

Learning and memory with complex synaptic plasticity

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What is a synapse?

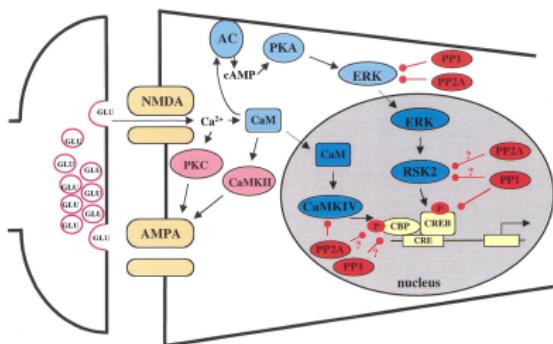
Experimentalists

Theorists

What is a synapse?

Experimentalists

Theorists

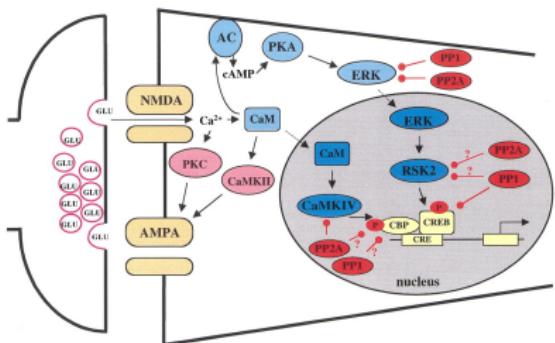


[Klann (2002)]

What is a synapse?

Experimentalists

Theorists



$$W_{ij}$$

[Klann (2002)]

Storage capacity of synaptic memory

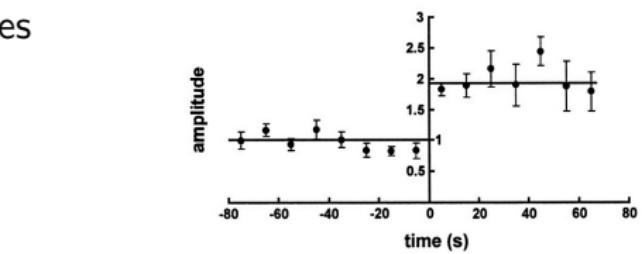
Hopfield, perceptron have capacity $\propto N$, (# synapses).

Assumes unbounded analogue synapses

With discrete, finite synapses:

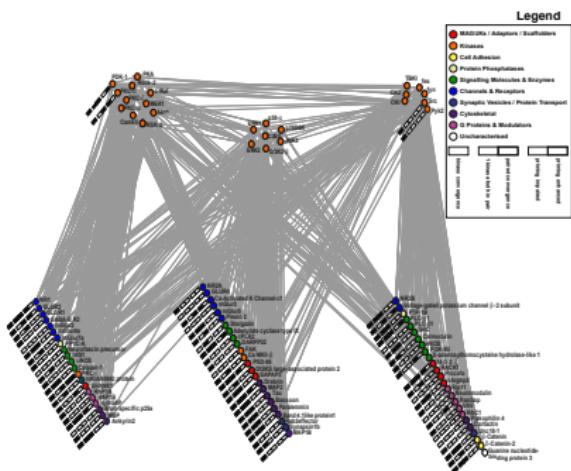
⇒ memory capacity $\sim \mathcal{O}(\log N)$.

[Amit and Fusi (1992), Amit and Fusi (1994)]

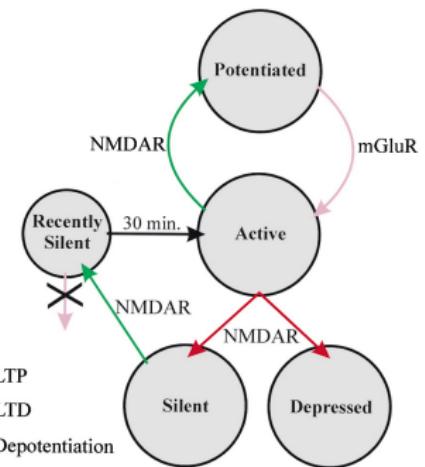


[Petersen et al. (1998), O'Connor et al. (2005)]

Synapses are complex

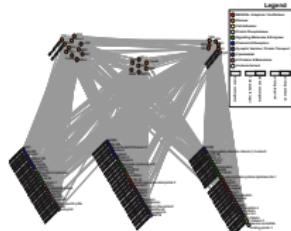


[Coba et al. (2009)]

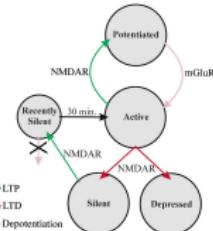


[Montgomery and Madison (2002)]

Synapses are complex

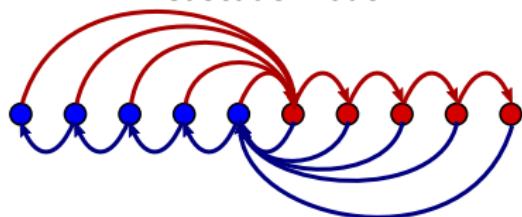


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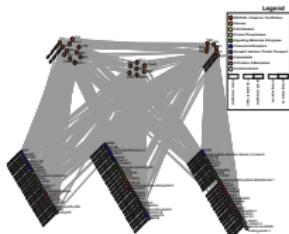
Cascade model



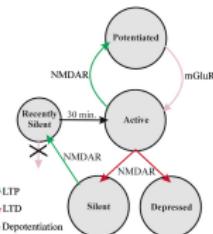
Capacity $\propto N^{2/3}$.

[Fusi et al. (2005)]

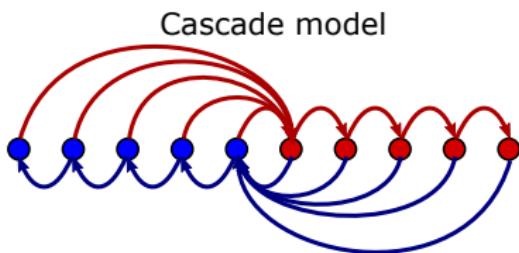
Synapses are complex



[Coba et al. (2009)]



[Montgomery and Madison (2002)]



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:

- underlying mechanisms and principles.
- trade-offs between aspects of performance (e.g. learning vs. memory).
- 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

Benefits of enhanced plasticity?

Learning requires synaptic plasticity.

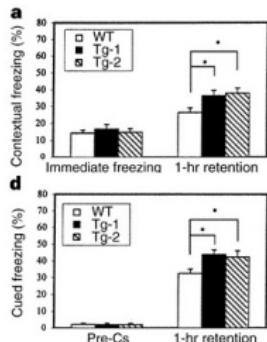


Can we enhance learning by enhancing plasticity?

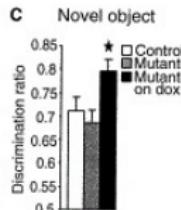
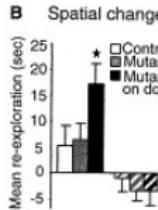


Enhanced plasticity can enhance learning

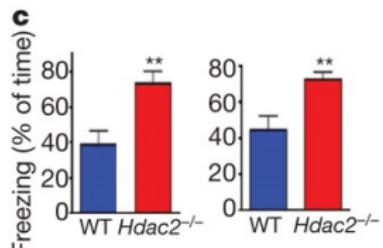
Overexpress NR2B



Inhibit CN



Knockout Hdac2



Fear conditioning

[Tang et al. (1999)]

Novel object recog.

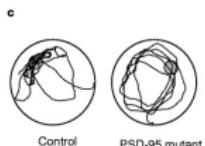
[Malleret et al. (2001)]

Fear conditioning

[Guan et al. (2009)]

Enhanced plasticity can *impair* learning

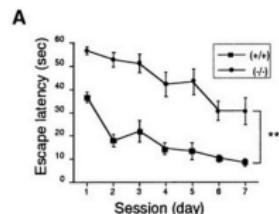
Mutate PSD-95



Water maze

[Migaud et al. (1998)]

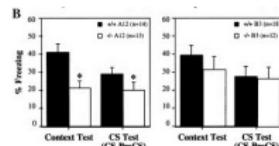
Knockout PTP δ



Water maze

[Uetani et al. (2000)]

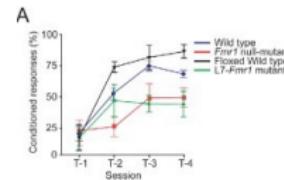
Delete Tmod2



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 → enhanced learning.
Sometimes enhanced plasticity → impaired learning.

Why? How? When?



Overview

Sometimes enhanced plasticity → enhanced learning.
Sometimes enhanced plasticity → impaired learning.

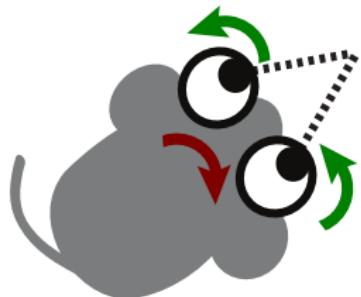


Why? How? When?

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

Simple synapses **cannot** explain behaviour. **Complex synapses** are required.
→ predictions for synaptic physiology.

Vestibulo-Occular Reflex



Eye movements compensate for head movements
⇒ stabilise image on retina.

Requires control of VOR gain = $\frac{\text{eye velocity}}{\text{head velocity}}$.

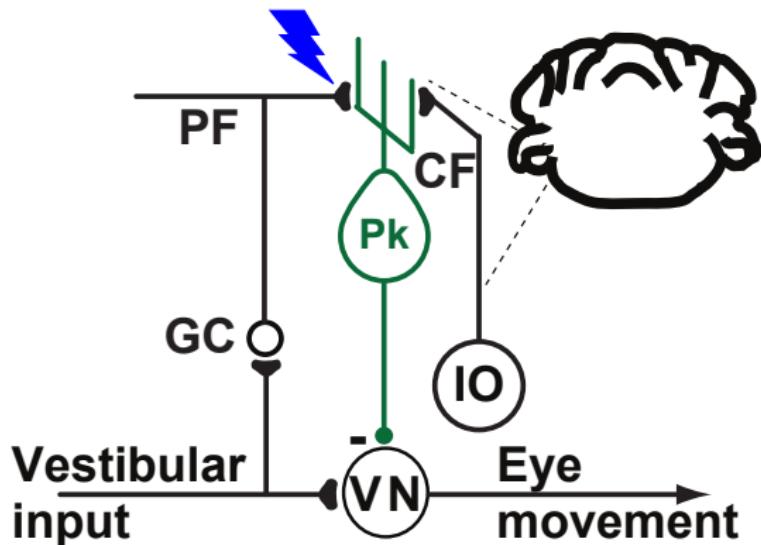
Needs to be adjusted as eye muscles age, etc.

