Learning and memory with complex synaptic plasticity

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What is a synapse?

Experimentalists

Theorists

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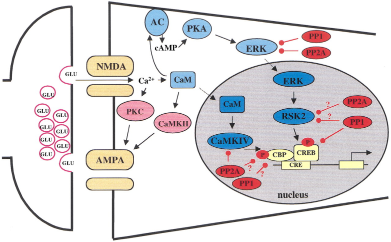

[Klann (2002)]

What is a synapse?

Experimentalists

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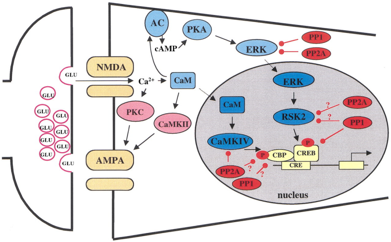


$$W_{ij}$$

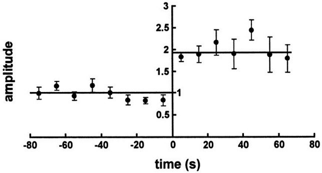
[Klann (2002)]

Storage capacity of synaptic memory

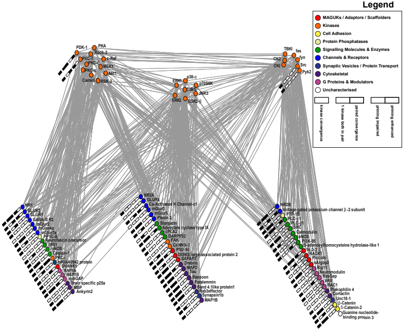
Hopfield, perceptron have capacity $\propto N$, ($\#$ synapses).

Assumes unbounded analogue synapses

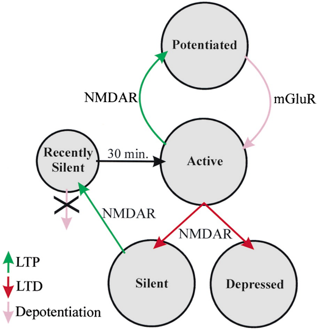
With discrete, finite synapses:
$\implies$ memory capacity $\sim \mathcal{O}(\log N)$.
[Amit and Fusi (1992), Amit and Fusi (1994)]



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



[Coba et al. (2009)]



[Montgomery and Madison (2002)]

Outline

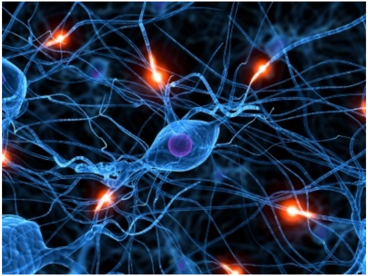
1. Learning with enhanced plasticity
   - Effects of enhanced plasticity on cerebellar learning
   - Synaptic models of cerebellar learning
   - Learning outcomes of mice and models
2. Memory over different timescales
   - Quantifying memory quality
   - Frontiers of memory
   - Implications of memory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

Section 1

Learning with enhanced plasticity

Benefits of enhanced plasticity?

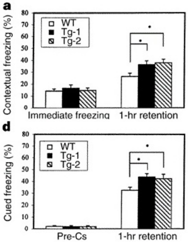
Learning requires synaptic plasticity.



Can we enhance learning by enhancing plasticity?

Enhanced plasticity *can* enhance learning

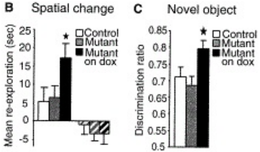
Overexpress NR2B



Fear conditioning

[Tang et al. (1999)]

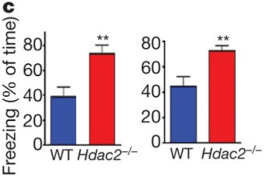
Inhibit CN



Novel object recog.

[Malleret et al. (2001)]

Knockout Hdac2

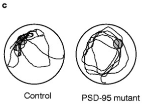


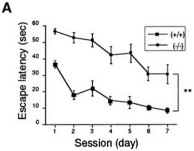
Fear conditioning

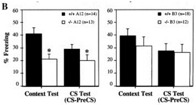
[Guan et al. (2009)]

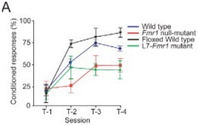
Enhanced plasticity can *impair* learning

Mutate PSD-95	Knockout PTPδ	Delete Tmod2	Knockout FMR1







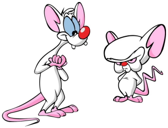


Water maze	Water maze	Fear cond.	Eyeblink
[Migaud et al. (1998)]	[Uetani et al. (2000)]	[Cox et al. (2003)]	[Koekkoek et al. (2005)]

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?

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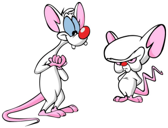
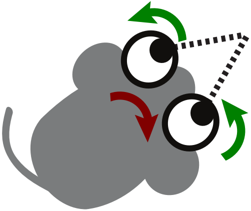


Why? How? When?

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.



Eye movements compensate for head movements $\implies$ stabilise image on retina.

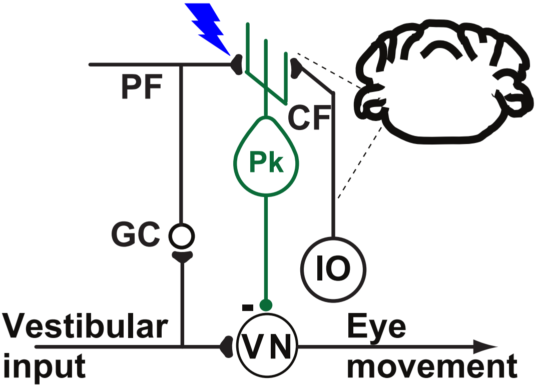
Requires control of VOR gain $= \frac{\text{eye velocity}}{\text{head velocity}}$.

Needs to be adjusted as eye muscles age, etc.

Vestibulo-Occular Reflex training

VOR Increase Training

VOR Decrease Training

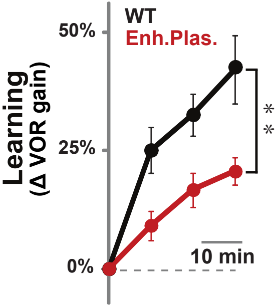


VOR increase:	LTD in PF-Pk synapses.
VOR decrease:	different mechanism, also reverses LTD in PF-Pk.

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

Enhanced plasticity impairs learning

Expectation: enhanced LTD → enhanced learning.

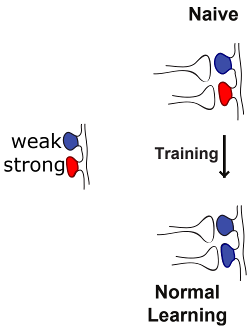


Experiment: enhanced plasticity → impaired learning.

Knockout of MHC-I $K^b D^b$ 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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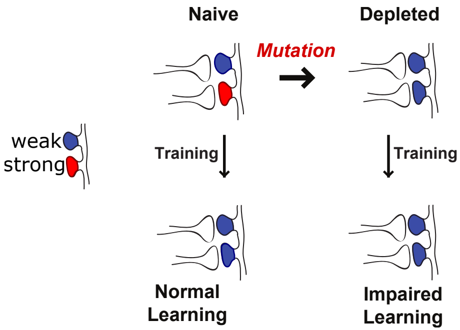

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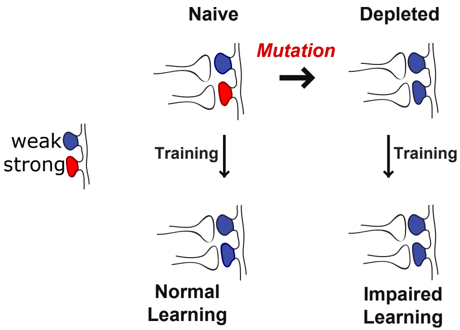

Question 1: depletion effect competes with enhanced intrinsic plasticity.
When is depletion effect stronger?

