Learning and memory with complex synaptic plasticity

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What is a synapse?

Experimentalists

Theorists

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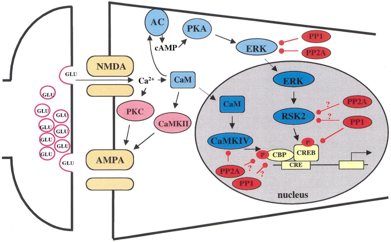
Experimentalists

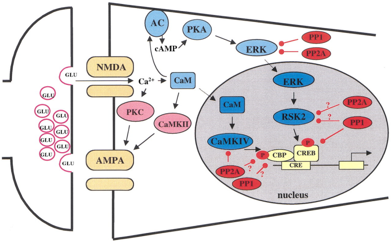
Theorists



[Klann (2002)]

What is a synapse?

Experimentalists



[Klann (2002)]

Theorists

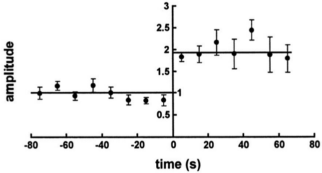
$$W_{ij}$$

Storage capacity of synaptic memory

Hopfield, perceptron have capacity $\propto N$, ($\#$ synapses).

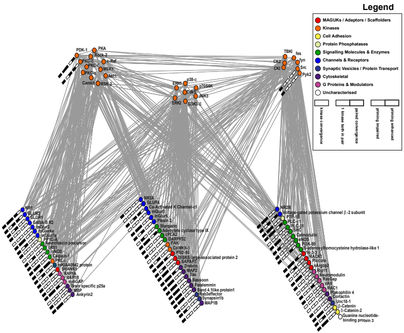
Assumes unbounded analogue synapses

With discrete, finite synapses:
$\implies$ memory capacity $\sim \mathcal{O}(\log N)$.
[Amit and Fusi (1992), Amit and Fusi (1994)]

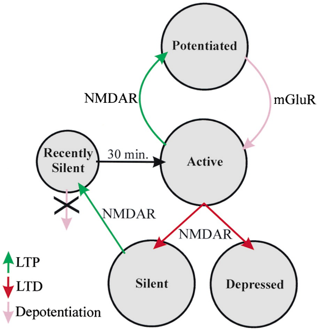


[Petersen et al. (1998), O'Connor et al. (2005)]

Synapses are complex



[Coba et al. (2009)]



[Montgomery and Madison (2002)]

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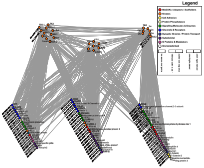

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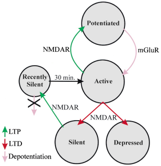
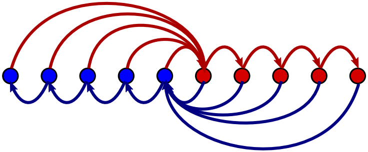


[Montgomery and Madison (2002)]

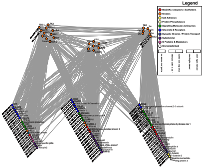
Cascade model



Capacity $\propto N^{2/3}$.

[Fusi et al. (2005)]

Synapses are complex



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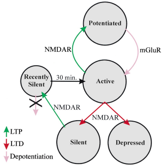

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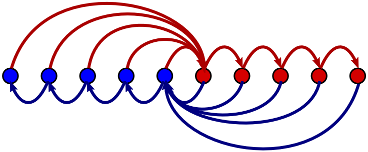


Capacity $\propto N^{2/3}$. [Fusi et al. (2005)]

Capacity $\propto N$. [Benna and Fusi (2016)]

My approach

We want to study the structure-function relationship of biological processes.

Not trying to build a model for "X".

Instead, we study a broad class of models to find:

- $\rightarrow$ underlying mechanisms and principles.
- $\rightarrow$ trade-offs between aspects of performance (e.g. learning vs. memory).
- $\rightarrow$ properties of models that best manage these trade-offs.

Outline

1. Learning with enhanced plasticity
   - Effects of enhanced plasticity on cerebellar learning
   - Synaptic models of cerebellar learning
   - Learning outcomes of mice and models
2. Memory over different timescales
   - Quantifying memory quality
   - Frontiers of memory
   - Implications of memory limits
3. Designing experiments

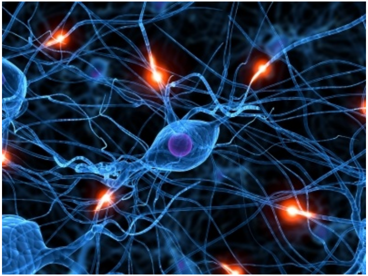
Section 1

Learning with enhanced plasticity

"A saturation hypothesis to explain both enhanced and impaired learning with enhanced plasticity", TDB Nguyen-Vu, GQ Zhao, S Lahiri, RR Kimpo, H Lee, S Ganguli, CJ Shatz, JL Raymond.
eLife, 6:e20147, (Feb., 2017).

Benefits of enhanced plasticity?

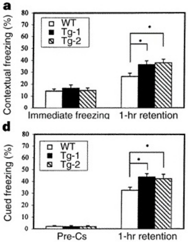
Learning requires synaptic plasticity.



Can we enhance learning by enhancing plasticity?

Enhanced plasticity *can* enhance learning

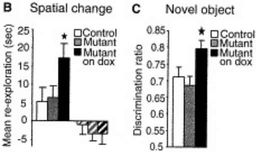
Overexpress NR2B



Fear conditioning

[Tang et al. (1999)]

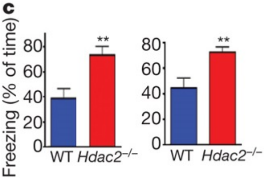
Inhibit CN



Novel object recog.

[Malleret et al. (2001)]

Knockout Hdac2

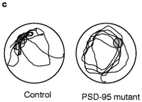


Fear conditioning

[Guan et al. (2009)]

Enhanced plasticity can *impair* learning

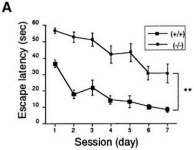
Mutate PSD-95



Water maze

[Migaud et al. (1998)]

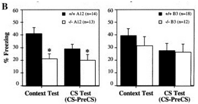
Knockout PTPδ



Water maze

[Uetani et al. (2000)]

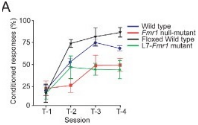
Delete Tmod2



Fear cond.

[Cox et al. (2003)]

Knockout FMR1



Eyeblink

[Koekkoek et al. (2005)]

also: [Hayashi et al. (2004), Rutten et al. (2008)]

Overview

Sometimes enhanced plasticity $\rightarrow$ enhanced learning.
Sometimes enhanced plasticity $\rightarrow$ impaired learning.

Why? How? When?

Overview

Sometimes enhanced plasticity $\rightarrow$ enhanced learning.
Sometimes enhanced plasticity $\rightarrow$ impaired learning.

Why? How? When?

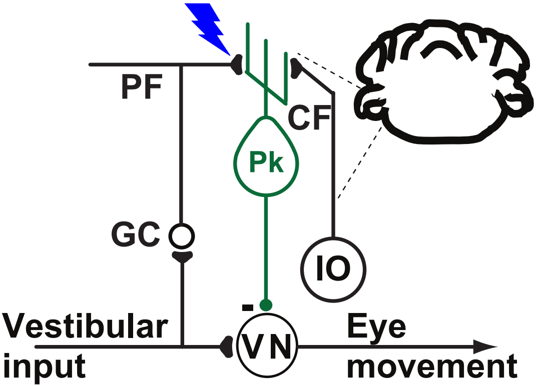
Mice with enhanced cerebellar plasticity can show both impaired and enhanced learning.