Vestibulo-Occular Reflex training

VOR Increase
Training



VOR Decrease
Training

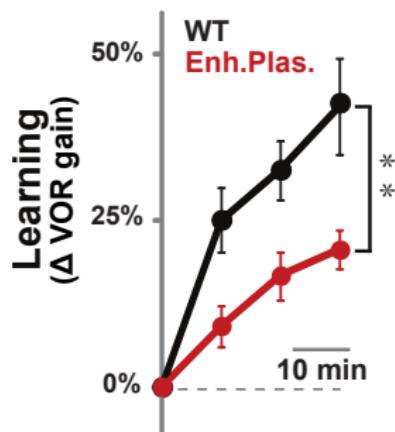


VOR increase: LTD in PF-Pk synapses.
VOR decrease: different mechanism,
also reverses LTD in PF-Pk.
[Marr (1969), Albus (1971), Ito (1972)]

Enhanced plasticity impairs learning

Expectation: enhanced LTD \rightarrow enhanced learning.

VOR Increase
Training



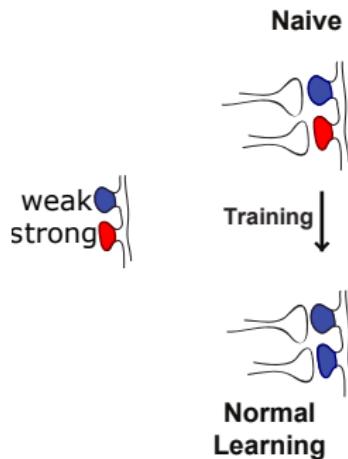
Experiment: enhanced plasticity \rightarrow impaired learning.

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

[McConnell et al. (2009)]

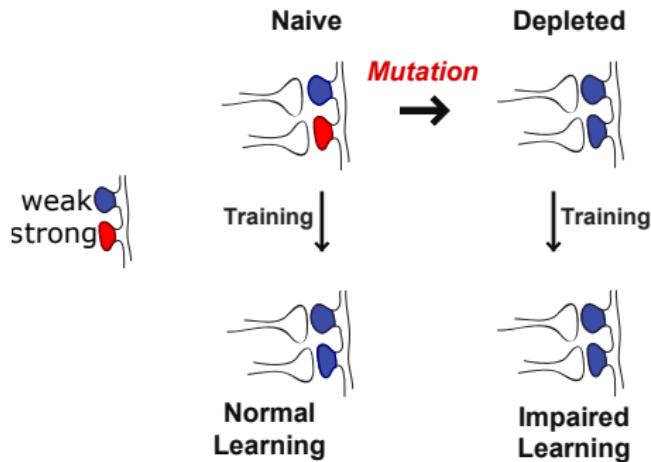
Depletion hypothesis

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



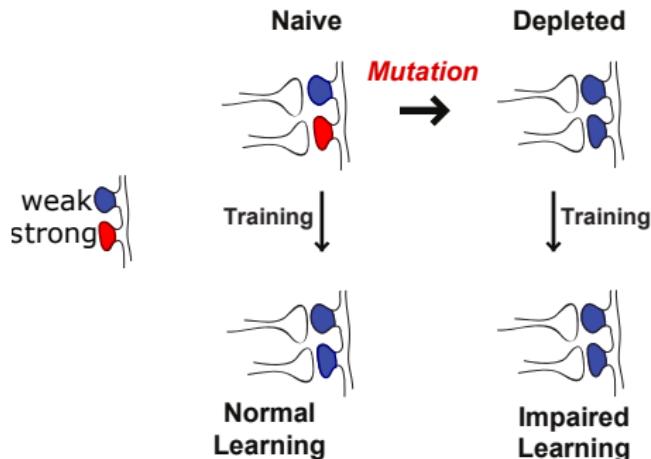
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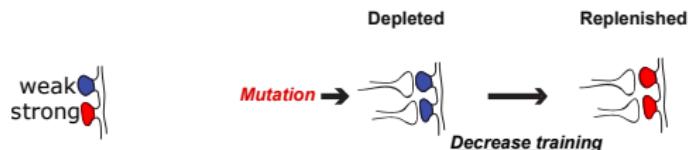


Question 1: depletion effect competes with enhanced intrinsic plasticity.
When is depletion effect stronger?

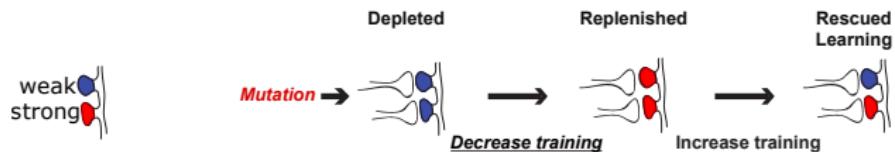
Replenishment by reverse-training



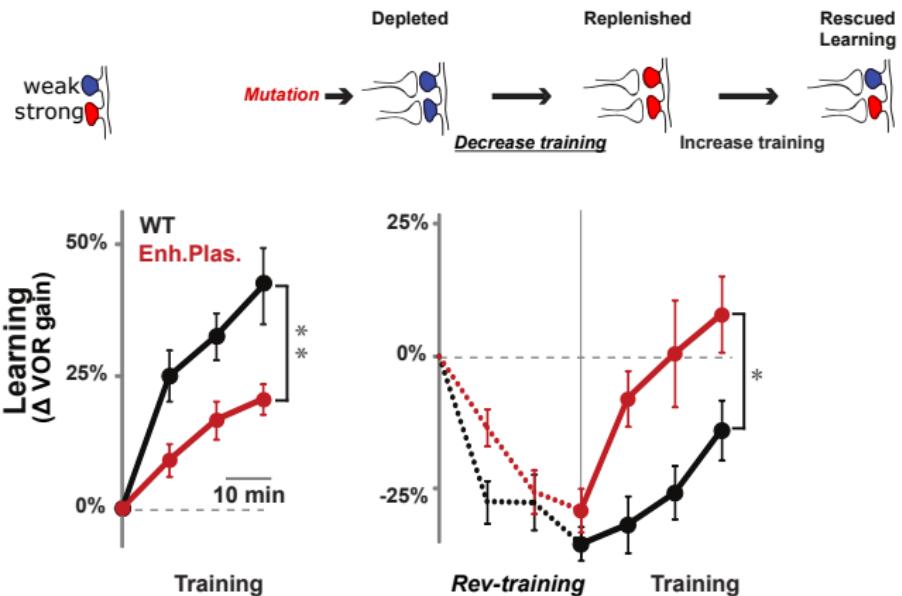
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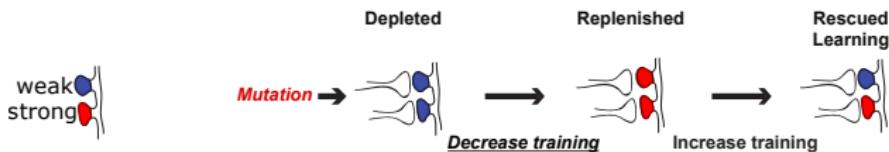
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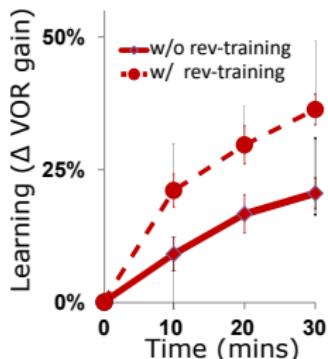
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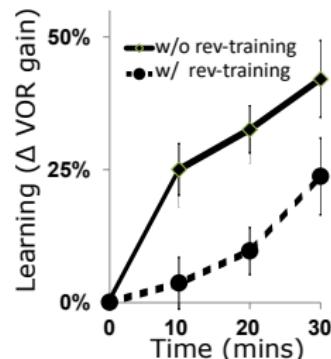
Replenishment by reverse-training



Enh. Plast.



WT



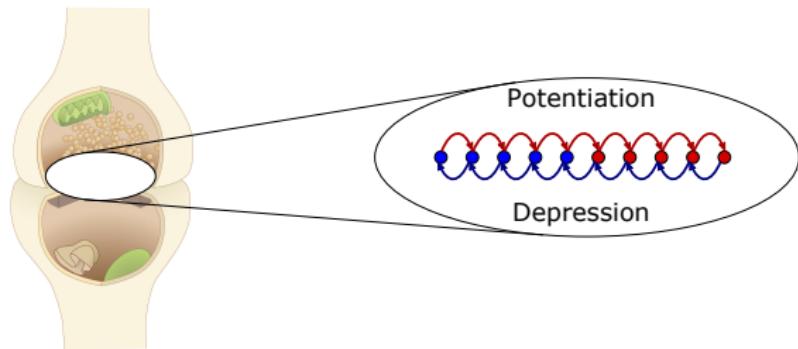
Question 2: How can replenishment ever impair learning?

Models of complex synaptic dynamics



Models of complex synaptic dynamics

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



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

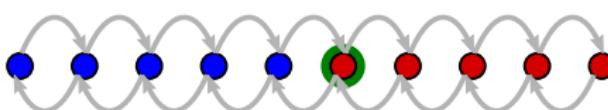
[Fusi et al. (2005), Fusi and Abbott (2007), Barrett and van Rossum (2008)]
[Smith et al. (2006), Lahiri and Ganguli (2013)]

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Potentiation event

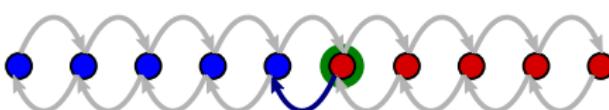


Depression event

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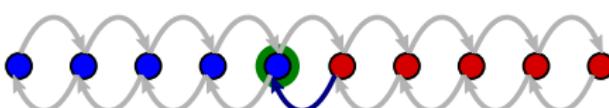


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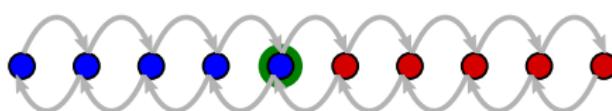


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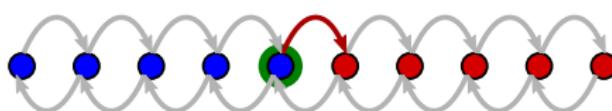


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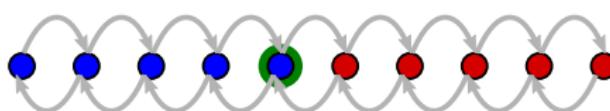


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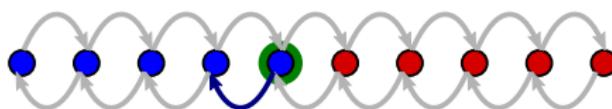


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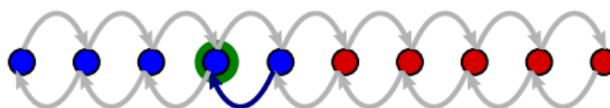
Metaplasticity: change propensity for plasticity
(independent of change in synaptic weight).

