

# Learning and memory with complex synaptic plasticity

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# My research areas

## **Learning and memory**

Structure of synapses & function.  
Learning v. remembering tradeoff.  
Success & failure in trying to enhance learning.

## **Energy use in living systems**

Energy cost of signalling/sensing.  
Tradeoffs with accuracy & speed.  
Thermodynamics  $\leftrightarrow$  information geometry.

## **High dimensional statistics**

Theory of random projections and the geometry of data.  
Neural recordings as projections.

# What is a synapse?

Theorists

Experimentalists

# What is a synapse?

Theorists

Experimentalists

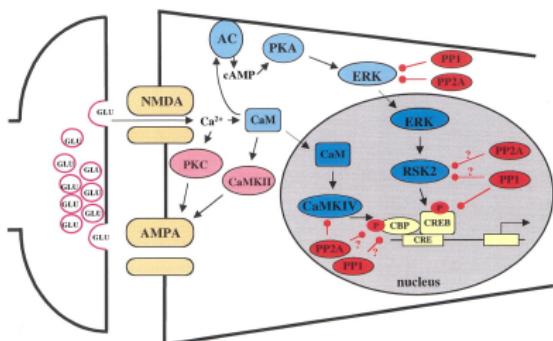
$$W_{ij}$$

# What is a synapse?

Theorists

$W_{ij}$

Experimentalists



[Klann (2002)]

# Storage capacity of synaptic memory

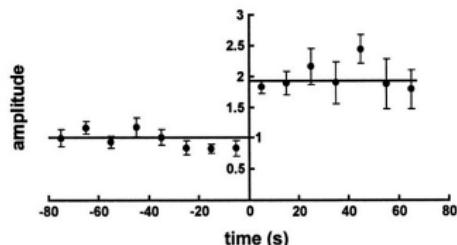
Hopfield, perceptron have capacity  $\propto N$ , (# synapses).

Assumes unbounded analogue synapses

With discrete, finite synapses:

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

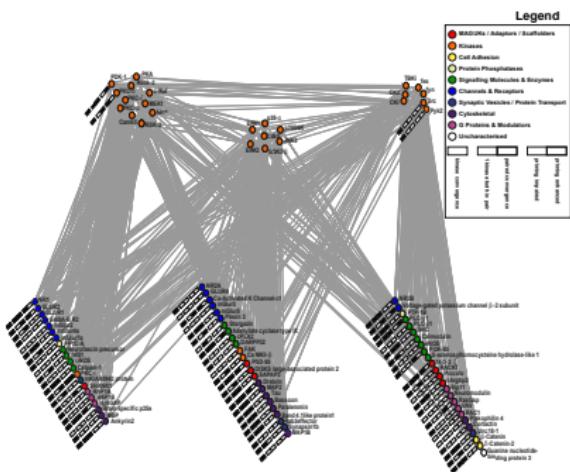
[Amit and Fusi (1992), Amit and Fusi (1994)]



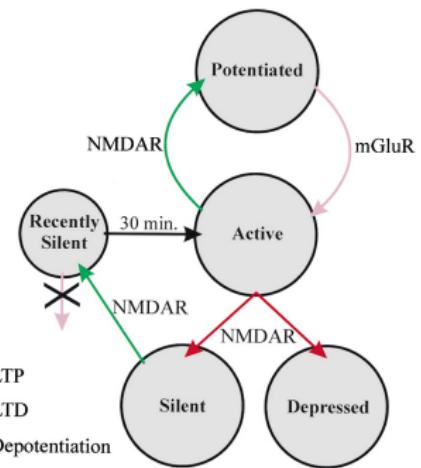
[Petersen et al. (1998), O'Connor et al. (2005)]

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

## Synapses are complex

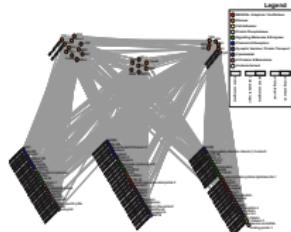


[Coba et al. (2009)]

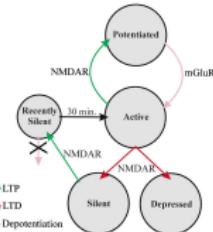


[Montgomery and Madison (2002)]

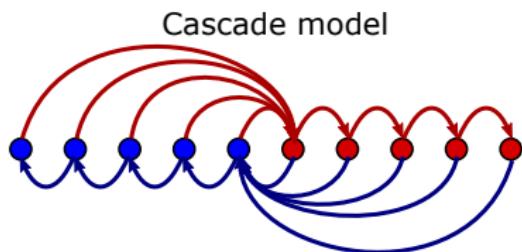
# Synapses are complex



[Coba et al. (2009)]



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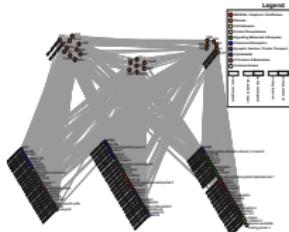


Cascade model

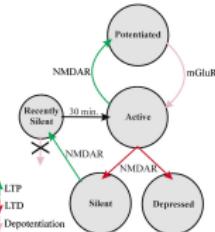
Capacity  $\propto N^{2/3}$ .

[Fusi et al. (2005)]

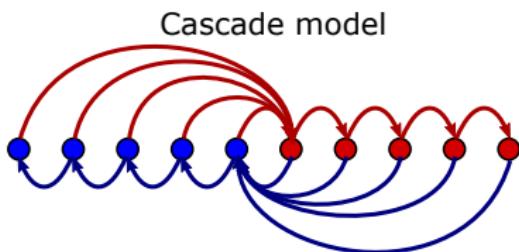
# Synapses are complex



[Coba et al. (2009)]



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Capacity  $\propto N^{2/3}$ . [Fusi et al. (2005)]  
Capacity  $\propto N$ . [Benna and Fusi (2016)]

## My approach

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

Not trying to build a *single* model.

