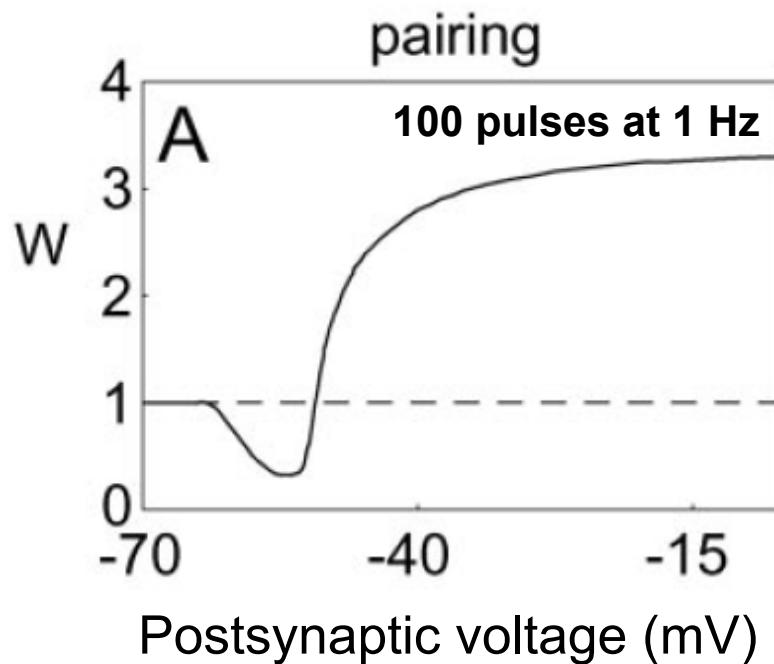
$$\dot{W}_j = \eta([Ca]_j)(\Omega([Ca]_j) - W_j)$$



Modeling NMDAR-dependent pairing and frequency-dependent synaptic plasticity

$$I_{NMDA}(t_i) = P_0 G_{NMDA} [I_f \theta(t) e^{-t/\tau_f} + I_s \theta(t) e^{-t/\tau_s}] H(V)$$

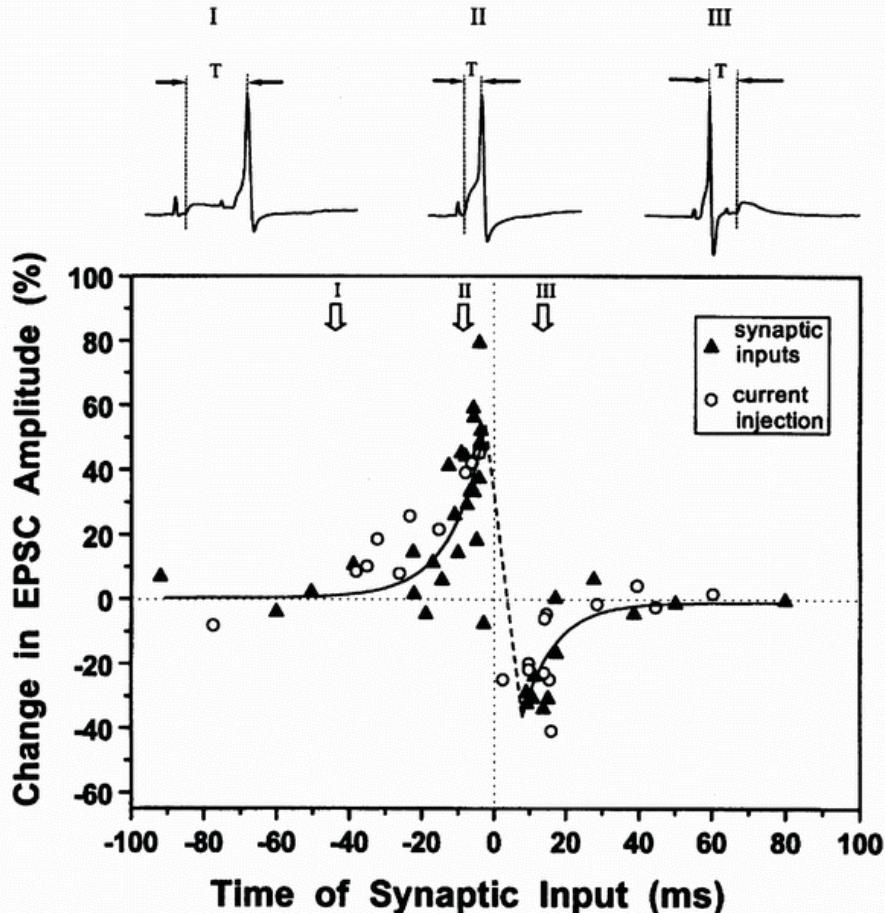
$$\frac{d[Ca(t)]}{dt} = I_{NMDA}(t) - (1/\tau_{Ca})[Ca(t)]$$



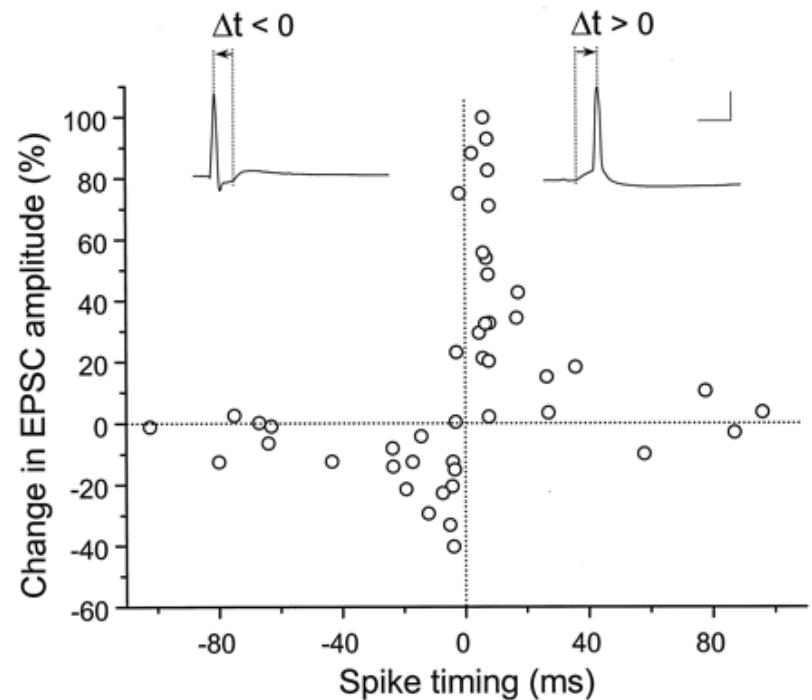
Modeling spike-timing dependent plasticity

STDP

Xenopus tectal neurons



Rat Hippocampal culture neurons



Bi and Poo, JNS, 1998

Zhang et al., Nature, 1998

Phenomenological model of STDP

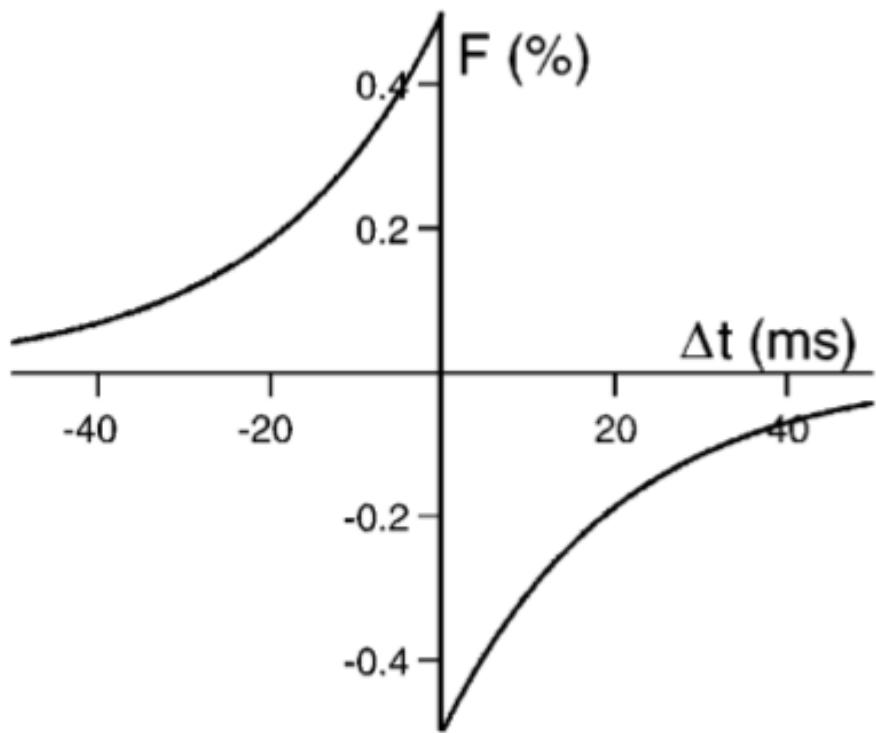
Competitive Hebbian learning through spike-timing-dependent synaptic plasticity

Sen Song¹, Kenneth D. Miller² and L. F. Abbott¹

nature neuroscience • volume 3 no 9 • september 2000

Phenomenological model of STDP

$$\tau_m \frac{dV}{dt} = V_{\text{rest}} - V + g_{\text{ex}}(t)(E_{\text{ex}} - V) + g_{\text{in}}(t)(E_{\text{in}} - V)$$



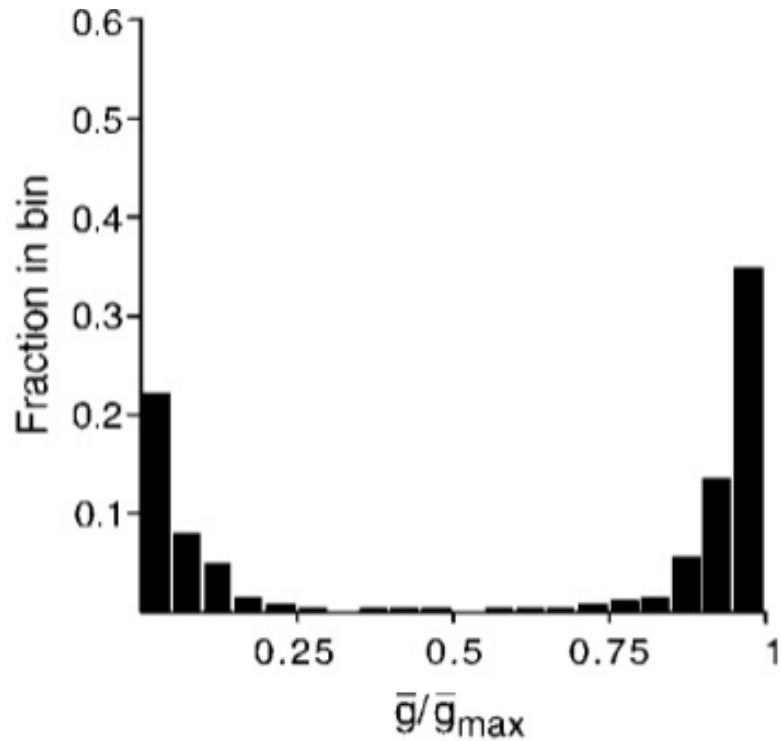
STDP in excitatory synapses

$$F(\Delta t) = \begin{cases} A_+ \exp(\Delta t / \tau_+) & \text{if } \Delta t < 0 \\ -A_- \exp(-\Delta t / \tau_-) & \text{if } \Delta t \geq 0 \end{cases}$$