Simple synapses cannot explain behaviour. Complex synapses are required.
$\rightarrow$ predictions for synaptic physiology.

Vestibulo-Occular Reflex training

VOR Increase Training

VOR Decrease Training

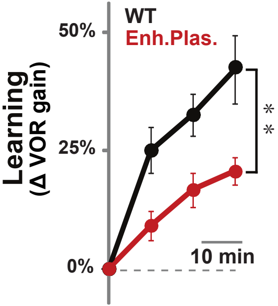


VOR increase:	LTD in PF-Pk synapses.
VOR decrease:	different mechanism, also reverses LTD in PF-Pk.

[Marr (1969), Albus (1971), Ito (1972)]

Enhanced plasticity impairs learning

Expectation: enhanced LTD → enhanced learning.



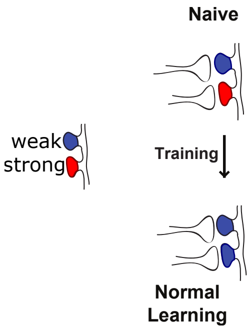
Experiment: enhanced plasticity → impaired learning.

Knockout of MHC-I K^bD^b molecules in PF-Pk synapses
→ lower threshold for LTD

[McConnell et al. (2009)]

Depletion hypothesis

Learning rate $\sim$ intrinsic plasticity rate $\times$ # synapses available for LTD.



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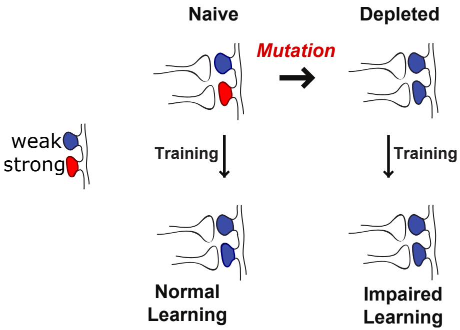

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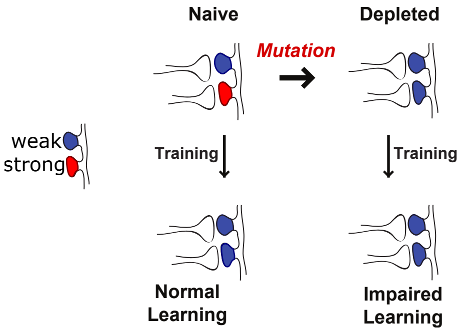
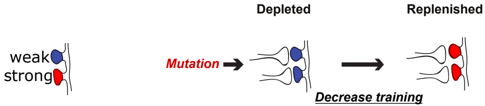


Question 1: depletion effect competes with enhanced intrinsic plasticity.
When is depletion effect stronger?

Replenishment by reverse-training

Replenishment by reverse-training



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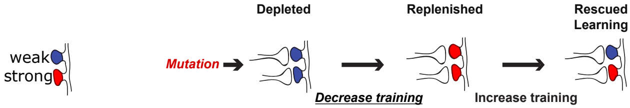

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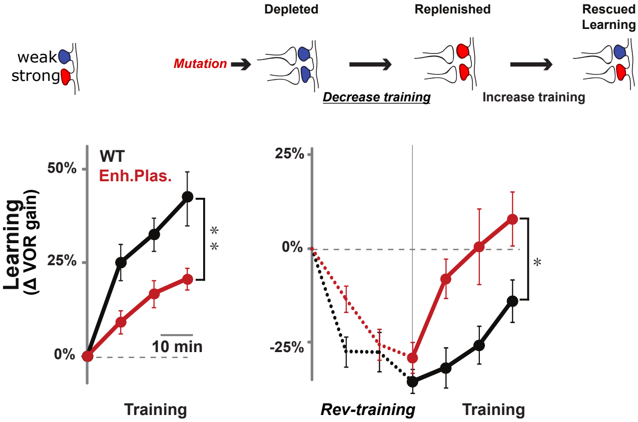

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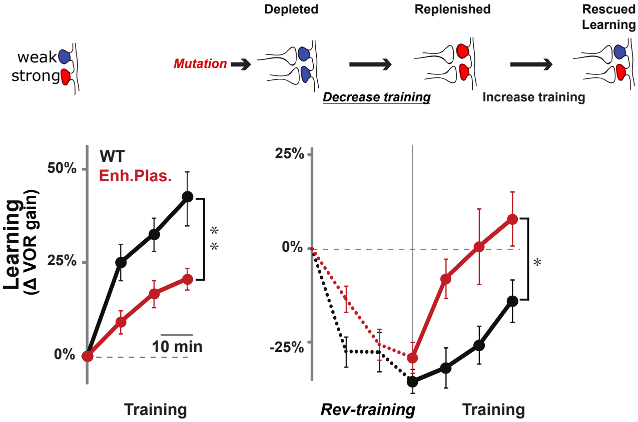
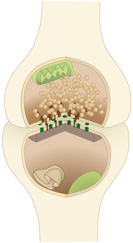


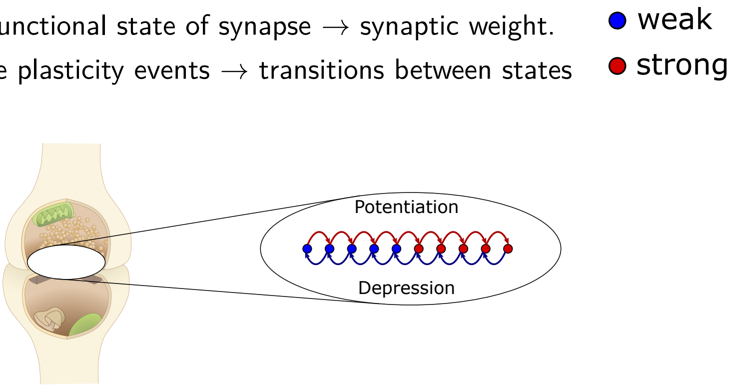
Question 2: When does enhanced plasticity impair learning?

Models of complex synaptic dynamics



Models of complex synaptic dynamics

- Internal functional state of synapse → synaptic weight.
- Candidate plasticity events → transitions between states



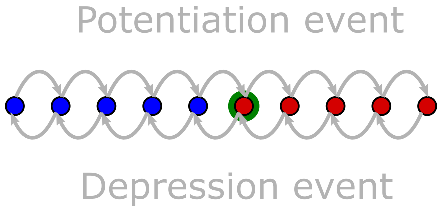
States: NMDAR subunit composition, CaMK II autophosphorylation, activating PKC, p38 MAPK,...

[Fusi et al. (2005), Fusi and Abbott (2007), Barrett and van Rossum (2008)]
[Smith et al. (2006), Lahiri and Ganguli (2013)]

Models of complex synaptic dynamics

- Internal functional state of synapse → synaptic weight.
- Candidate plasticity events → transitions between states

● weak
● strong



Models of complex synaptic dynamics

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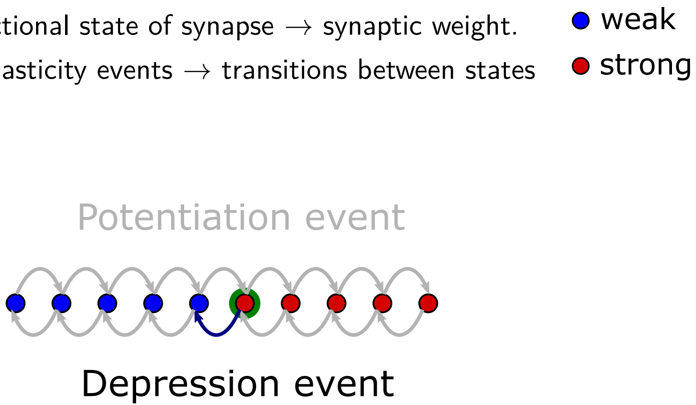