Instead, we build a broad framework 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 Memory over different timescales

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

## 2 Learning with enhanced plasticity

- Effects of enhanced plasticity on cerebellar learning
- Synaptic models of cerebellar learning
- Learning outcomes of mice and models

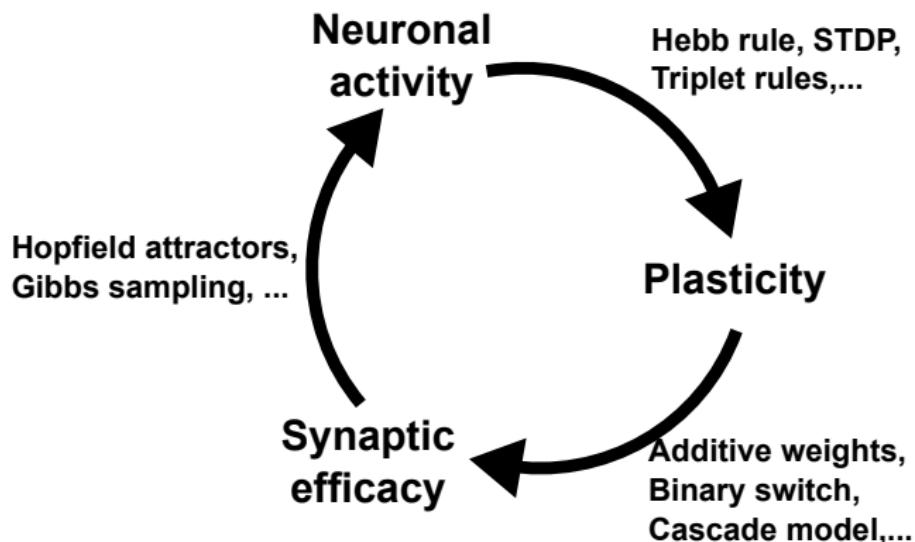
## 3 Designing experiments

# Section 1

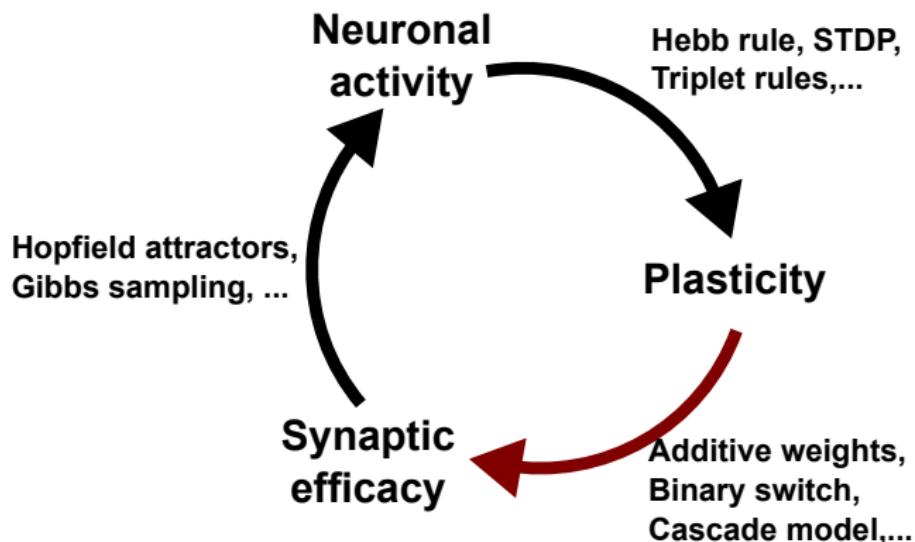
## Memory over different timescales

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

# Synaptic learning and memory



# Synaptic learning and memory



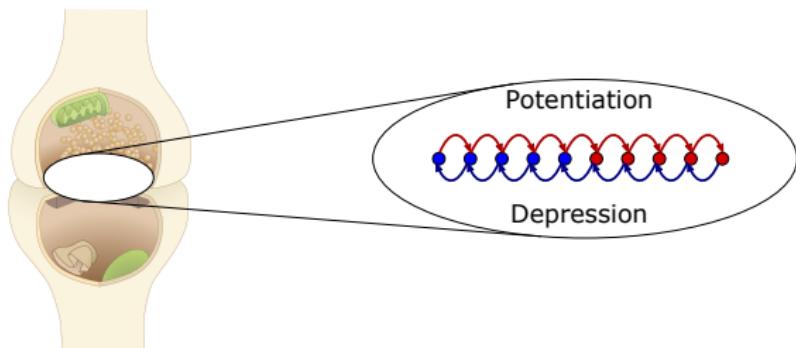
# Models of complex synaptic dynamics



# Models of complex synaptic dynamics

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

weak  
strong



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

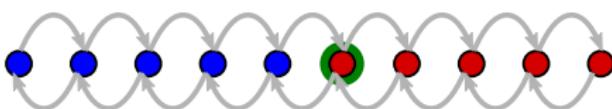
[Fusi et al. (2005), Fusi and Abbott (2007), Barrett and van Rossum (2008)]

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

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Potentiation event

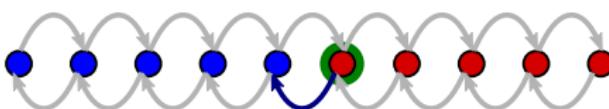


Depression event

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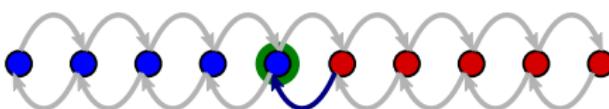