Models of complex synaptic dynamics

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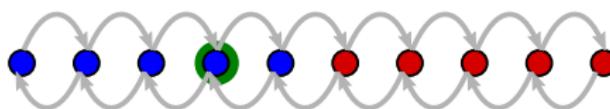
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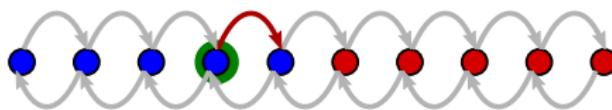
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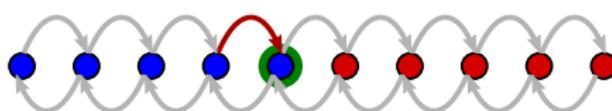
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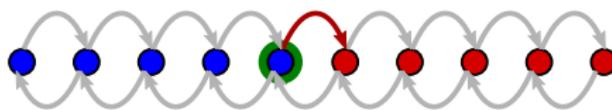
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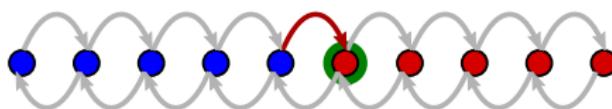
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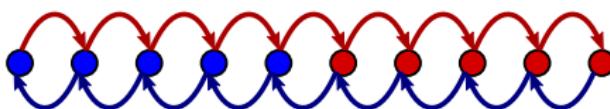
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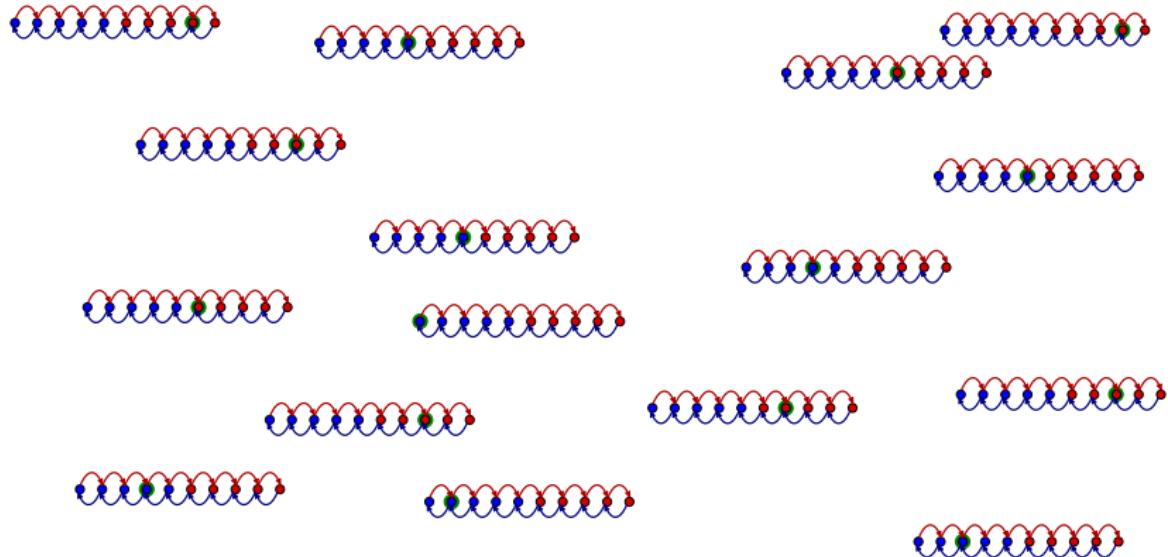
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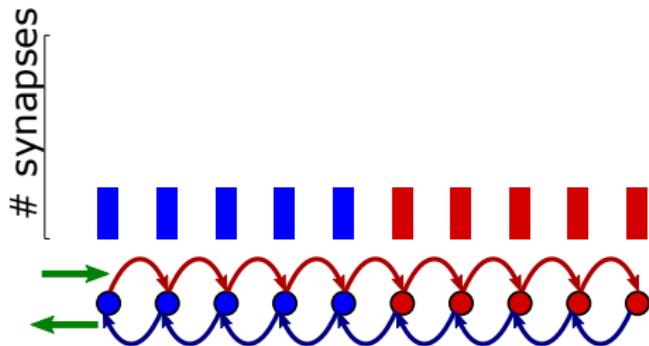
Depression

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Modelling VOR experiments

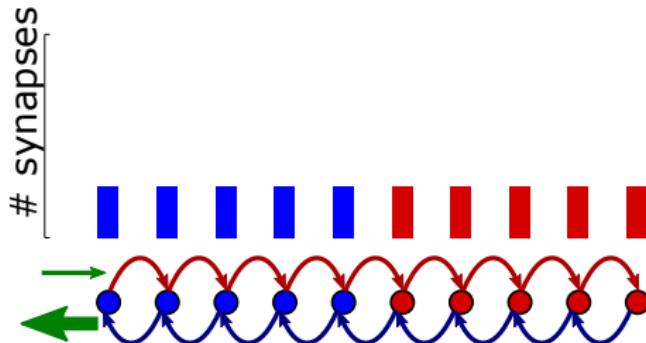


Modelling VOR experiments



Modelling VOR experiments

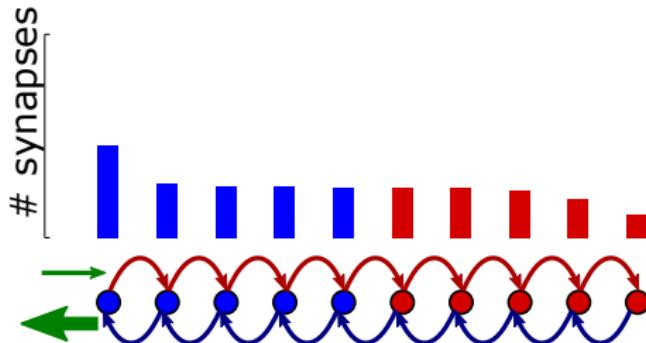
PF-Pk LTD → VOR increase



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

Modelling VOR experiments

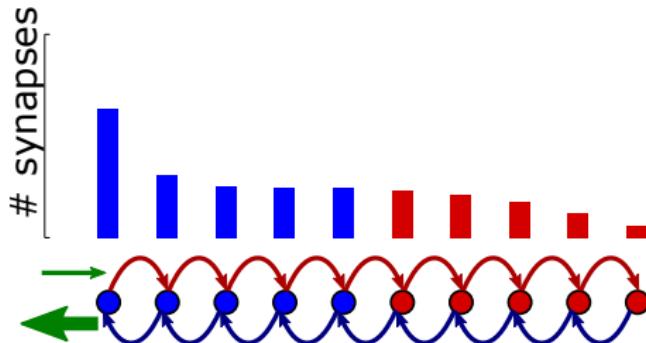
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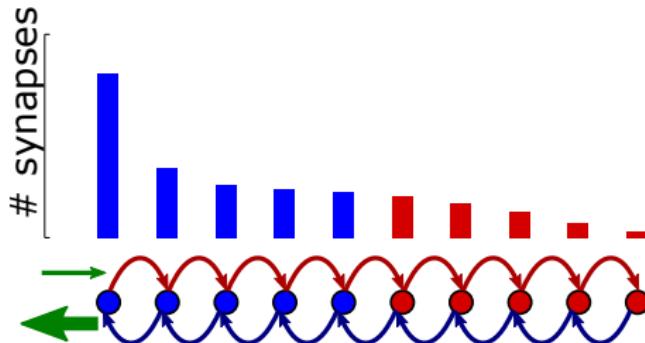
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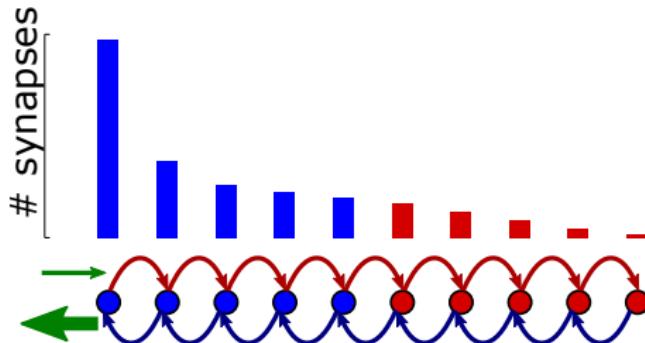
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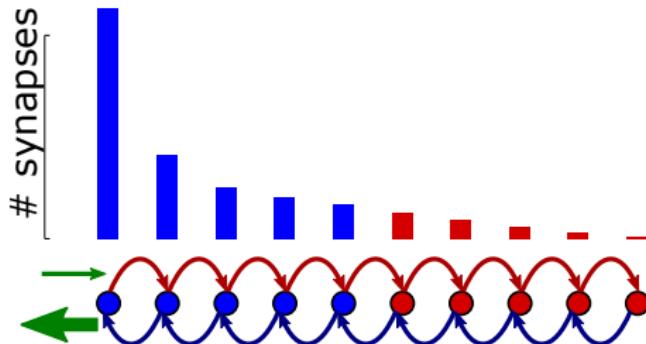
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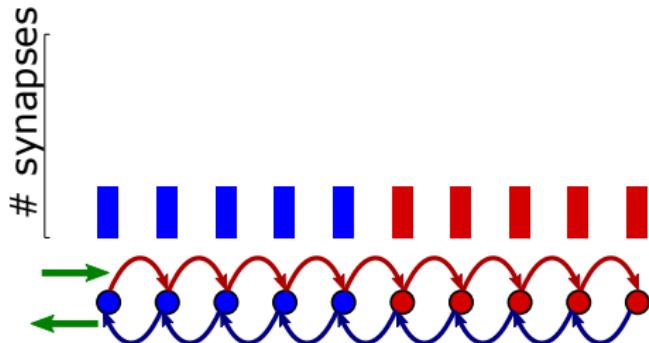


Training: different CF activity \implies
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Learning: decrease in average synaptic weight.

Modelling VOR experiments

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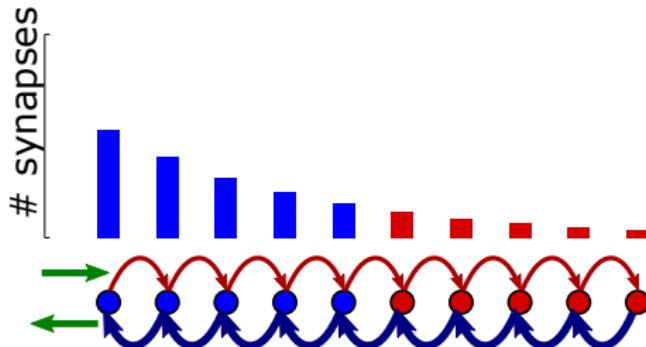
Training: different CF activity \Rightarrow
change frequency of pot/dep events.