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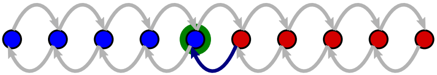
Potentiation event



Depression event

Models of complex synaptic dynamics

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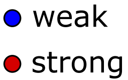

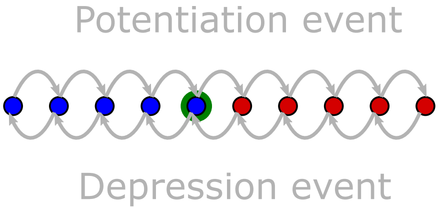

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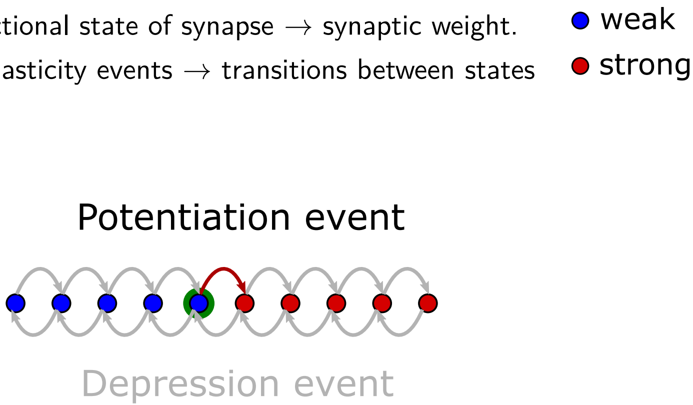

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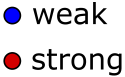

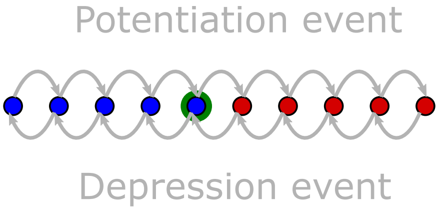

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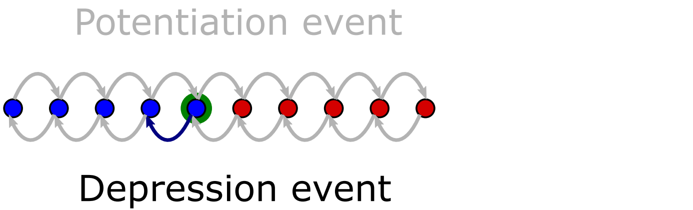

Metaplasticity: change propensity for plasticity
(independent of change in synaptic weight).

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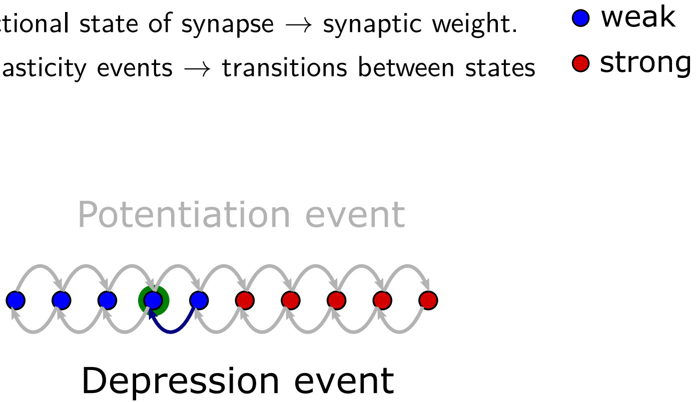

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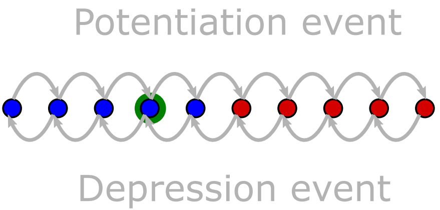

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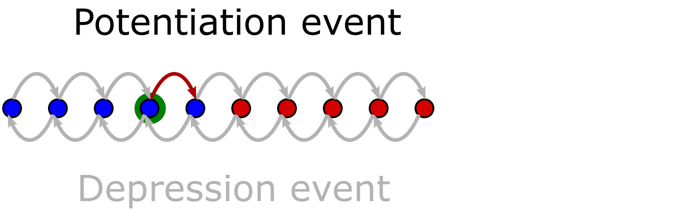

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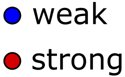
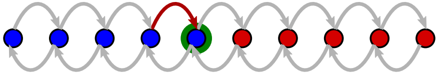


Potentiation event



Depression event

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weak

strong

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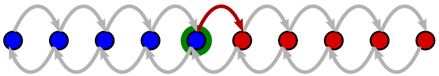

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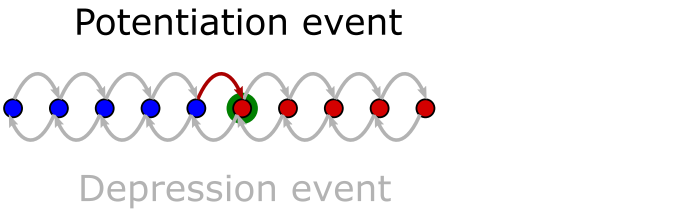

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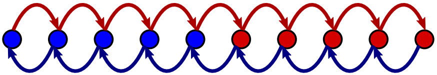

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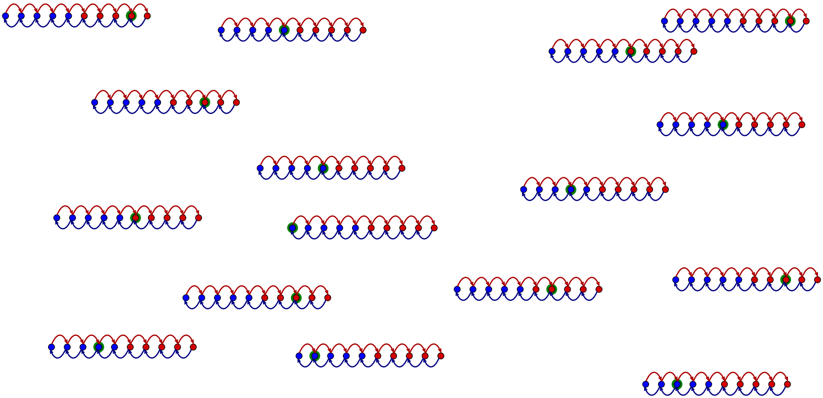
Modelling VOR experiments



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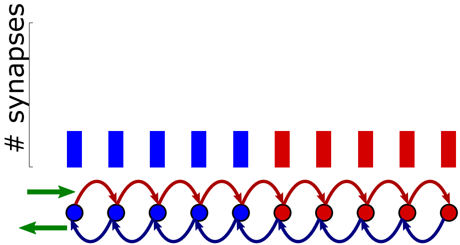
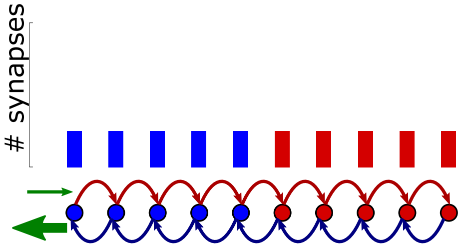


Modelling VOR experiments

PF-Pk LTD $\rightarrow$ VOR increase



Training: different CF activity $\Longrightarrow$
change frequency of pot/dep events.