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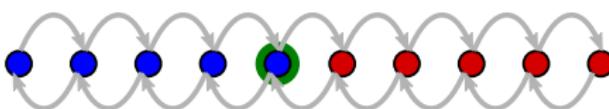


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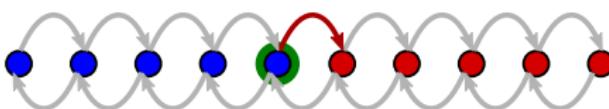


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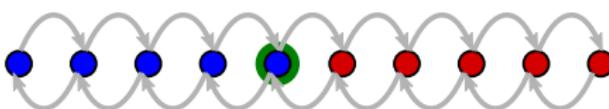


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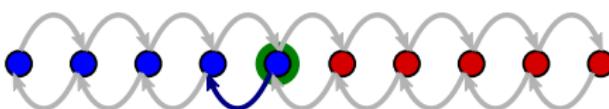
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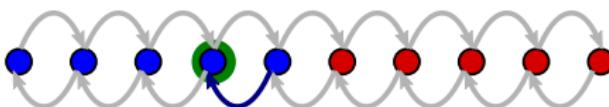
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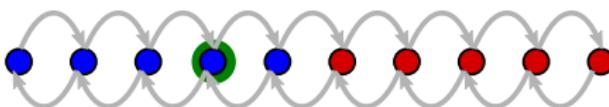
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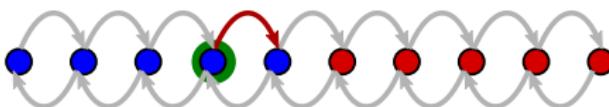
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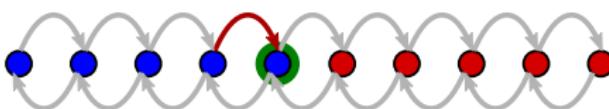
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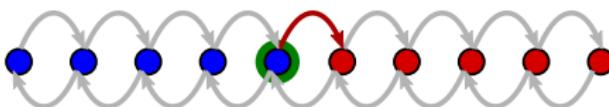
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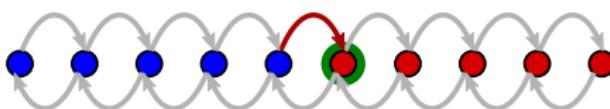
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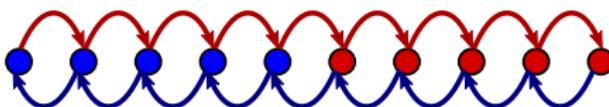
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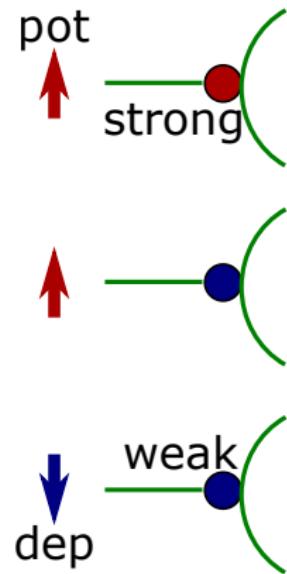
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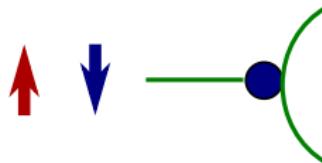
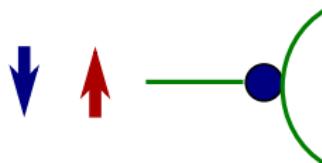
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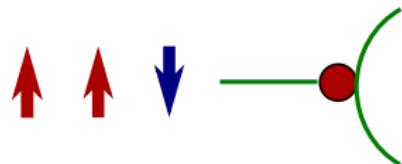
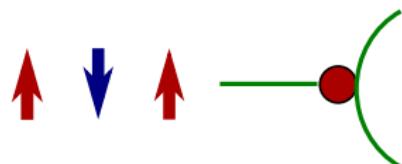
## Synaptic memory curves