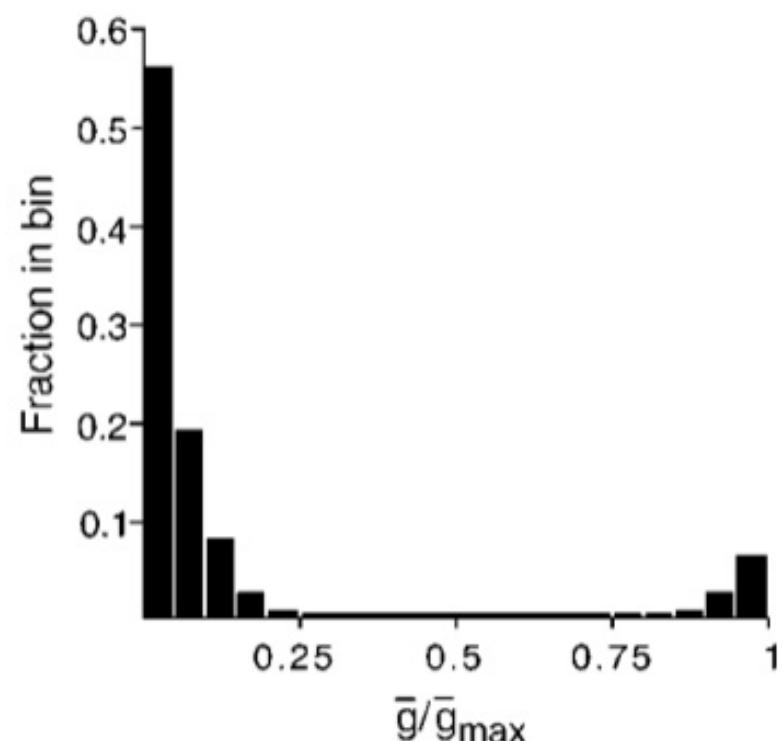
Inhibitory synapses were held constant

Balance of excitation-inhibition by STDP

Average excitatory input firing rate: 10 Hz

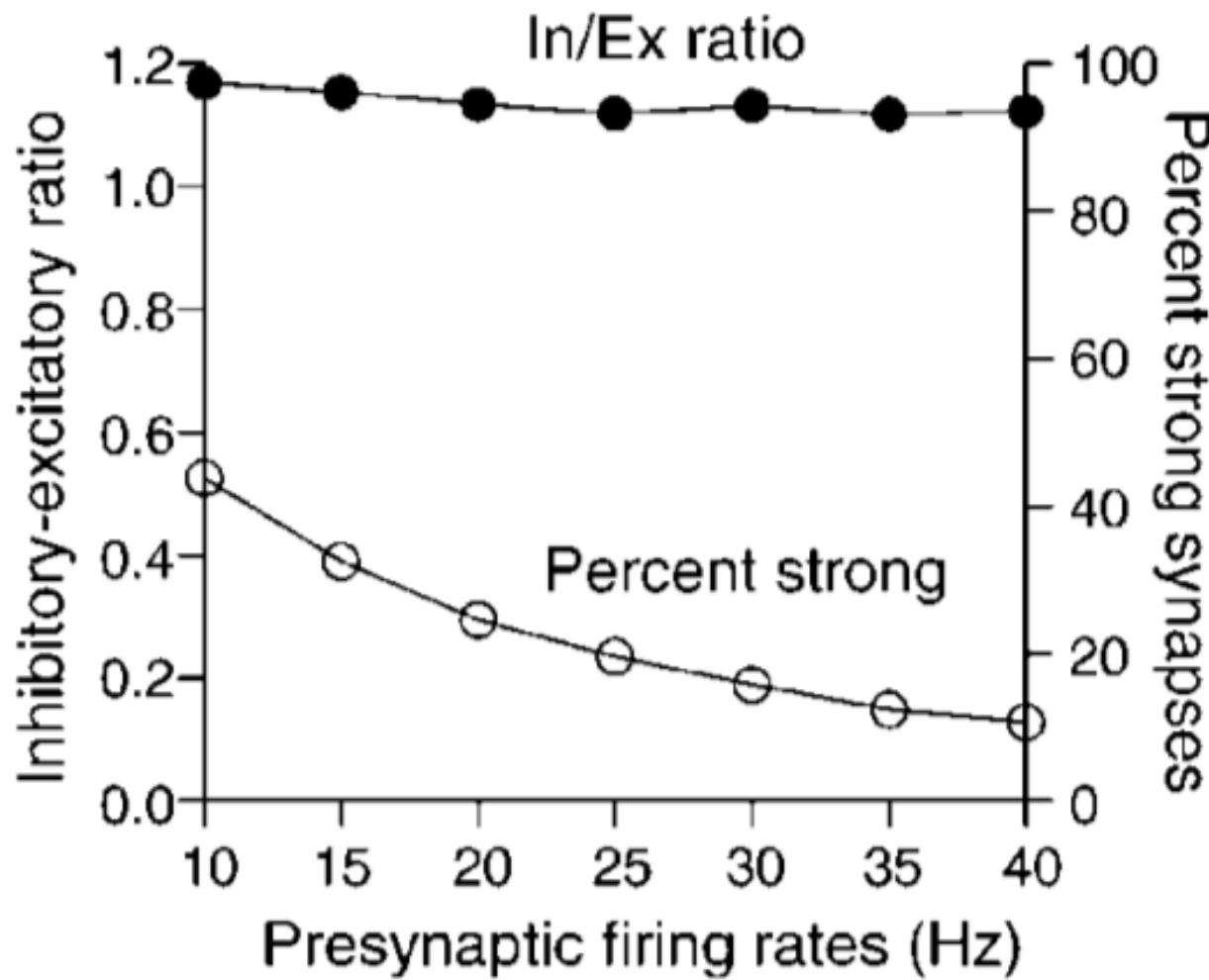


Average excitatory input firing rate: 40 Hz

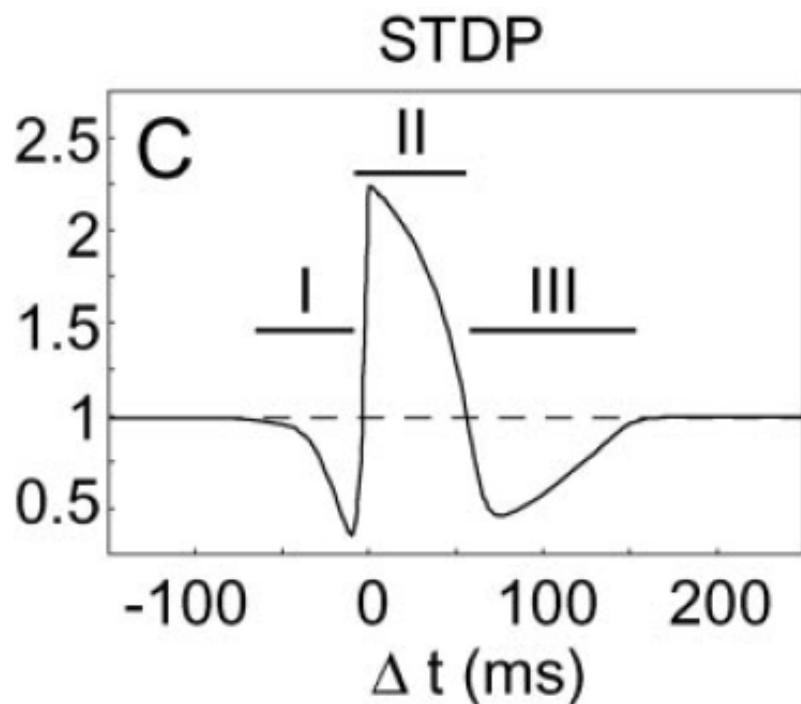


Initially all synapses were set to g_{\max}

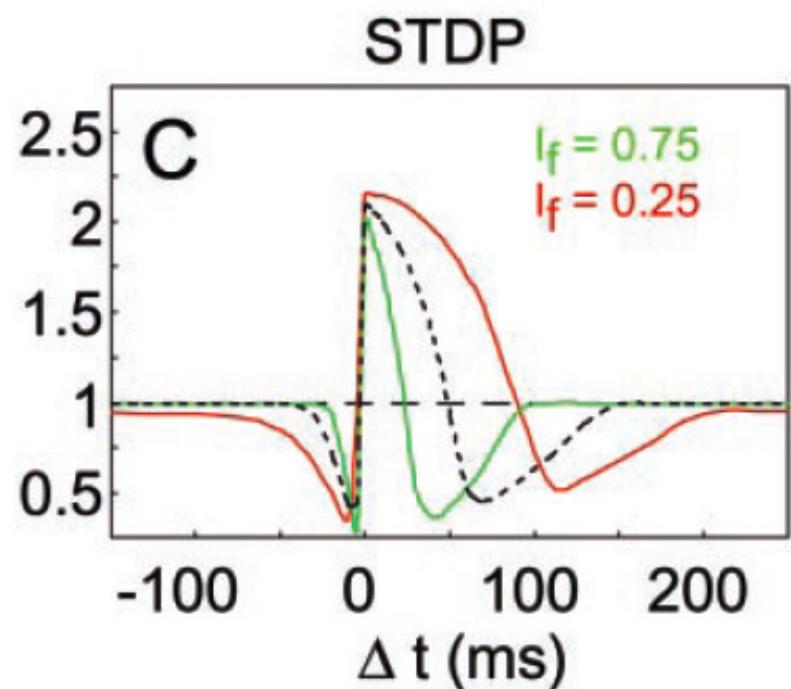
Balance of excitation-inhibition by STDP



STDP within the calcium-dependent framework



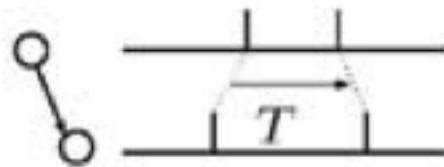
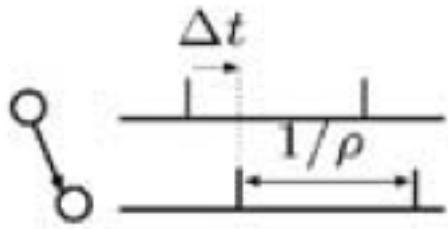
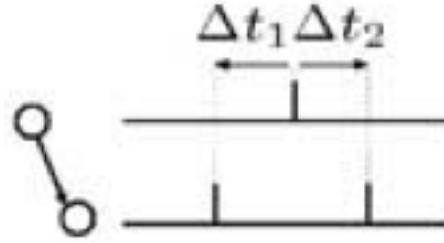
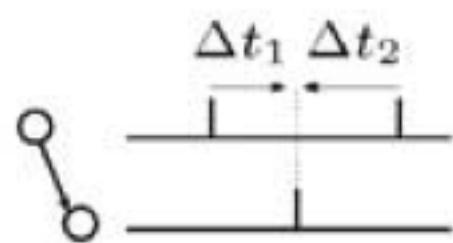
Dependence on NMDAR kinetics



Shouval et al., PNAS, 2002

Other issues in modeling spike-timing dependent plasticity

Triplets and quadruplets



Additive STDP

Multiplicative STDP

Suppression additive STDP

Nearest-Neighbor additive STDP

Nearest-spike additive STDP

...

Triplets and quadruplets: More information

Spike-timing-dependent synaptic modification induced by natural spike trains

Robert C. Froemke & Yang Dan

NATURE | VOL 416 | 28 MARCH 2002

Relating STDP to BCM

Eugene M. Izhikevich

Eugene.Izhikevich@nsi.edu, www.nsi.edu/users/izhikevich

Niraj S. Desai

desai@nsi.edu

Neural Computation 15, 1511–1523 (2003)

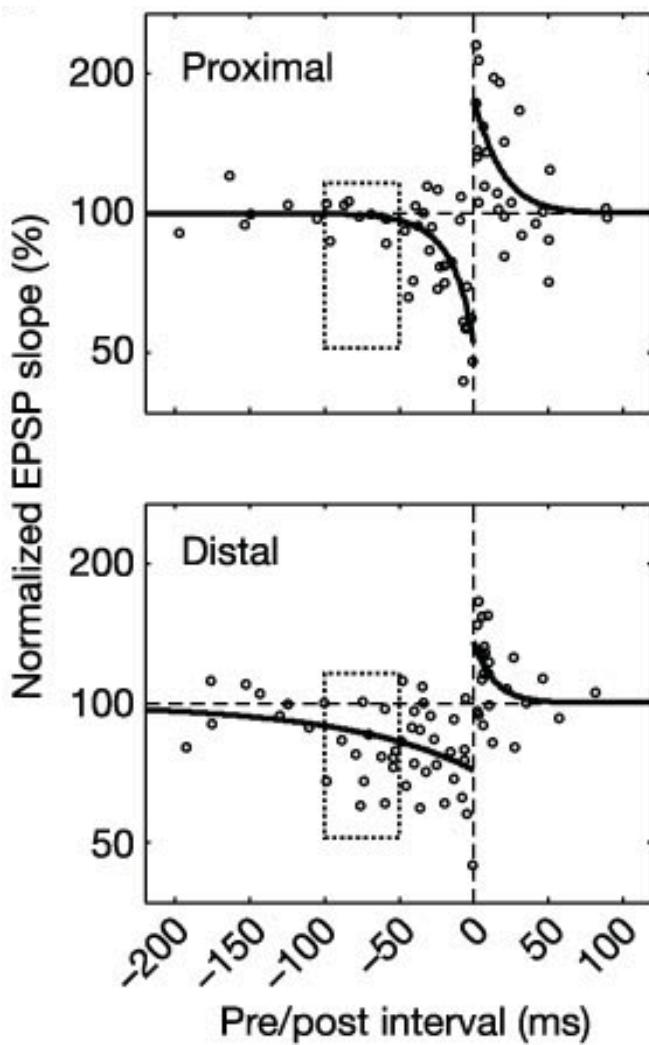
Triplets of Spikes in a Model of Spike Timing-Dependent Plasticity

Jean-Pascal Pfister and Wulfram Gerstner

The Journal of Neuroscience, September 20, 2006 • 26(38):9673–9682

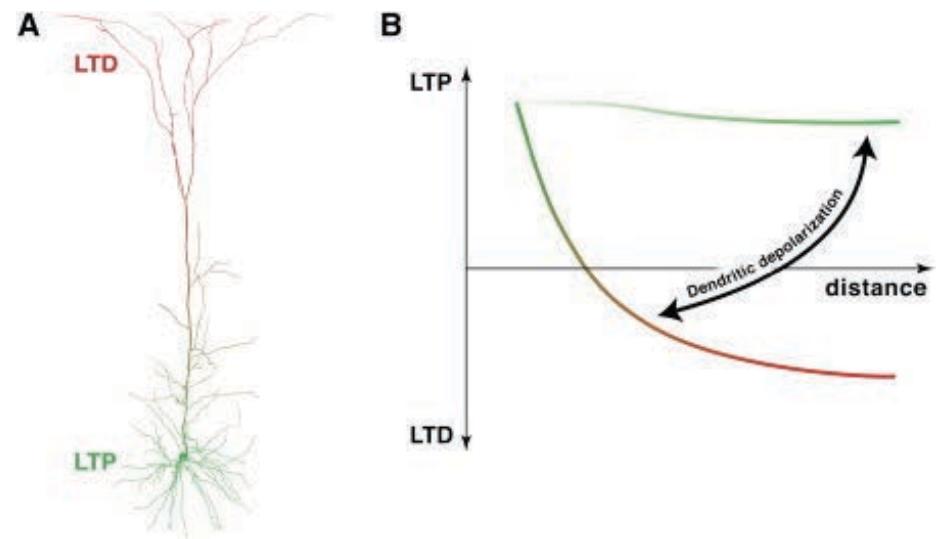
Location-dependence of STDP

Layer 2/3 neocortex



Froemke et al., Nature, 2005

Layer 5 neocortex



Sjostrom and Häusser, Neuron, 2006

Both are controlled by the spread of backpropagating action potentials

Location-dependence of STDP: Model

Learning Rules for Spike Timing-Dependent Plasticity Depend on Dendritic Synapse Location

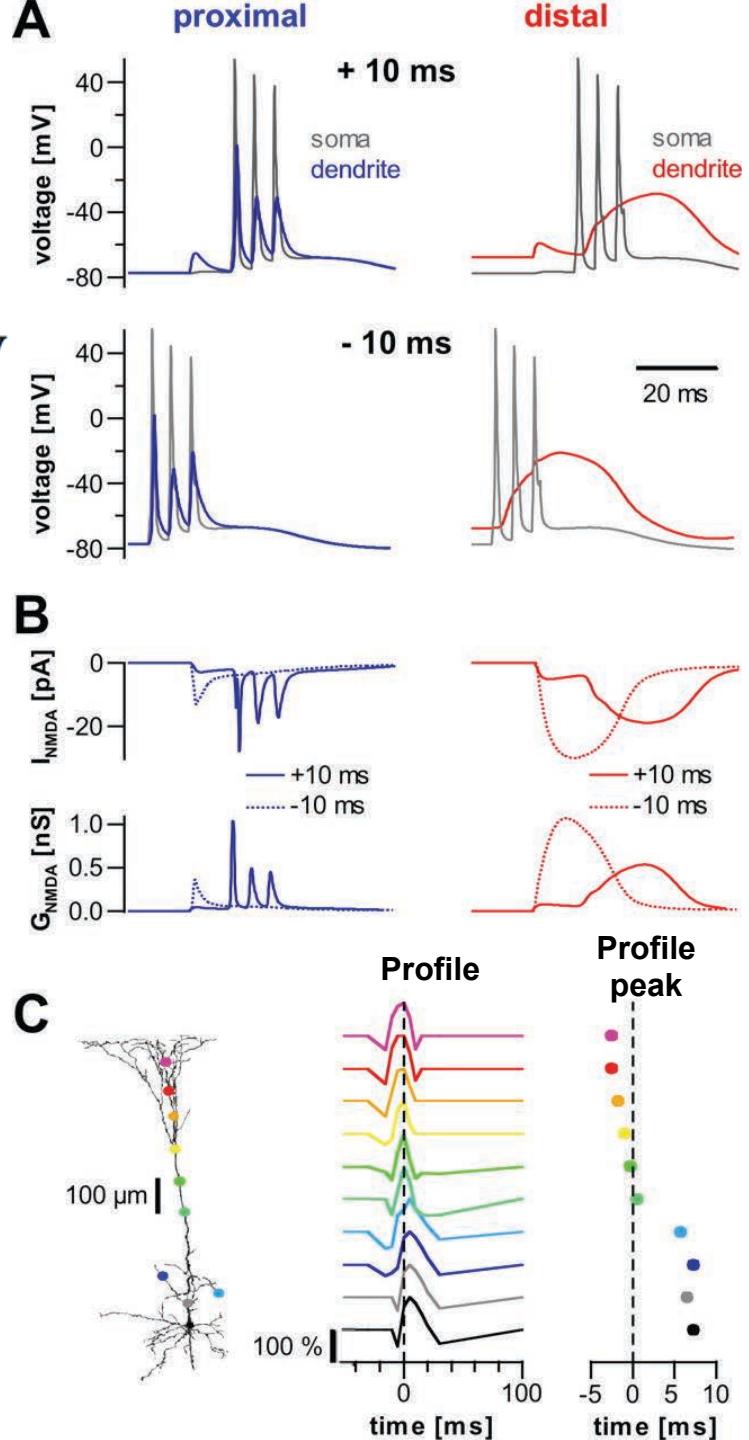
Johannes J. Letzkus, Björn M. Kampa, and Greg J. Stuart

The Journal of Neuroscience, October 11, 2006 • 26(41):10420–10429

Morphologically realistic model

Six different VGICs distributed with experimentally-assessed gradients

Conversion from calcium to plasticity done through the (Shouval et al., PNAS, 2002) model.