Modelling VOR experiments

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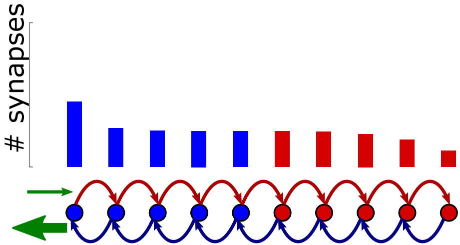

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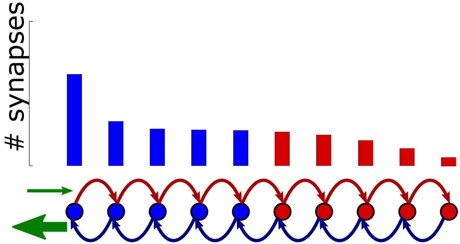

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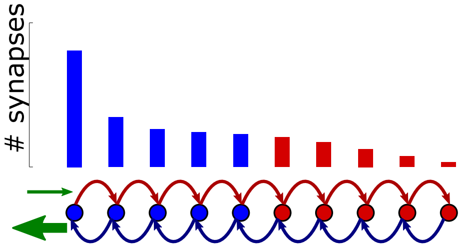

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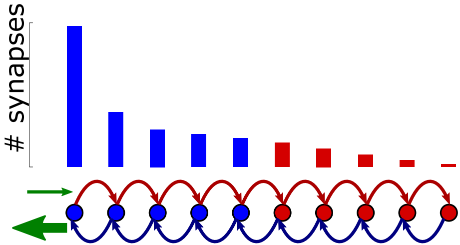

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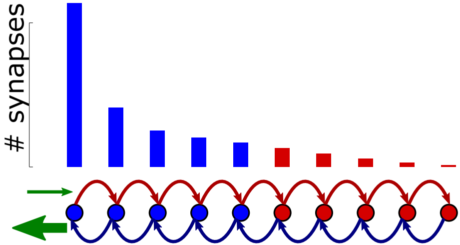

Training: different CF activity $\implies$
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Learning: decrease in average synaptic weight.

Modelling VOR experiments

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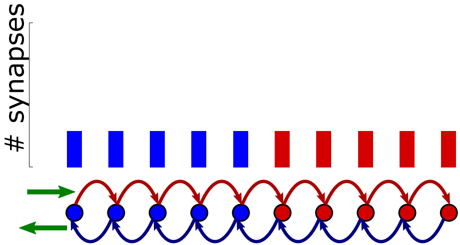

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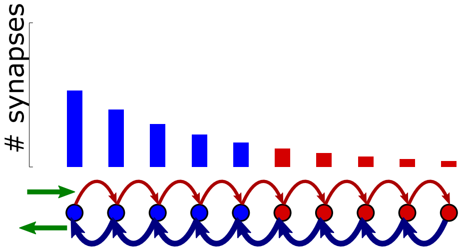
change frequency of pot/dep events.

Learning: decrease in average synaptic weight.

Mutation: lower threshold for LTD $\Longrightarrow$
increase transition probability for depression events.

Modelling VOR experiments

PF-Pk LTD $\rightarrow$ VOR increase



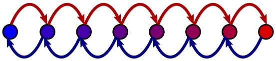
Training: different CF activity $\Longrightarrow$
change frequency of pot/dep events.

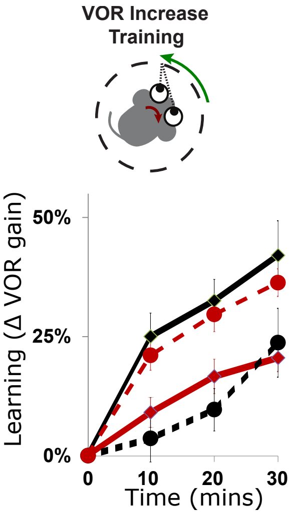
Learning: decrease in average synaptic weight.

Mutation: lower threshold for LTD $\Longrightarrow$
increase transition probability for depression events.

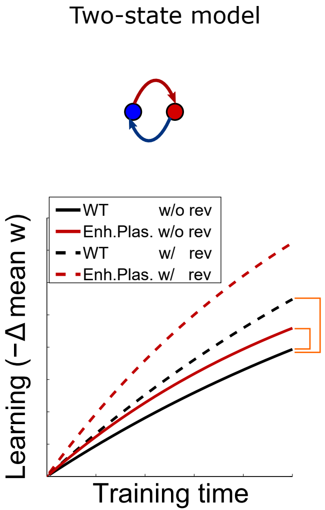
Simple synapses cannot explain the data

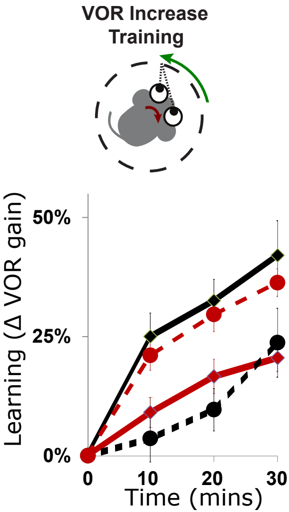
Multistate synapse





Simple synapses cannot explain the data





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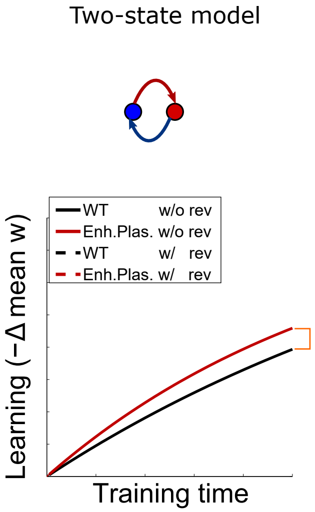

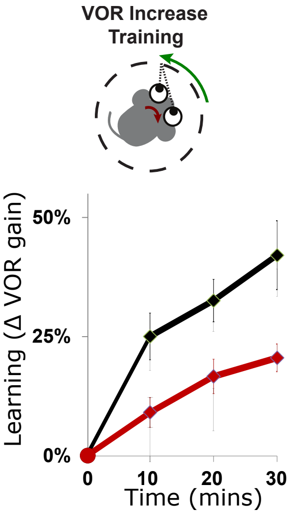

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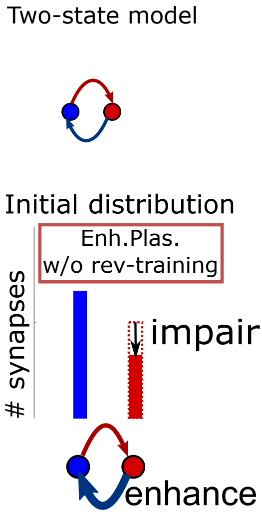

depletion effect

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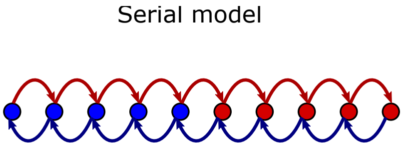
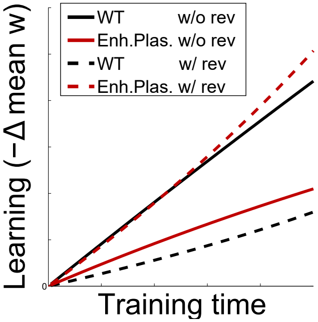
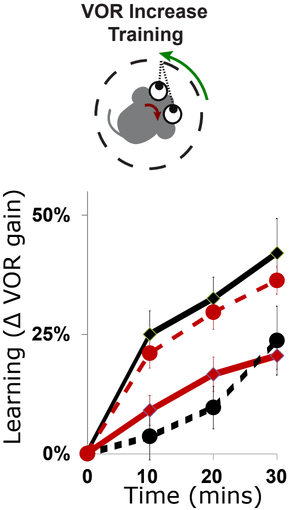
enhanced plasticity