Replenishment by reverse-training

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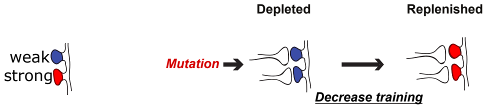

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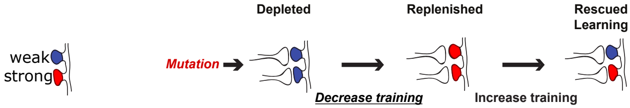

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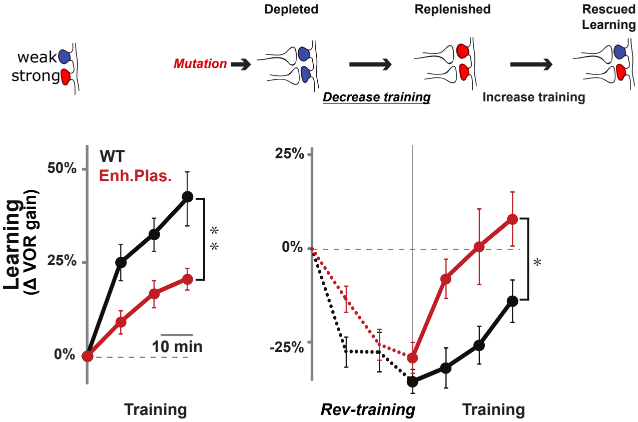

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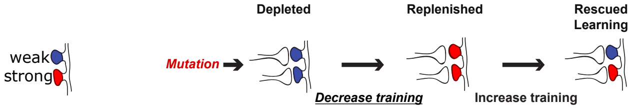
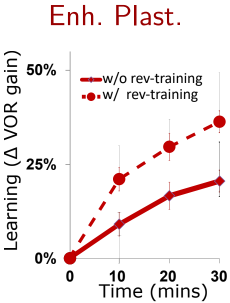
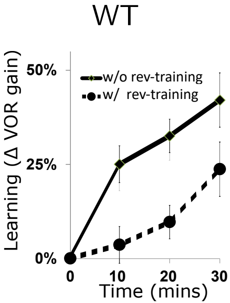
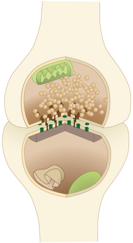






Question 2: How can replenishment *ever* impair learning?

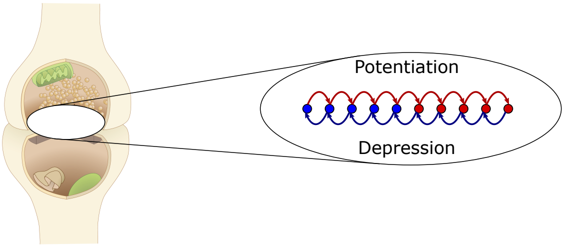
Models of complex synaptic dynamics



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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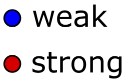

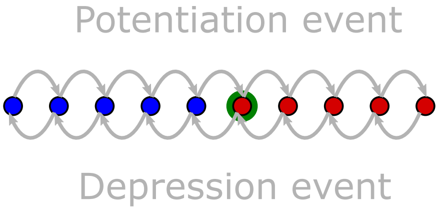

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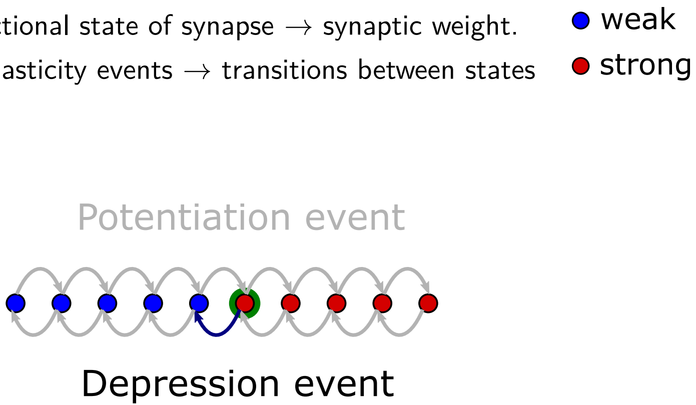

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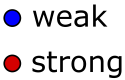
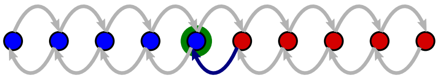


Potentiation event



Depression event

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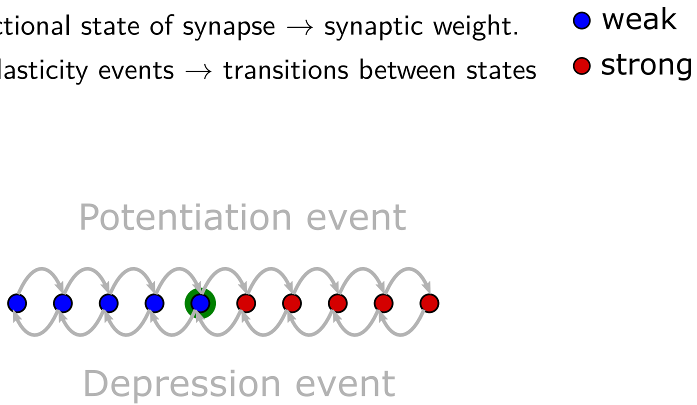

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weak
strong

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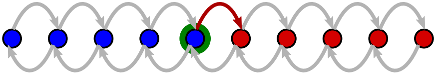

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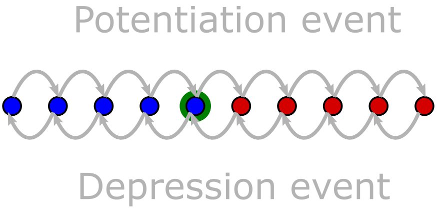

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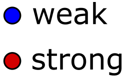

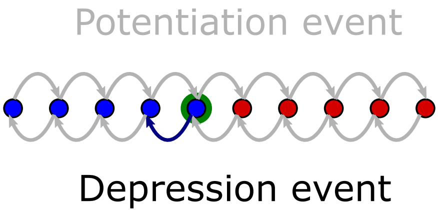

Metaplasticity: change propensity for plasticity
(independent of change in synaptic weight).

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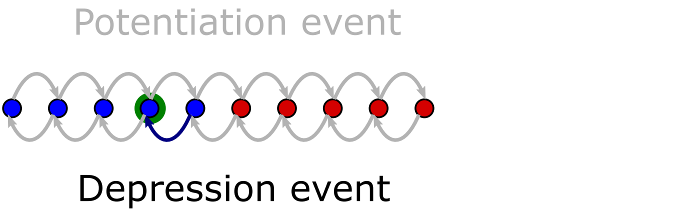

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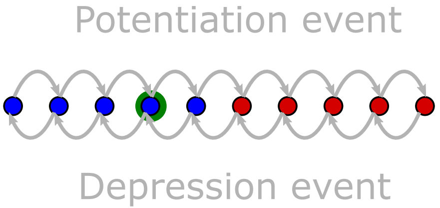

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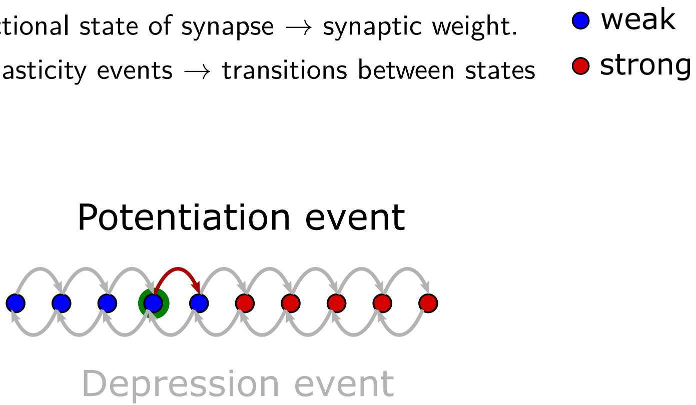