Learning: decrease in average synaptic weight.

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

Modelling VOR experiments

PF-Pk LTD → VOR increase



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

Learning: decrease in average synaptic weight.

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

Questions

Depletion effect competes with enhanced intrinsic plasticity.

Question 1: When is the depletion effect stronger?

Reverse training impairs learning in wild-type.

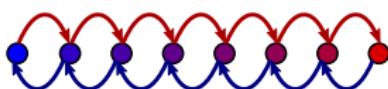
Question 2: How can replenishment ever impair learning?

Enhanced plasticity → enhanced/impaired learning

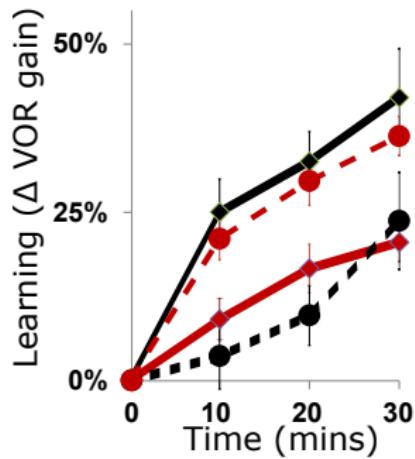
Big question: Why? When?

Simple synapses cannot explain the data

Multistate synapse

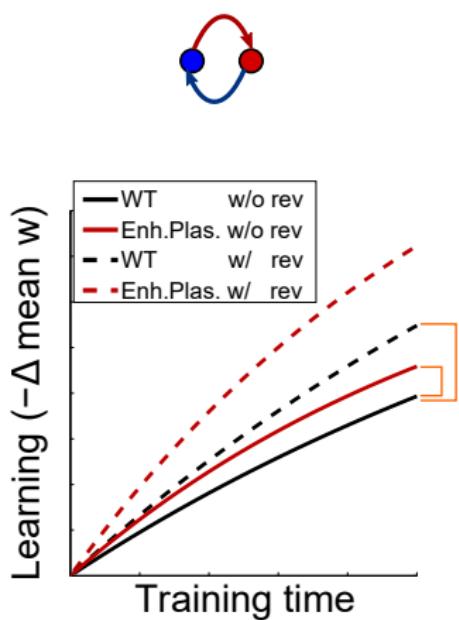


VOR Increase
Training

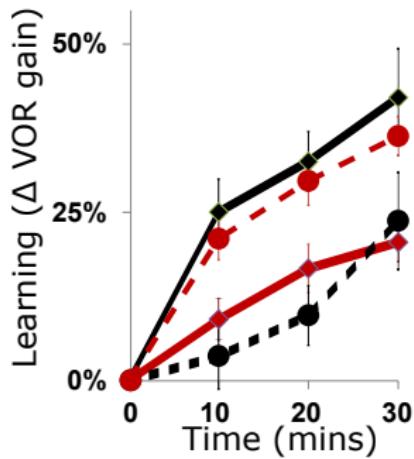


Simple synapses cannot explain the data

Two-state model

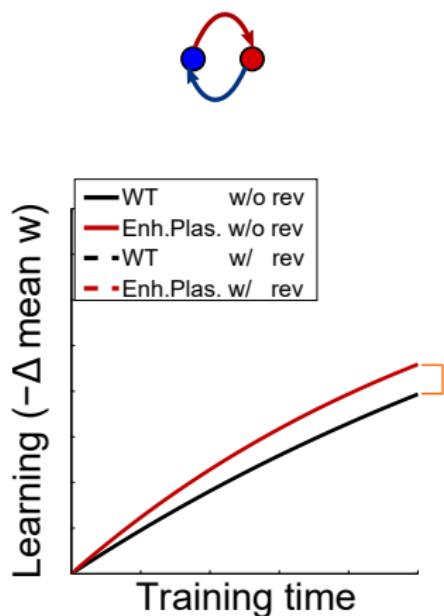


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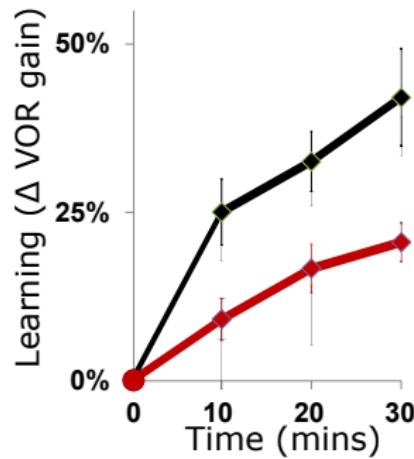


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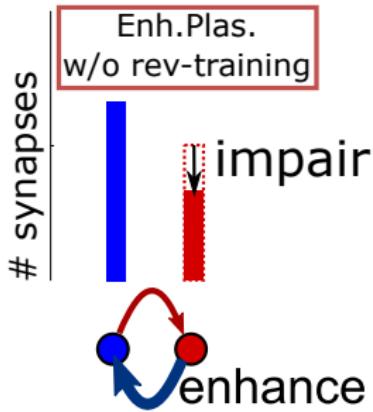


Simple synapses cannot explain the data

Two-state model



Initial distribution



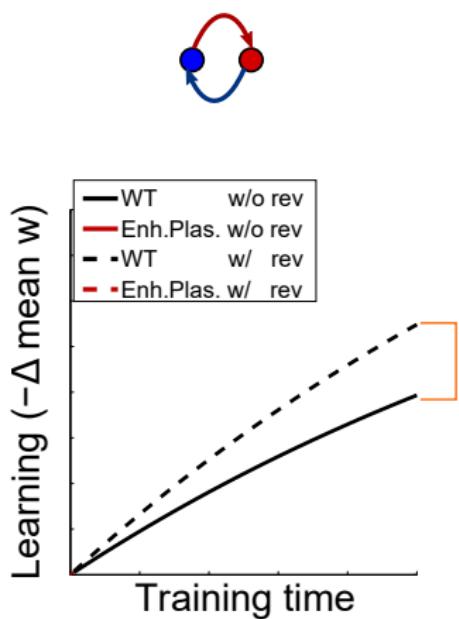
depletion effect

<
enhanced plasticity

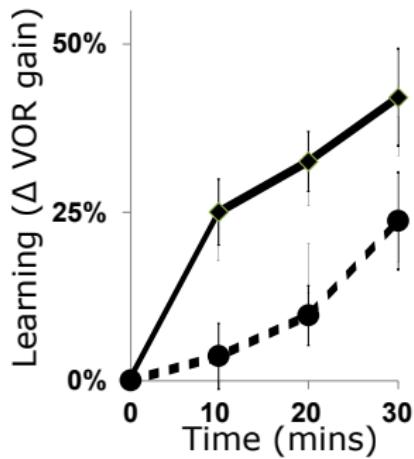
⇒ enhanced learning

Simple synapses cannot explain the data

Two-state model



VOR Increase
Training



Simple synapses cannot explain the data

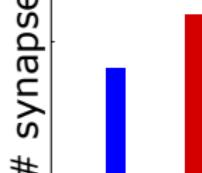
Two-state model



Initial distribution

WT
w/ rev-training

synapses



reverse training

⇒

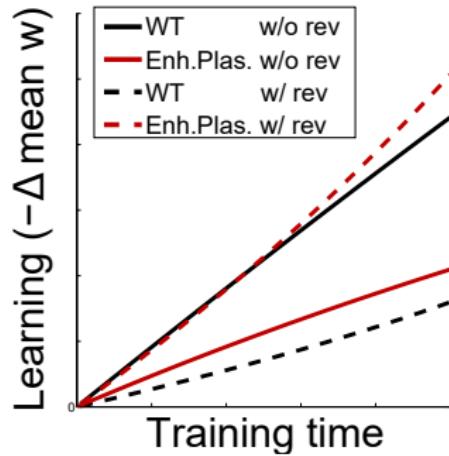
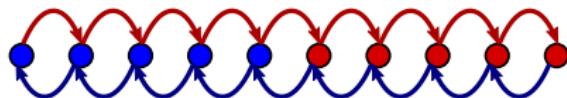
replenishment

⇒

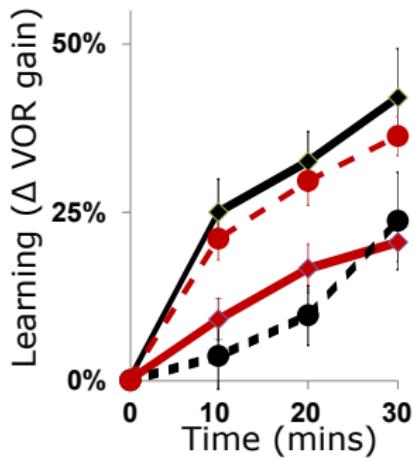
enhanced learning

Complex metaplastic synapses can explain the data

Serial model

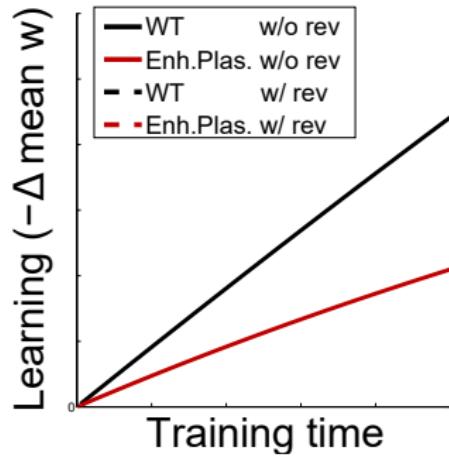
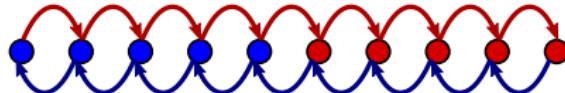


VOR Increase
Training

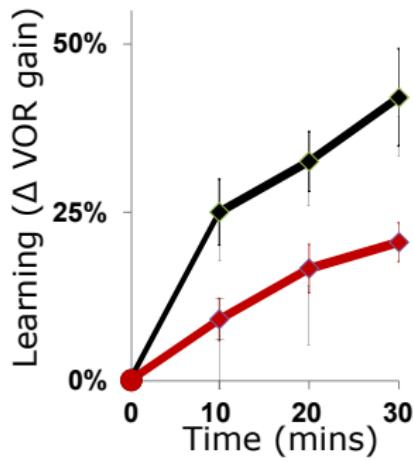


Complex metaplastic synapses can explain the data

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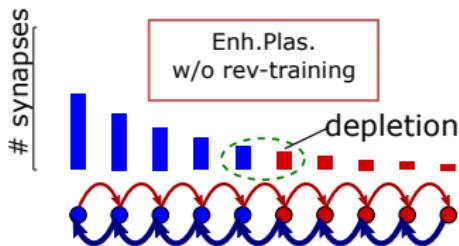
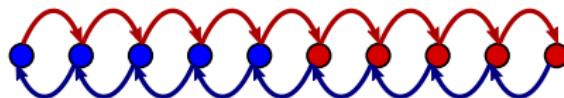


