

# Learning and memory with complex synaptic plasticity

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Stanford University, Applied Physics

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# What is a synapse?

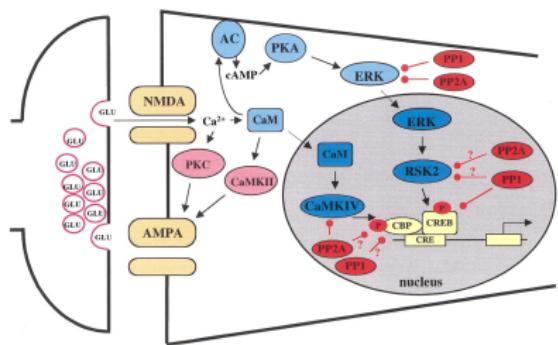
Experimentalists

Theorists

# What is a synapse?

Experimentalists

Theorists

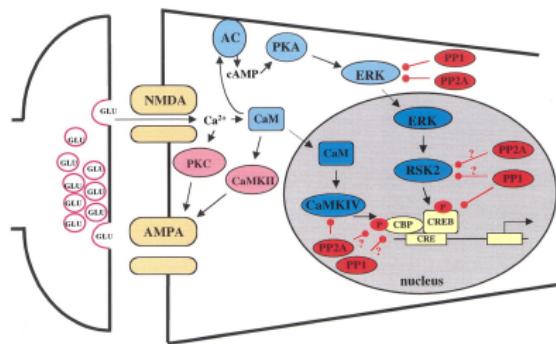


[Klann (2002)]

# What is a synapse?

Experimentalists

Theorists



$$W_{ij}$$

[Klann (2002)]

# Storage capacity of synaptic memory

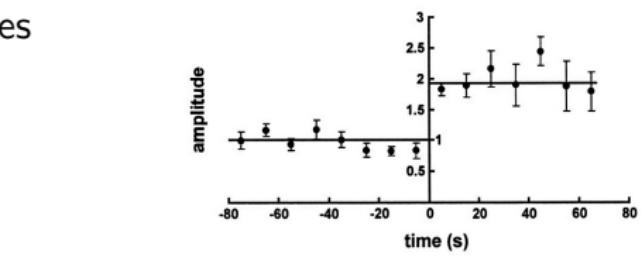
Hopfield, perceptron models have capacity  $\propto N$ , (# synapses).

Assumes unbounded analogue synapses

With discrete, finite synapses:

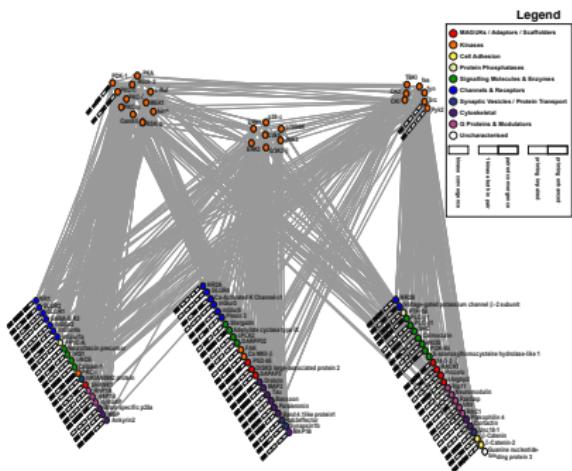
$\implies$  memory capacity  $\sim \mathcal{O}(\log N)$ .

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

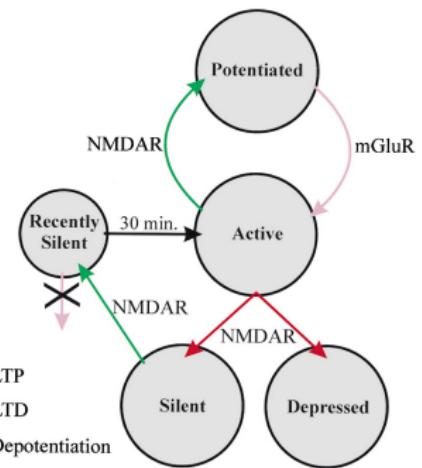


[Petersen et al. (1998), O'Connor et al. (2005)]

# Synapses are complex

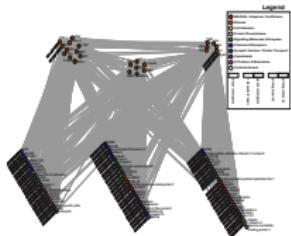


[Coba et al. (2009)]

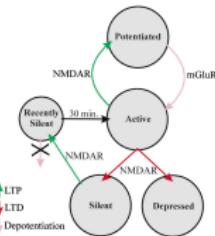


[Montgomery and Madison (2002)]

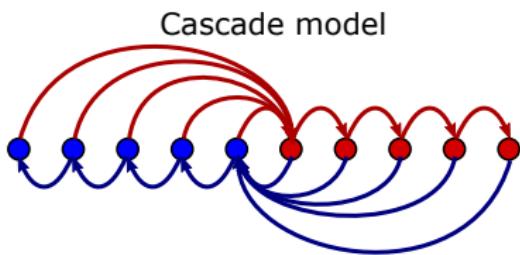
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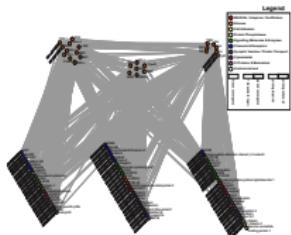


Cascade model

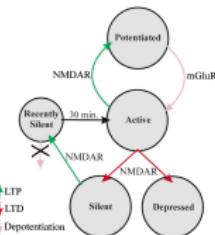
$$\text{Capacity} \propto N^{2/3}.$$

[Fusi et al. (2005)]

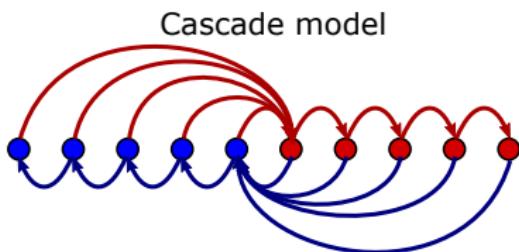
# Synapses are complex



[Coba et al. (2009)]



[Montgomery and Madison (2002)]



Cascade model

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 learning
- Learning outcomes of mice and models

## 2 Memory over different timescales

- Quantifying memory quality
- Frontiers of memory
- Implications of memory limits

## 3 Designing experiments

# Section 1

## Learning with enhanced plasticity

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

# Overview

Learning requires synaptic plasticity.

Expect: enhanced plasticity → enhanced learning.

[Tang et al. (1999), Malleret et al. (2001), Guan et al. (2009)]



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[Migaud et al. (1998), Uetani et al. (2000), Hayashi et al. (2004)]

[Cox et al. (2003), Rutten et al. (2008), Koekkoek et al. (2005)]



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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 training

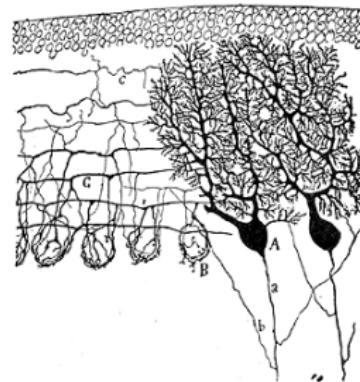
## VOR Increase Training



## VOR Decrease Training



VOR increase:  
VOR decrease:



[Cajal]

LTD in PF-Pk synapses.  
different mechanism,  
also reverses LTD in PF-Pk.

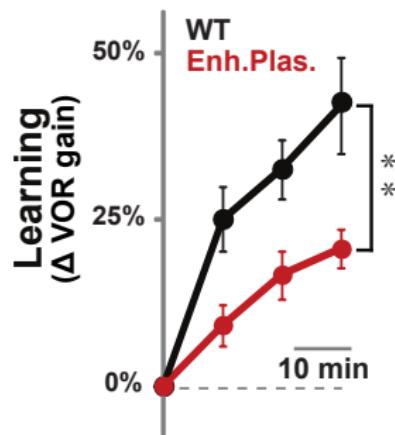
[Marr (1969), Albus (1971), Ito (1972)]

# Depletion hypothesis

Knockout of MHC-I K<sup>b</sup>D<sup>b</sup> molecules in PF-Pk synapses

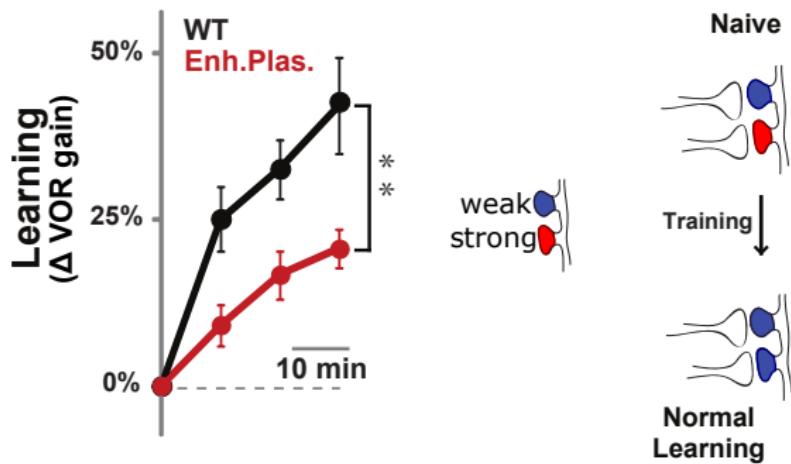
→ lower threshold for LTD → enhanced learning of Rotarod task.