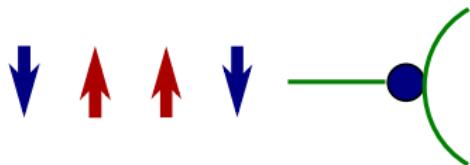
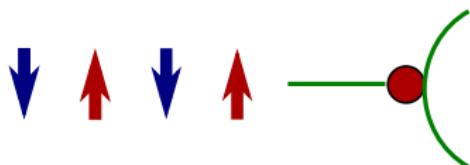
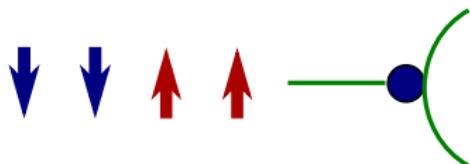
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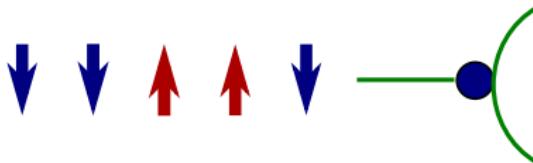
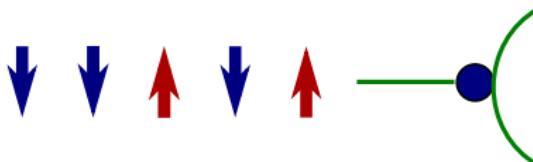
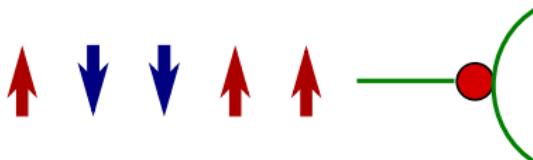
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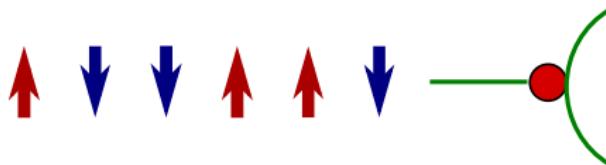
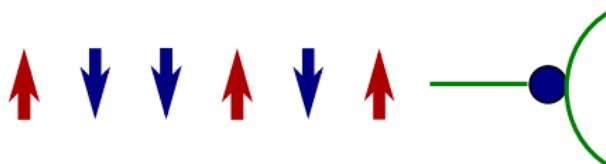
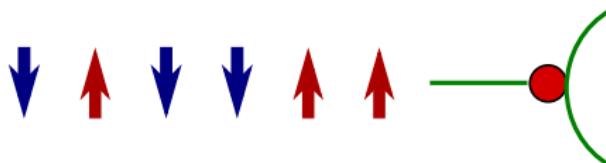
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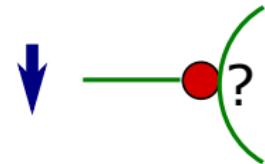
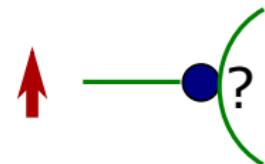
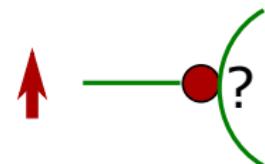
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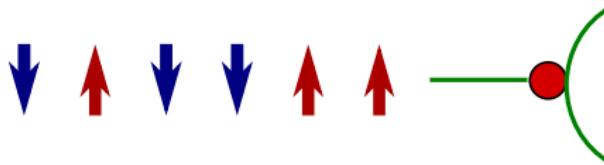
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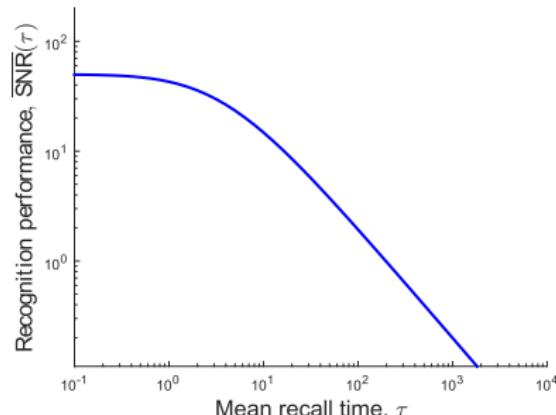
# Synaptic memory curves



Synapses store a sequence of memories.

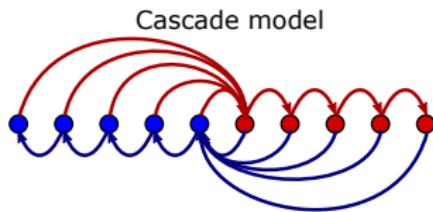
Recognition memory: has this pattern been seen before?

Performance described by SNR of  $\vec{w}(t) \cdot \vec{w}_{\text{test}}$ .

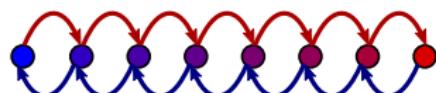


# Specific models of complex synaptic dynamics

Two example models of complex synapses.

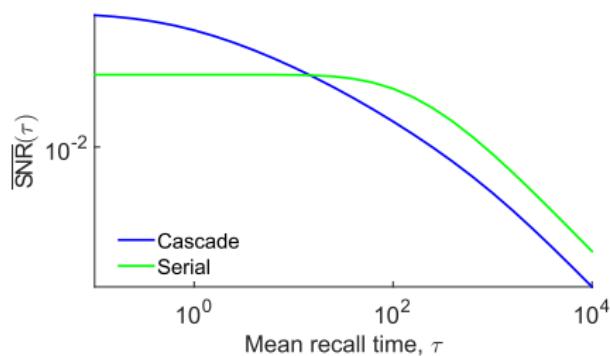


Multistate synapse



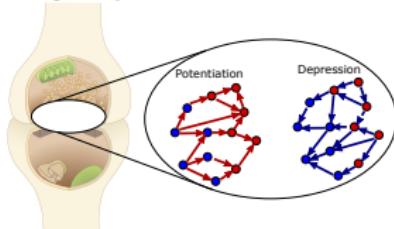
[Fusi et al. (2005), Leibold and Kempfer (2008), Ben-Dayan Rubin and Fusi (2007)]