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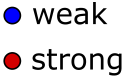

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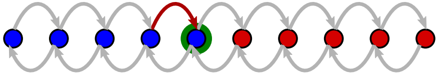

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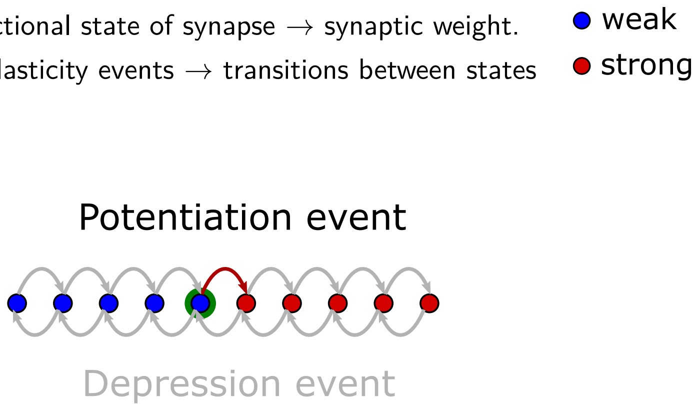

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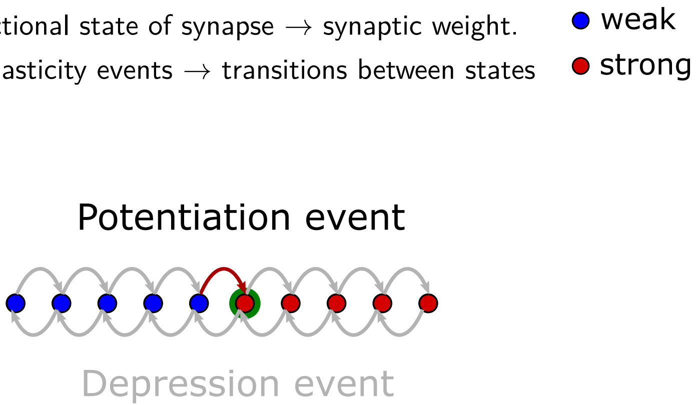

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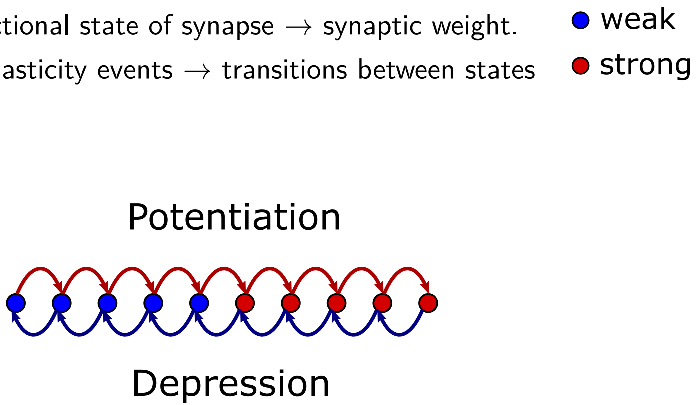

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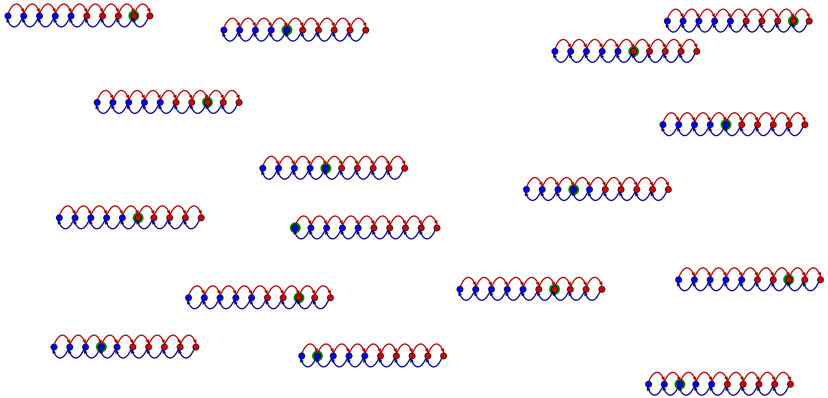
Modelling VOR experiments



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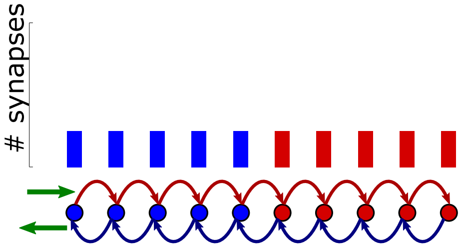
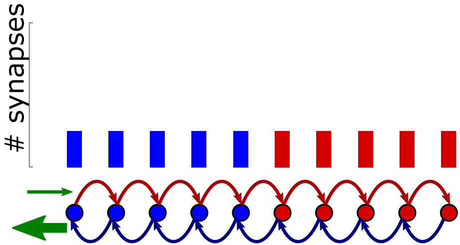


Modelling VOR experiments

PF-Pk LTD $\rightarrow$ VOR increase



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

Modelling VOR experiments

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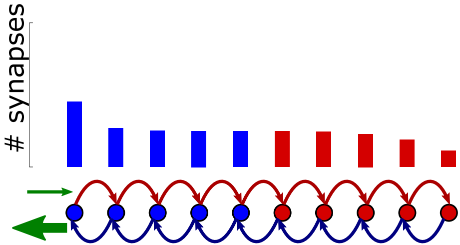

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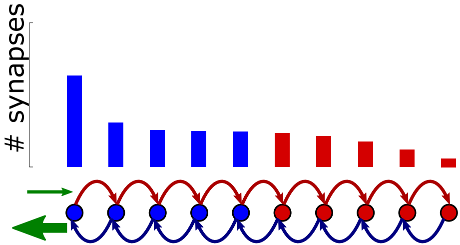

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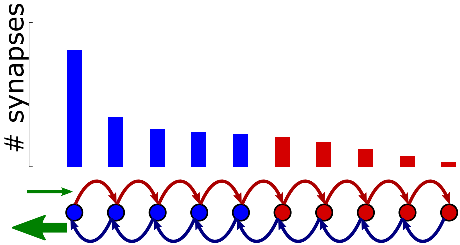

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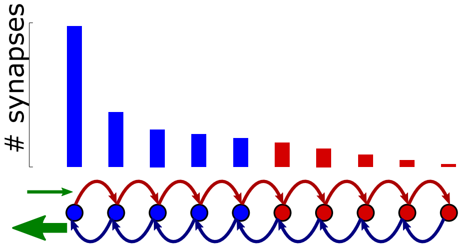

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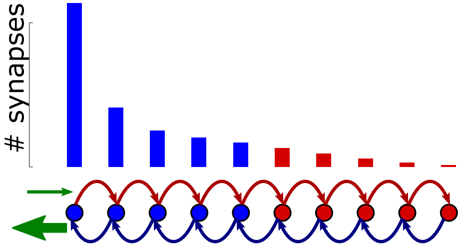

Training: different CF activity $\implies$
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Learning: decrease in average synaptic weight.

Modelling VOR experiments

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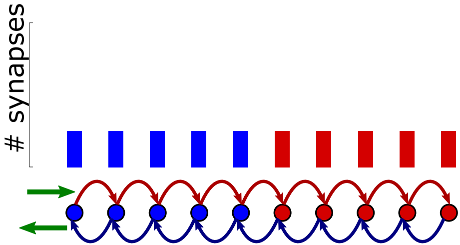

Training: different CF activity $\Longrightarrow$
change frequency of pot/dep events.