[McConnell et al. (2009)]



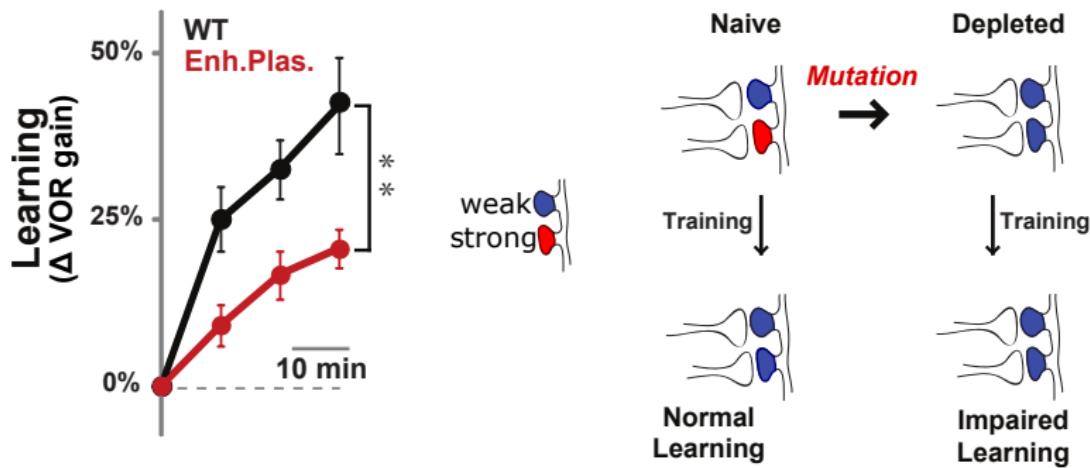
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Learning rate  $\sim$  intrinsic plasticity rate  $\times$  # synapses available for LTD.



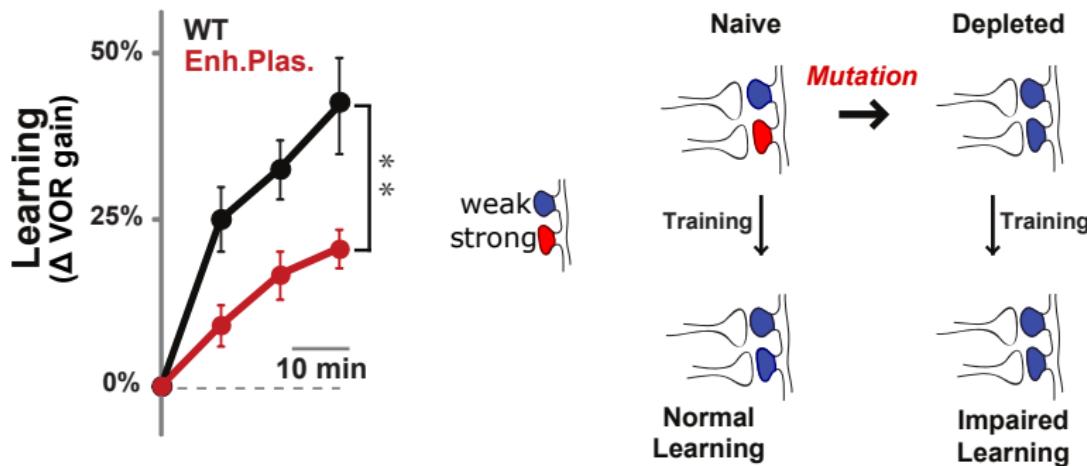
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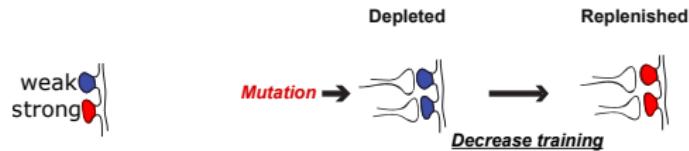


Question 1: depletion effect competes with enhanced intrinsic plasticity.  
When is depletion effect stronger?

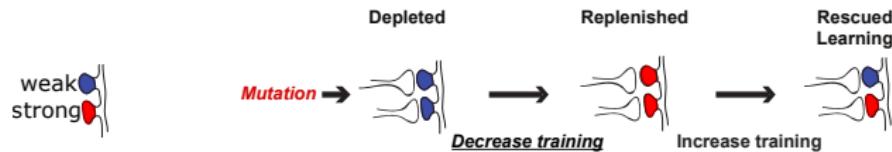
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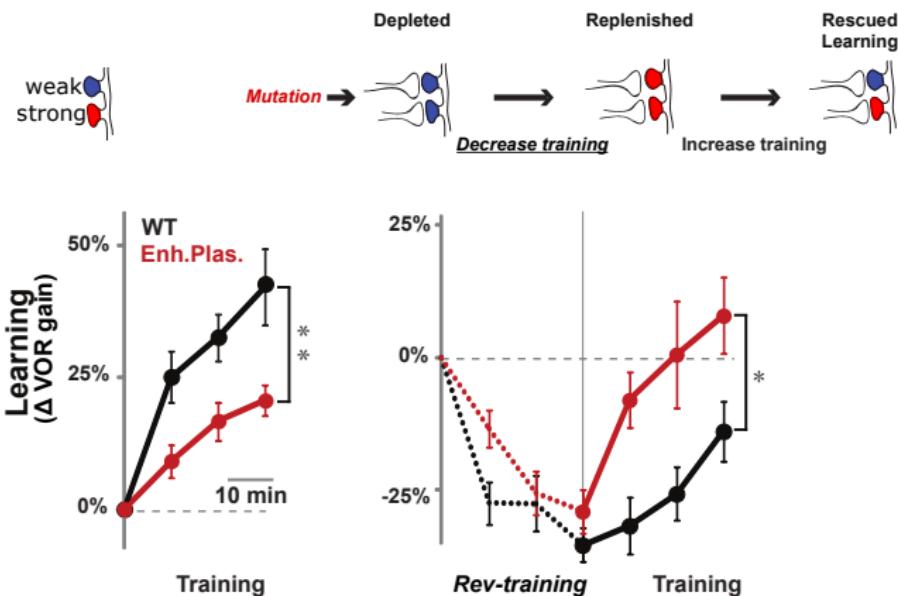
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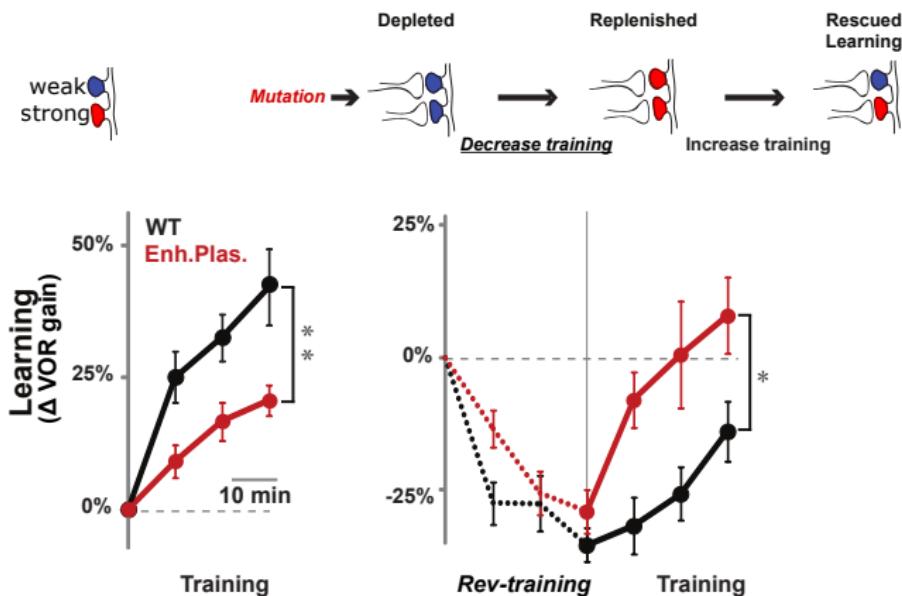
# Replenishment by reverse-training



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# Replenishment by reverse-training



Question 2: When does enhanced plasticity impair learning?

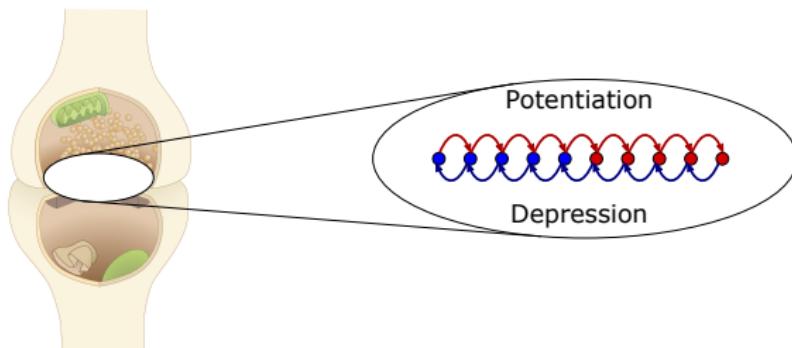
# Models of complex synaptic dynamics



# Models of complex synaptic dynamics

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

weak  
strong



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

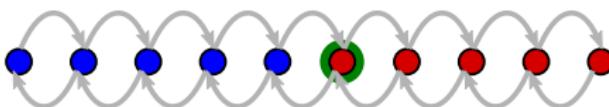
[Fusi et al. (2005), Fusi and Abbott (2007), Barrett and van Rossum (2008)]

[Smith et al. (2006); Lahiri and Ganguli (2013)]