These have different memory storage properties

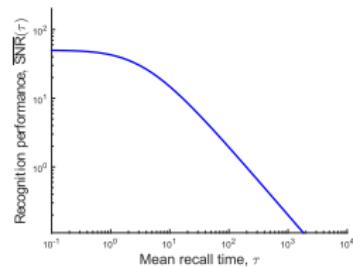


# General principles relating structure and function?

## Synaptic structure



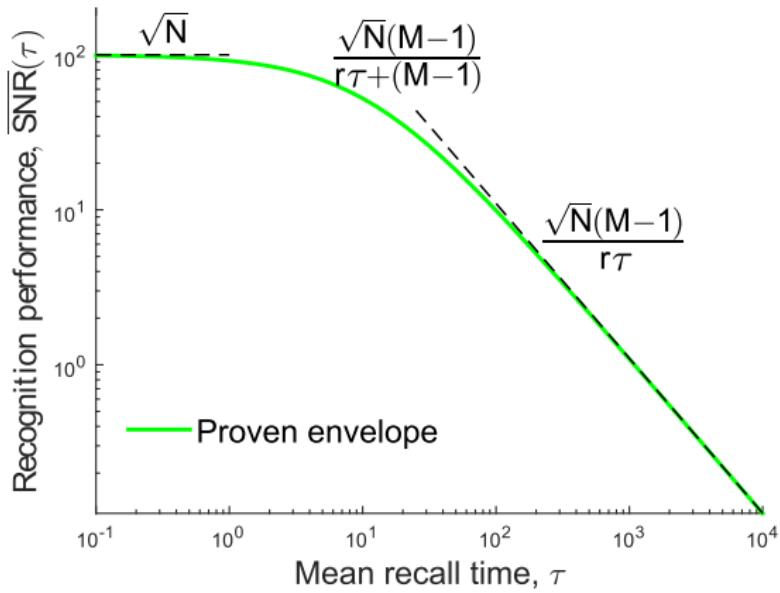
## Synaptic function



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

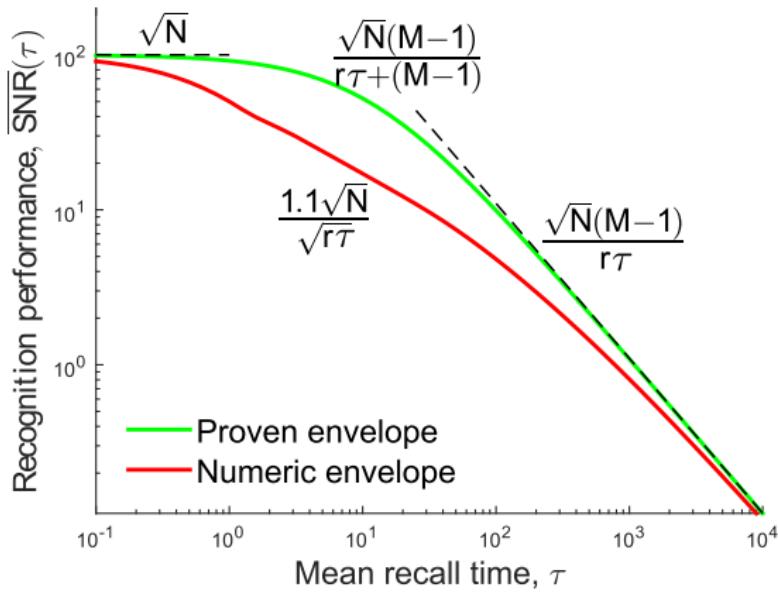
## Proven envelope: memory frontier

Upper bound on memory curve at *any* timescale.