$\Longrightarrow$ enhanced learning

Complex metaplastic synapses can explain the data

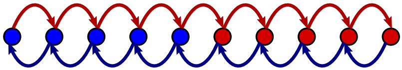


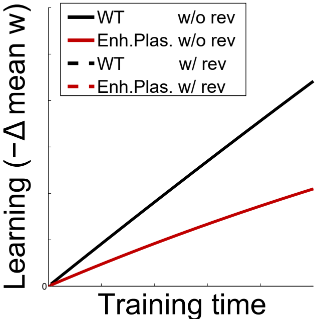




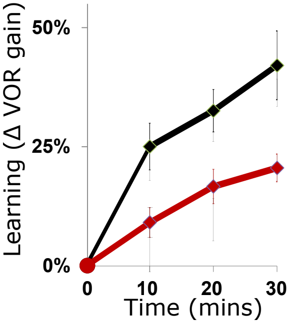
Complex metaplastic synapses can explain the data

Serial model





VOR Increase Training



Complex metaplastic synapses can explain the data

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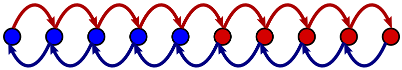

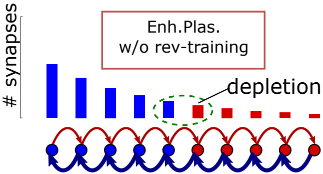

amplified depletion

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enhanced plasticity

$\Longrightarrow$ impaired learning

Complex metaplastic synapses can explain the data

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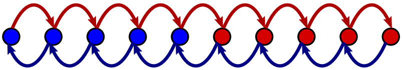
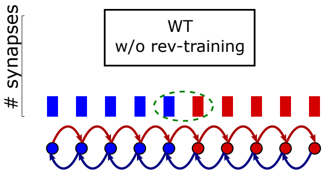
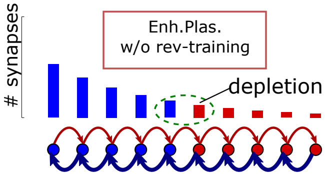
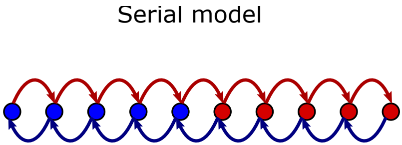
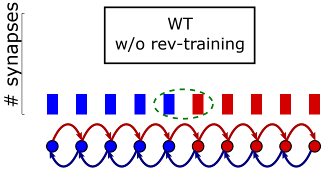






Complex metaplastic synapses can explain the data





start in: labile states

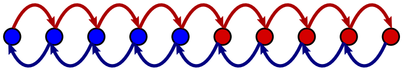
$\Downarrow$

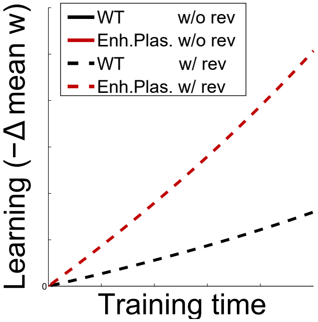
enhanced plasticity

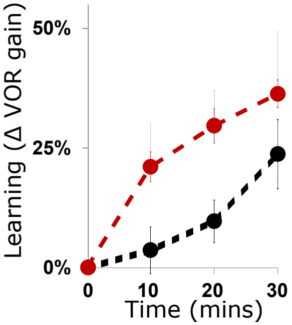
$\Longrightarrow$ impaired learning

Complex metaplastic synapses can explain the data

Serial model

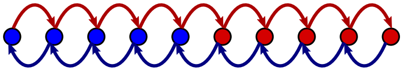


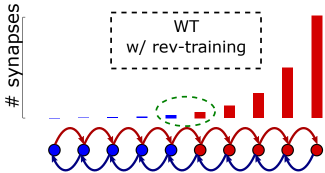


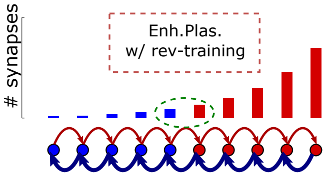


Complex metaplastic synapses can explain the data

Serial model

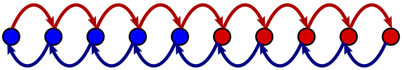


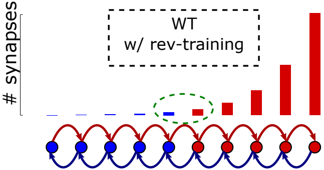




Complex metaplastic synapses can explain the data

Serial model





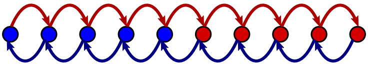
start in: stubborn states

$\Downarrow$

enhanced plasticity

$\Longrightarrow$ enhanced learning

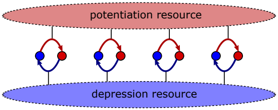
Essential features of successful models

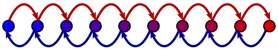


The success of the serial model relies on two features:

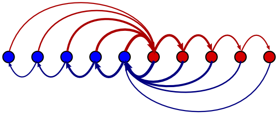
- Complexity - needed for depletion to dominate enhanced plasticity,
- Stubbornness - repeated potentiation impairs subsequent depression.

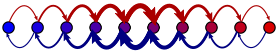
Fail:





Succeed:





Conclusions

- In VOR learning, depending on prior experience:
  Enhanced plasticity $\rightarrow$ enhance/impair learning.
- enhanced LTD vs. depletion $\rightarrow$ learning outcome.
- Predictions for synaptic physiology:
  Complexity: necessary to amplify depletion.
  Stubbornness: repeated potentiation impairs subsequent depression.
- We used behaviour to constrain the dynamics of synaptic plasticity.

Section 2

Memory over different timescales

"A memory frontier for complex synapses", S Lahiri and S Ganguli.
Adv. Neural Inf. Process. Syst. 26, pp. 1034–1042., (2013).

Storage capacity of synaptic memory

Hopfield, perceptron have capacity $\propto N$, (# synapses).

Assumes unbounded analog synapses

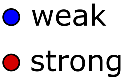
With discrete, finite synapses: $\implies$ memory capacity $\sim \mathcal{O}(\log N)$.
[Amit and Fusi (1992), Amit and Fusi (1994)]

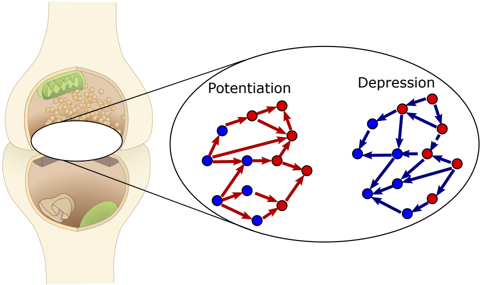
New memories overwrite old $\implies$ stability-plasticity dilemma.

Models of complex synaptic dynamics

There are N identical synapses with M internal functional states.

- Internal functional state of synapse $\to$ synaptic weight.
- Candidate plasticity events $\to$ transitions between states



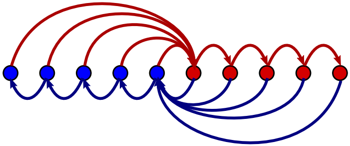


States: #AMPAR, #NMDAR, NMDAR subunit composition,
CaMK II autophosphorylation, activating PKC, p38 MAPK,...