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Potentiation event

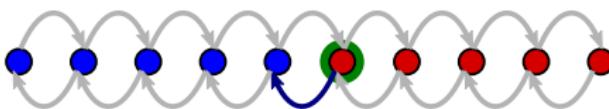


Depression event

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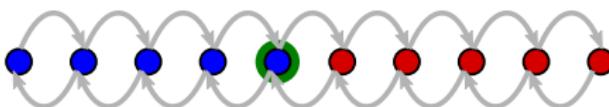


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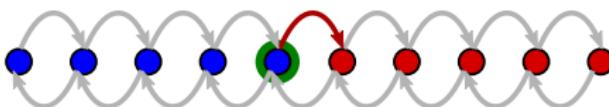


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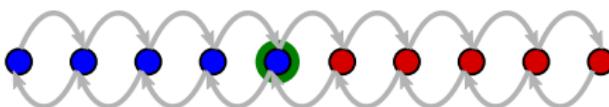


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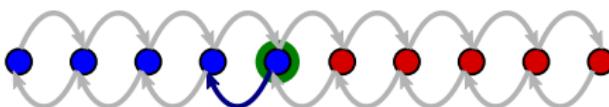


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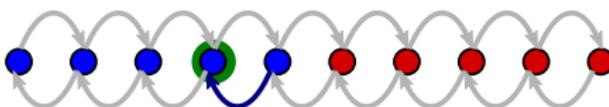
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Metaplasticity: change propensity for plasticity  
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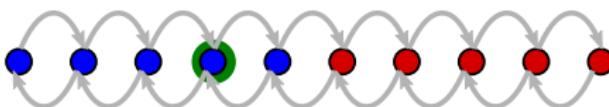
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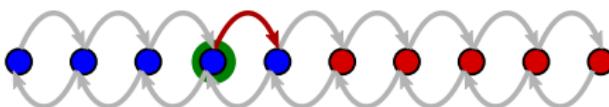
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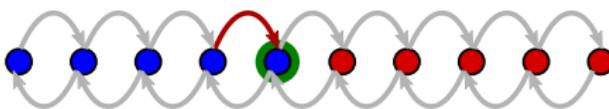
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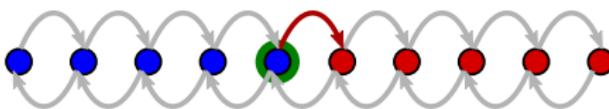
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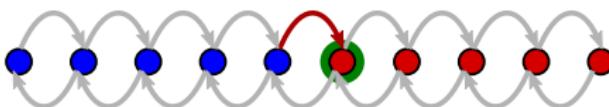
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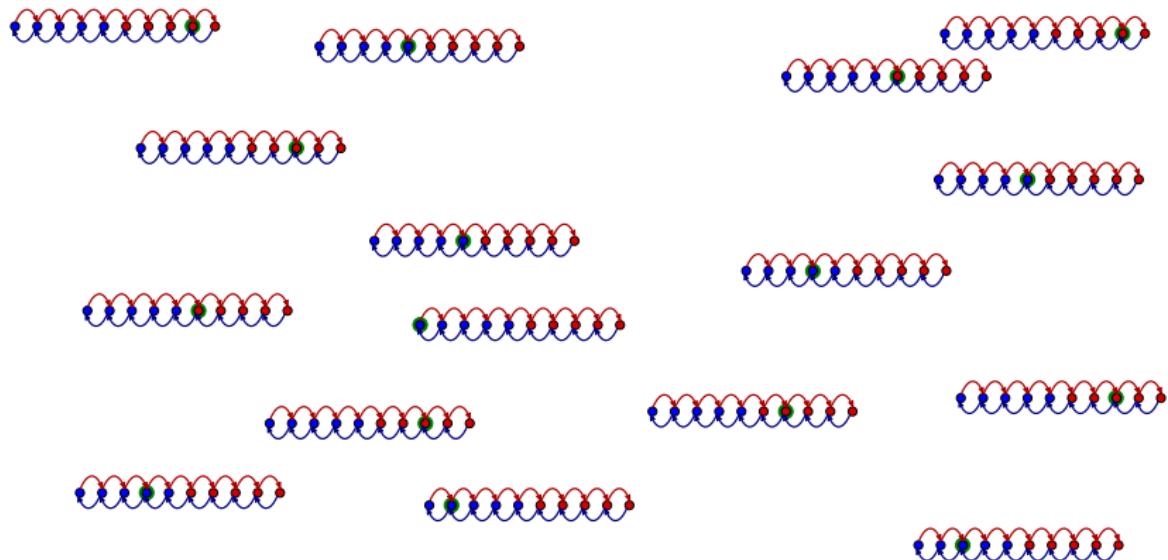
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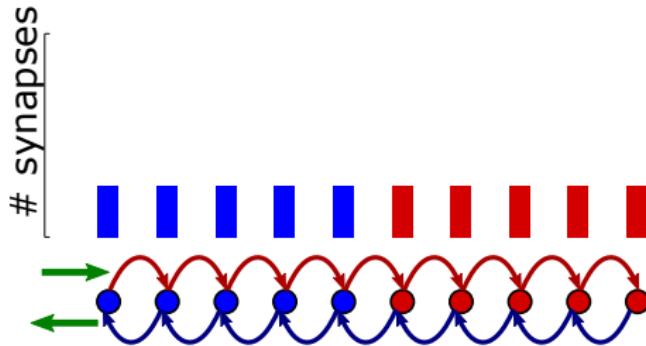
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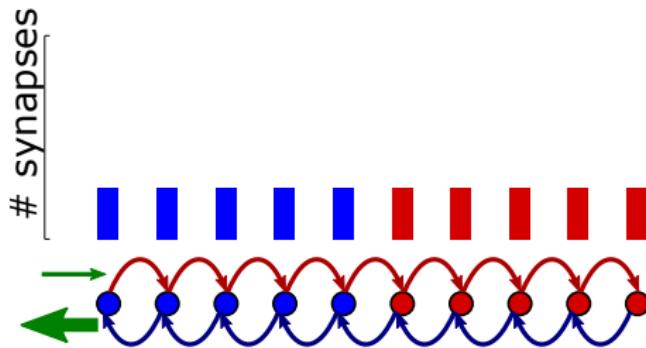
# Modelling VOR experiments



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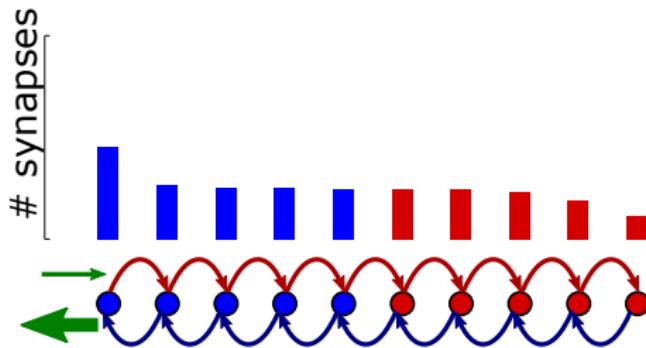


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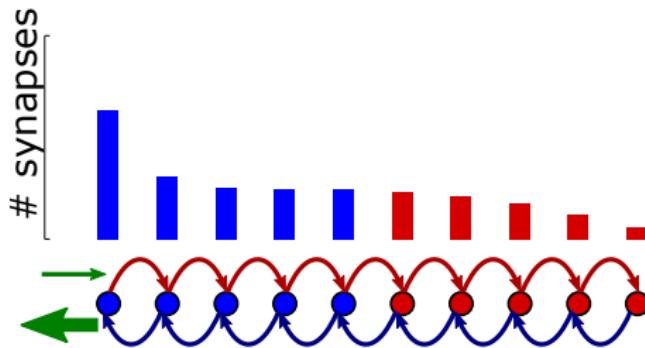
Training: change frequency of pot/dep events.

# Modelling VOR experiments



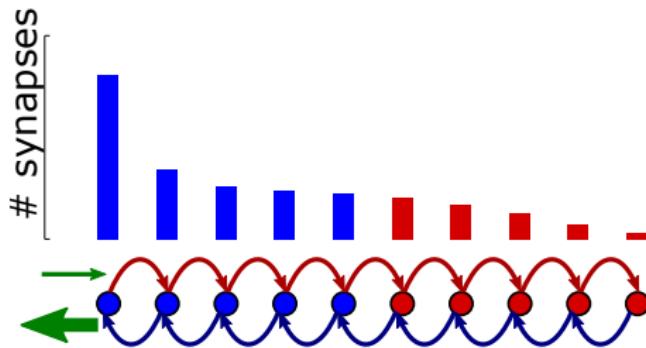
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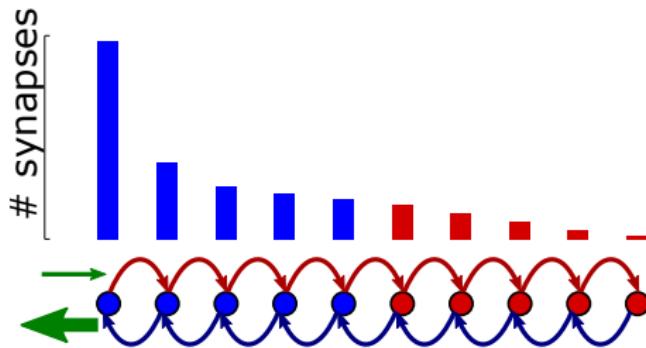
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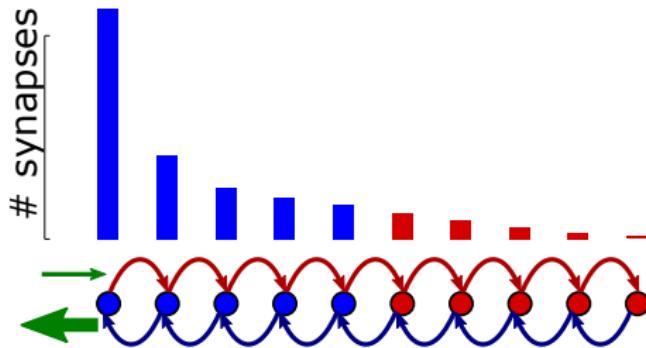
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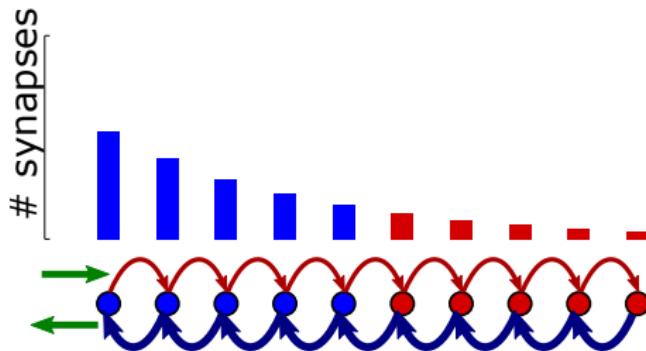
# Modelling VOR experiments



Training: change frequency of pot/dep events.