VOR Increase
Training



Complex metaplastic synapses can explain the data

Serial model



amplified depletion

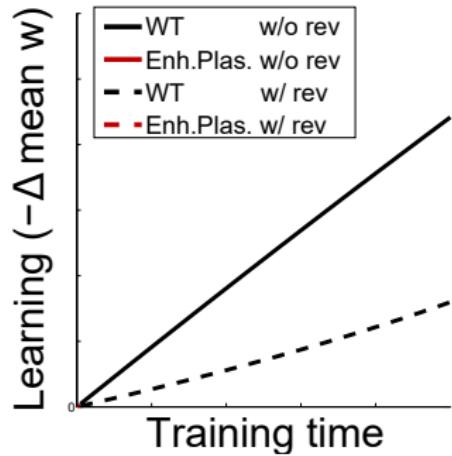
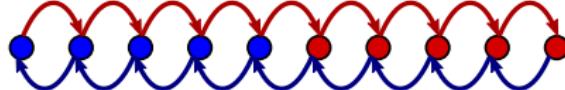
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enhanced plasticity

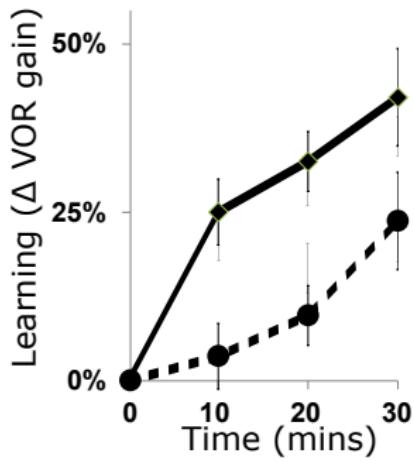
⇒ impaired learning

Complex metaplastic synapses can explain the data

Serial model

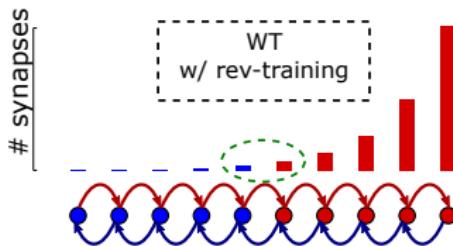
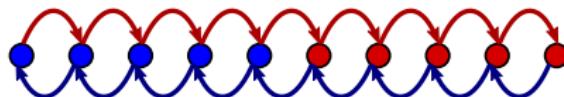


VOR Increase
Training



Complex metaplastic synapses can explain the data

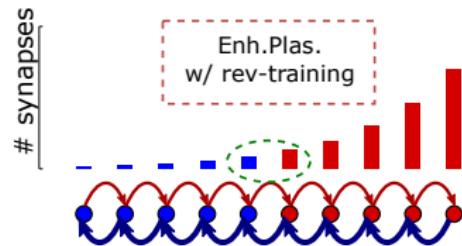
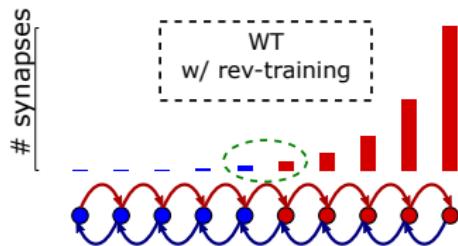
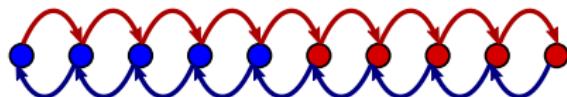
Serial model



reverse training
+
“stubborn” metaplasticity
⇒ impaired learning

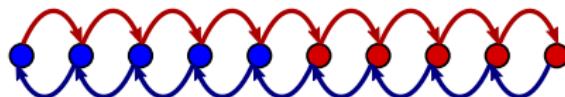
Complex metaplastic synapses can explain the data

Serial model



Complex metaplastic synapses can explain the data

Serial model



starting point:
labile states



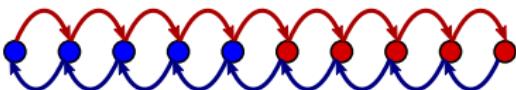
enhanced plasticity
⇒ impaired learning

starting point:
stubborn states



enhanced plasticity
⇒ enhanced learning

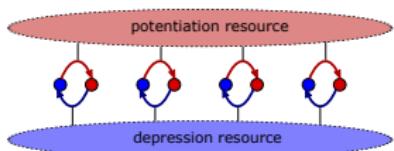
Essential features



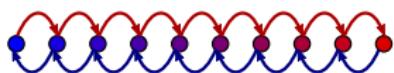
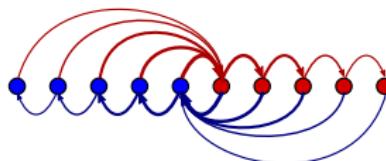
The success of the serial model relies on two features:

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

Fail:



Succeed:



Conclusions

- Diverse behavioural patterns:
Enhanced plasticity → enhance/impair learning (prior experience).
Reverse-training → enhance/impair learning (plasticity rates).
- enhanced LTD vs. depletion → 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.



Storage capacity of synaptic memory

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

Assumes unbounded analog synapses

With discrete, finite synapses:

\implies memory capacity $\sim \mathcal{O}(\log N)$.

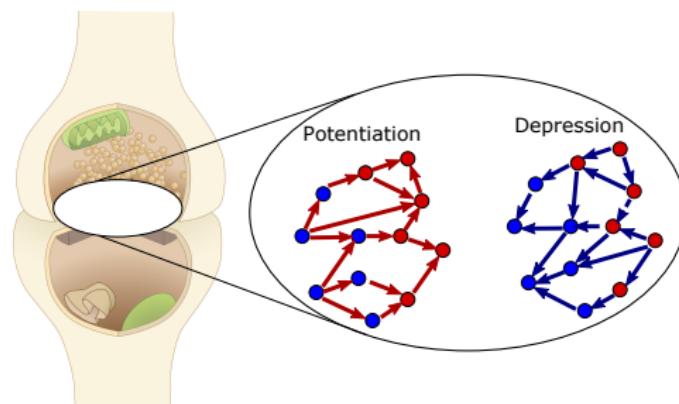
[Amit and Fusi (1992), Amit and Fusi (1994)]

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 → synaptic weight.
● weak
● strong
- Candidate plasticity events → transitions between states

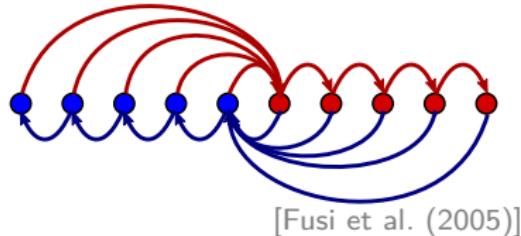


States: #AMPAR, #NMDAR, NMDAR subunit composition,
CaMK II autophosphorylation, activating PKC, p38 MAPK,...

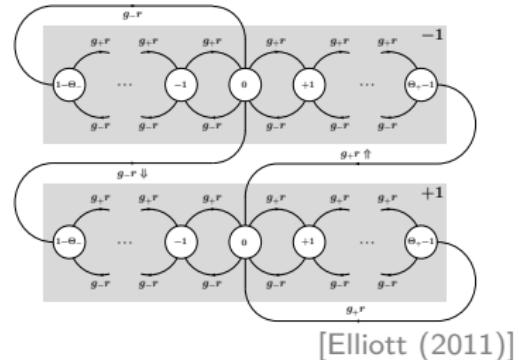
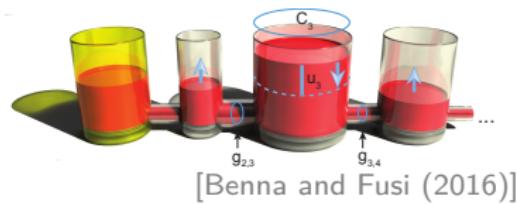
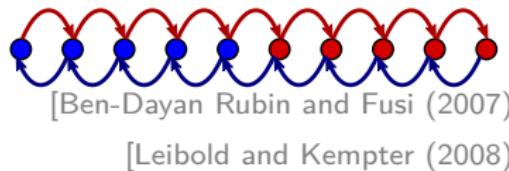
[Fusi et al. (2005), Fusi and Abbott (2007), Barrett and van Rossum (2008)]

Specific models of complex synaptic dynamics

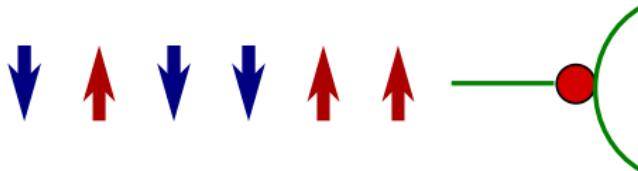
Cascade model



Serial model

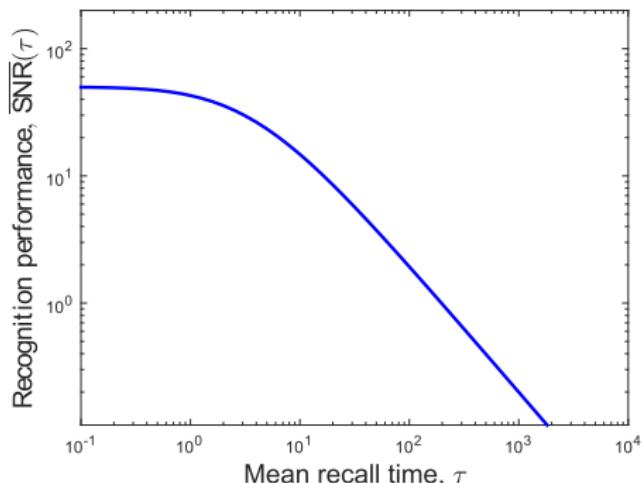


Synaptic memory curves



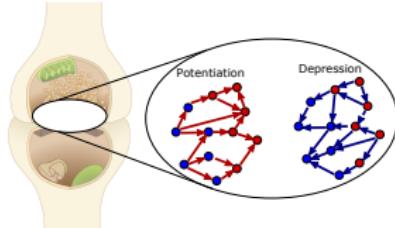
Synapses store a sequence of memories.

Recognition memory performance described by SNR.

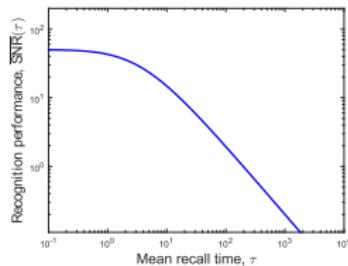


General principles relating structure and function?