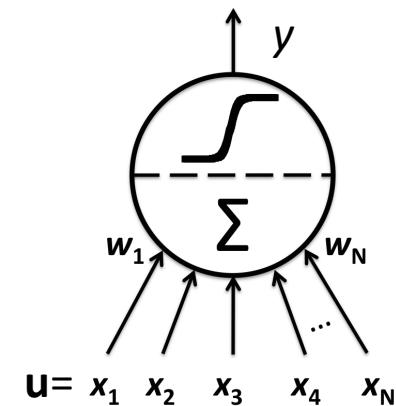
**Studying different forms of long-term
plasticity and interactions among them**

A more abstract model for coupling between intrinsic and synaptic plasticity

Synergies Between Intrinsic and Synaptic Plasticity Mechanisms

Jochen Triesch

Neural Computation 19, 885–909 (2007)



$$y = g_{ab}(x) = \frac{1}{1 + \exp(-(ax + b))}$$

Synaptic plasticity learning rule:

$$\Delta \mathbf{w} = \eta_{\text{Hebb}} \mathbf{u} y(\mathbf{u}) = \eta_{\text{Hebb}} \mathbf{u} g_{ab}(\mathbf{w}^T \mathbf{u})$$

Intrinsic plasticity learning rule:

$$\Delta a = \eta_{\text{IP}} \left(\frac{1}{a} + x - \left(2 + \frac{1}{\mu} \right) xy + \frac{1}{\mu} xy^2 \right)$$

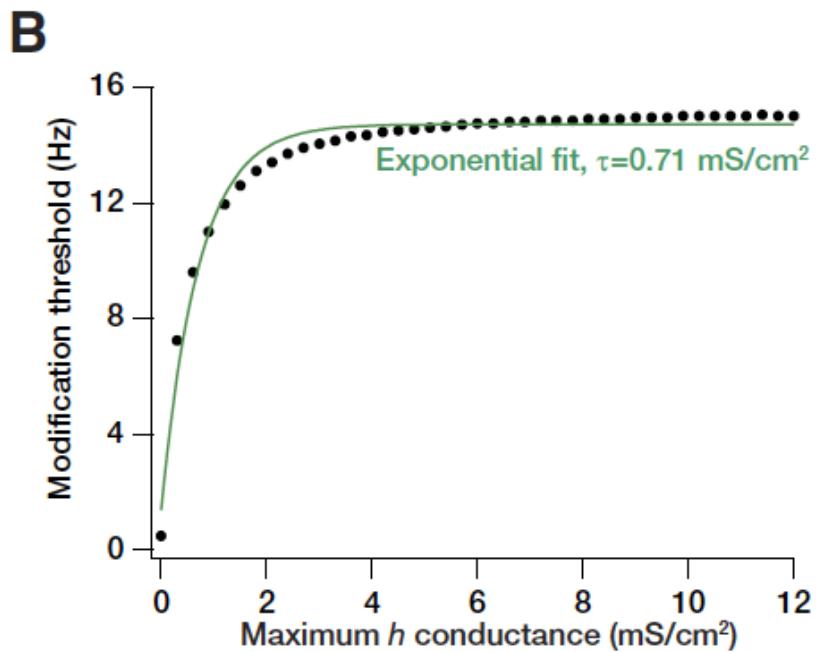
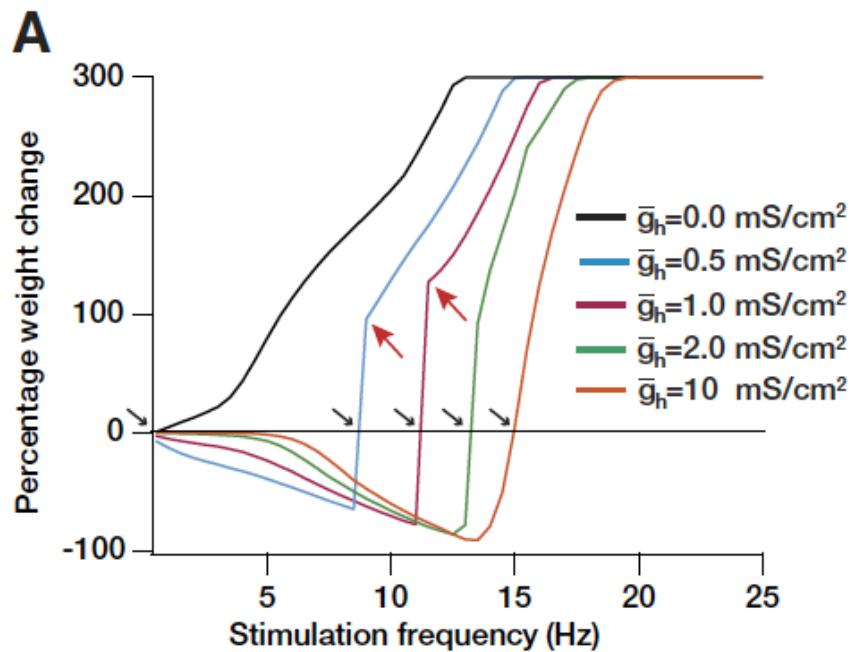
$$\Delta b = \eta_{\text{IP}} \left(1 - \left(2 + \frac{1}{\mu} \right) y + \frac{1}{\mu} y^2 \right),$$

Derived such that μ is the neuron's desired mean activity and η_{IP} is a small learning rate

Also see Naude et al., J. Neurosci., 2013

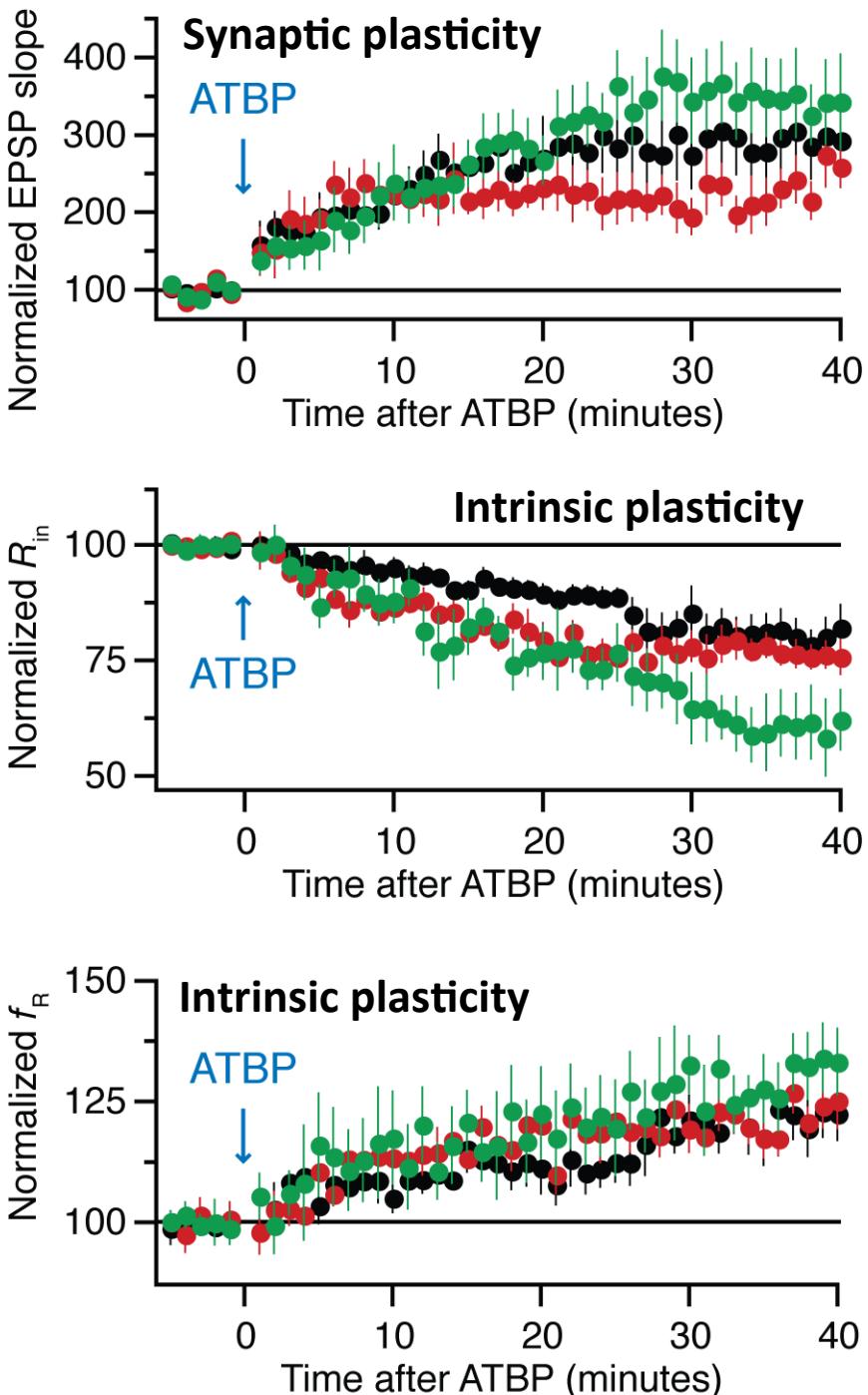
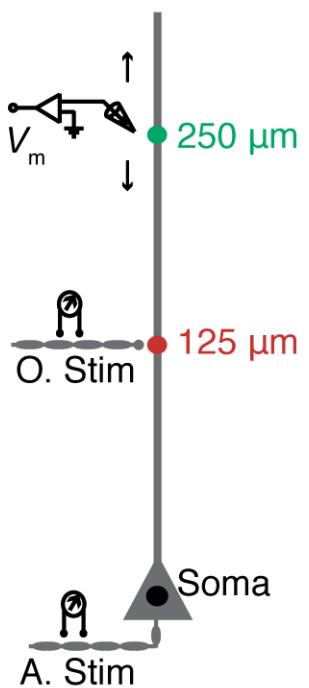
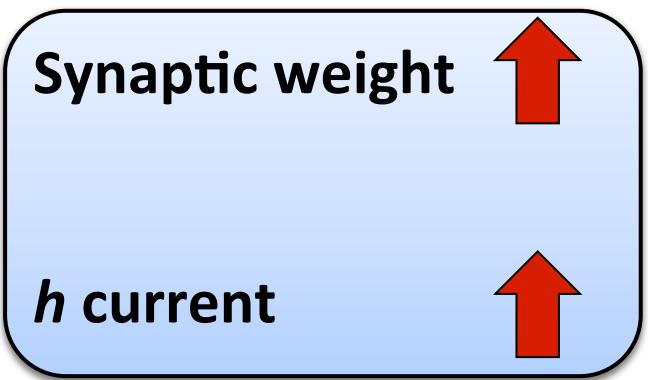
Plasticity in HCN channels alters synaptic plasticity rules

Impact of intrinsic properties/plasticity on synaptic plasticity rules



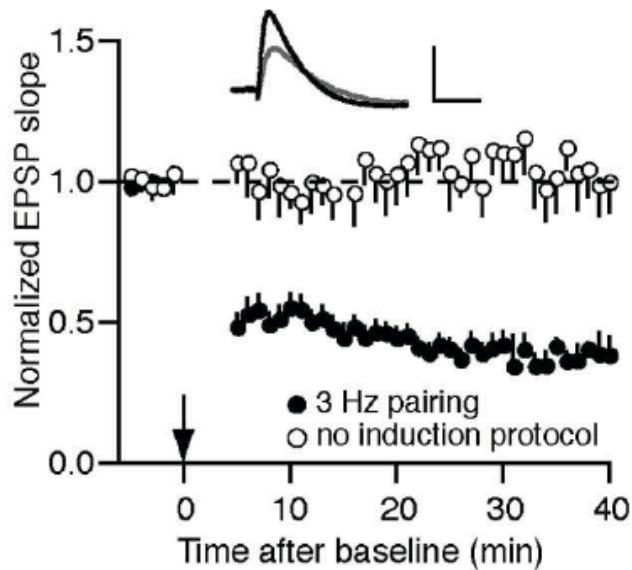
Global plasticity in resonance frequency map accompanies synaptic plasticity

This is consequent to increases in a specific ion channel conductance: The h conductance



Bidirectionality: Decrease in h current accompanies decrease in synaptic strength