Learning: decrease in average synaptic weight.

# Modelling VOR experiments



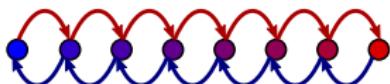
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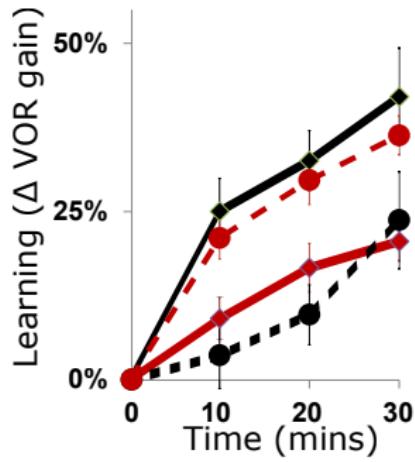
Mutation: increase transition probability for depression events.

# Simple synapses cannot explain the data

Multistate synapse

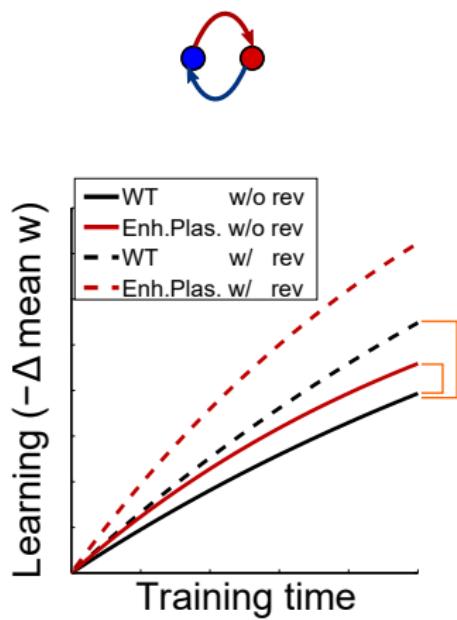


VOR Increase  
Training

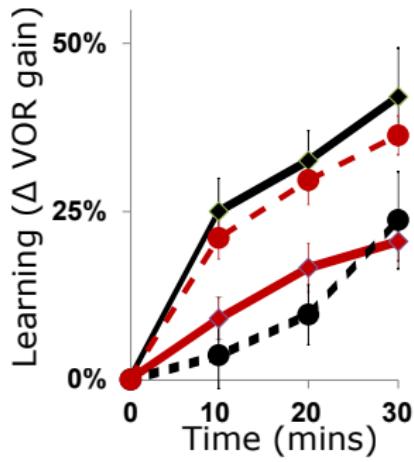


# Simple synapses cannot explain the data

Two-state model

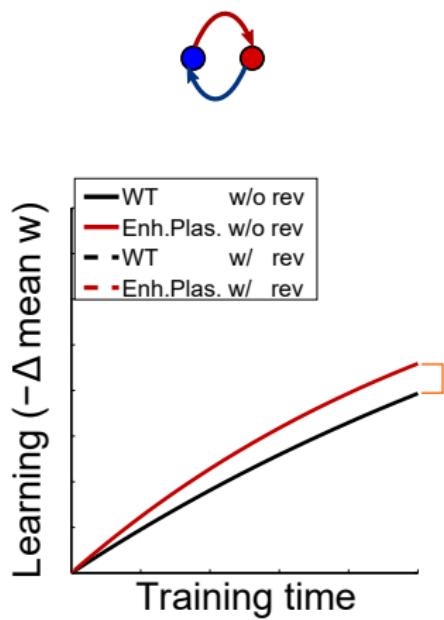


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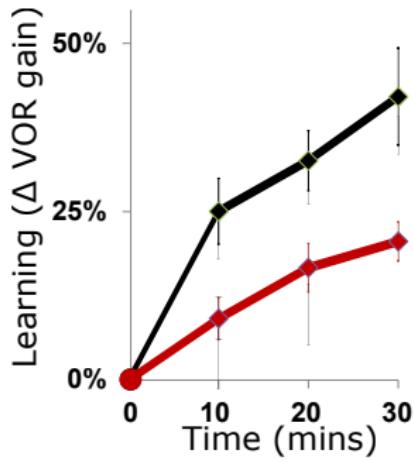


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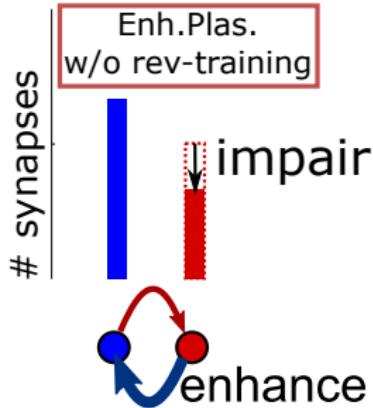


# Simple synapses cannot explain the data

## Two-state model



Initial distribution

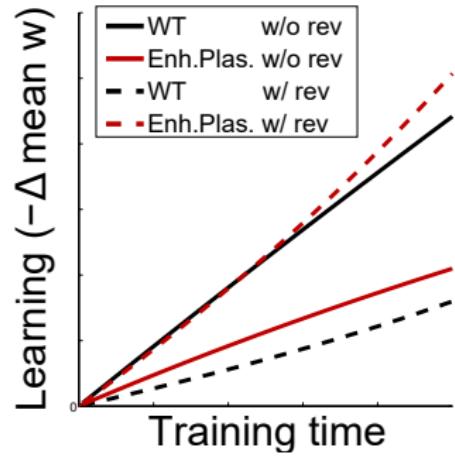
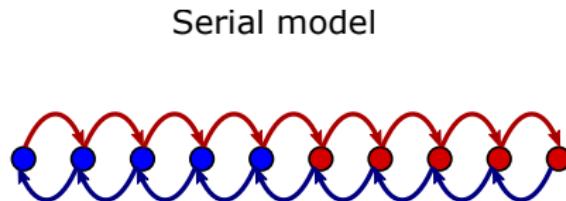


depletion effect

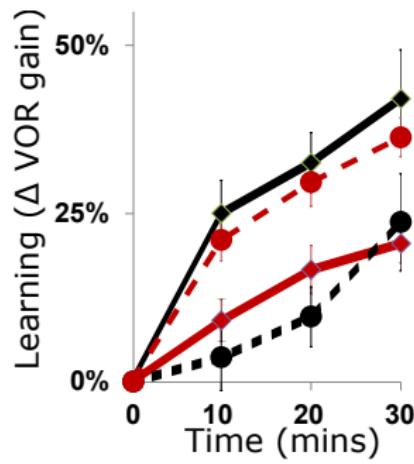
<  
enhanced plasticity

⇒ enhanced learning

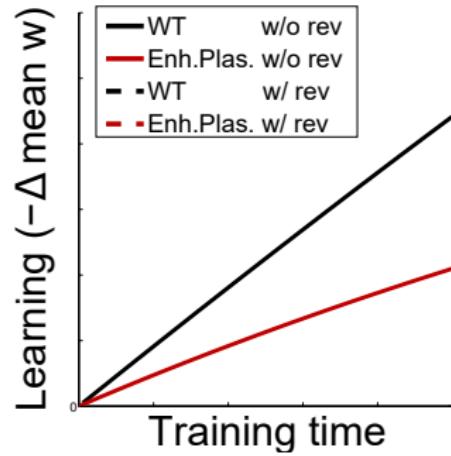
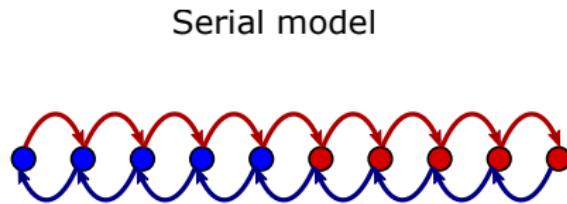
# Complex metaplastic synapses can explain the data