Learning: decrease in average synaptic weight.

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

Modelling VOR experiments

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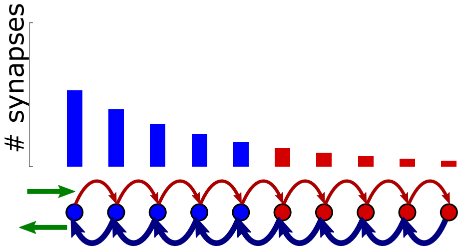

Training: different CF activity $\implies$
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Questions

Depletion effect competes with enhanced intrinsic plasticity.

Question 1: When is the depletion effect stronger?

Reverse training impairs learning in wild-type.

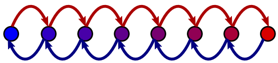
Question 2: How can replenishment *ever* impair learning?

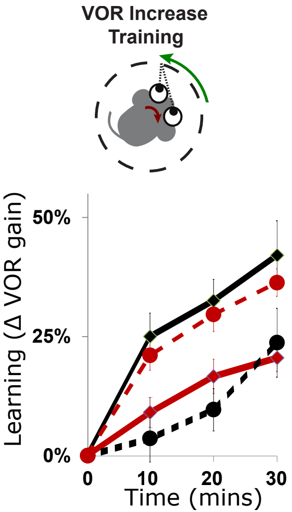
Enhanced plasticity $\rightarrow$ enhanced/impaired learning

Big question: Why? When?

Simple synapses cannot explain the data

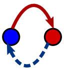
Multistate synapse

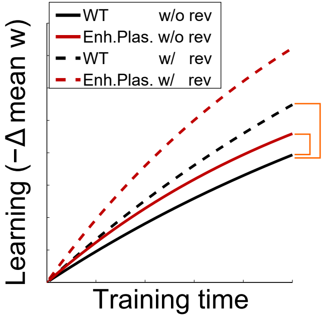




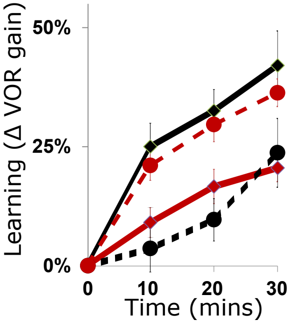
Simple synapses cannot explain the data

Two-state model

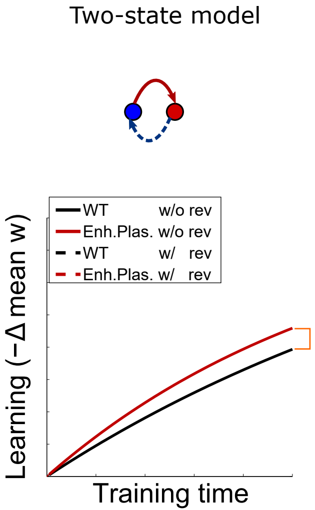


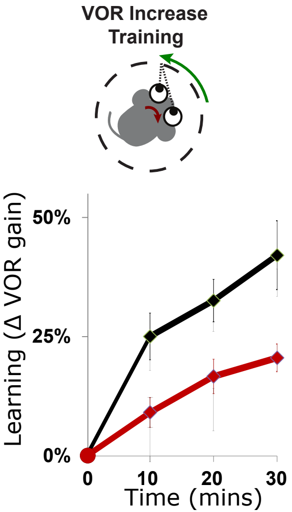


VOR Increase Training

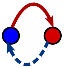


Simple synapses cannot explain the data

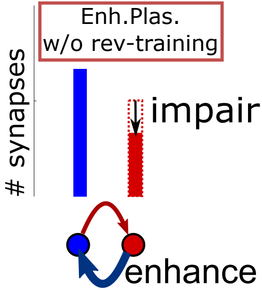




Two-state model



Initial distribution



depletion effect

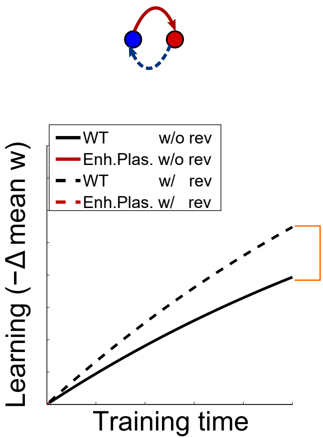
$<$

enhanced plasticity

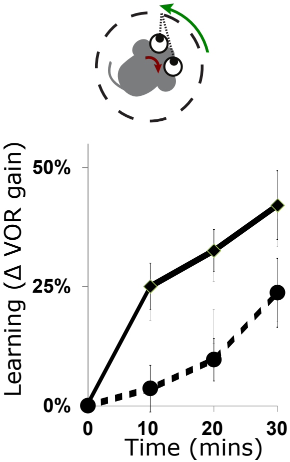
$\Longrightarrow$ enhanced learning

Simple synapses cannot explain the data

Two-state model

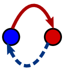


VOR Increase Training

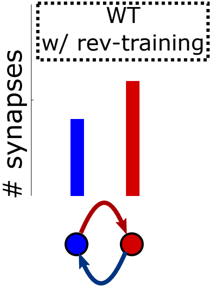


Simple synapses cannot explain the data

Two-state model



Initial distribution



reverse training

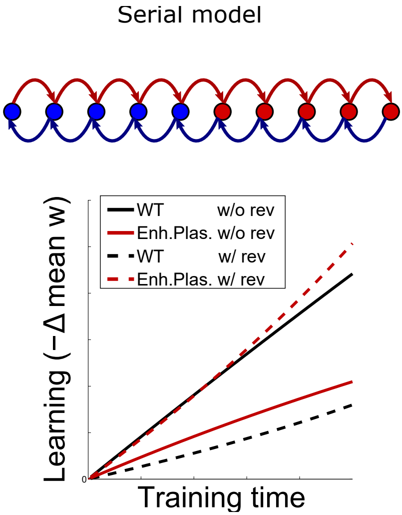
$\Longrightarrow$

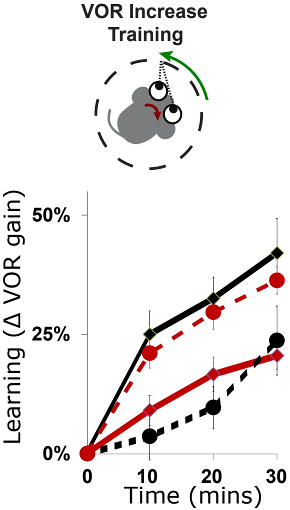
replenishment

$\Longrightarrow$

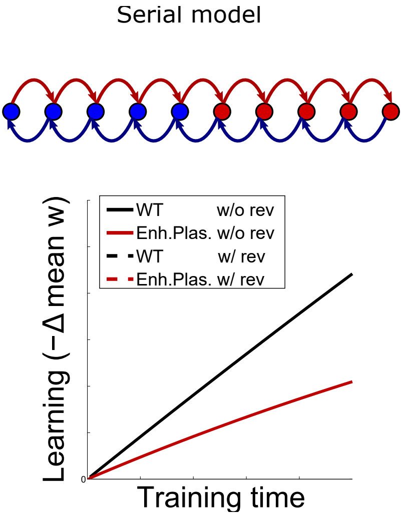
enhanced learning

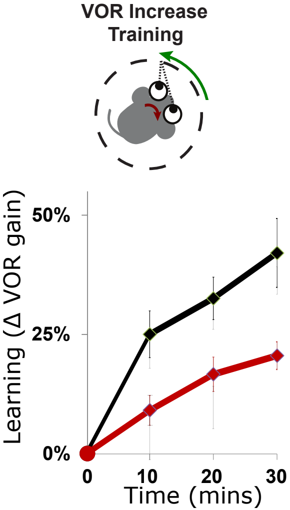
Complex metaplastic synapses can explain the data