Synaptic plasticity



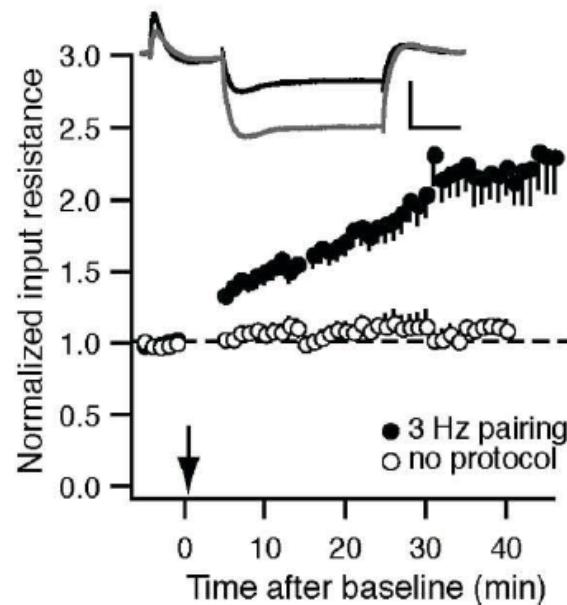
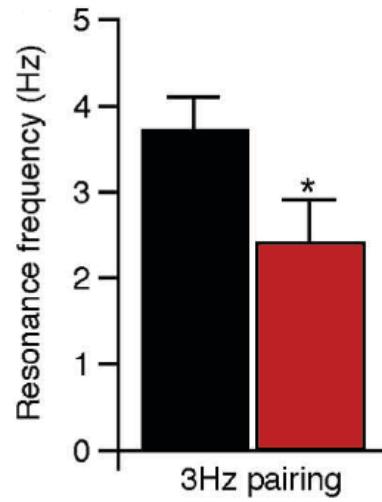
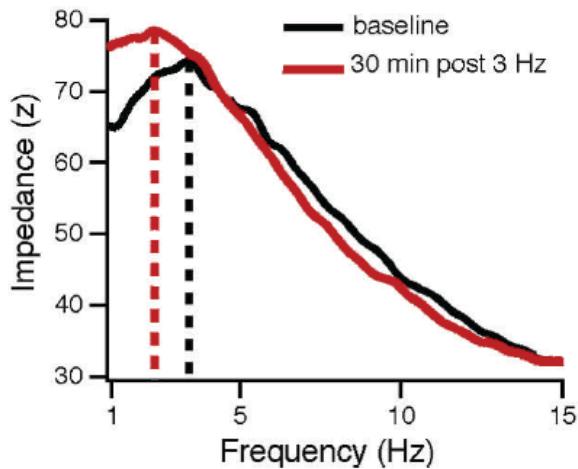
Synaptic weight



h current

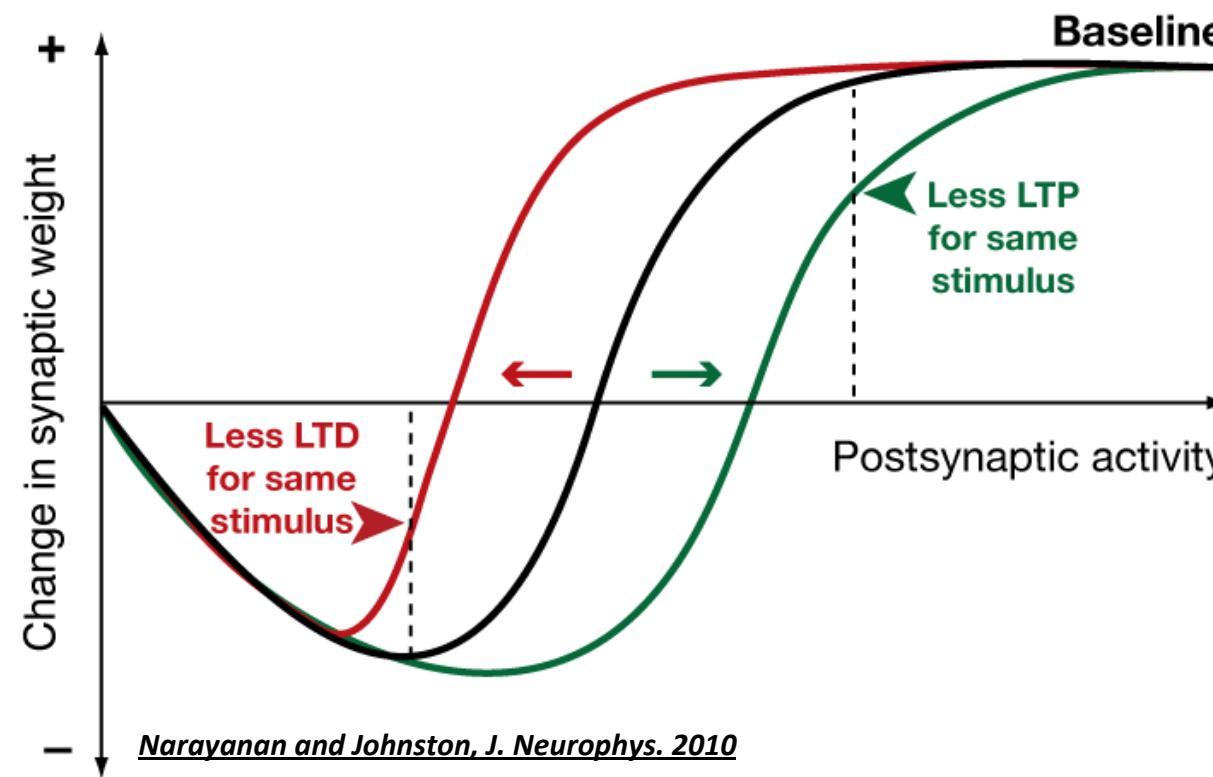


Intrinsic Plasticity



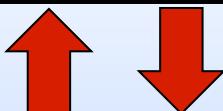
The *h* Current Is a Candidate Mechanism for Regulating the Sliding Modification Threshold in a BCM-Like Synaptic Learning Rule

Rishikesh Narayanan and Daniel Johnston

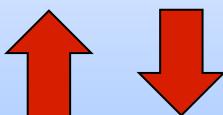


This shape and the ensuing analysis hold only for hippocampal SC synapses and a few others — do not generalize!

Synaptic weight



h current



Incorporating plasticity in h channels into this framework

Goal: To derive experimentally-driven rules for plasticity in voltage-gated ion channels and explore their synergy with synaptic plasticity



A Calcium-Dependent Plasticity Rule for HCN Channels Maintains Activity Homeostasis and Stable Synaptic Learning

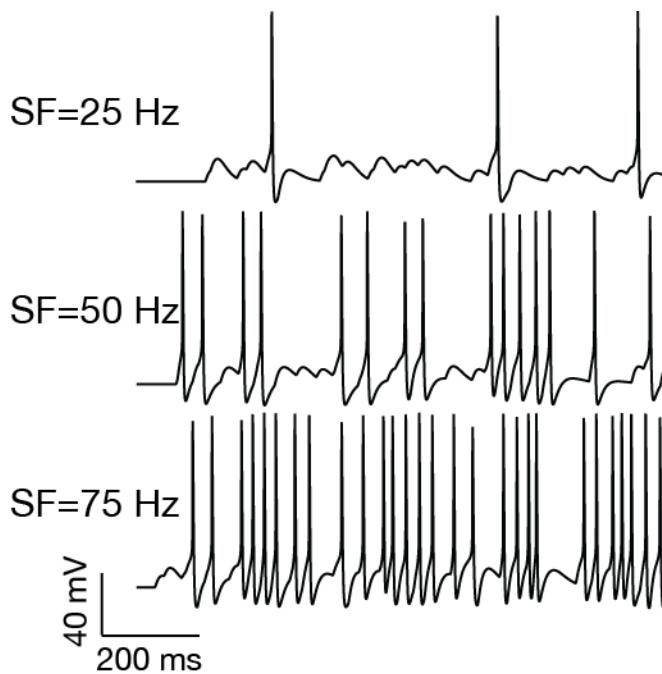
Suraj Honnuraiah[✉], Rishikesh Narayanan*

Cellular Neurophysiology Laboratory, Molecular Biophysics Unit, Indian Institute of Science, Bangalore, India

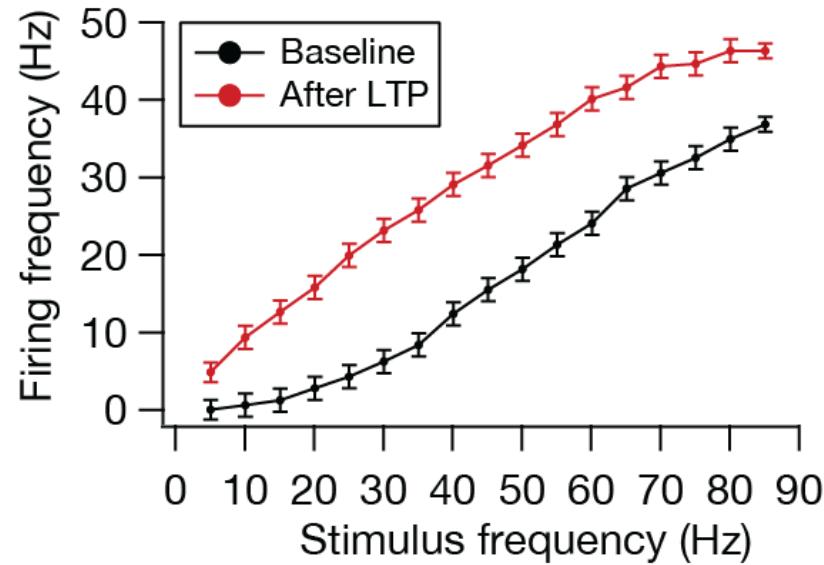
February 2013 | Volume 8 | Issue 2 | e55590

LTP increases firing rate of neurons

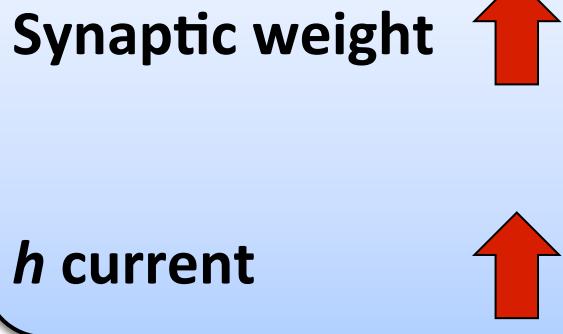
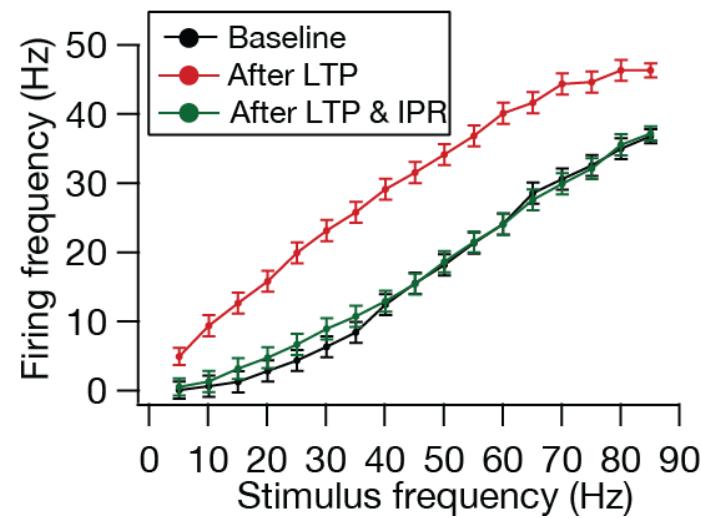
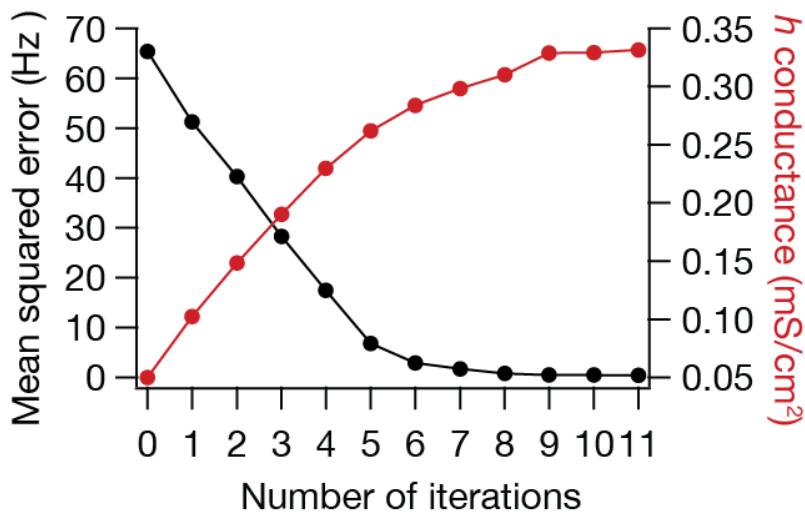
Baseline



After LTP

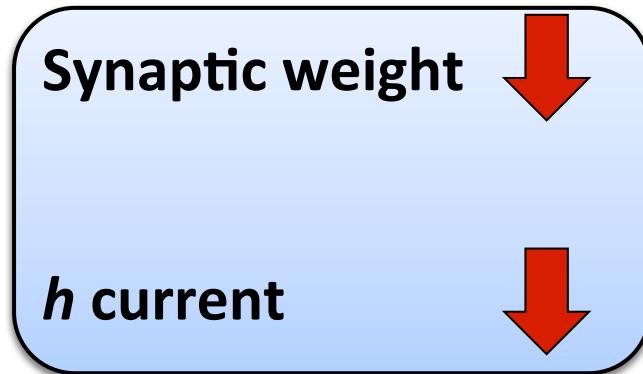
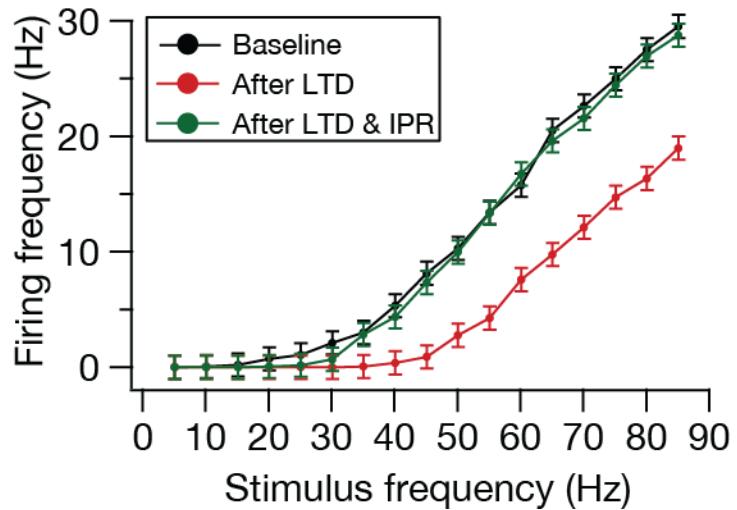
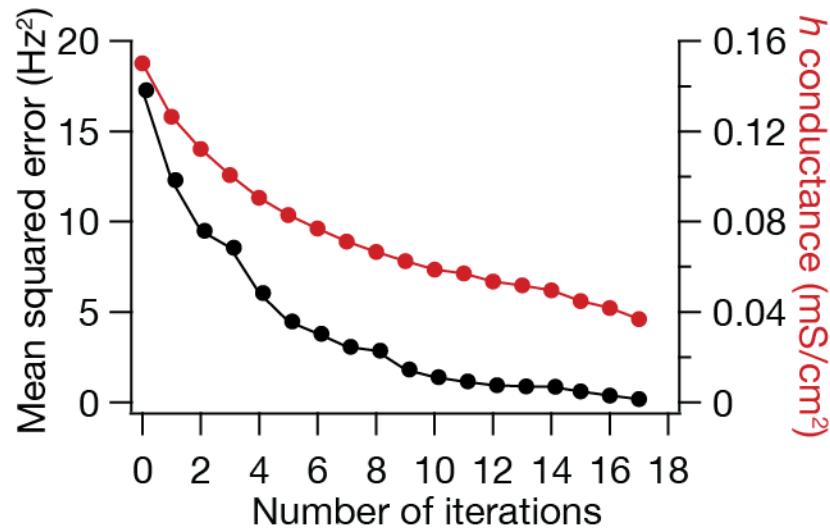


Plasticity in h conductance through the plasticity rule maintained firing rate after increase in synaptic weight