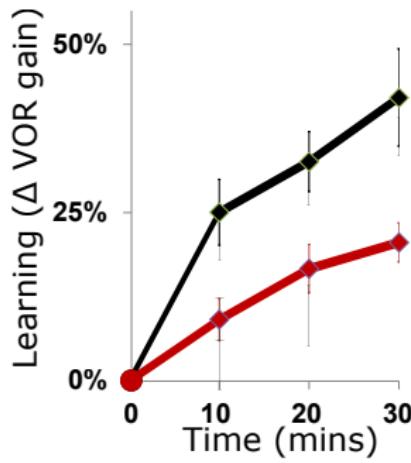
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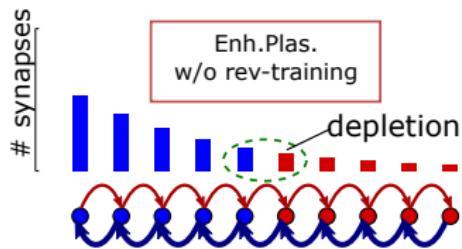
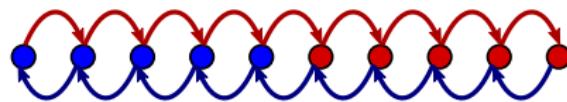


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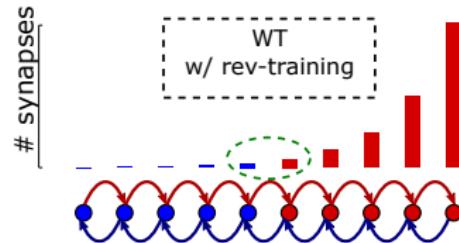
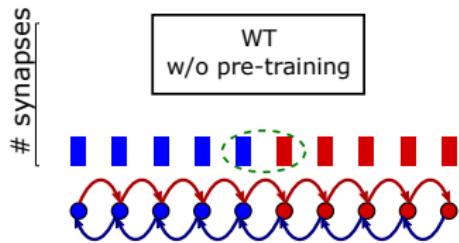
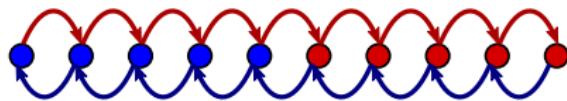
Serial model



amplified depletion  
>  
enhanced plasticity  
⇒ impaired learning

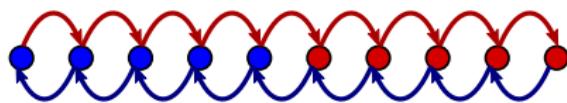
# Complex metaplastic synapses can explain the data

Serial model



# Complex metaplastic synapses can explain the data

Serial model



starting point:  
labile states



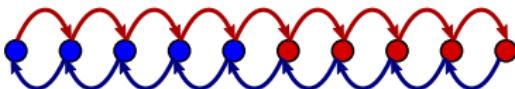
enhanced plasticity  
⇒ impaired learning

starting point:  
stubborn states



enhanced plasticity  
⇒ enhanced learning

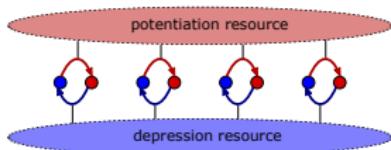
# Essential features



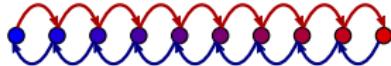
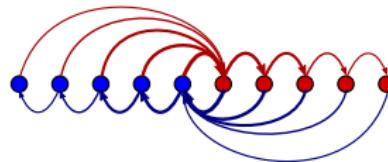
The success of the serial model relies on two features:

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

Fail:



Succeed:



## Section 2

### Memory over different timescales

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

# Storage capacity of synaptic memory

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

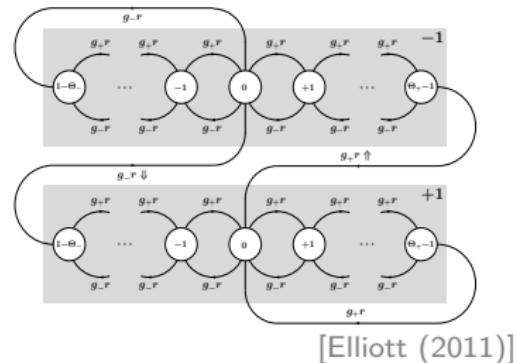
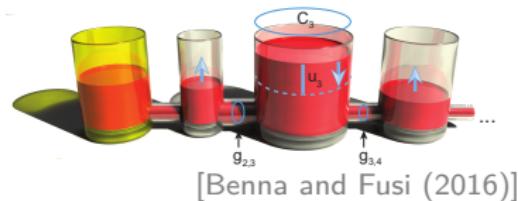
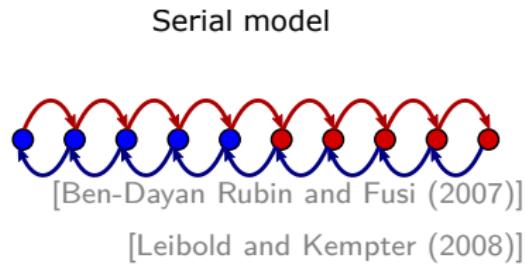
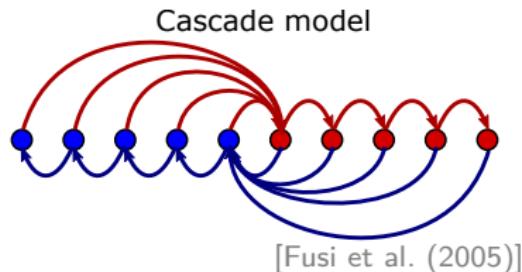
Assumes unbounded analogue synapses

With discrete, *finite* synapses:  $\implies$  memory capacity  $\sim \mathcal{O}(\log N)$ .

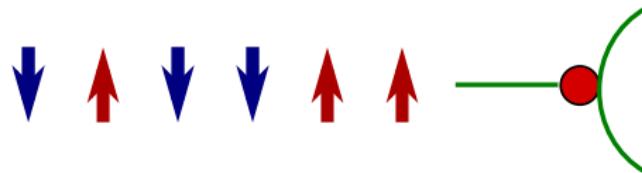
[Amit and Fusi (1992), Amit and Fusi (1994)]

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

# Specific models of complex synaptic dynamics

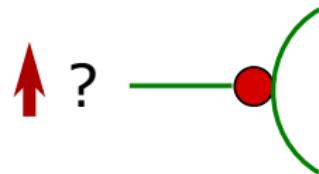


# Synaptic memory curves



Synapses store a sequence of memories.

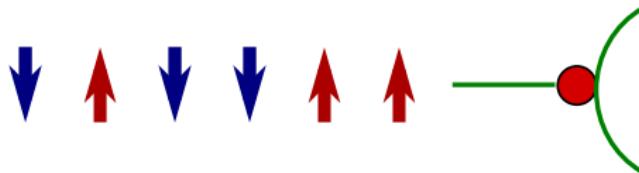
# Synaptic memory curves



Synapses store a sequence of memories.

Recognition memory: has this pattern been seen before?

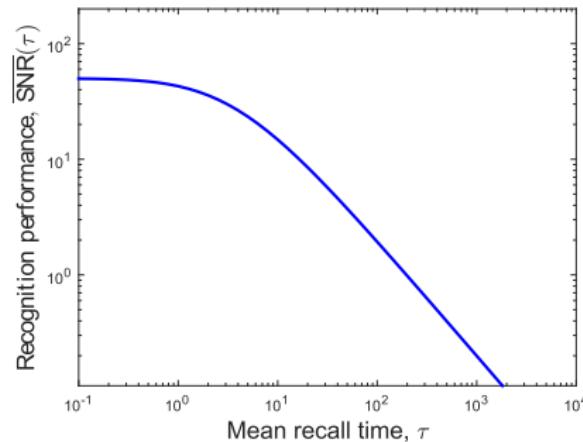
# Synaptic memory curves



Synapses store a sequence of memories.

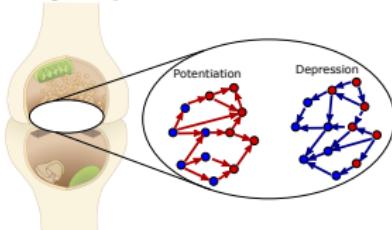
Recognition memory: has this pattern been seen before?

Performance described by SNR.