[Fusi et al. (2005), Fusi and Abbott (2007), Barrett and van Rossum (2008)]

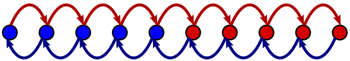
Specific models of complex synaptic dynamics

Cascade model



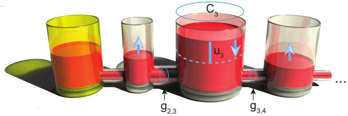
[Fusi et al. (2005)]

Serial model

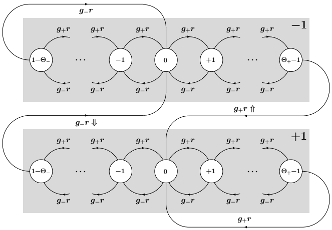


[Ben-Dayan Rubin and Fusi (2007)]

[Leibold and Kempter (2008)]

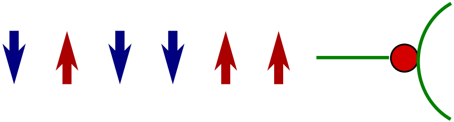


[Benna and Fusi (2016)]

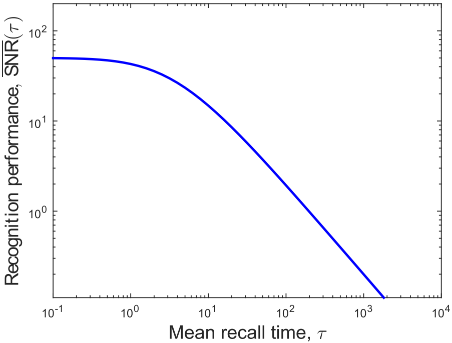


[Elliott (2011)]

Synaptic memory curves

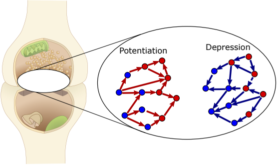


Synapses store a sequence of memories.
Recognition memory performance described by SNR.

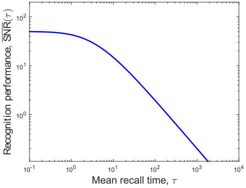


General principles relating structure and function?

Synaptic structure



Synaptic function

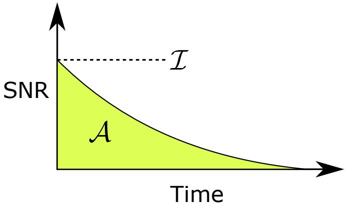


- What are the fundamental limits of memory?
- Which models achieve these limits?
- What are the theoretical principles behind the optimal models?

Upper bounds on measures of memory

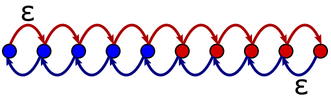
Initial SNR:

$$\mathcal{I} = \mathrm{SNR}(0) = \sum_a \mathcal{I}_a \leq \sqrt{N}.$$



Area under curve:

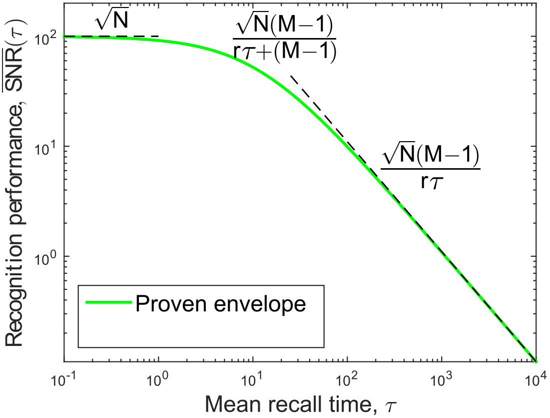
$$\mathcal{A} = \int_0^\infty \mathrm{SNR}(t)\,\mathrm{d}t = \sum_a \mathcal{I}_a \tau_a \leq \sqrt{N}(M-1)/r.$$



[Lahiri and Ganguli (2013)]

Proven envelope: memory frontier

Upper bound on memory curve at *any* timescale.



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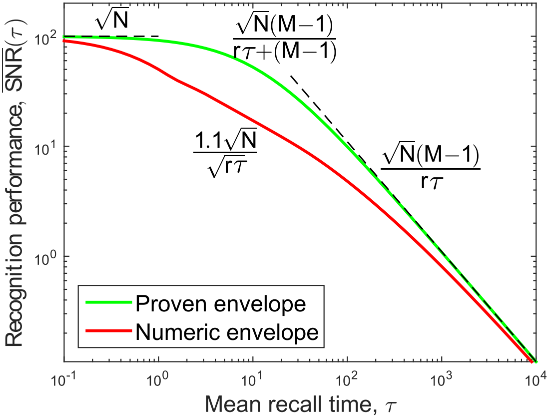
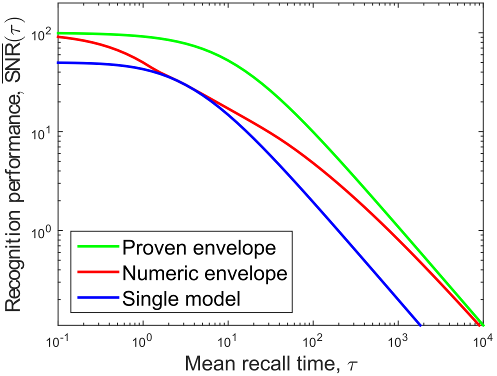
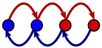


Models that maximize memory for one timescale





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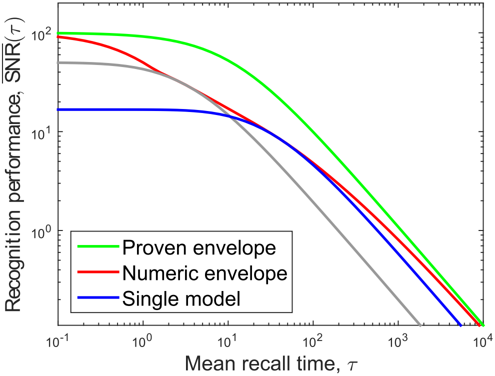

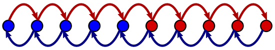

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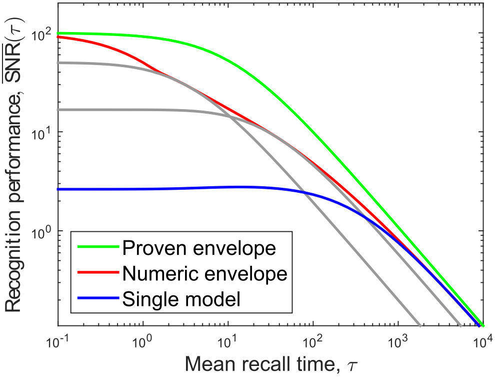
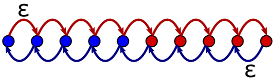
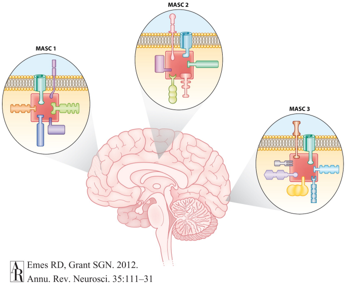




Synaptic diversity and timescales of memory

Different synapses have different molecular structures.



[Emes and Grant (2012)]

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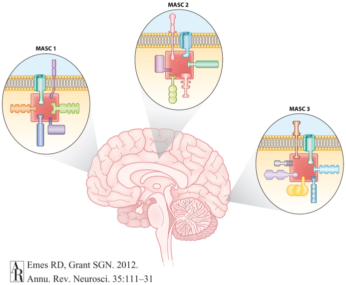
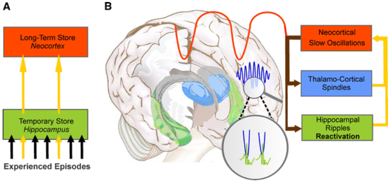


[Emes and Grant (2012)]

Memories stored in different places for different timescales

[Squire and Alvarez (1995)]

[McClelland et al. (1995)]



[Born and Wilhelm (2012)]

Also: Cerebellar cortex $\rightarrow$ nuclei.

[Attwell et al. (2002)]

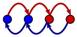
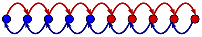
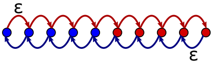
[Cooke et al. (2004)]

Synaptic structure and function: general principles

Real synapses limited by molecular building blocks.
Evolution had larger set of priorities.

What can we conclude?