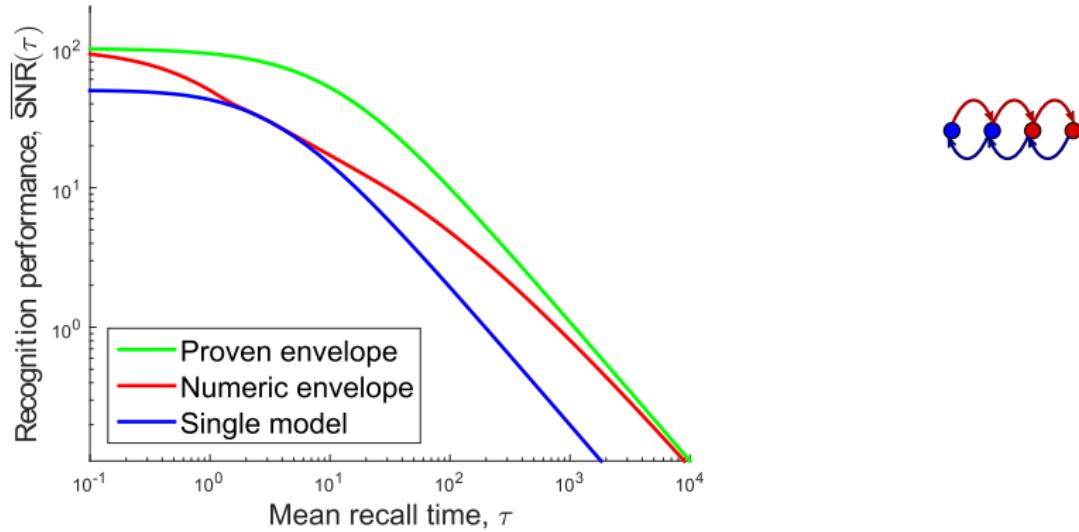


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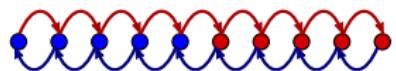
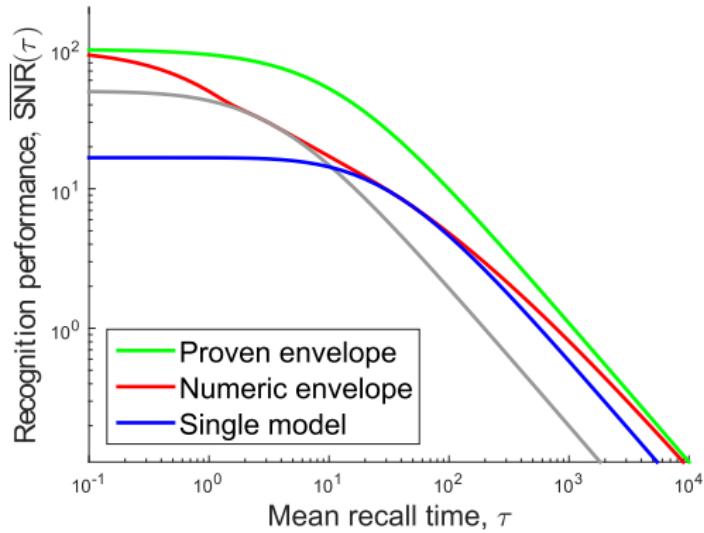
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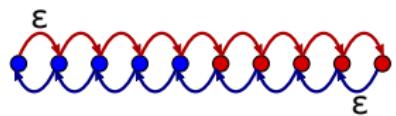
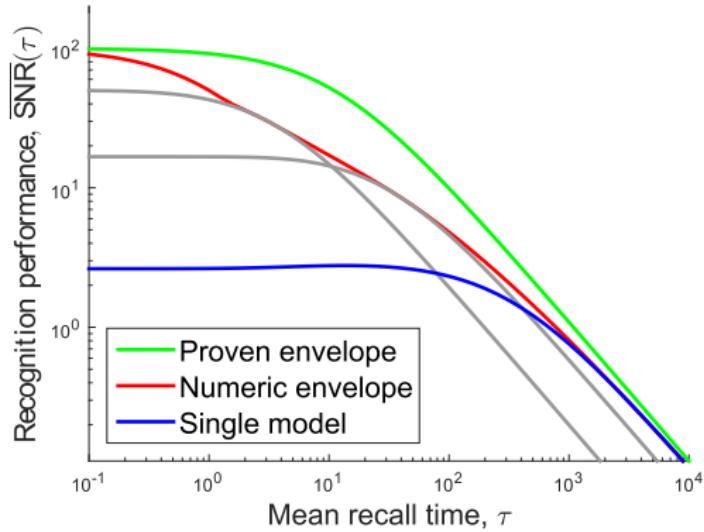
## Models that maximize memory for one timescale



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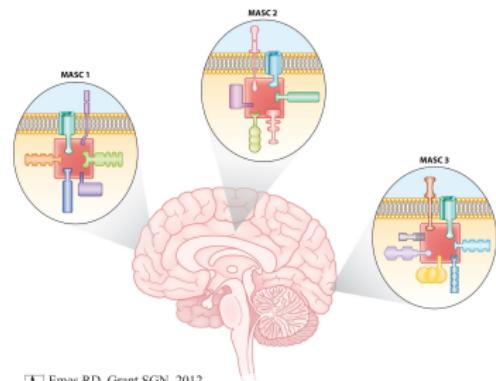


# Models that maximize memory for one timescale



# Synaptic diversity and timescales of memory

Different synapses have different molecular structures.

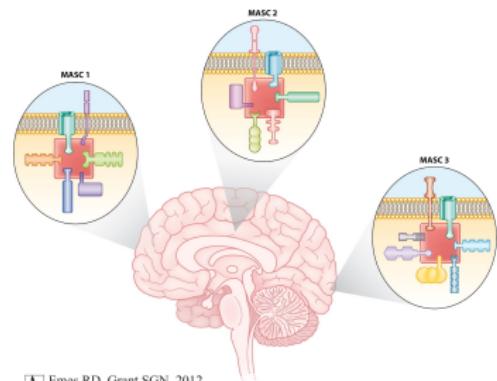


[A] Emes RD, Grant SGN. 2012.  
Annu. Rev. Neurosci. 35:111–31

[Emes and Grant (2012)]

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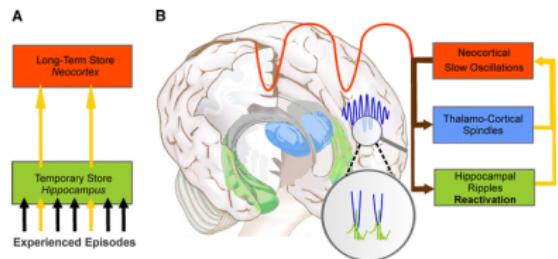
[Emes RD, Grant SGN. 2012.  
Annu. Rev. Neurosci. 35:111–31]

[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.

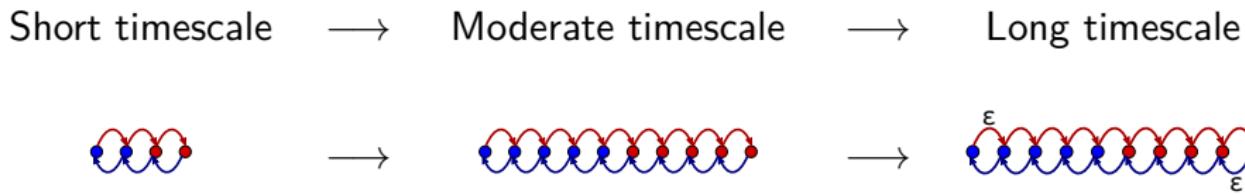
[Attwell et al. (2002)]

[Cooke et al. (2004)]

# Synaptic structure and function: general principles

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

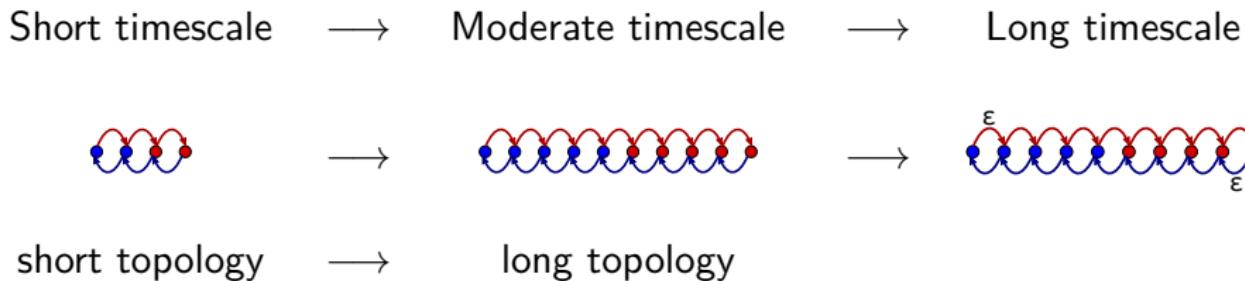
What can we conclude?