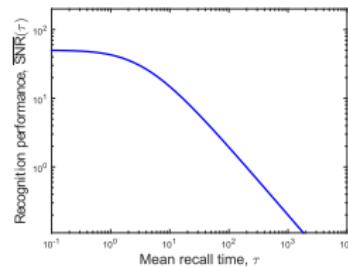


# General principles relating structure and function?

## Synaptic structure



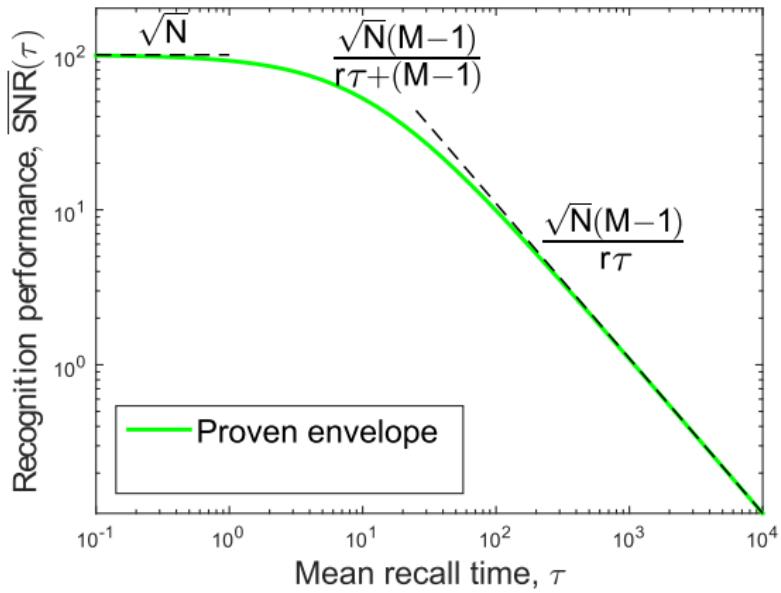
## Synaptic function



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

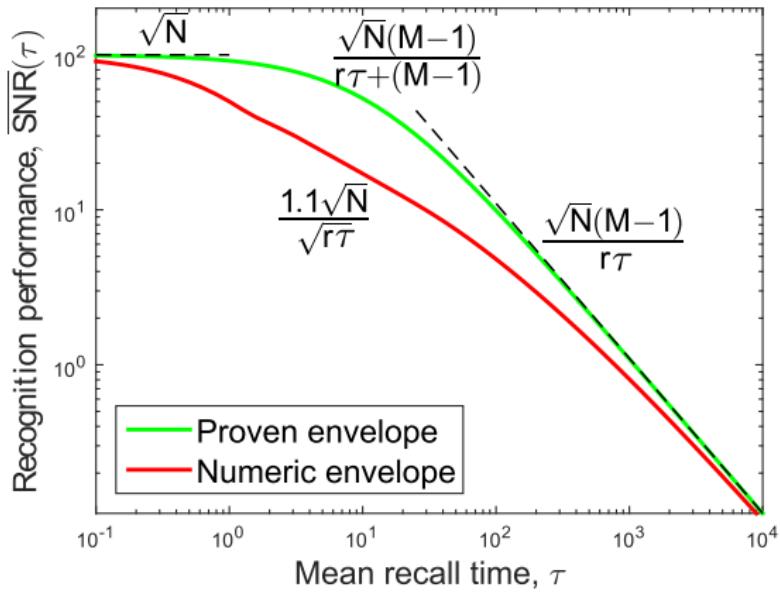
# Proven envelope: memory frontier

Upper bound on memory curve at *any* timescale.

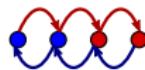
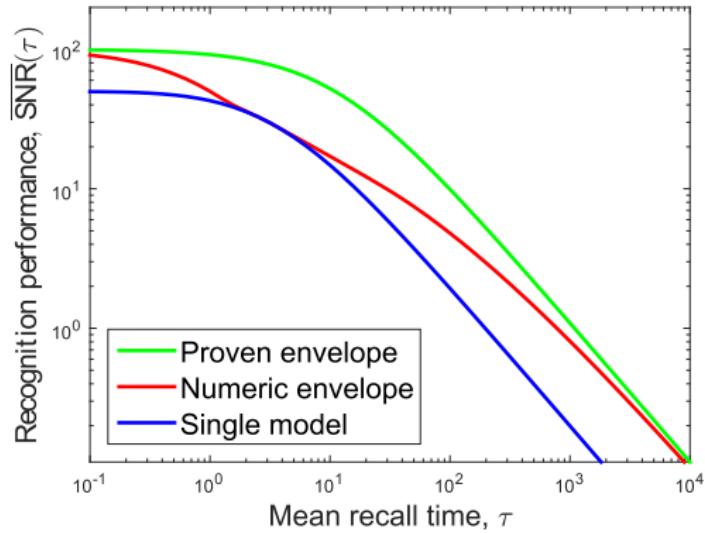


# Proven envelope: memory frontier

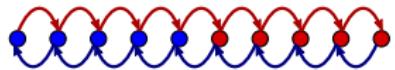
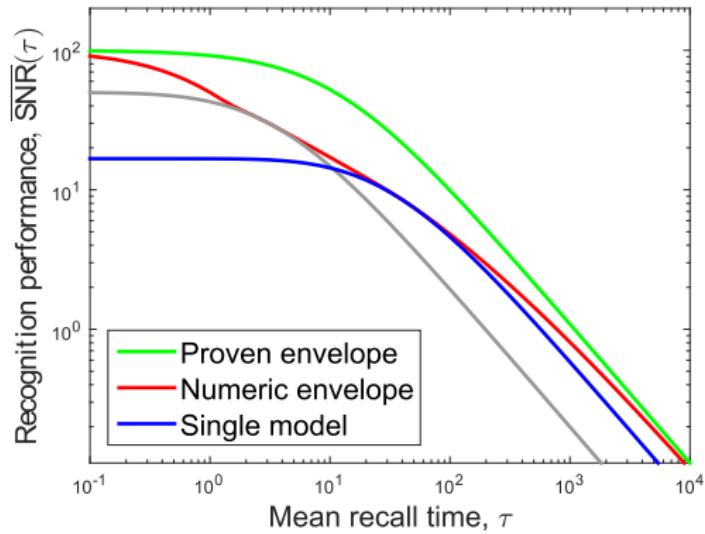
Upper bound on memory curve at *any* timescale.



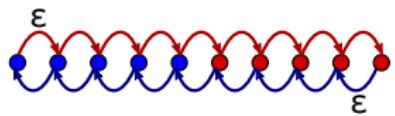
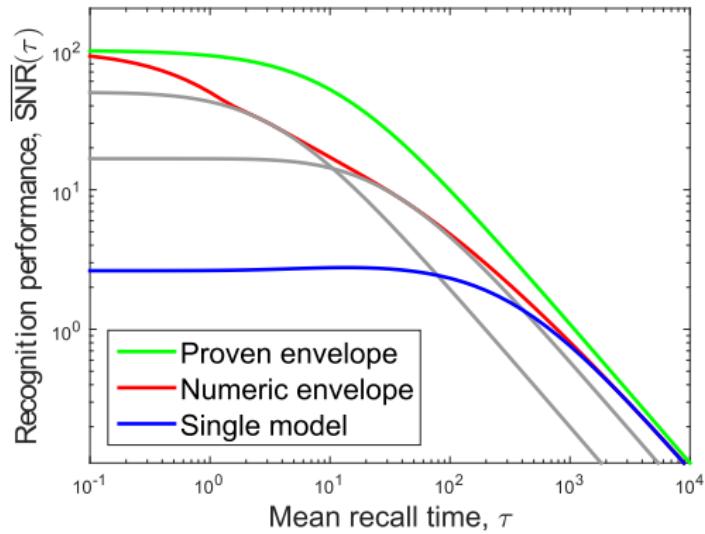
# Models that maximize memory for one timescale



# Models that maximize memory for one timescale

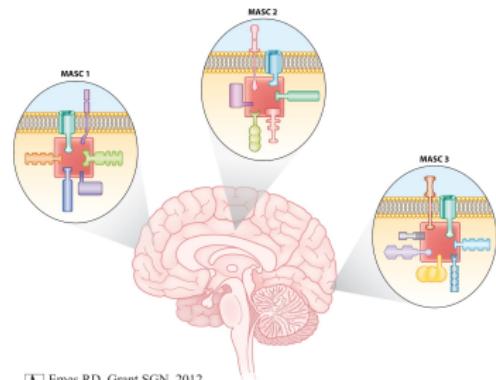


# Models that maximize memory for one timescale



# Synaptic diversity and timescales of memory

Different synapses have different molecular structures.

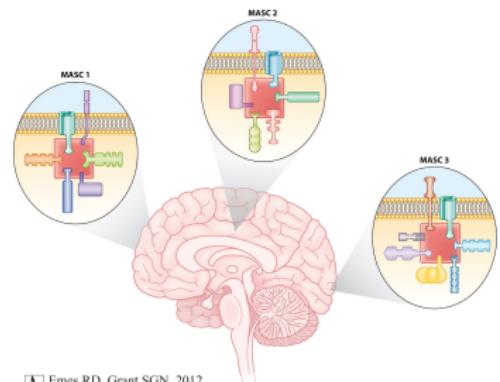


[A] Emes RD, Grant SGN. 2012.  
Annu. Rev. Neurosci. 35:111–31

[Emes and Grant (2012)]

# Synaptic diversity and timescales of memory

Different synapses have different molecular structures.



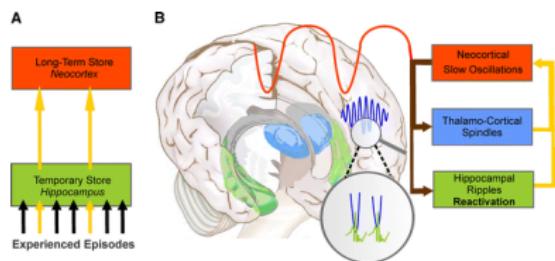
[Emes RD, Grant SGN. 2012.  
Annu. Rev. Neurosci. 35:111–31]

[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.