Synaptic structure



Synaptic function

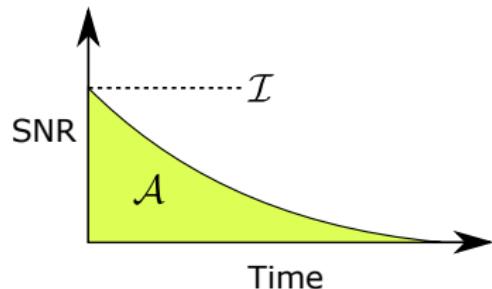


- What are the fundamental limits of memory?
- Which models achieve these limits?
- What are the theoretical principles behind the optimal models?

Upper bounds on measures of memory

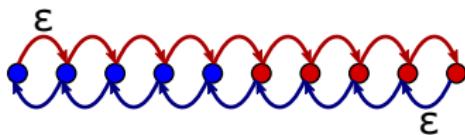
Initial SNR:

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



Area under curve:

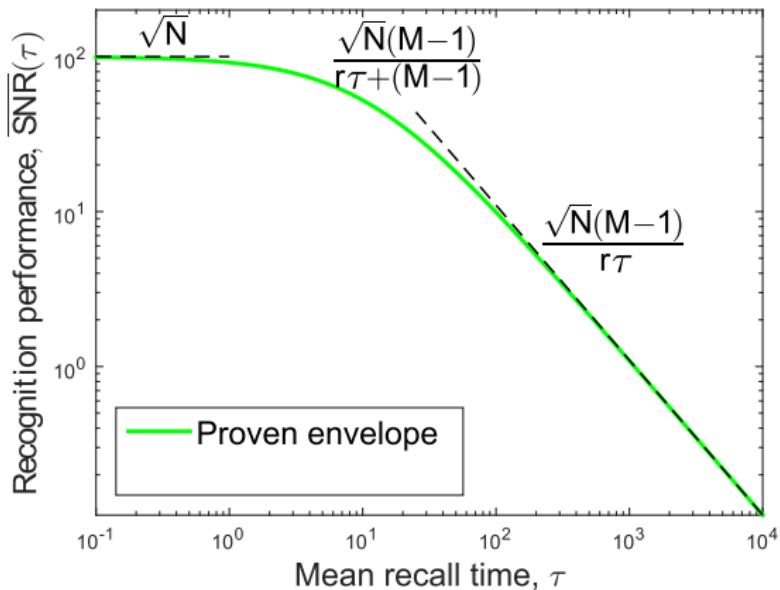
$$\mathcal{A} = \int_0^\infty \text{SNR}(t) dt = \sum_a \mathcal{I}_a \tau_a \leq \sqrt{N}(M-1)/r.$$



[Lahiri and Ganguli (2013)]

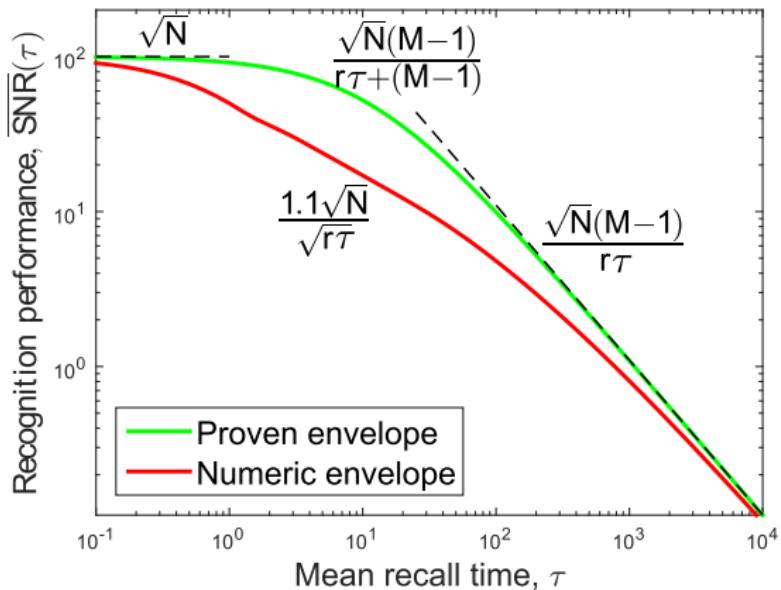
Proven envelope: memory frontier

Upper bound on memory curve at *any* timescale.

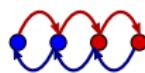
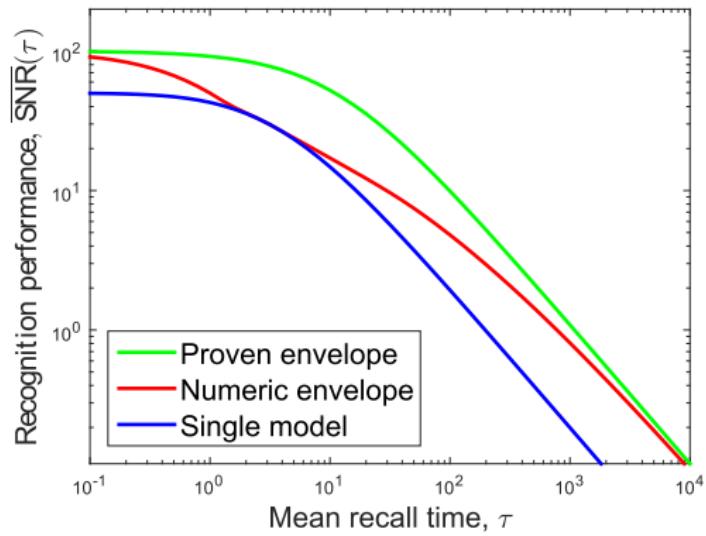


Proven envelope: memory frontier

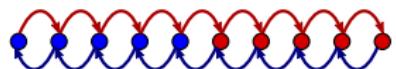
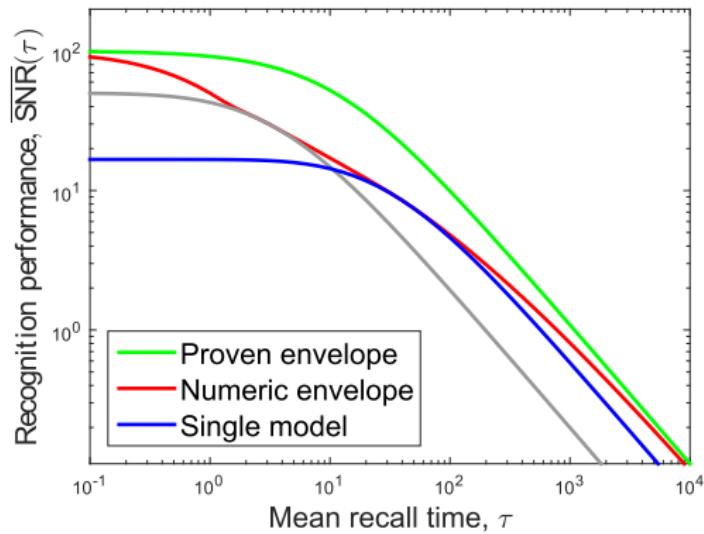
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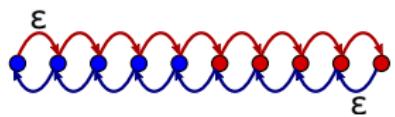
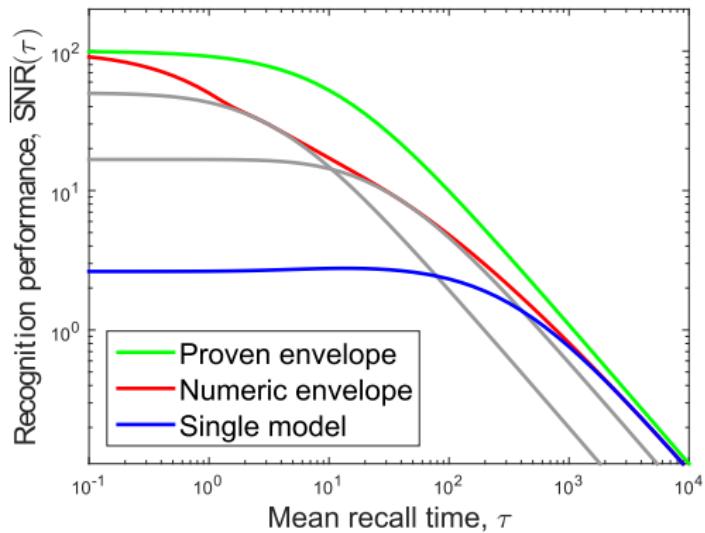
Models that maximize memory for one timescale



Models that maximize memory for one timescale

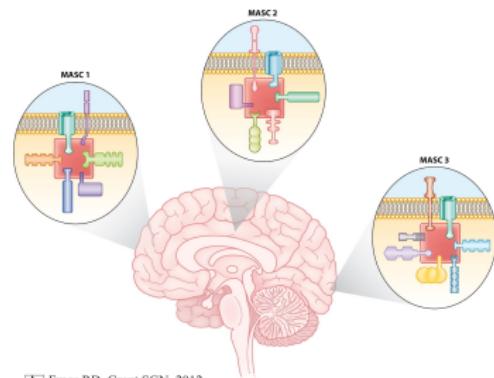


Models that maximize memory for one timescale



Synaptic diversity and timescales of memory

Different synapses have different molecular structures.

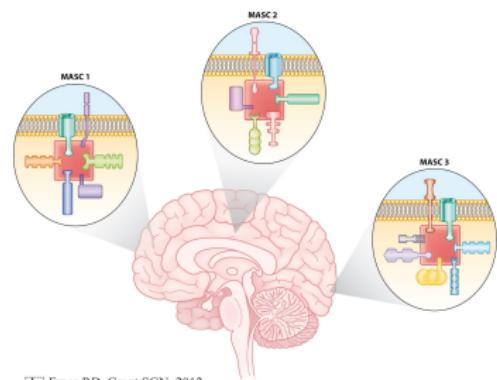


[A] Emes RD, Grant SGN. 2012.
Annu. Rev. Neurosci. 35:111–31

[Emes and Grant (2012)]

Synaptic diversity and timescales of memory

Different synapses have different molecular structures.



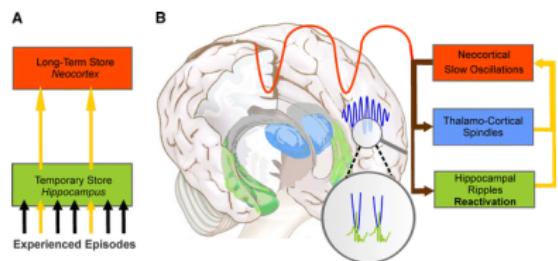
[Emes RD, Grant SGN. 2012.
Annu. Rev. Neurosci. 35:111–31]

[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 → nuclei.