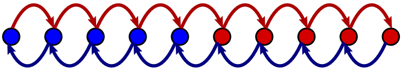
Complex metaplastic synapses can explain the data

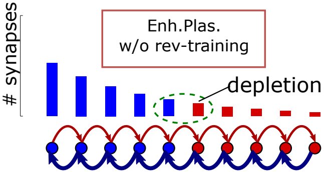




Complex metaplastic synapses can explain the data

Serial model





amplified depletion

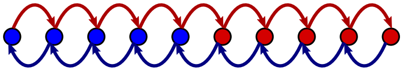
$>$

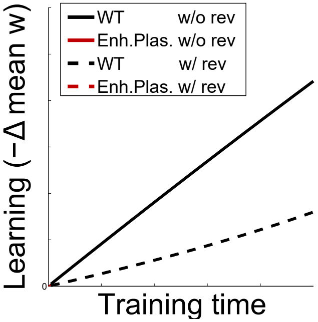
enhanced plasticity

$\Longrightarrow$ impaired learning

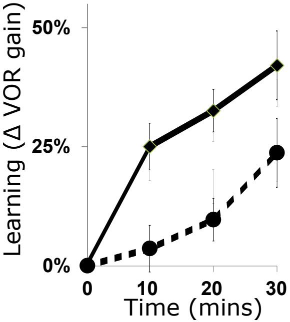
Complex metaplastic synapses can explain the data

Serial model



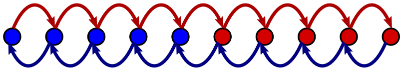


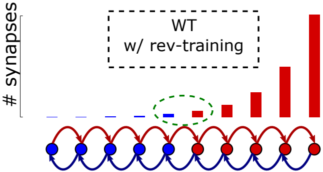
VOR Increase Training



Complex metaplastic synapses can explain the data

Serial model





reverse training

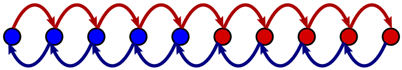
$+$

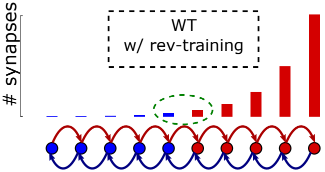
"stubborn" metaplasticity

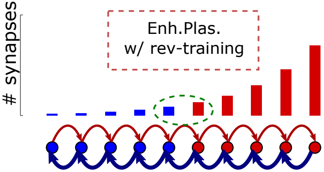
$\Longrightarrow$ impaired learning

Complex metaplastic synapses can explain the data

Serial model

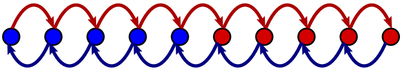






Complex metaplastic synapses can explain the data

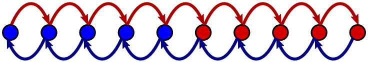
Serial model



starting point:
labile states
$\downarrow$
enhanced plasticity
$\implies$ impaired learning

starting point:
stubborn states
$\downarrow$
enhanced plasticity
$\implies$ enhanced learning

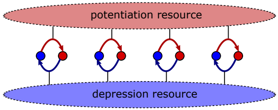
Essential features

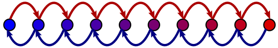


The success of the serial model relies on two features:

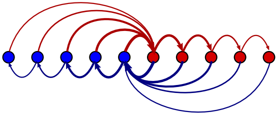
- Complexity - needed for depletion to dominate enhanced plasticity,
- Stubbornness - repeated potentiation impairs subsequent depression.

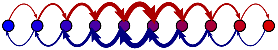
Fail:





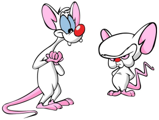
Succeed:





Conclusions

- Diverse behavioural patterns:
  Enhanced plasticity $\rightarrow$ enhance/impair learning (prior experience).
  Reverse-training $\rightarrow$ enhance/impair learning (plasticity rates).



- 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

Storage capacity of synaptic memory

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

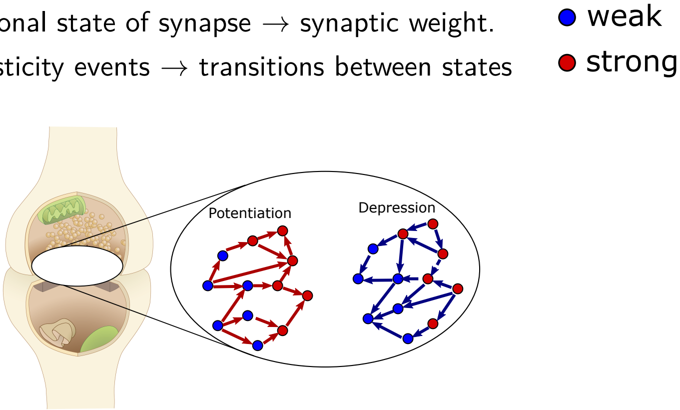
Assumes unbounded analog synapses

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.

There are N identical synapses with M internal functional states.

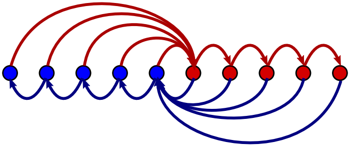
- Internal functional state of synapse → synaptic weight.
- Candidate plasticity events → transitions between states



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

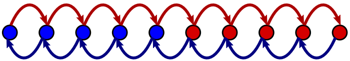
[Fusi et al. (2005), Fusi and Abbott (2007), Barrett and van Rossum (2008)]

Cascade model



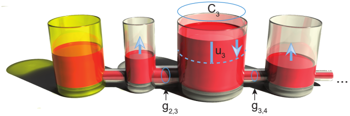
[Fusi et al. (2005)]

Serial model

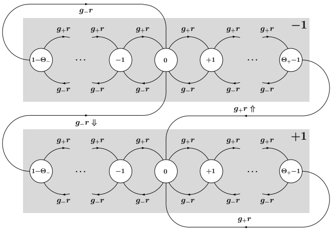


[Ben-Dayan Rubin and Fusi (2007)]

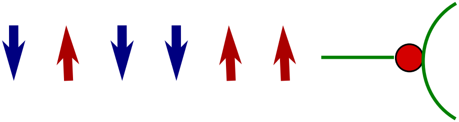
[Leibold and Kempter (2008)]



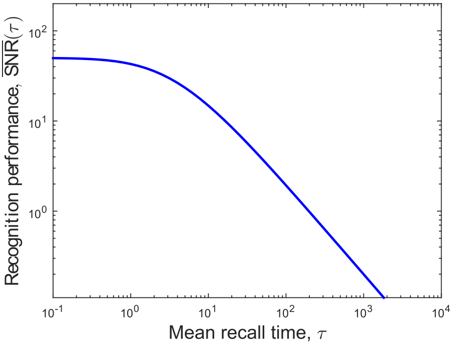
[Benna and Fusi (2016)]



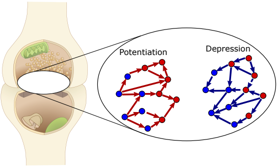
[Elliott (2011)]



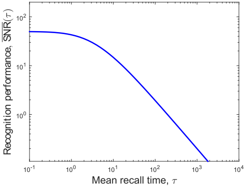
Synapses store a sequence of memories.
Recognition memory performance described by SNR.



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?