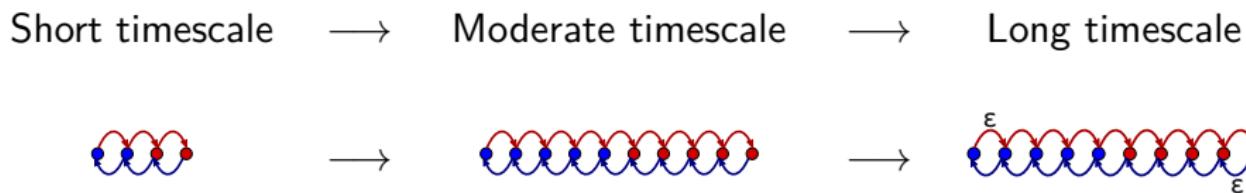
[Attwell et al. (2002)]

[Cooke et al. (2004)]

# Synaptic structure and function: general principles

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

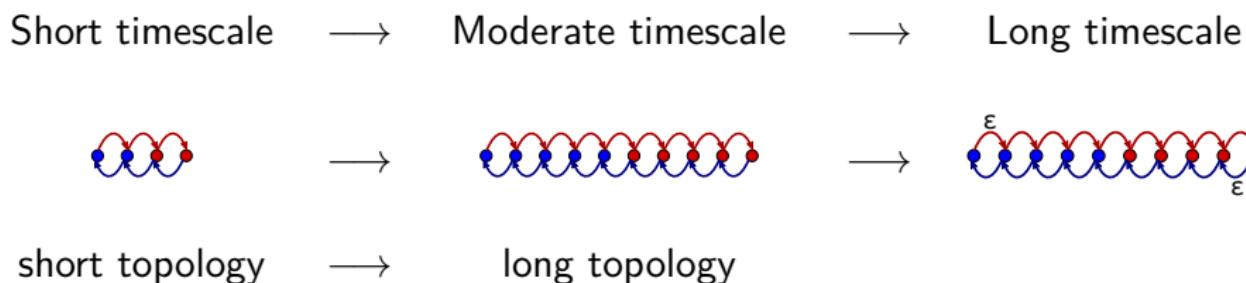
What can we conclude?



# Synaptic structure and function: general principles

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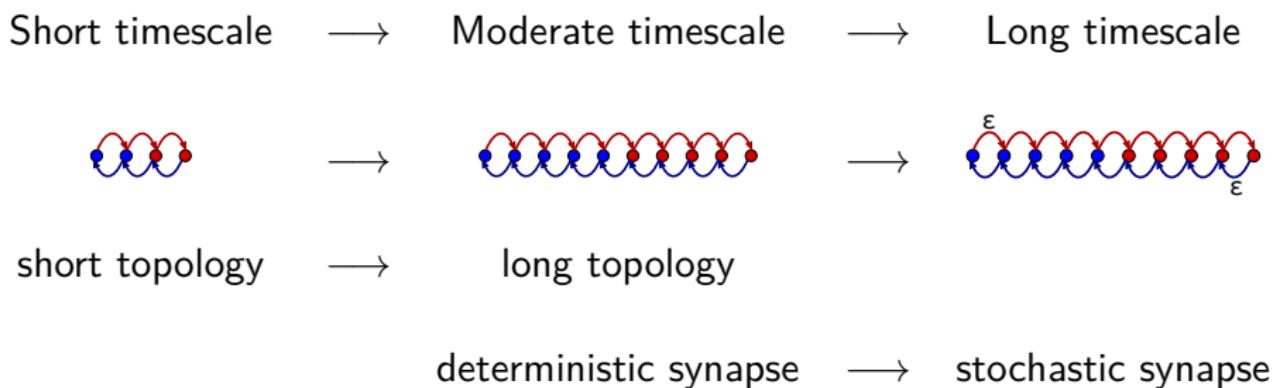
What can we conclude?



# 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:

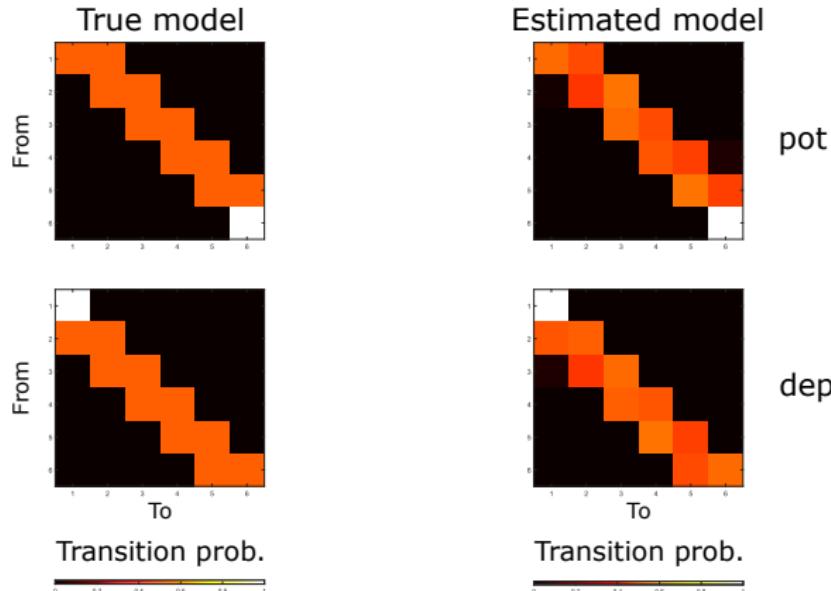


To fit a model: long sequence of small plasticity events.

Observe the changes in synaptic efficacy.



# Simulated experiment



Problem: need *long* sequences.

Whole cell patch of postsynaptic neuron → Ca washout.

# Summary

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

# Acknowledgements

## **Surya Ganguli**

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Christopher Stock  
Sarah Harvey  
Aran Nayebi

Stefano Fusi

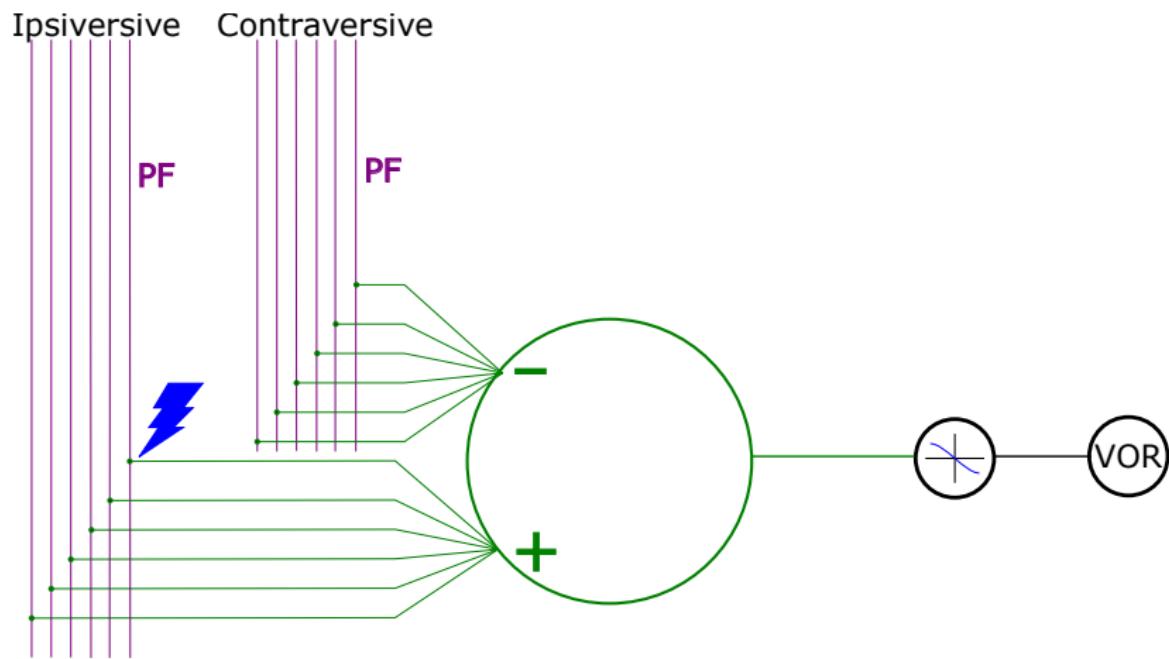
## **Jennifer Raymond**

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Grace Zhao  
Aparna Suvrathan  
Rhea Kimpo  
**Carla Shatz**  
Hanmi Lee

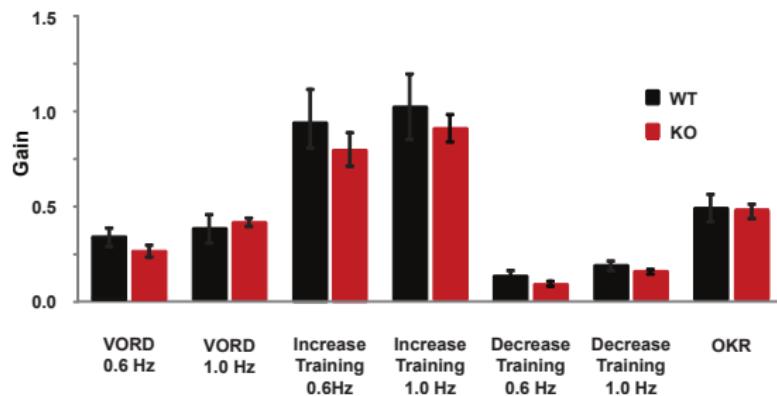
Marcus Benna

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

# Model of circuit

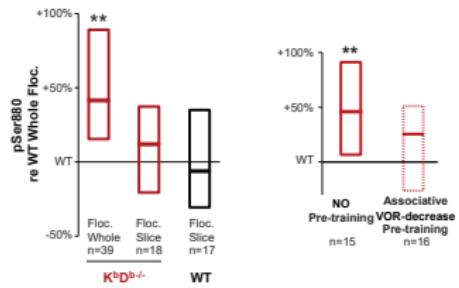


# Baseline



# Evidence: level of depression

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

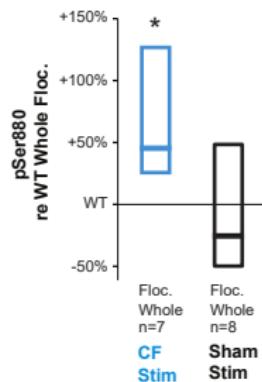
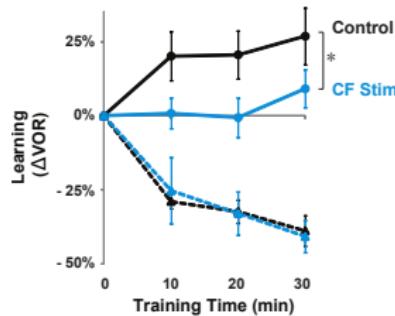
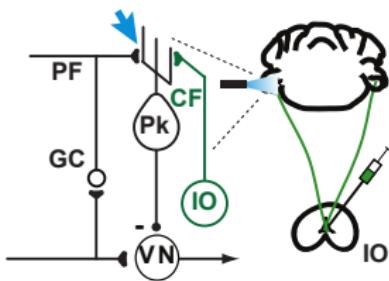


Biochemical signature of PF-Pk LTD.