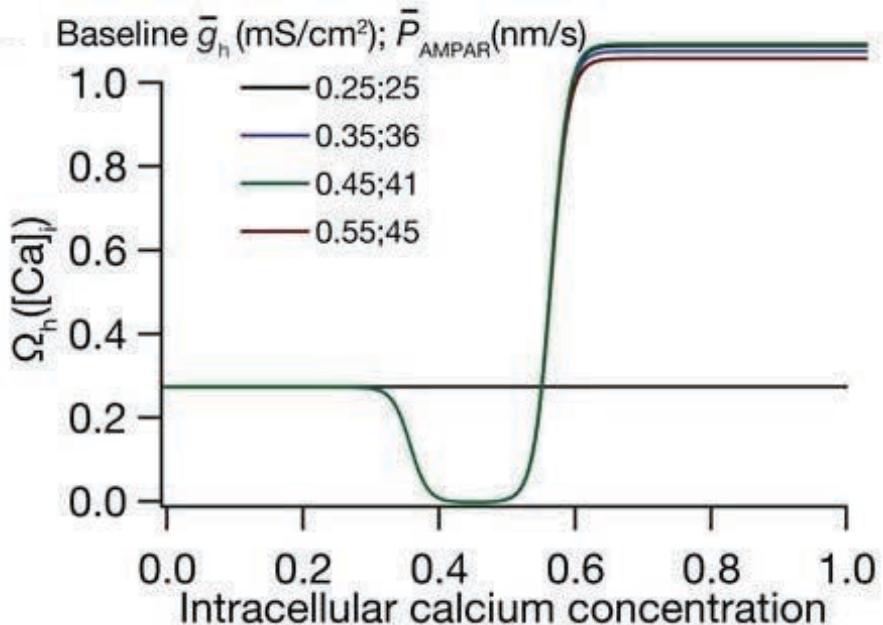
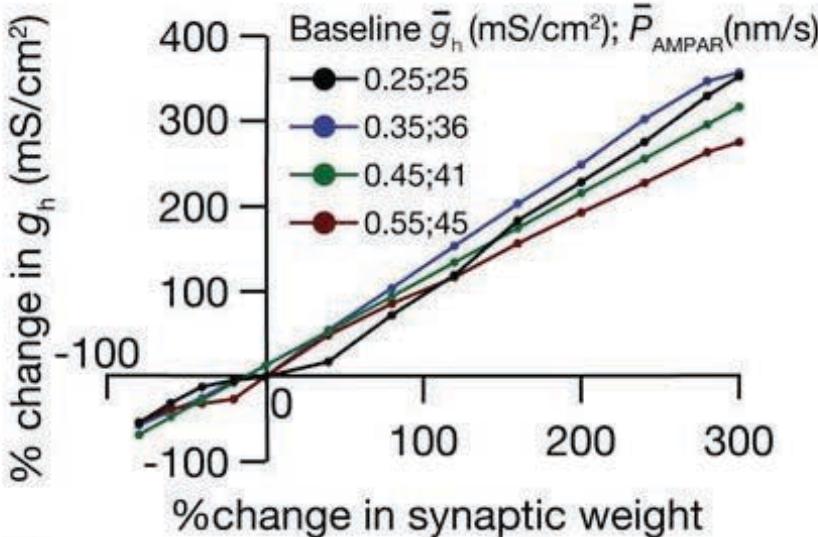


IPR: iterative plasticity rule

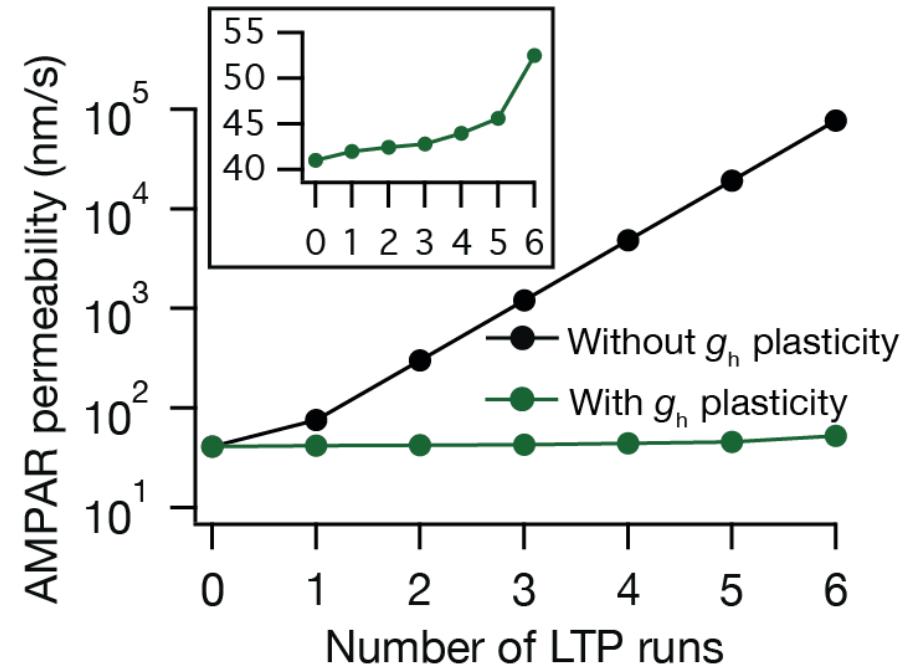
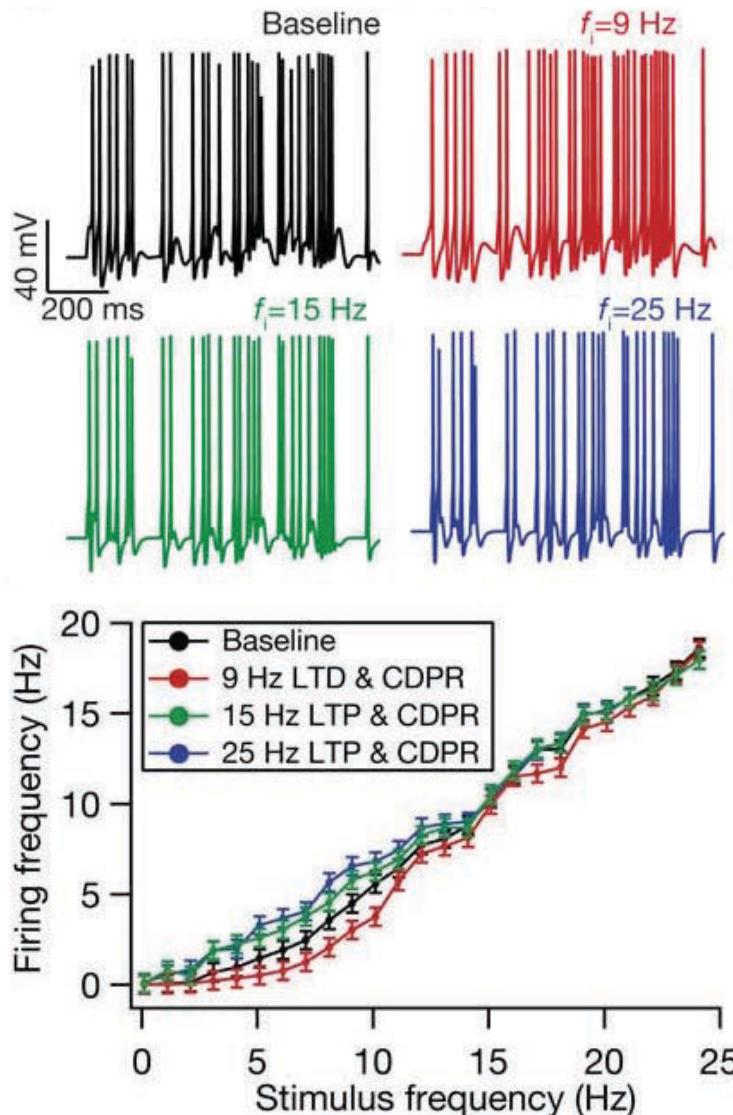
Plasticity in h conductance through the plasticity rule maintained firing rate after decrease in synaptic weight



Plasticity in HCN-channels was linearly related to synaptic plasticity, leading to a calcium-dependent plasticity rule for HCN channels



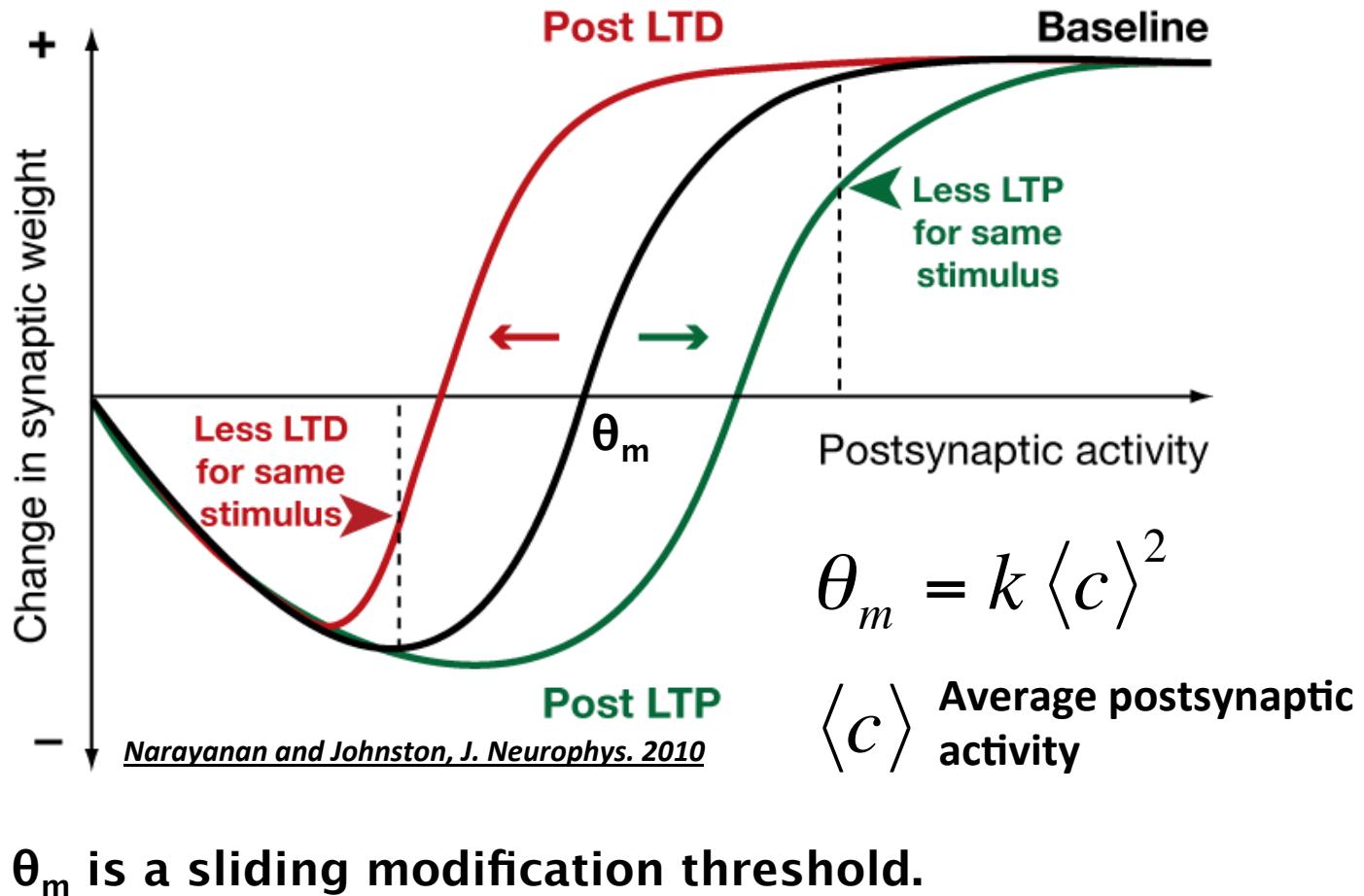
Firing rate homeostasis is maintained and runaway increase in synaptic weight is prevented if h channel plasticity accompanies synaptic plasticity



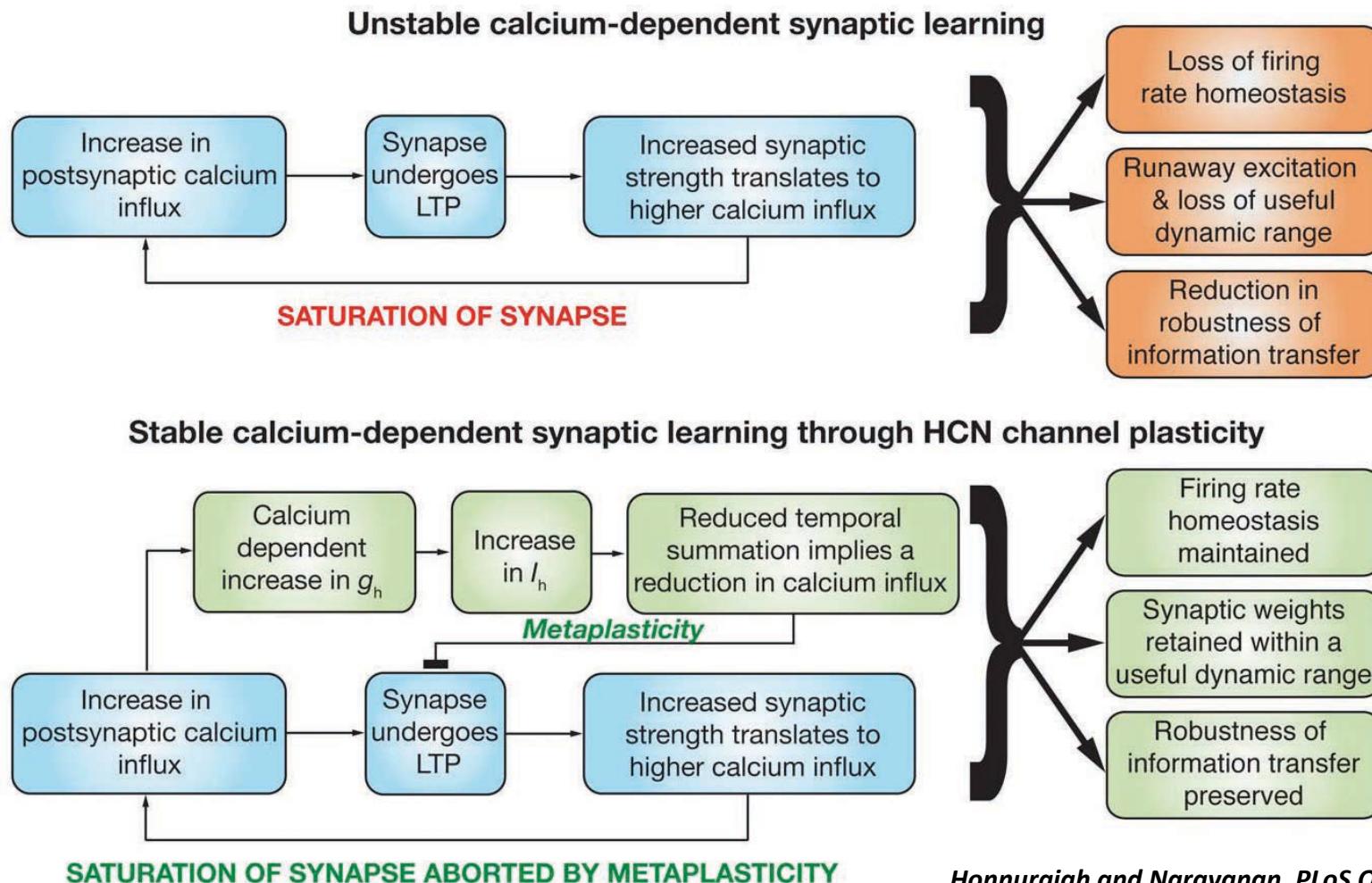
CDPR: Calcium-Dependent Plasticity Rule

Metaplasticity brings about stability!