Parameters for synaptic dynamics

$$f^{\text{pot/dep}} = \text{fraction of events that are pot/dep},$$

pot. event: $M_{ij}^{\text{pot}} = \text{transition prob. } i \to j,$ $\qquad \mathbf{W}^{\text{pot}} = f^{\text{pot}}(\mathbf{M}^{\text{pot}} - I),$

dep. event: $M_{ij}^{\text{dep}} = \text{transition prob. } i \to j,$ $\qquad \mathbf{W}^{\text{dep}} = f^{\text{dep}}\left(\mathbf{M}^{\text{dep}} - I\right).$

Constraints:

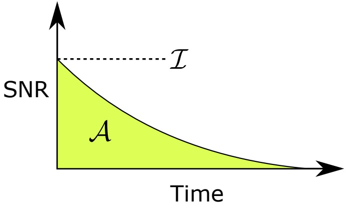
$$f^{\text{pot/dep}}, \mathbf{M}_{ij}^{\text{pot/dep}} \in [0, 1], \qquad f^{\text{pot}} + f^{\text{dep}} = \sum_j \mathbf{M}_{ij}^{\text{pot/dep}} = 1.$$

Memory curve given by

$$\begin{aligned} \overline{\text{SNR}}(\tau) &= \sqrt{N}\, \boldsymbol{\pi} \left(\mathbf{W}^{\text{pot}} - \mathbf{W}^{\text{dep}}\right) \left[\mathbf{I} - r\tau \left(\mathbf{W}^{\text{pot}} + \mathbf{W}^{\text{dep}}\right)\right]^{-1} \mathbf{w}. \\ &= \sqrt{N} \sum_a \frac{\mathcal{I}_a}{1 + r\tau/\tau_a}. \end{aligned}$$

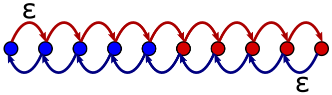
Initial SNR:

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



Area under curve:

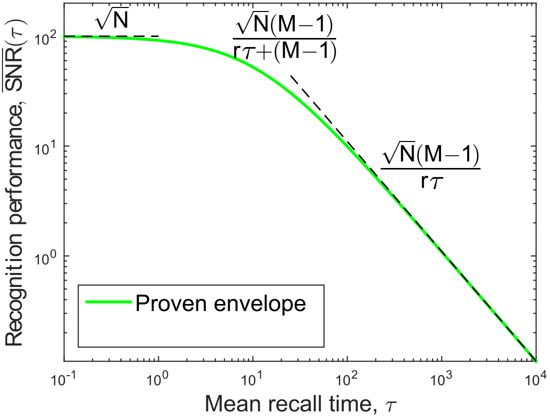
$$\mathcal{A} = \int_0^\infty \mathrm{SNR}(t)\,\mathrm{d}t = \sum_a \mathcal{I}_a \tau_a \leq \sqrt{N}(M-1)/r.$$



[Lahiri and Ganguli (2013)]

Proven envelope: memory frontier

Upper bound on memory curve at *any* timescale.



Proven envelope: memory frontier

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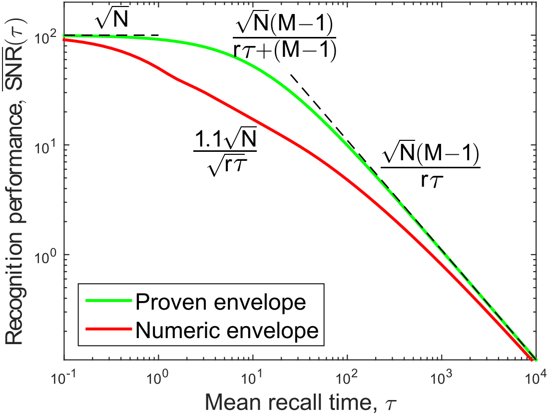
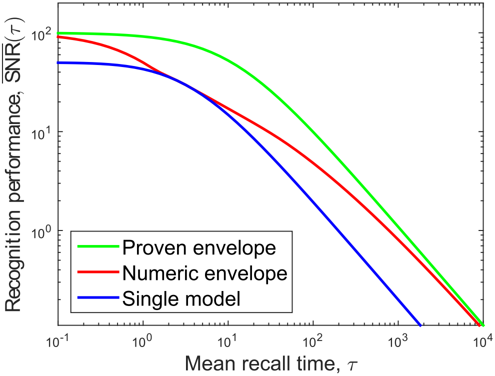
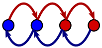
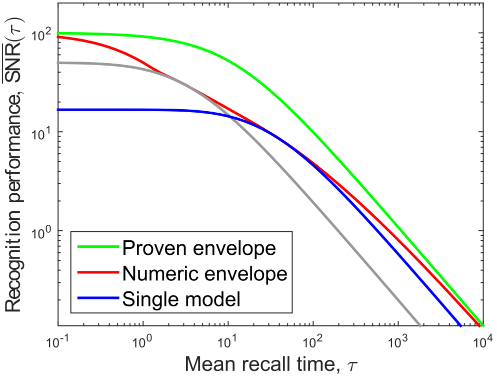
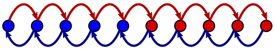


Models that maximize memory for one timescale






Recognition performance, $\overline{\mathrm{SNR}}(\tau)$
10^2
10^1
10^0
Proven envelope
Numeric envelope
Single model
10^{-1}
10^0
10^1
10^2
10^3
10^4
Mean recall time, τ



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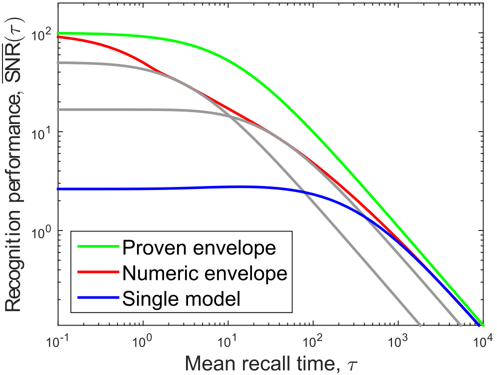
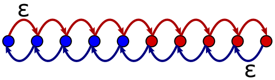
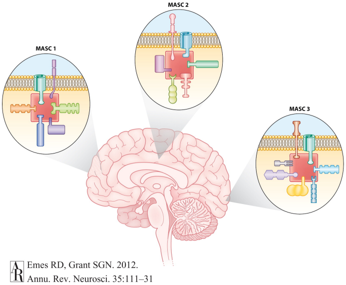




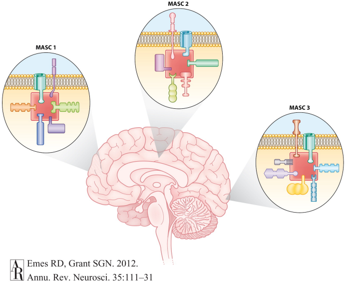
Synaptic diversity and timescales of memory

Different synapses have different molecular structures.



[Emes and Grant (2012)]

Different synapses have different molecular structures.

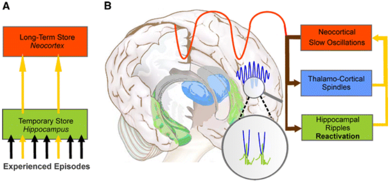


[Emes and Grant (2012)]

Memories stored in different places for different timescales

[Squire and Alvarez (1995)]

[McClelland et al. (1995)]



[Born and Wilhelm (2012)]

Also: Cerebellar cortex $\to$ nuclei.

[Attwell et al. (2002)]

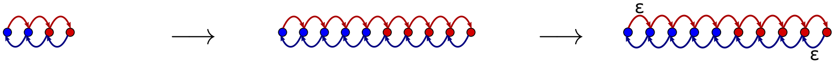
[Cooke et al. (2004)]

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



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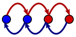
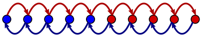
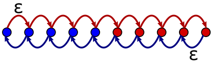
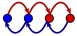
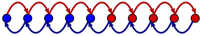
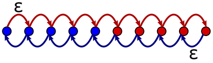
 $\longrightarrow$  $\longrightarrow$ 

short topology $\longrightarrow$ long topology

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
	$\longrightarrow$		$\longrightarrow$	
short topology	$\longrightarrow$	long topology		
		deterministic synapse	$\longrightarrow$	stochastic synapse

Section 3

Designing experiments

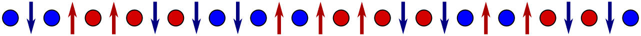
Experimental tests?