Short timescale $\longrightarrow$ Moderate timescale $\longrightarrow$ Long timescale

 $\longrightarrow$  $\longrightarrow$ 

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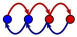
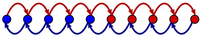
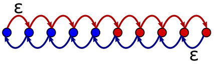
 $\longrightarrow$  $\longrightarrow$ 

short topology $\longrightarrow$ long topology

Synaptic structure and function: general principles

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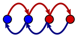
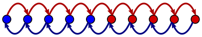
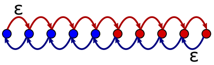
What can we conclude?

Short timescale $\longrightarrow$ Moderate timescale $\longrightarrow$ Long timescale

 $\longrightarrow$  $\longrightarrow$ 

short topology $\longrightarrow$ long topology

deterministic synapse $\longrightarrow$ stochastic synapse

Conclusions

- We have formulated a general theory of learning and memory with complex synapses.
- We find a memory envelope: a single curve that cannot be exceeded by the memory curve of *any* synaptic model.
- We understood which types of synaptic structure are useful for storing memories for different timescales.
- We studied more than a single model. We studied *all possible models*, to extract general principles relating synaptic structure to function

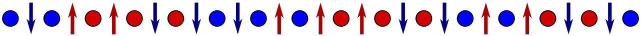
Experimental tests?

Traditional experiments:

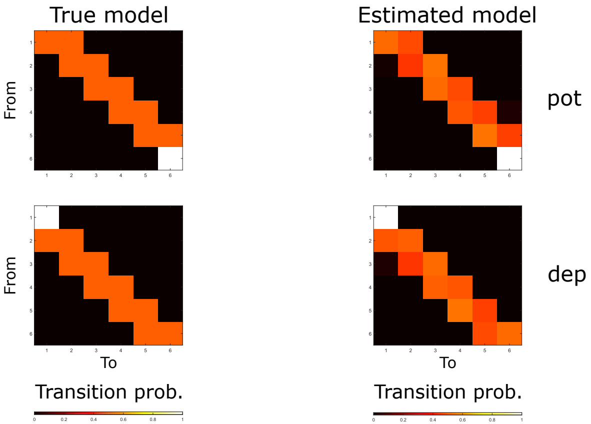
Experimental tests?

Traditional experiments:

To fit a model: long sequence of small plasticity events.
Observe the changes in synaptic efficacy.



Simulated experiment



Problem: need *long* sequences.
Whole cell patch of postsynaptic neuron $\rightarrow$ Ca washout.

Experimental problems

- Need single synapses.
- Need long sequences of plasticity events.
- Need to control types of candidate plasticity events.
- Need to measure synaptic efficacies.

When we patch the postsynaptic neuron $\rightarrow$ Ca washout.

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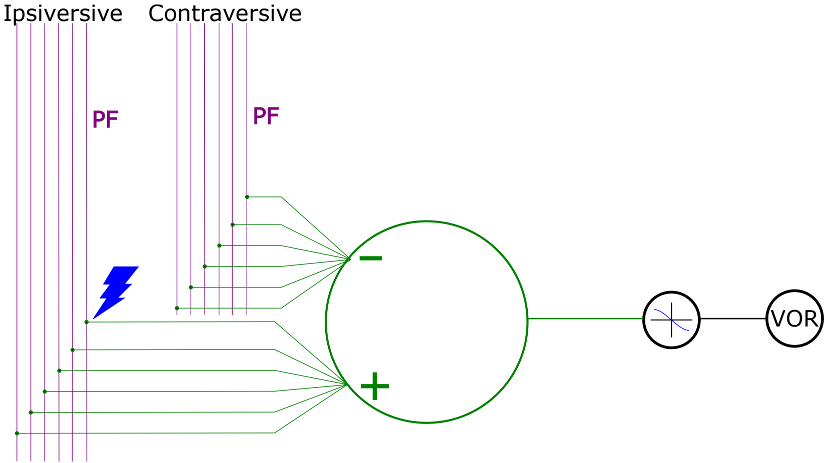
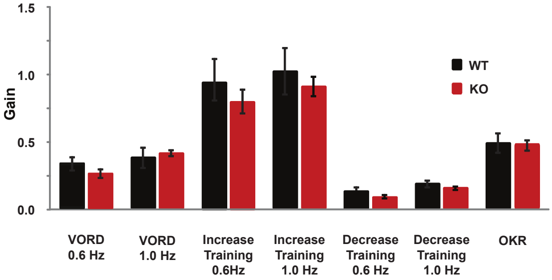
Summary

- Internal dynamics of synaptic plasticity
  $\rightarrow$ understand learning and memory.
- Behaviour $\rightarrow$ subcellular dynamics of synapses.
- Why & when enhanced plasticity $\rightarrow$ enhanced/impaired learning.
- Memory envelope: cannot be exceeded by *any* model's memory curve.
- Which synaptic structures are useful for different memory timescales.
- Not just a single model, *all possible models*
  $\rightarrow$ general principles relating synaptic structure to function.

Model of circuit

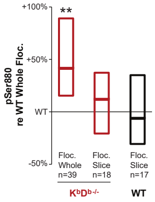


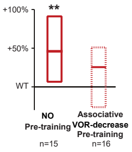
Baseline



1.5
1.0
0.5
0.0
Gain
WT
KO
VORD 0.6 Hz
VORD 1.0 Hz
Increase Training 0.6Hz
Increase Training 1.0 Hz
Decrease Training 0.6 Hz
Decrease Training 1.0 Hz
OKR

Evidence: level of depression





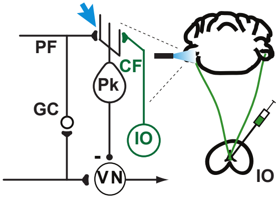
Basal level of GluR2 phosphorylation at serine 880 in AMPA receptor.

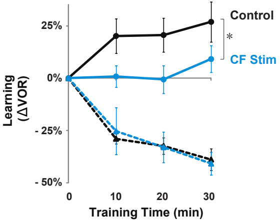
Biochemical signature of PF-Pk LTD.

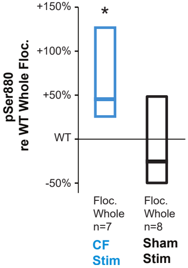
Shows that # depressed synapses in flocculus is larger in KO than WT.

Evidence: saturation by CF stimulation

Use Channelrhodopsin to stimulate CF →increase LTD in PF-Pk synapses
→simulate saturation in WT.

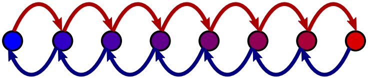




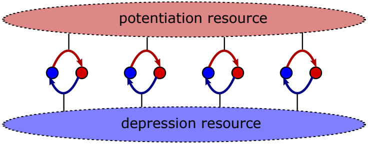


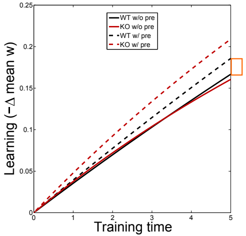
Other models that fail

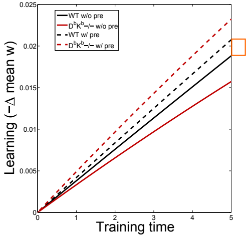
Multistate synapse



Pooled resource model



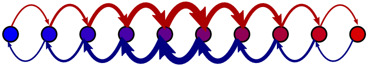


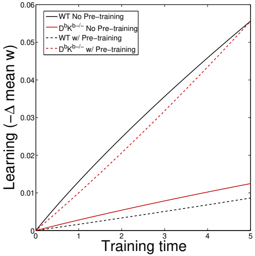


[Amit and Fusi (1994)]

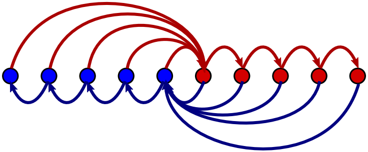
Other models that work

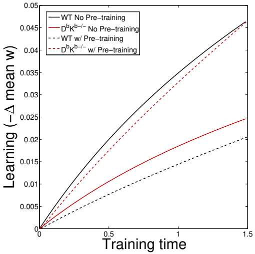
Non-uniform multistate model





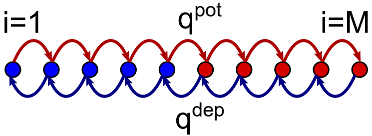
Cascade model





[Fusi et al. (2005)]

Mathematical explanation



Serial synapse: $\pi_i \sim \mathcal{N} \left(\frac{q^{\text{pot}}}{q^{\text{dep}}} \right)^i$.