Bienenstock, Cooper, Munro (BCM) plasticity framework



Calcium-dependent intrinsic plasticity enables retention of stability in a synaptic learning system: Implications



Honnuraiah and Narayanan, PLoS One, 2013

Dynamic range of the synapses retained by the negative feedback mechanism induced by the h channel plasticity

Modeling plasticity of intrinsic conductances

Activity-Dependent Regulation of Conductances in Model Neurons

Gwendal LeMasson, Eve Marder, L. F. Abbott*

SCIENCE • VOL. 259 • 26 MARCH 1993

The modeling paper whose experimental counterpart came a year later

Activity-Dependent Changes in the Intrinsic Properties of Cultured Neurons

Gina Turrigiano,* L. F. Abbott, Eve Marder

SCIENCE • VOL. 264 • 13 MAY 1994

Also see Abbott and LeMasson, Neural Computation, 1993; Liu et al., J. Neurosci., 1998

The base model

Single compartmental model

$$C \frac{dV}{dt} = - \sum_i I_i$$

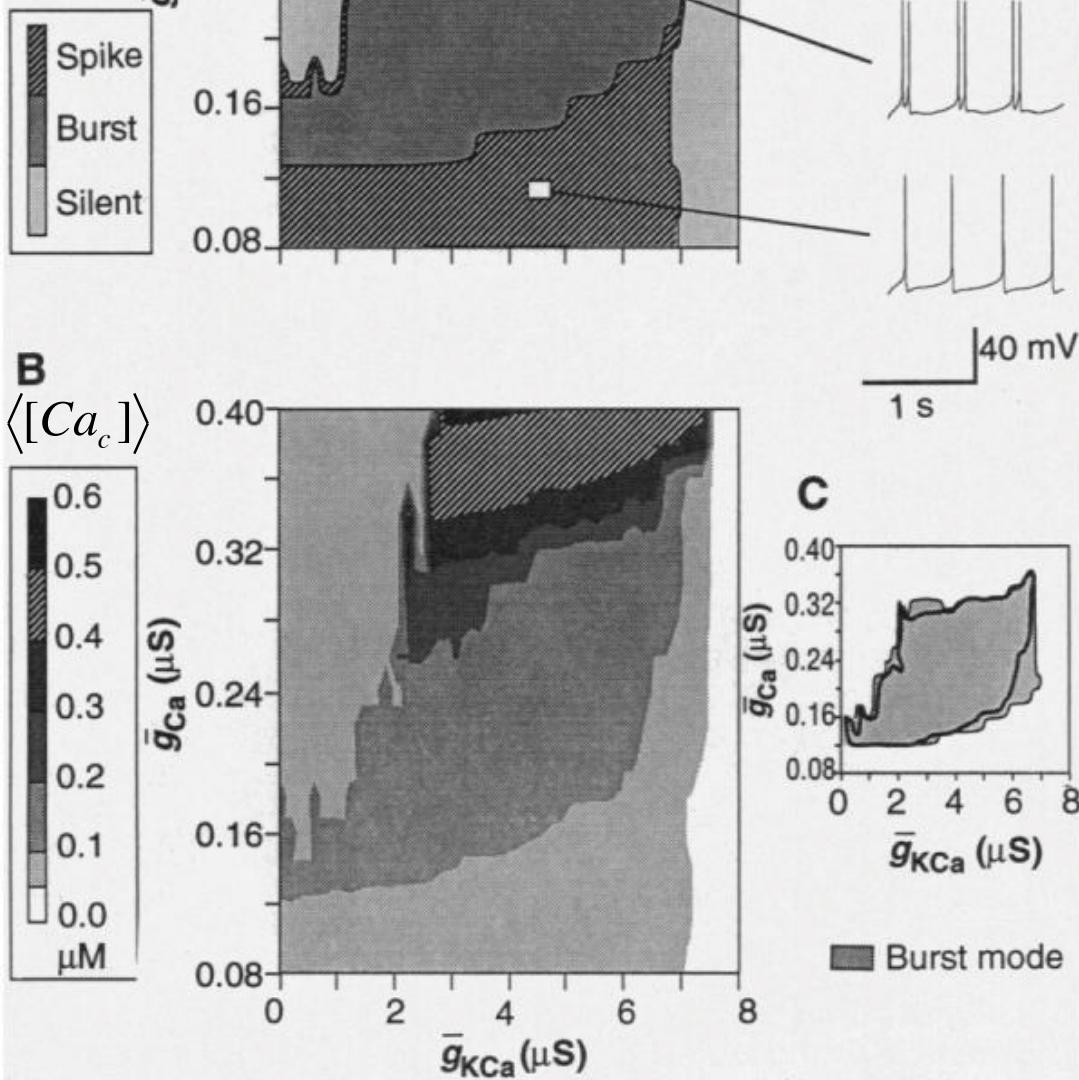
A passive leak current, and seven active currents modeled with the HH formulation: fast Na⁺, delayed rectifier K⁺, fast and slow transient K⁺, hyperpolarization-activated inward H, transient Ca²⁺, Ca²⁺-dependent K⁺

Calcium ON and OFF mechanisms:

$$\frac{d[\text{Ca}]}{dt} = -k(AI_{\text{Ca}} - [\text{Ca}])$$

A

Firing patterns and calcium concentrations as functions of intrinsic conductances



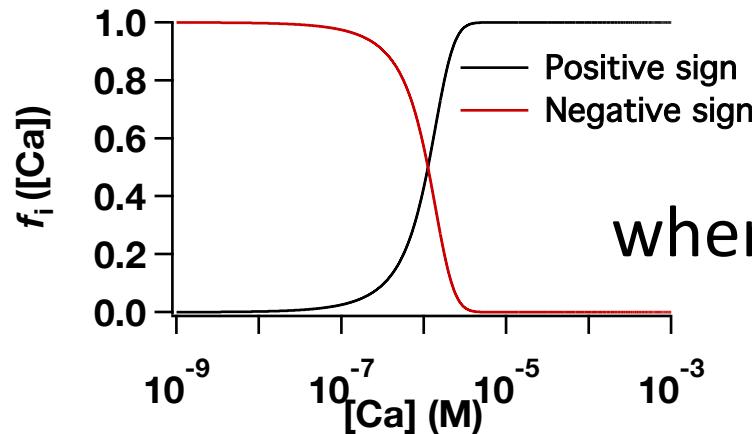
Bursting activity occurs in this model when the calcium concentration is between 0.1–0.3 μM

Calcium homeostasis drives self-regulation of ionic conductances

Use calcium as a feedback signal because it reliably reflects intrinsic firing patterns

For all conductances g_i

$$\tau_i \frac{d\bar{g}_i}{dt} = f_i([Ca]) - \bar{g}_i$$



where

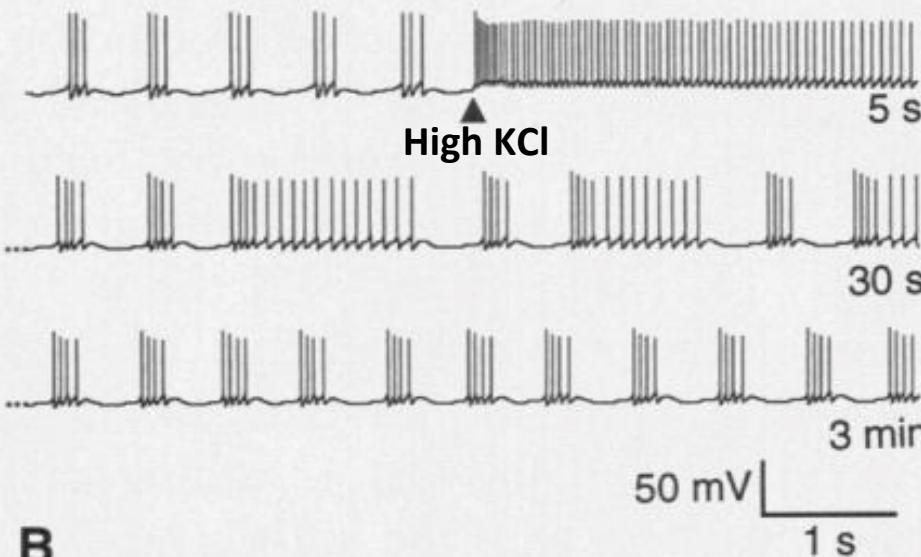
$$f_i([Ca]) = \frac{G_i}{1 + \exp\{\pm ([Ca] - C_T)/\Delta\}}$$

$$\text{All } \tau_i = 50 \text{ s}$$

C_T is the target calcium concentration

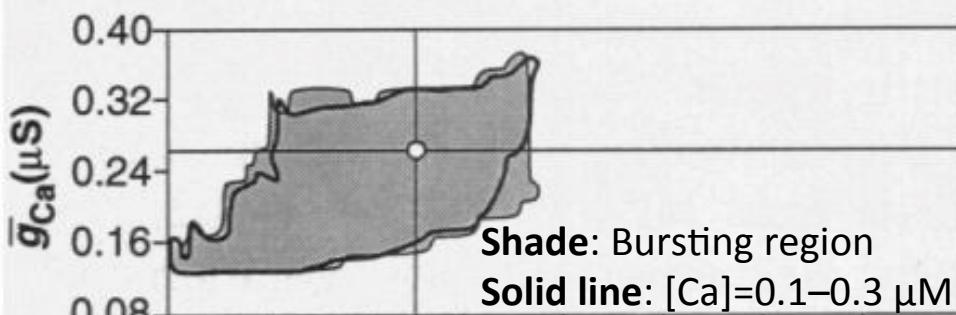
Signs are wrong in the paper!
Changed below!

Heuristic towards stability: Negative sign for inward currents, and positive sign for outward currents in $f_i([Ca])$

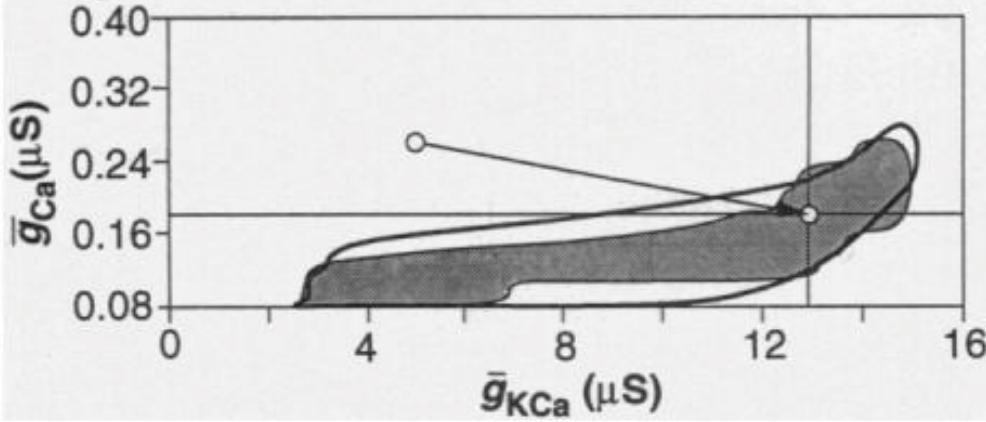
A

Intrinsic plasticity in response to change in afferent activity

High KCl: Change potassium reversal from -80 mV to -65 mV

B

Target calcium, $C_T=0.2 \mu M$

C

Bursting activity and calcium concentrations were restored but with different conductance values!

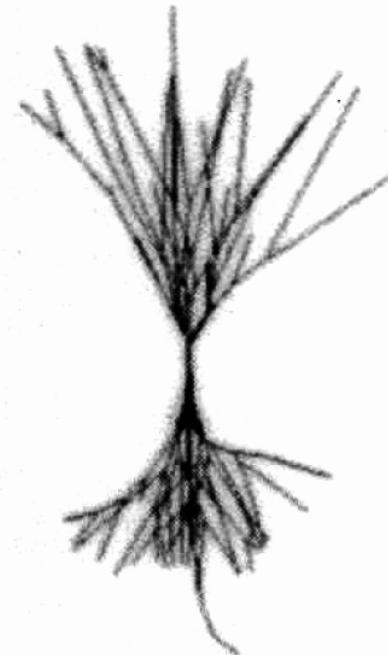
Taking the model to morphological realism and channel gradients!

Proc. Natl. Acad. Sci. USA
Vol. 91, pp. 11308–11312, November 1994
Neurobiology

Activity-dependent current distributions in model neurons

(activity-dependent regulation/neuronal plasticity/calcium-dependent modulation/channel density)

MICAH SIEGEL*, EVE MARDER, AND L. F. ABBOTT†



A passive leak current, and four active currents modeled with the HH formulation: fast Na^+ , delayed rectifier K^+ , transient K^+ and Ca^{2+}

Calcium ON and OFF mechanisms and diffusion:

$$\frac{\partial[\text{Ca}^{2+}]}{\partial t} = D \frac{\partial^2[\text{Ca}^{2+}]}{\partial x^2} - k[\text{Ca}] - \gamma I_{\text{Ca}}$$

Calcium homeostasis drives self-regulation of ionic conductances

$$\tau \frac{d\bar{g}}{dt} = \frac{G}{1 + \exp[\pm([Ca^{2+}] - C_T)/\Delta]} - \bar{g},$$

$$C_T = 0.5 \mu M$$

where the variable sign is plus with $G = 360 \text{ mS/cm}^2$ for I_{Na} and minus with $G = 180 \text{ mS/cm}^2$ for I_K .