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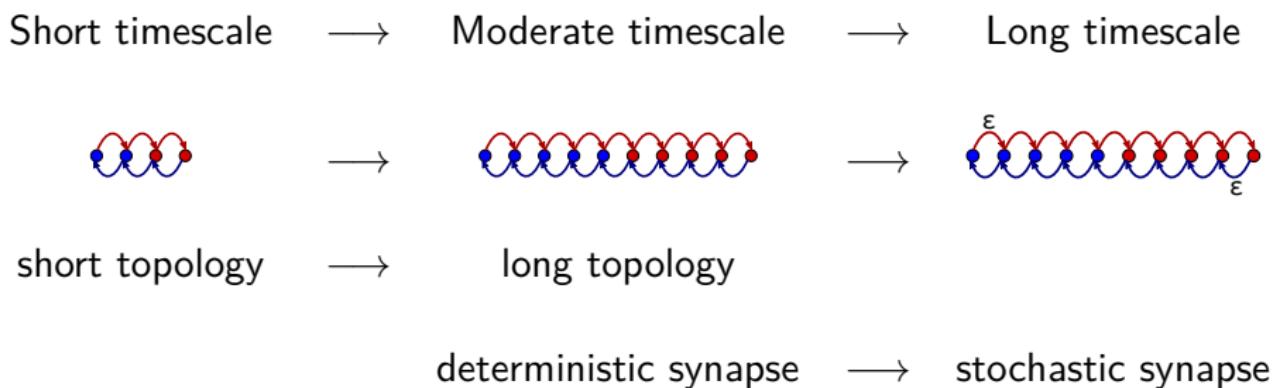
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What can we conclude?



# Conclusions

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

## Section 2

### 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).

Highest rated abstract at Cosyne 2014.

# Benefits of enhanced plasticity?

Learning requires synaptic plasticity.

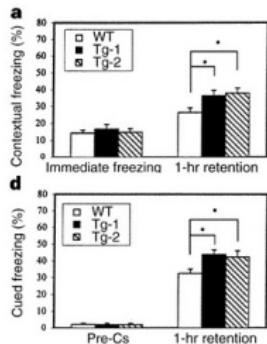


Can we enhance learning by enhancing plasticity?

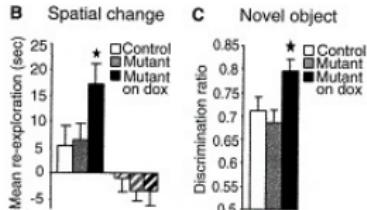


# Enhanced plasticity can enhance learning

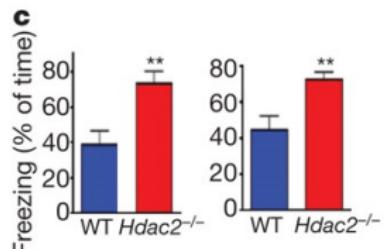
## Overexpress NR2B



## Inhibit CN



## Knockout Hdac2



## Fear conditioning

[Tang et al. (1999)]

## Novel object recog.

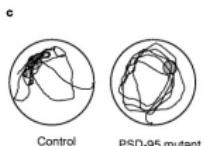
[Malleret et al. (2001)]

## Fear conditioning

[Guan et al. (2009)]

# Enhanced plasticity can *impair* learning

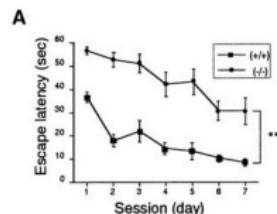
Mutate PSD-95



Water maze

[Migaud et al. (1998)]

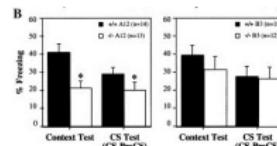
Knockout PTP $\delta$



Water maze

[Uetani et al. (2000)]

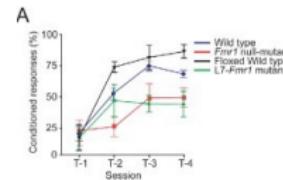
Delete Tmod2



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.

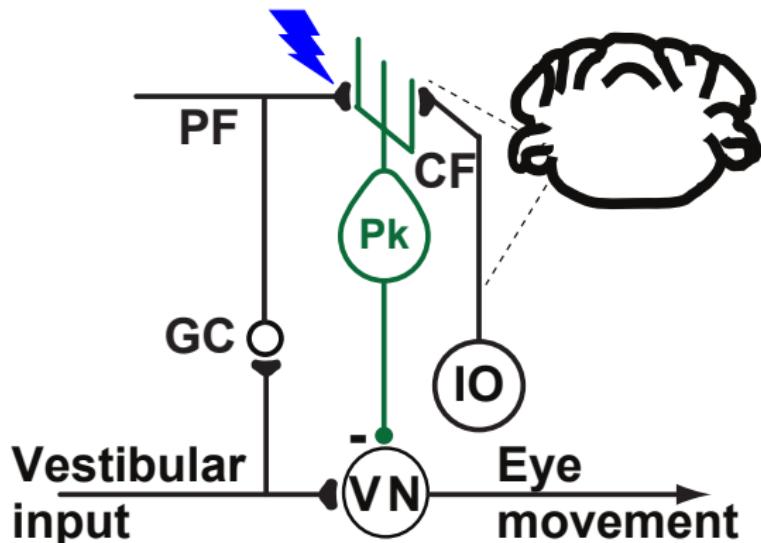
Simple synapses **cannot** explain behaviour. **Complex synapses** are required.  
→ predictions for synaptic physiology.