Traditional experiments:

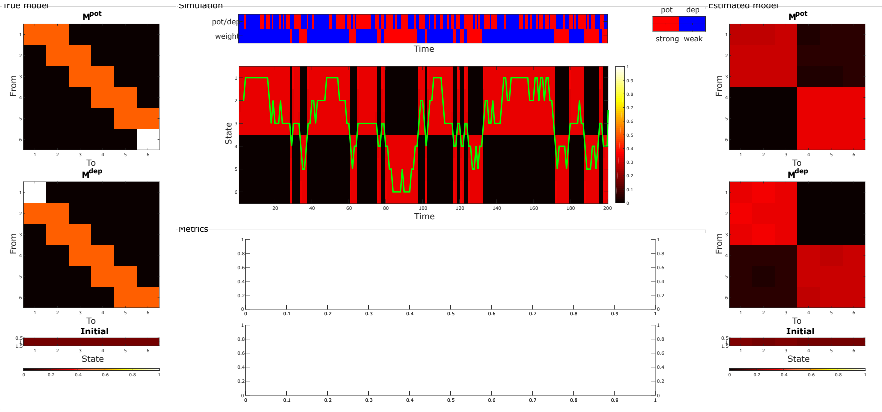
Experimental tests?

Traditional experiments:

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



Simulated experiment



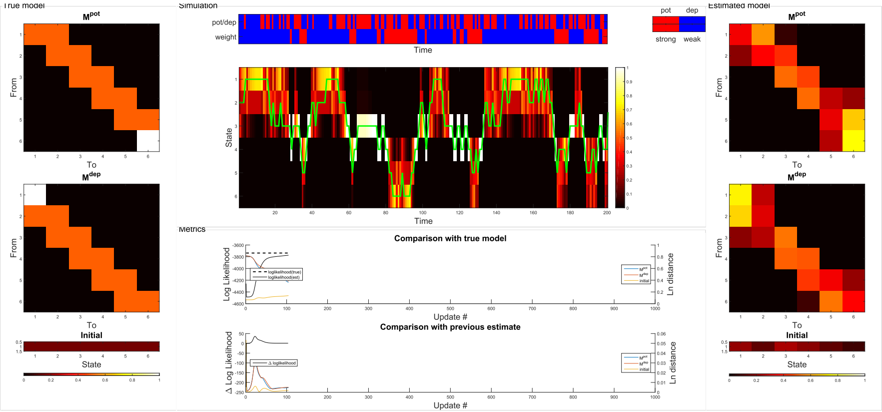
EM algorithms:

Sequence of hidden states → estimate transition probabilities

Transition probabilities → estimate sequence of hidden states

[Baum et al. (1970), Rabiner and Juang (1993), Dempster et al. (2007)]

Simulated experiment



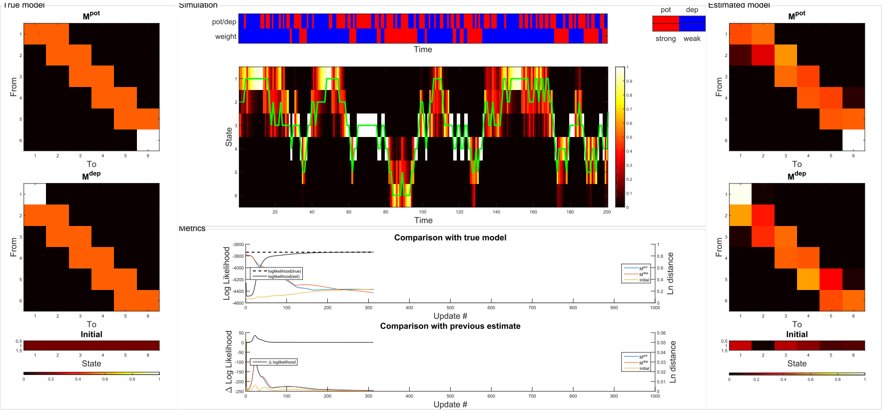
EM algorithms:

Sequence of hidden states → estimate transition probabilities

Transition probabilities → estimate sequence of hidden states

[Baum et al. (1970), Rabiner and Juang (1993), Dempster et al. (2007)]

Simulated experiment



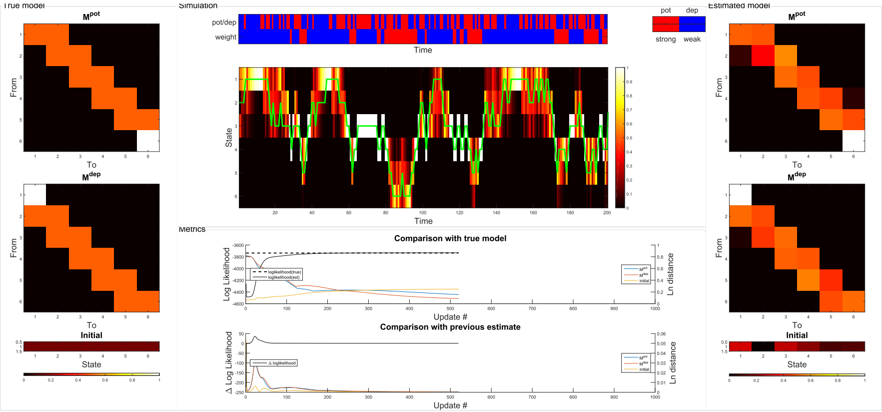
EM algorithms:

Sequence of hidden states $\rightarrow$ estimate transition probabilities

Transition probabilities $\rightarrow$ estimate sequence of hidden states

[Baum et al. (1970), Rabiner and Juang (1993), Dempster et al. (2007)]

Simulated experiment

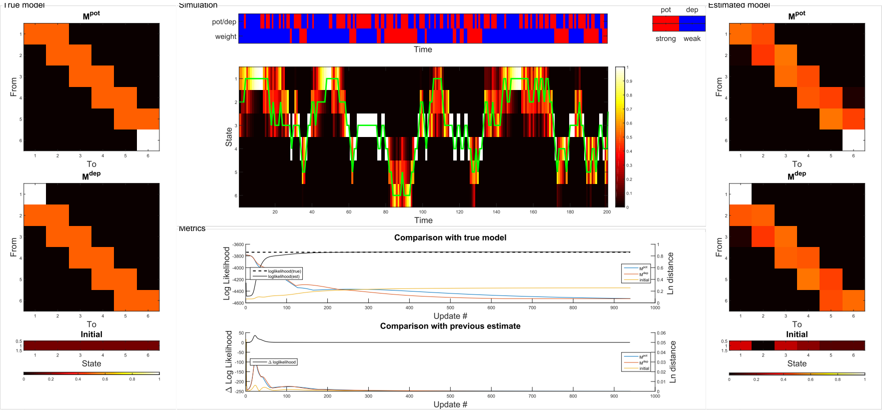


EM algorithms:

Sequence of hidden states → estimate transition probabilities

Transition probabilities → estimate sequence of hidden states

[Baum et al. (1970), Rabiner and Juang (1993), Dempster et al. (2007)]



EM algorithms:

Sequence of hidden states → estimate transition probabilities

Transition probabilities → estimate sequence of hidden states

[Baum et al. (1970), Rabiner and Juang (1993), Dempster et al. (2007)]

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.