Signs are wrong, again! Should be opposite for I_{Na} and I_K

Random Poisson-distributed synaptic inputs spread over the apical and basal trees of the model neuron, and the evolution monitored

Self-organizing Conductance Distributions

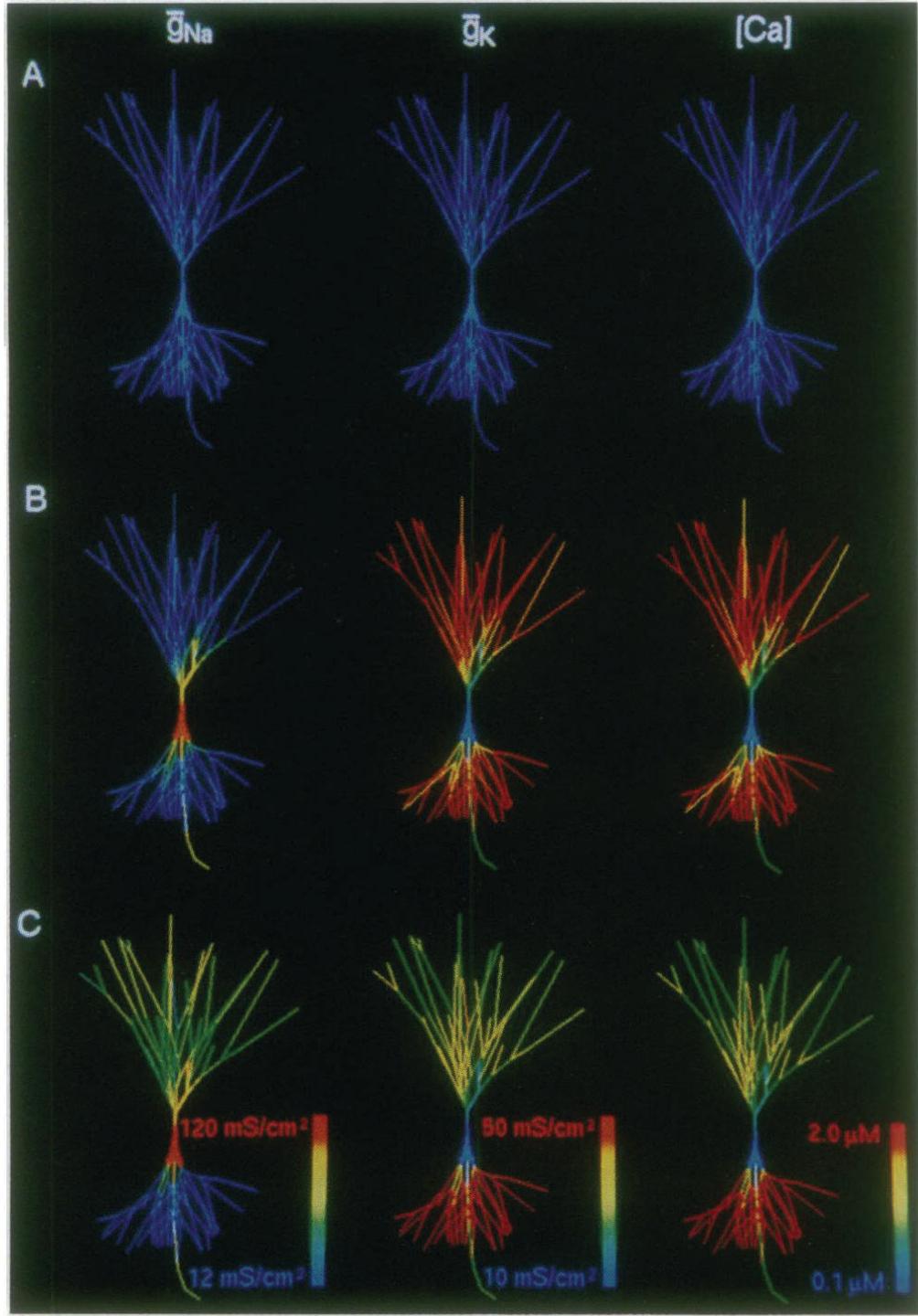
Baseline

Randomly placed 100-Hz stimulation of synapses with 2-nS peak conductance spanning apical and basal trees

Interactions between synaptic and intrinsic properties are also studied

Randomly placed 2-nS synapses with 100-Hz stimulation of synapses on basal dendrites and 5Hz on apical dendrites

The dependence of [Ca] on Surface area-to-volume ratio translates to conductance gradients



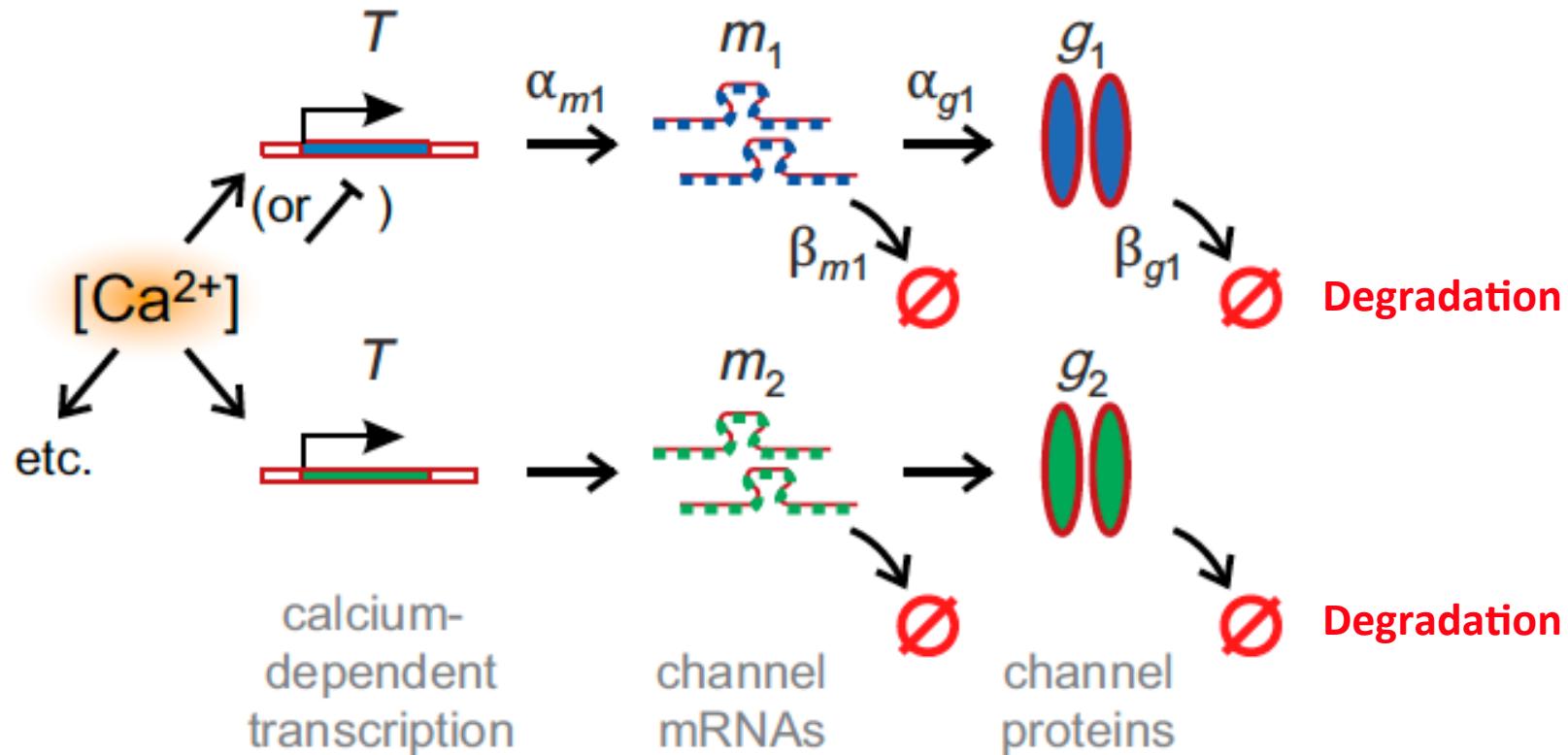
Update within the central dogma of molecular biology

Cell Types, Network Homeostasis, and Pathological Compensation from a Biologically Plausible Ion Channel Expression Model

Timothy O'Leary,^{1,*} Alex H. Williams,¹ Alessio Franci,^{2,3} and Eve Marder^{1,*}

Neuron 82, 809–821, May 21, 2014

Update within the central dogma of molecular biology



$$\dot{T} = \alpha_T([Ca^{2+}]) - \beta_T$$

$$\text{If } \alpha_T([Ca^{2+}]) = \alpha_T \cdot [Ca^{2+}]$$

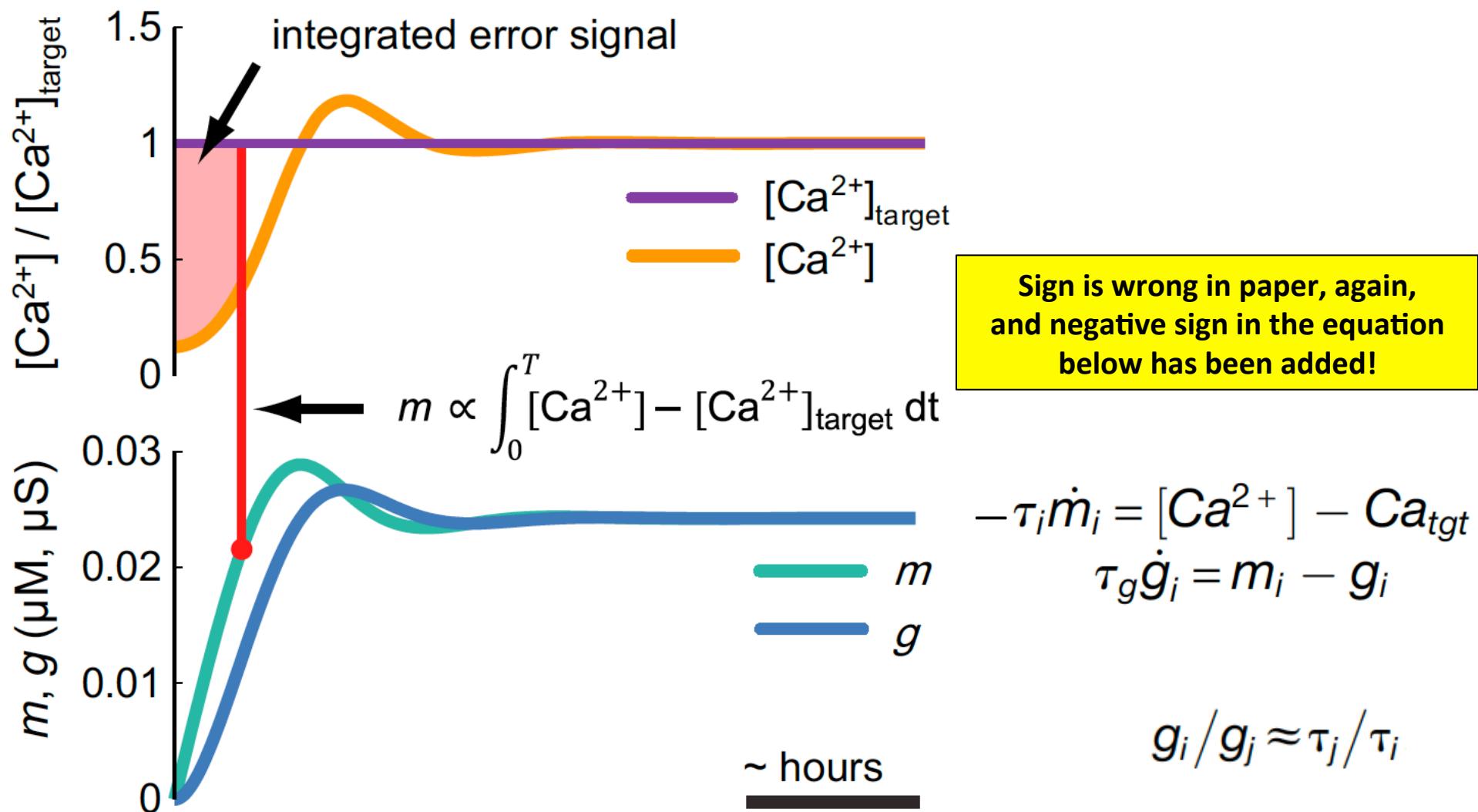
$$\text{Then } T = \int (\alpha_T \cdot [Ca^{2+}] - \beta_T) dt = \alpha_T \int ([Ca^{2+}] - Ca_{tgt}) dt$$

$$Ca_{tgt} = \beta_T / \alpha_T$$

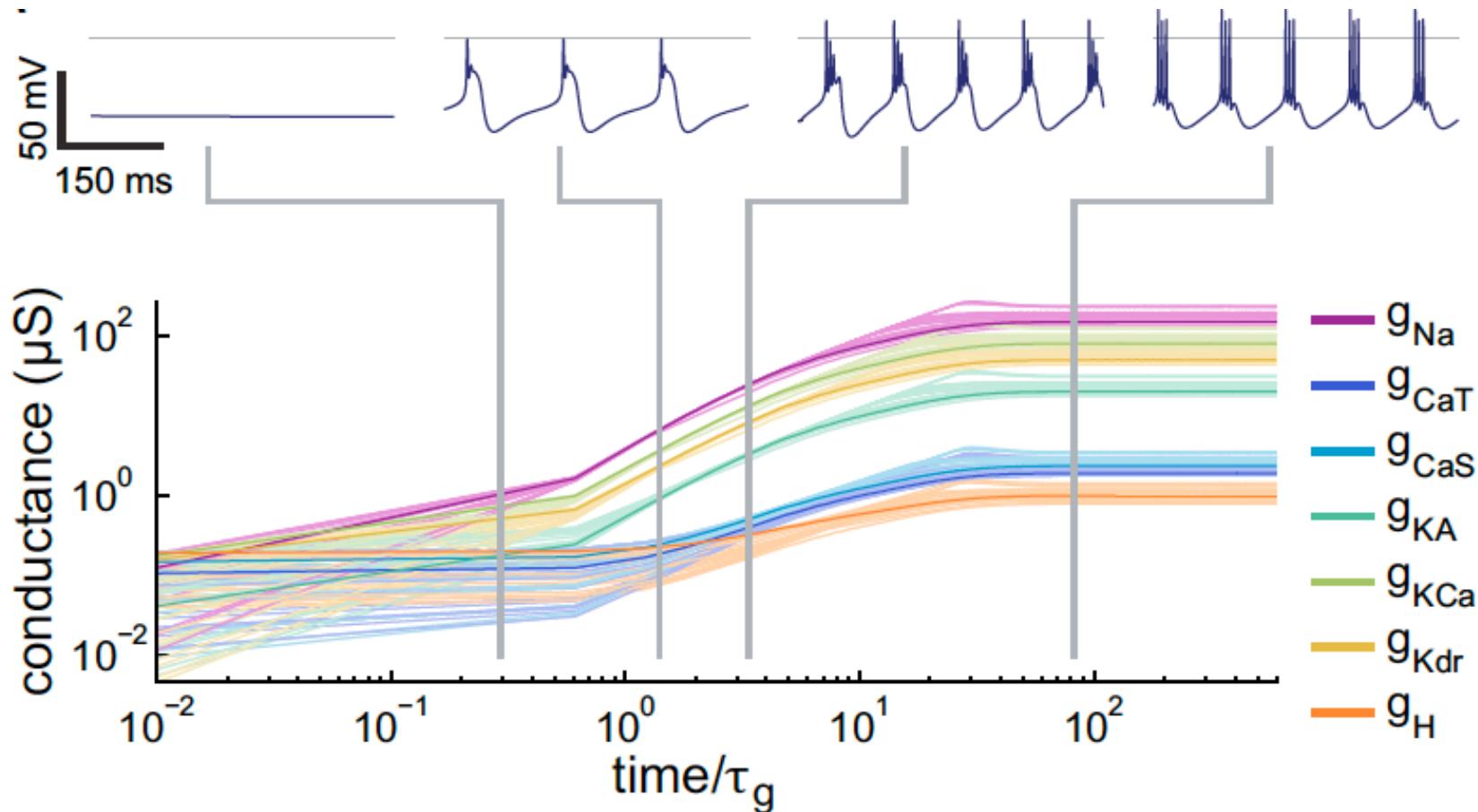
The transcription factor T is considered to be driven by the integral of the difference between the actual calcium and a target calcium