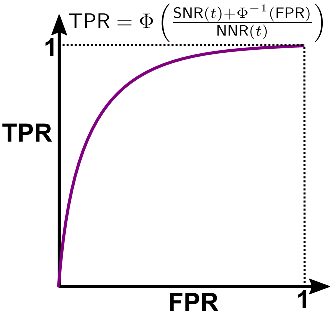
Learning rate $\sim \pi_{M/2} \left(\frac{q^{\text{dep}}}{q^{\text{pot}}} \right) = \mathcal{N} \left(\frac{q^{\text{pot}}}{q^{\text{dep}}} \right)^{\frac{M}{2}-1}$.

For $M > 2$: larger $q^{\text{dep}} \implies$ slower learning.

For $M = 2$: larger $q^{\text{dep}} \implies$ larger $\mathcal{N} \implies$ faster learning.

Quantifying memory quality

Test if $\vec{w}_{\text{ideal}} \cdot \vec{w}(t) \gtrless \theta$?



$$\mathrm{SNR}(t) = \frac{\langle \vec{w}_{\text{ideal}} \cdot \vec{w}(t) \rangle - \langle \vec{w}_{\text{ideal}} \cdot \vec{w}(\infty) \rangle}{\sqrt{\mathrm{Var}(\vec{w}_{\text{ideal}} \cdot \vec{w}(\infty))}},$$

$$\overline{\mathrm{SNR}}(\tau) = \int \mathrm{d}\tau \, \frac{\mathrm{e}^{-t/\tau}}{\tau} \, \mathrm{SNR}(t).$$

$$\mathrm{NNR}(t) = \sqrt{\frac{\mathrm{Var}(\vec{w}_{\text{ideal}} \cdot \vec{w}(t))}{\mathrm{Var}(\vec{w}_{\text{ideal}} \cdot \vec{w}(\infty))}}.$$

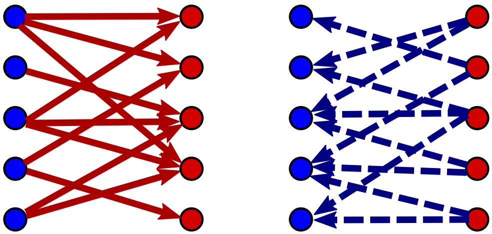
Also: KL divergence, Chernoff distance, . . .

Initial SNR as flux

Initial SNR is closely related to flux between strong & weak states

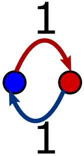
$$\mathrm{SNR}(0) \leq \frac{4\sqrt{N}}{r}\,\mathbf{\Phi}_{-+}.$$

Max when potentiation guarantees $\mathbf{w} \to +1$,
depression guarantees $\mathbf{w} \to -1$.



Two-state model

Two-state model equivalent to previous slide:

Transitions: 

$$\implies \mathrm{SNR}(t) = \sqrt{N}\,(4f^{\mathrm{pot}}f^{\mathrm{dep}})\,\mathrm{e}^{-rt}.$$

Maximal initial SNR:

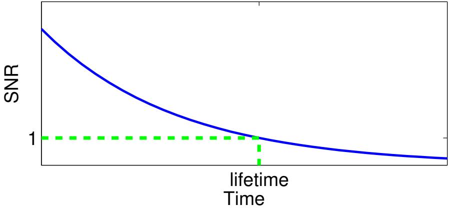
$$\mathrm{SNR}(0) \leq \sqrt{N}.$$

Area under memory curve

$$\mathcal{A} = \int_0^\infty \mathrm{d}t\ \mathrm{SNR}(t), \qquad \overline{\mathrm{SNR}}(\tau) \to \frac{\mathcal{A}}{\tau} \quad \text{as} \quad \tau \to \infty.$$

Area bounds memory lifetime:

$$\mathrm{SNR}(\text{lifetime}) = 1$$
$$\implies \quad \text{lifetime} < \mathcal{A}.$$



This area has an upper bound:

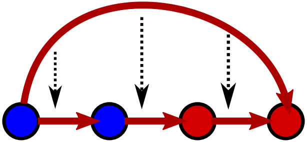
$$\mathcal{A} \leq \sqrt{N}(M-1)/r.$$

Saturated by a model with linear chain topology.

Proof of area bound

For any model, we can construct perturbations that

- preserve equilibrium distribution,
- increase area.



details

e.g. decrease "shortcut" transitions, increase bypassed "direct" ones.
Endpoint: linear chain

The area of this model is

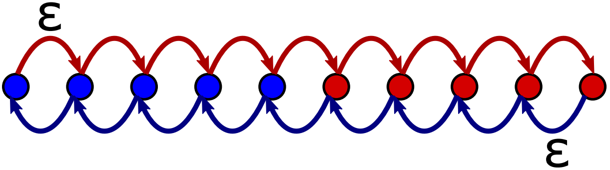
$$A = \frac{2\sqrt{N}}{r} \sum_k \pi_k \left| k - \langle k \rangle \right| .$$

Max: equilibrium probability distribution concentrated at both ends.

[Barrett and van Rossum (2008)]

Saturating model

Make end states "sticky"



Has long decay time, but terrible initial SNR.

$$\lim_{\varepsilon \to 0} A = \sqrt{N}(M-1)/r.$$

Technical detail: ordering states

Let $\mathbf{T}_{ij}$ = mean first passage time from state i to state j. Then:

$$\eta = \sum_j \mathbf{T}_{ij} \boldsymbol{\pi}_j,$$

is independent of the initial state i (Kemeney's constant).

[Kemeny and Snell (1960)]

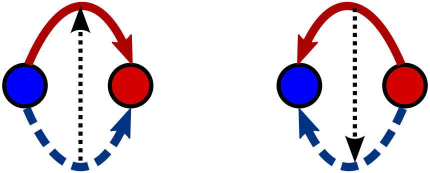
We define:

$$\eta_i^+ = \sum_{j \in \text{strong}} \mathbf{T}_{ij} \boldsymbol{\pi}_j, \qquad \eta_i^- = \sum_{j \in \text{weak}} \mathbf{T}_{ij} \boldsymbol{\pi}_j.$$

They can be used to arrange the states in an order (increasing η^- or decreasing η^+). back

Technical detail: upper/lower triangular

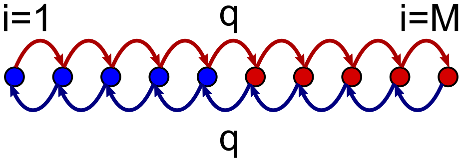
With states in order:



Endpoint: potentiation goes right, depression goes left.

back

Intuition for using topology



$$\mathcal{I} \propto q, \qquad \max_a \tau_a \propto \frac{1}{q},$$

$$\mathcal{I} \propto \frac{1}{M}, \qquad \max_a \tau_a \propto M^2,$$

$$\Longrightarrow$$

Stochasticity: $\mathcal{I} \propto \dfrac{1}{\tau_{\max}}$,

Topology: $\mathcal{I} \propto \dfrac{1}{\sqrt{\tau_{\max}}}$.

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