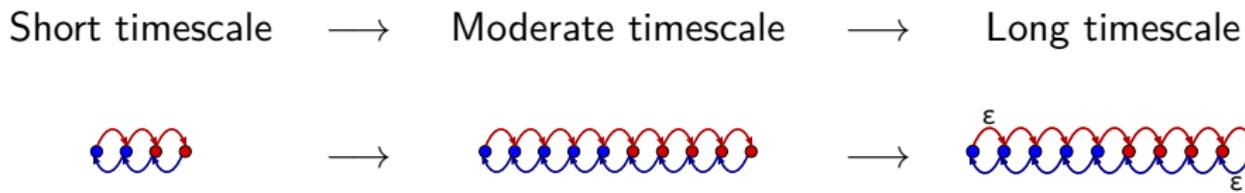
[Attwell et al. (2002)]

[Cooke et al. (2004)]

Synaptic structure and function: general principles

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

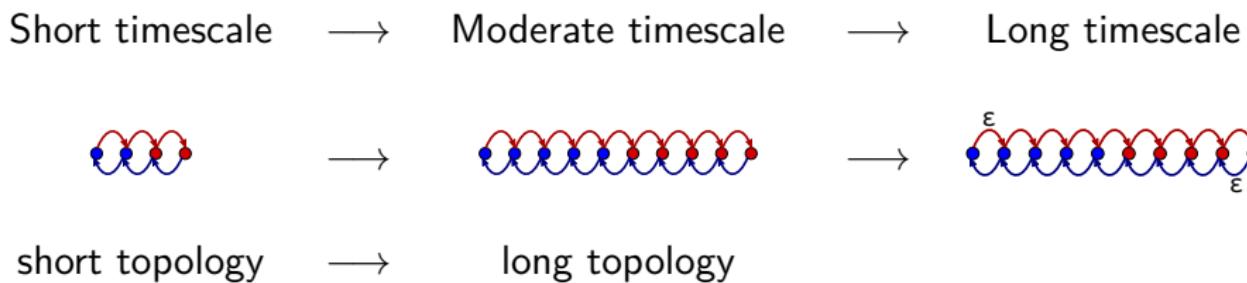
What can we conclude?



Synaptic structure and function: general principles

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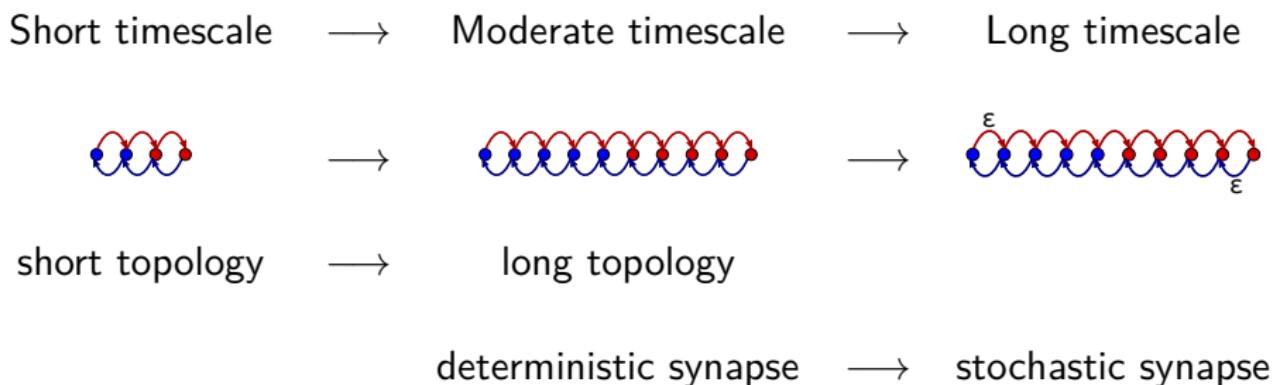
What can we conclude?



Synaptic structure and function: general principles

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

What can we conclude?



Experimental tests?

Traditional experiments:



Experimental tests?

Traditional experiments:

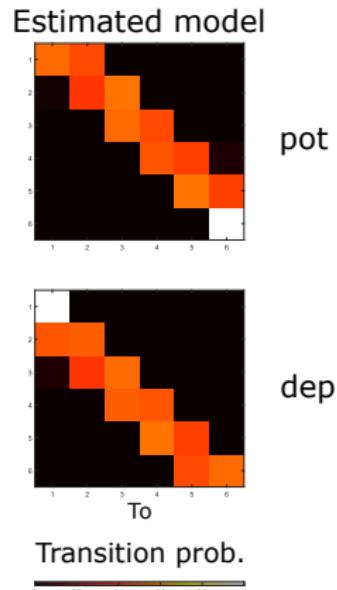
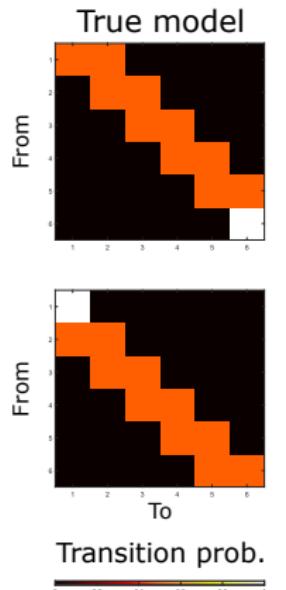


To fit a model: long sequence of small plasticity events.

Observe the changes in synaptic efficacy.



Simulated experiment



Problem: need *long* sequences.

Whole cell patch of postsynaptic neuron → 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 → Ca washout.

Summary

- 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

Acknowledgements

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Alex Williams

Christopher Stock

Sarah Harvey

Aran Nayebi

Stefano Fusi

Jennifer Raymond

Barbara Nguyen-Vu

Grace Zhao

Aparna Suvrathan

Rhea Kimpo

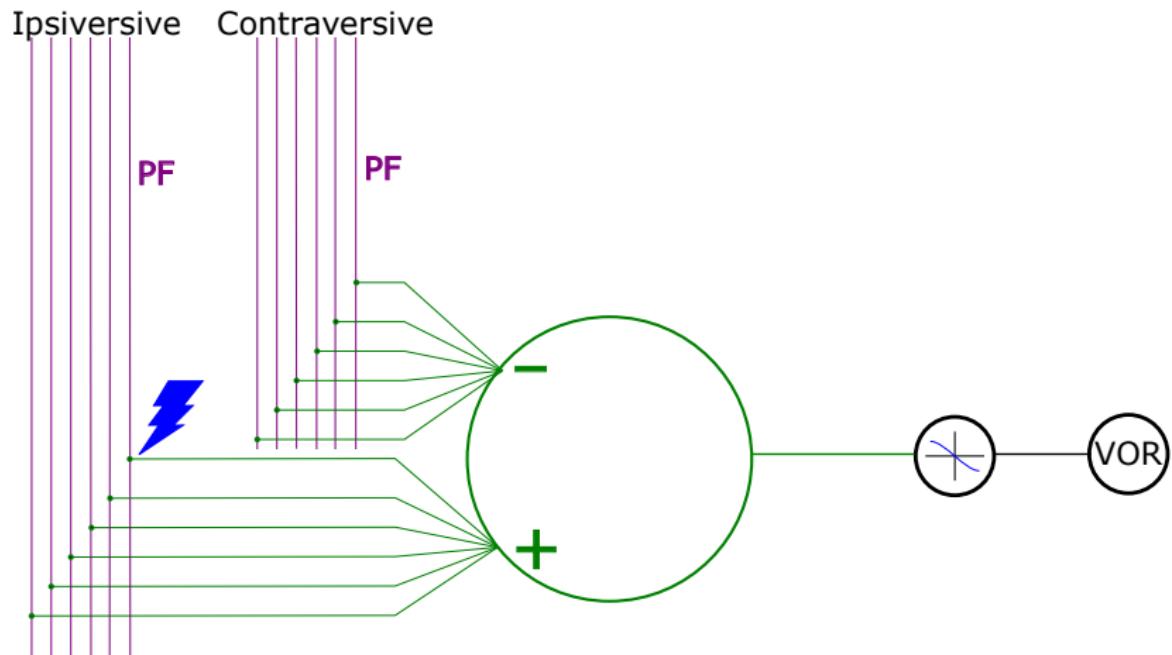
Carla Shatz

Hanmi Lee

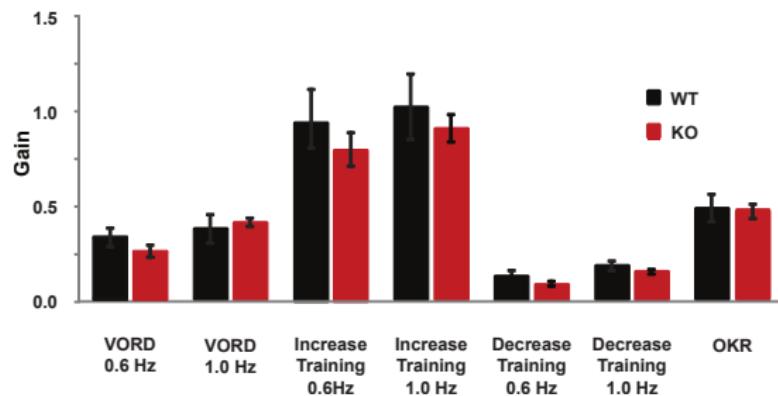
Marcus Benna

Funding: Swartz Foundation, Stanford Bio-X Genentech fellowship.

Model of circuit

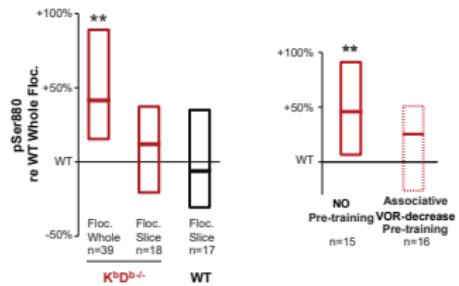


Baseline



Evidence: level of depression

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

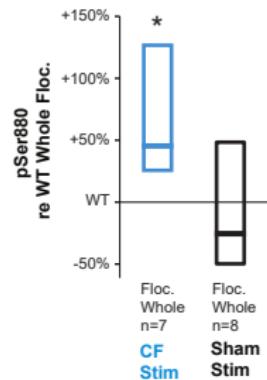
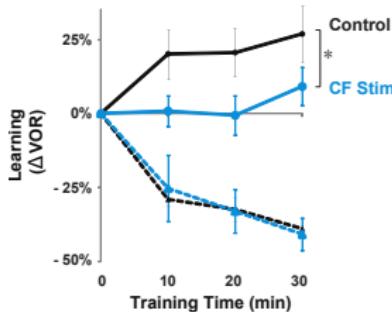
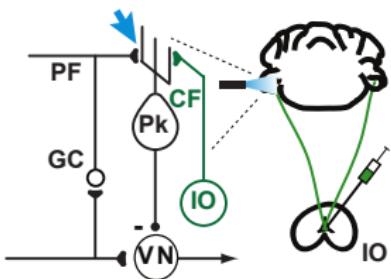


Biochemical signature of PF-Pk LTD.