Update within the central dogma of molecular biology

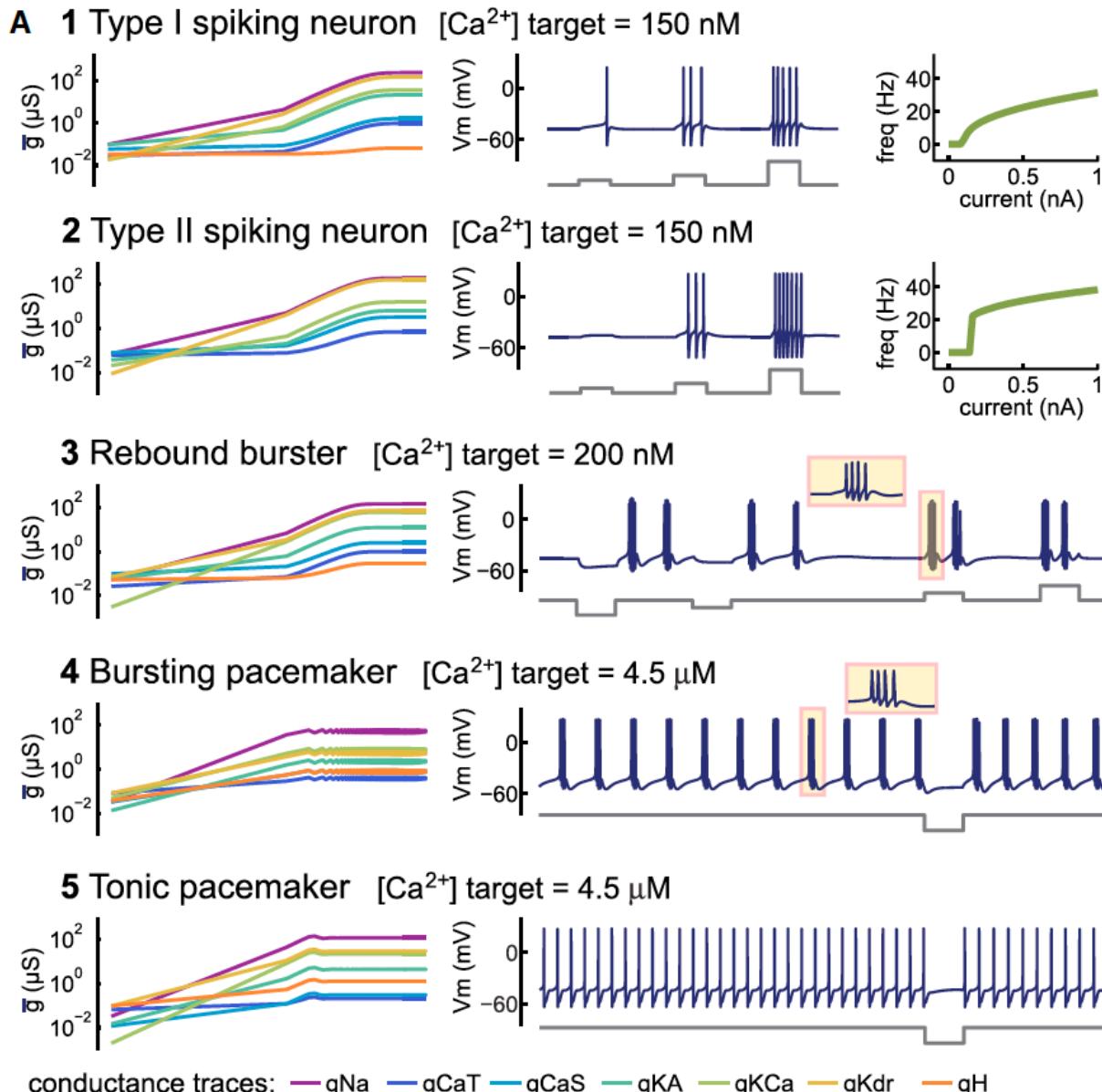
This error signal between observed and target calcium drives mRNA and protein formation



The temporal evolution of the different channels, and the consequent changes in firing rates



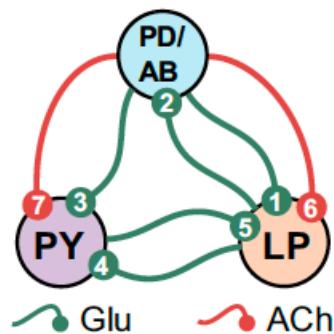
Different types of firing patterns can be designed within the same framework just by altering the target calcium!



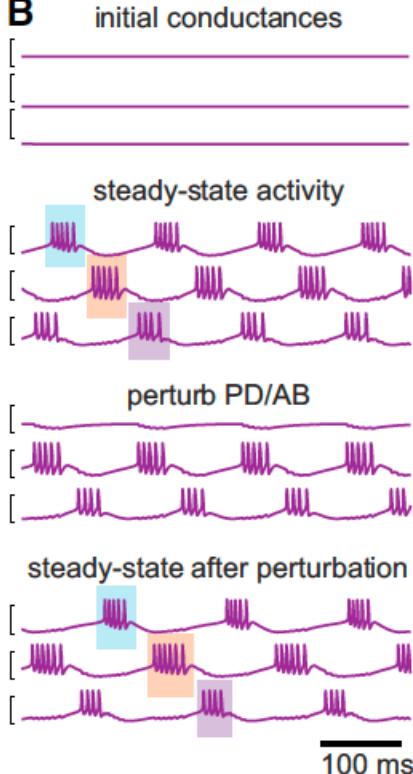
Add synaptic conductances also and make a network!

Self-assembling self-regulating CPG network!

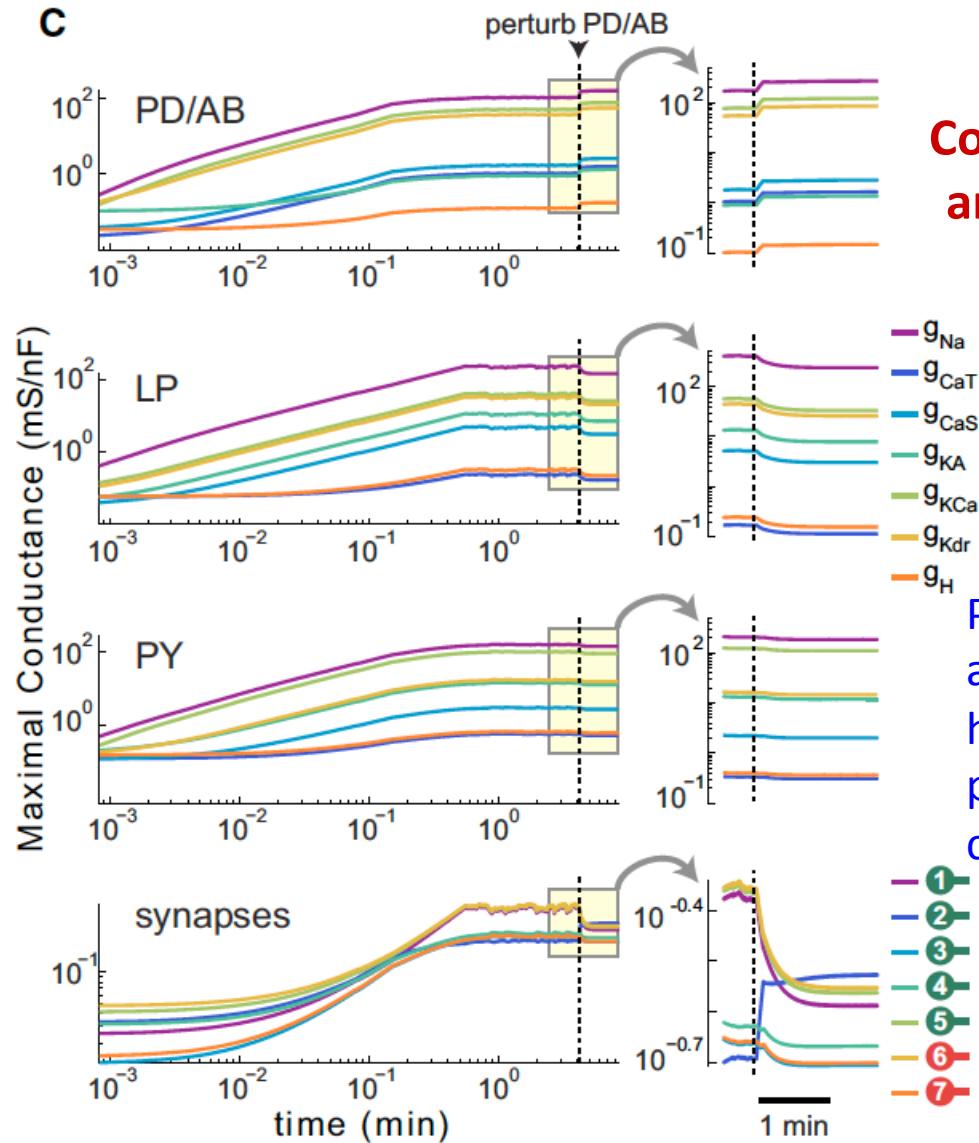
A



B



C



Coexistence of synaptic
and intrinsic plasticity

Perturbation of network
activity by addition of a
hyperpolarizing (reversal
potential = -80 mV)
conductance to PD

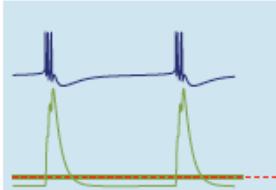
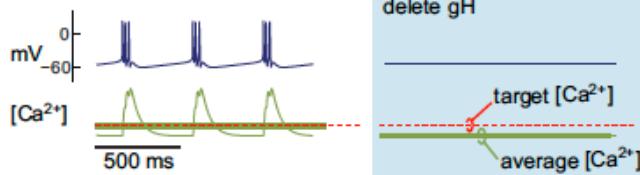
- 1
- 2
- 3
- 4
- 5
- 6
- 7

'wildtype'

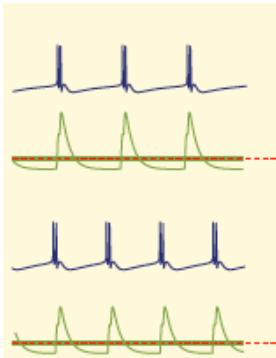
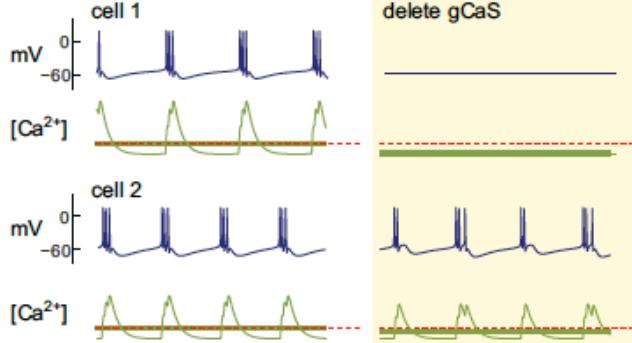
acute KO

compensated KO

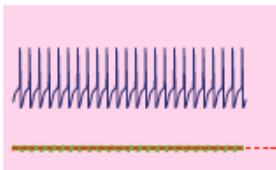
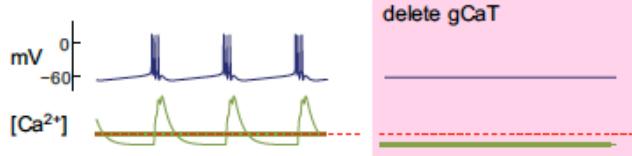
A Sensitivity to deletion, compensation restores function



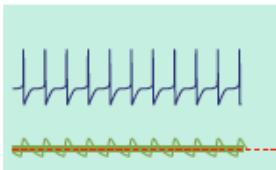
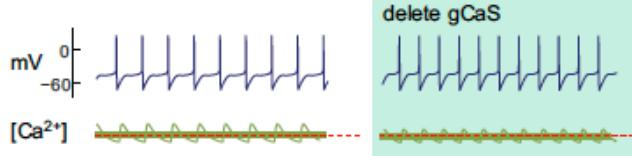
B Population variability in sensitivity to deletion, compensation preserves function



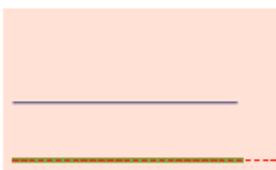
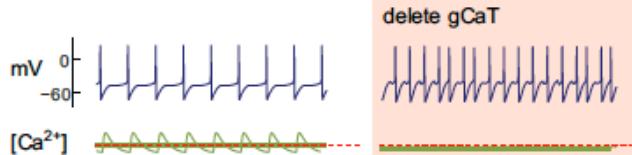
C Sensitivity to deletion, compensation is pathological



D Robustness to deletion, compensation preserves function



E Robustness to deletion, compensation is pathological



Activity-Dependent Regulation Can Be Compensatory or Pathological

Summary and Conclusions

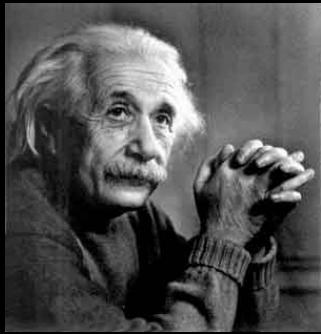
There are phenomenological models for synaptic plasticity of different complexities: abstract rules, calcium-dependent rules, STDP rules, etc.

Rules for plasticity in HCN channels can help maintenance of firing rate homeostasis and enable stability in synaptic learning

The important thing to account for in plasticity modeling is the ubiquitous nature of plasticity: Plasticity has to cover **ALL** the different components that are changing, not just one of them of our choice!!

Some open questions in plasticity modeling:

- All these are about homeostasis of certain functions (CPG, firing rate, calcium, plasticity, etc.)! But the important question is how to code new incoming information while maintaining homeostasis AND ensuring that the homeostatic process does not disturb the new code!
- How to construct rules for the several ion channels that express in neuronal dendrites and assess how they contribute to neural coding and homeostasis? How do these different forms of plasticity in such a dendritic tree come together synergistically to robustly encode new information AND maintaining homeostasis?

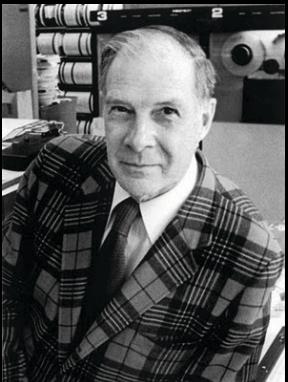
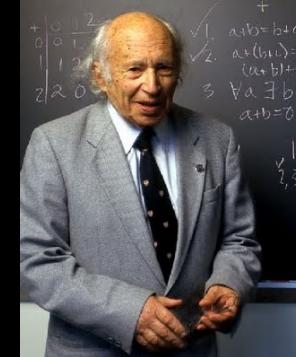


How can it be that mathematics, being after all a product of human thought which is independent of experience, is so admirably appropriate to the objects of reality?

—Albert Einstein

There is only one thing which is more unreasonable than the unreasonable effectiveness of mathematics in physics, and this is the unreasonable ineffectiveness of mathematics in biology.

—Israel Gelfand



The purpose of computing is insight, not numbers!

—Richard Hamming

Experiments without theory are blind.
Theory without experiments is empty.