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

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Christopher Stock
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Aparna Suvrathan
Rhea Kimpo

Carla Shatz
Hanmi Lee

Marcus Benna

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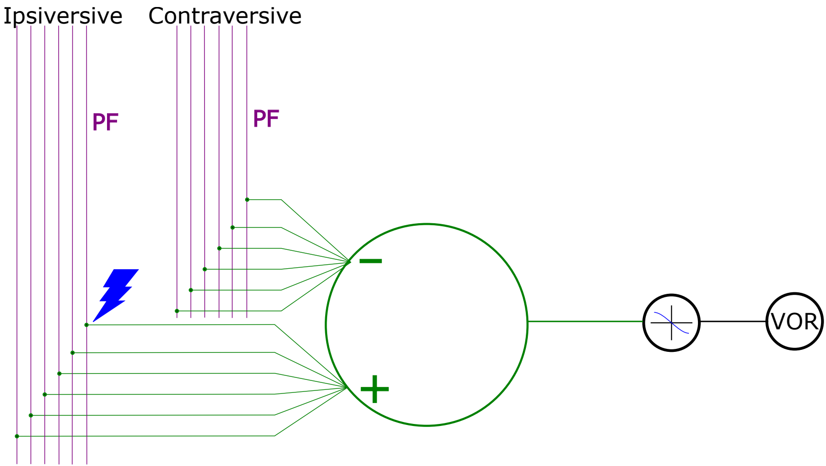
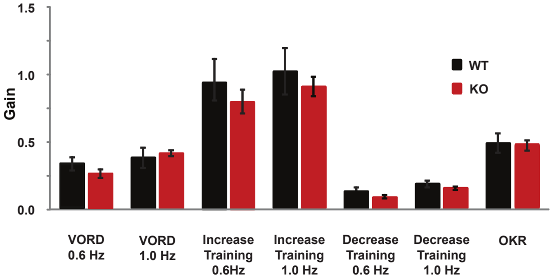
Model of circuit

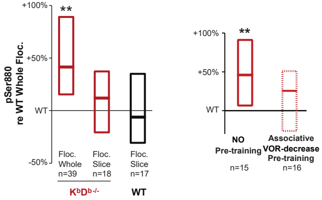


Baseline



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



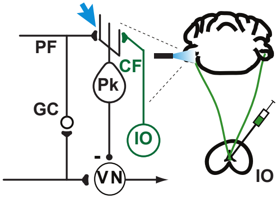
Basal level of GluR2 phosphorylation at serine 880 in AMPA receptor.

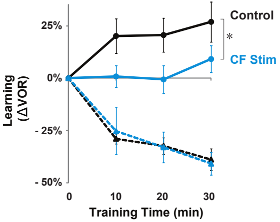
Biochemical signature of PF-Pk LTD.

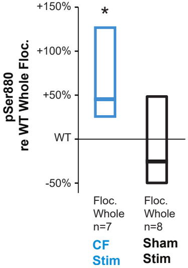
Shows that # depressed synapses in flocculus is larger in KO than WT.

Evidence: saturation by CF stimulation

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

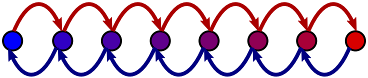




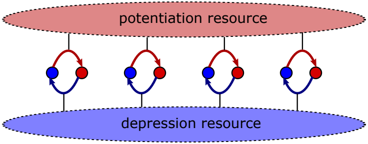


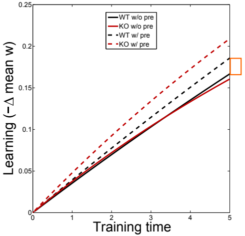
Other models that fail

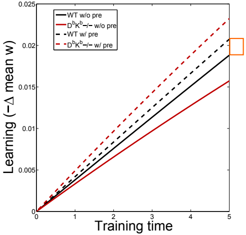
Multistate synapse



Pooled resource model



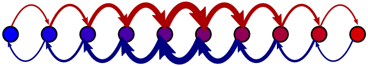


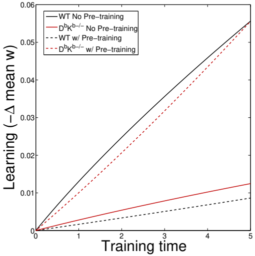


[Amit and Fusi (1994)]

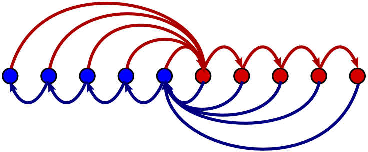
Other models that work

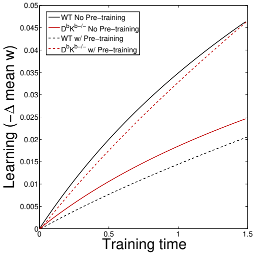
Non-uniform multistate model





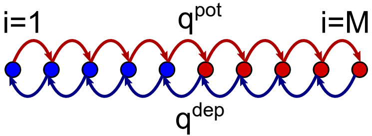
Cascade model





[Fusi et al. (2005)]

Mathematical explanation



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

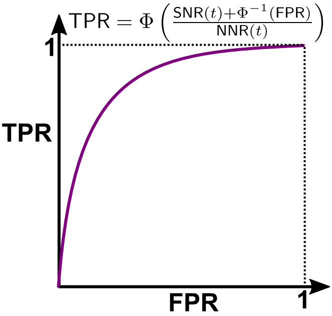
Learning rate $\sim \pi_{M/2}\left(\frac{q^{\text{dep}}}{q^{\text{pot}}}\right) = \mathcal{N}\left(\frac{q^{\text{pot}}}{q^{\text{dep}}}\right)^{\frac{M}{2}-1}$.

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



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

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

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

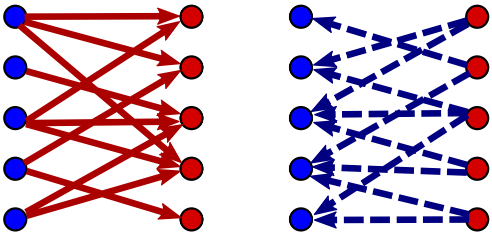
Also: KL divergence, Chernoff distance, ...

Initial SNR as flux

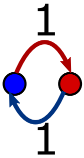
Initial SNR is closely related to flux between strong & weak states

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

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



Two-state model equivalent to previous slide:

Transitions: 

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

Maximal initial SNR:

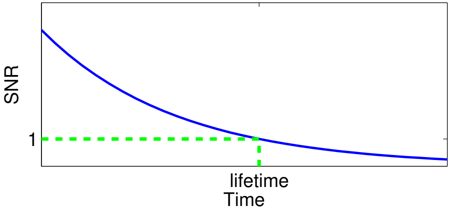
$$\mathrm{SNR}(0) \leq \sqrt{N}.$$

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:

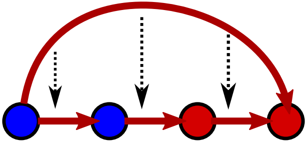
$$\mathcal{A} \leq \sqrt{N}(M-1)/r.$$

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

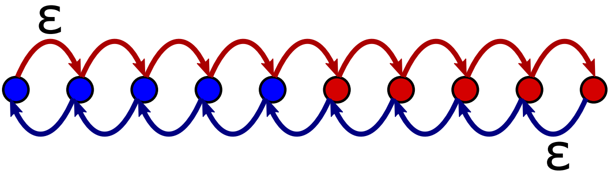
$$A = \frac{2\sqrt{N}}{r} \sum_k \pi_k \left| k - \langle k \rangle \right| .$$

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)]

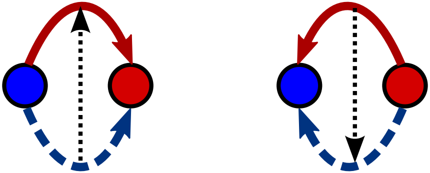
We define:

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

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

Technical detail: upper/lower triangular

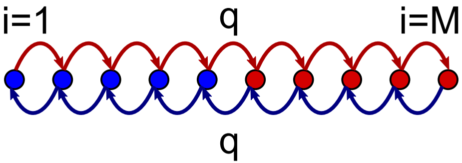
With states in order:



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

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

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