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

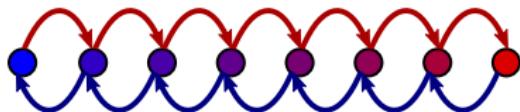
Evidence: saturation by CF stimulation

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

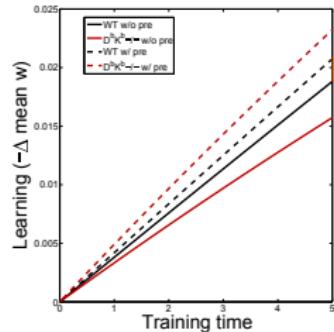
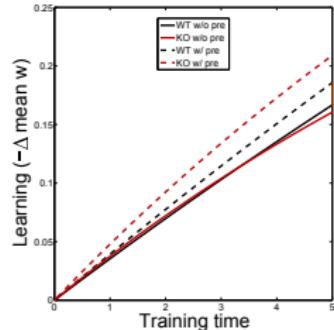
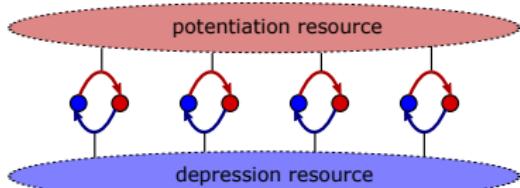


Other models that fail

Multistate synapse



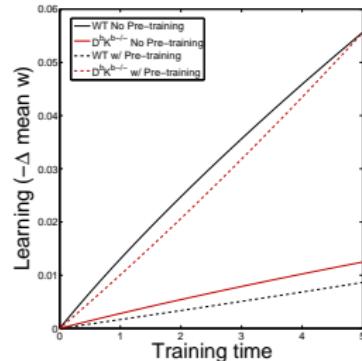
Pooled resource model



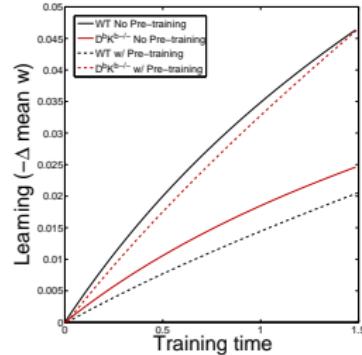
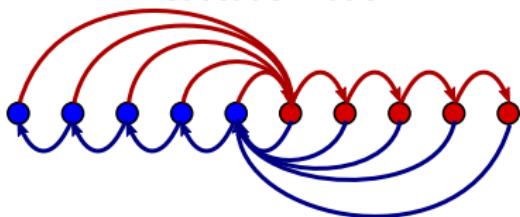
[Amit and Fusi (1994)]

Other models that work

Non-uniform multistate model

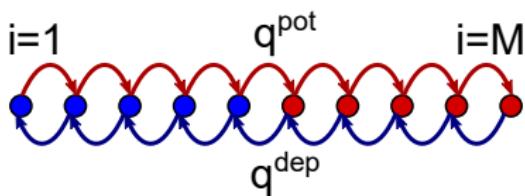


Cascade model



[Fusi et al. (2005)]

Mathematical explanation



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

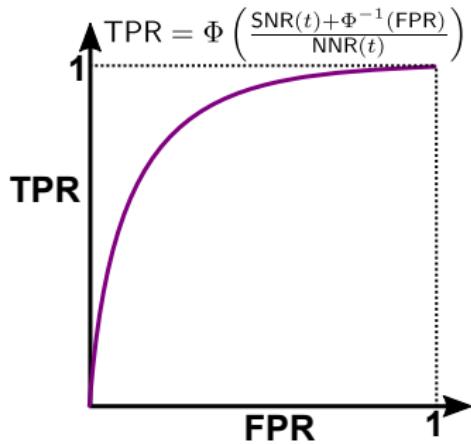
Learning rate $\sim \pi_{M/2} \left(\frac{q^{\text{dep}}}{q^{\text{pot}}} \right) = \mathcal{N} \left(\frac{q^{\text{pot}}}{q^{\text{dep}}} \right)^{\frac{M}{2}-1}$.

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

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

Quantifying memory quality

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



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

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

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

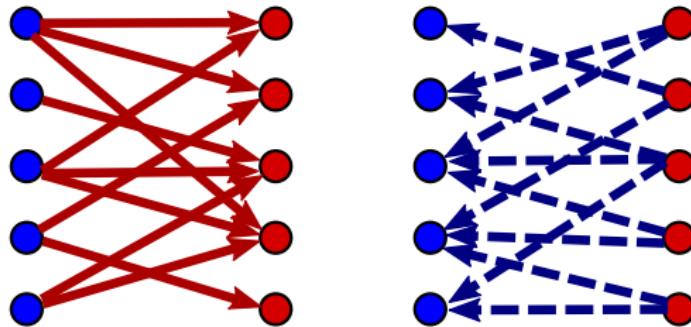
Also: KL divergence, Chernoff distance, . . .

Initial SNR as flux

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

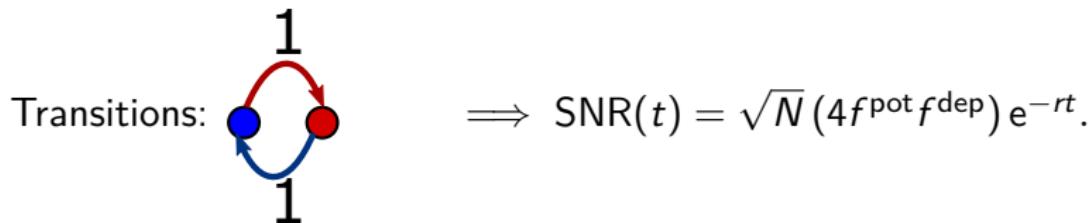
$$\text{SNR}(0) \leq \frac{4\sqrt{N}}{r} \Phi_{-+}.$$

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



Two-state model

Two-state model equivalent to previous slide:



Maximal initial SNR:

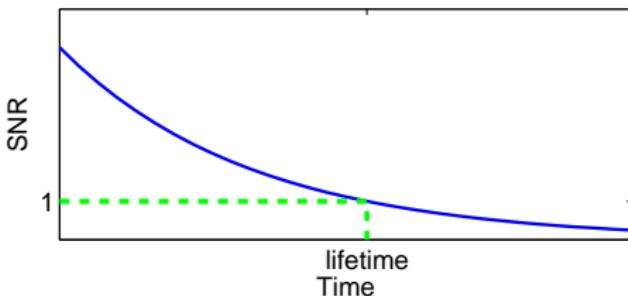
$$\text{SNR}(0) \leq \sqrt{N}.$$

Area under memory curve

$$\mathcal{A} = \int_0^\infty dt \text{ SNR}(t), \quad \overline{\text{SNR}}(\tau) \rightarrow \frac{\mathcal{A}}{\tau} \quad \text{as} \quad \tau \rightarrow \infty.$$

Area bounds memory lifetime:

$$\begin{aligned}\text{SNR(lifetime)} &= 1 \\ \implies \text{lifetime} &< \mathcal{A}.\end{aligned}$$



This area has an upper bound:

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

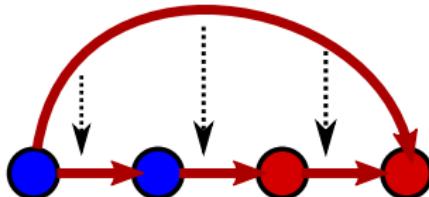
Saturated by a model with linear chain topology.

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

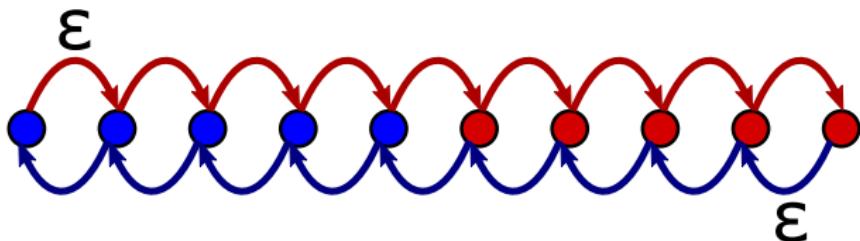
$$A = \frac{2\sqrt{N}}{r} \sum_k \pi_k |k - \langle k \rangle|.$$

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.

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

Technical detail: ordering states

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

$$\eta = \sum_j \mathbf{T}_{ij} \pi_j,$$

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

[Kemeny and Snell (1960)]

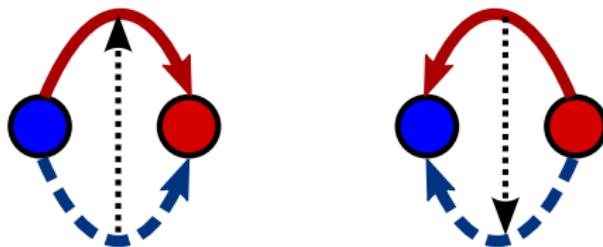
We define:

$$\eta_i^+ = \sum_{j \in \text{strong}} \mathbf{T}_{ij} \pi_j, \quad \eta_i^- = \sum_{j \in \text{weak}} \mathbf{T}_{ij} \pi_j.$$

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

Technical detail: upper/lower triangular

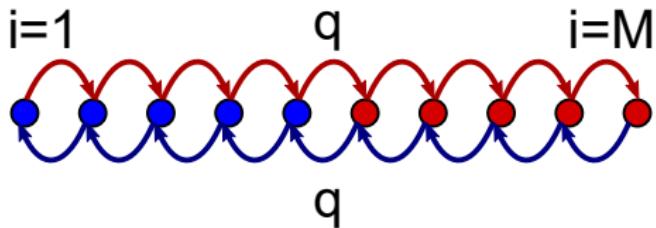
With states in order:



Endpoint: potentiation goes right, depression goes left.

back

Intuition for using topology



$$\begin{array}{ll} \mathcal{I} \propto q, & \max_a \tau_a \propto \frac{1}{q}, \\ \mathcal{I} \propto \frac{1}{M}, & \max_a \tau_a \propto M^2, \end{array} \quad \Rightarrow \quad \begin{array}{ll} \text{Stochasticity: } \mathcal{I} \propto \frac{1}{\tau_{\max}}, \\ \text{Topology: } \mathcal{I} \propto \frac{1}{\sqrt{\tau_{\max}}}. \end{array}$$

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