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

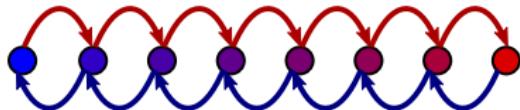
# Evidence: saturation by CF stimulation

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

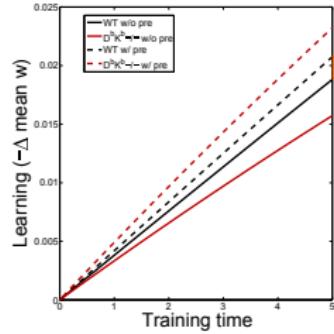
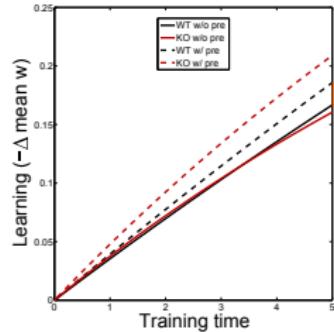
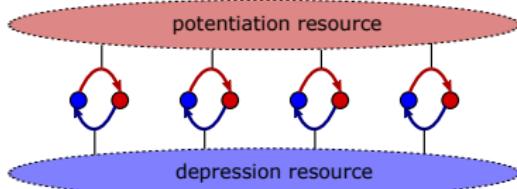


# Other models that fail

## Multistate synapse



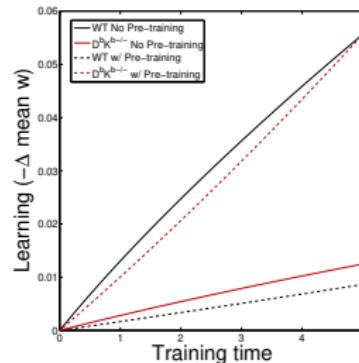
Pooled resource model



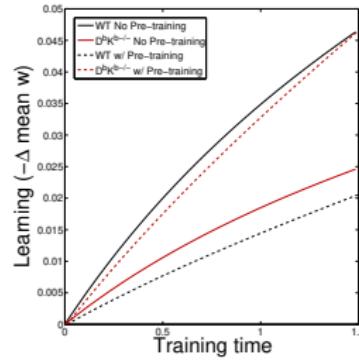
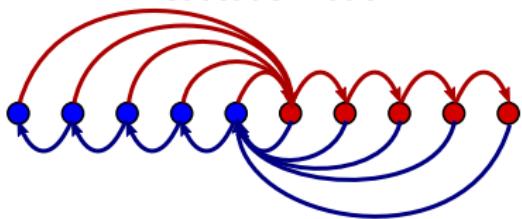
[Amit and Fusi (1994)]

# Other models that work

Non-uniform multistate model

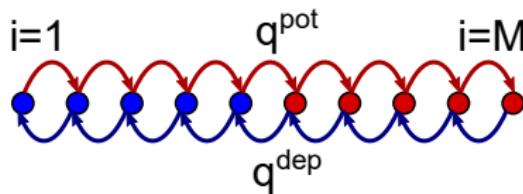


Cascade model



[Fusi et al. (2005)]

# Mathematical explanation



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

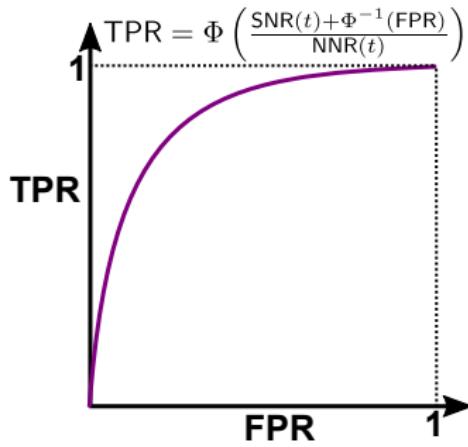
Learning rate  $\sim \pi_{M/2} \left( \frac{q^{dep}}{q^{pot}} \right) = \mathcal{N} \left( \frac{q^{pot}}{q^{dep}} \right)^{\frac{M}{2}-1}$ .

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



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

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

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

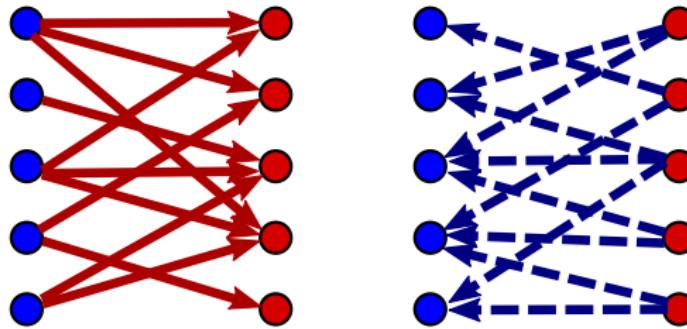
Also: KL divergence, Chernoff distance, . . .

# Initial SNR as flux

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

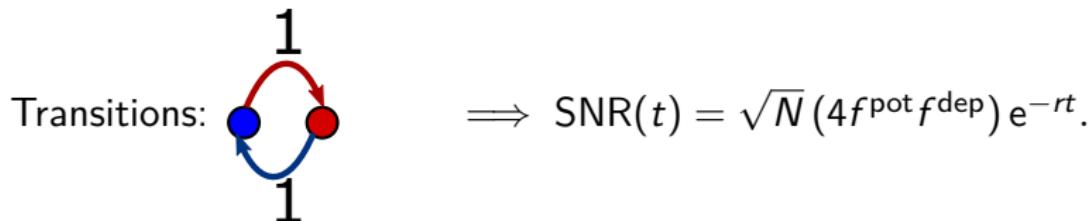
$$\text{SNR}(0) \leq \frac{4\sqrt{N}}{r} \Phi_{-+}.$$

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:

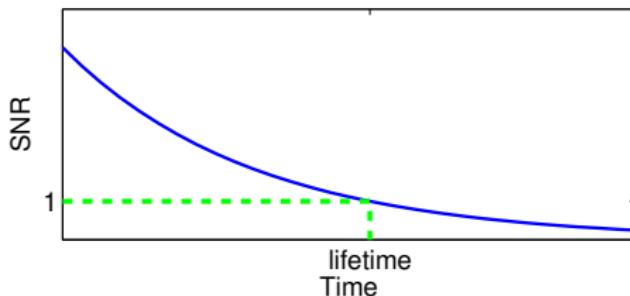
$$\text{SNR}(0) \leq \sqrt{N}.$$

# 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:

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

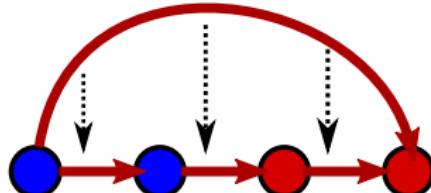
Saturated by a model with linear chain topology.

# 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

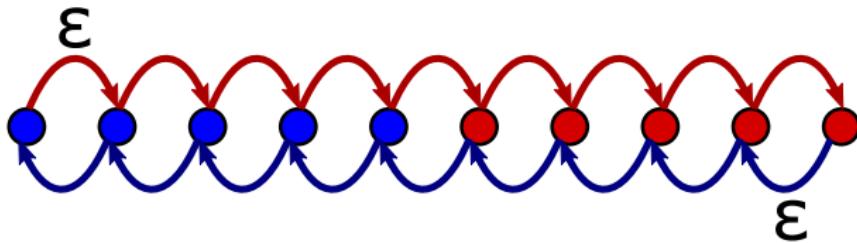
$$A = \frac{2\sqrt{N}}{r} \sum_k \pi_k |k - \langle k \rangle|.$$

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)]

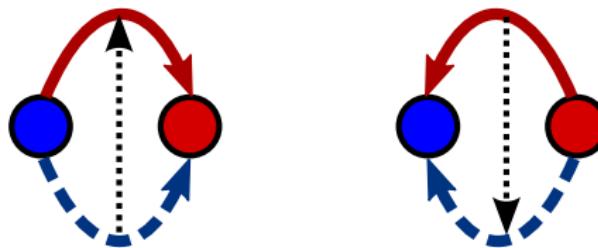
We define:

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

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

## Technical detail: upper/lower triangular

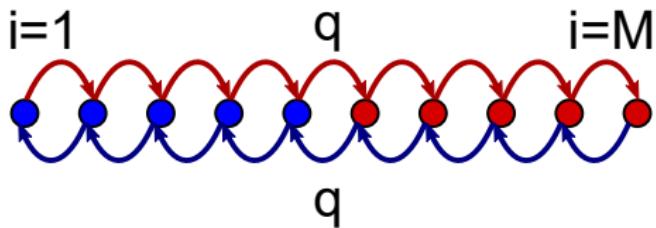
With states in order:



Endpoint: potentiation goes right, depression goes left.

[back](#)

# Intuition for using topology



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

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