# Vestibulo-Occular Reflex training

VOR Increase  
Training



VOR Decrease  
Training



VOR increase: LTD in PF-Pk synapses.

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

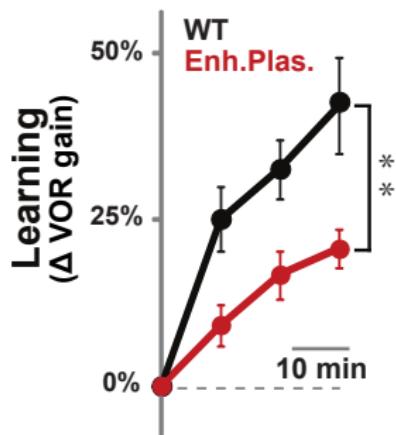
[Marr (1969), Albus (1971), Ito (1972)]

# Enhanced plasticity impairs learning

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

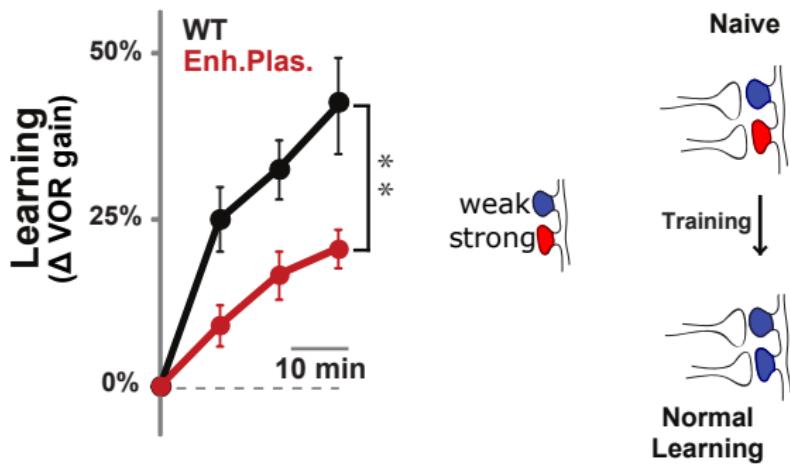
→ lower threshold for LTD → enhanced learning of Rotarod task.

[McConnell et al. (2009)]



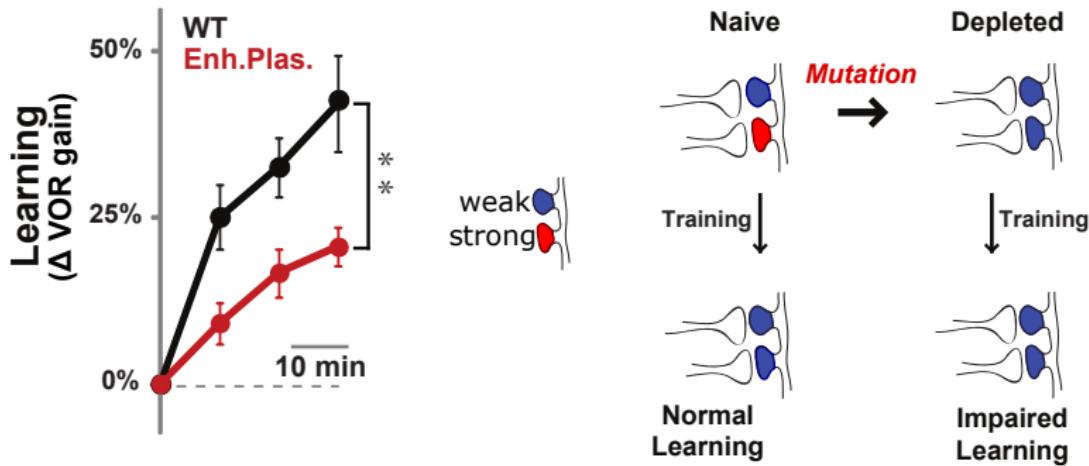
# Enhanced plasticity impairs learning

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



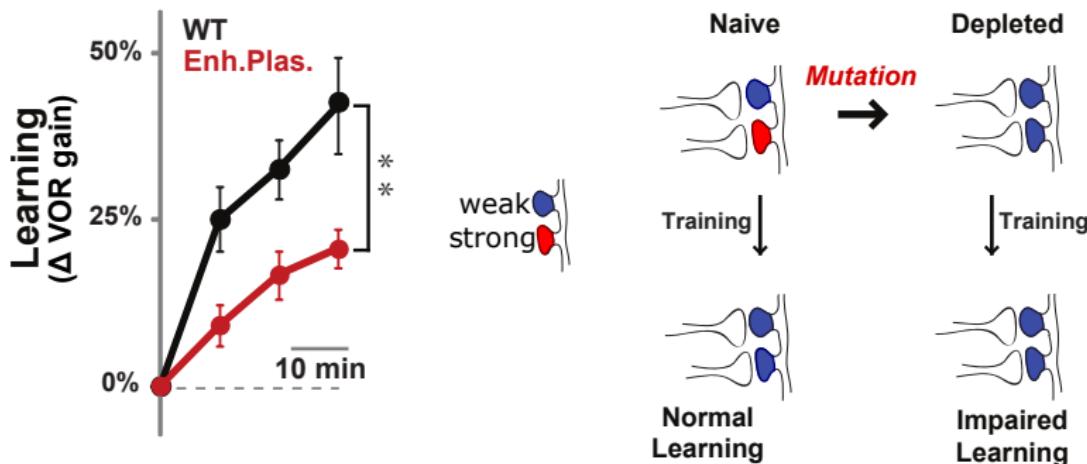
# Enhanced plasticity impairs learning

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



# Enhanced plasticity impairs learning

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

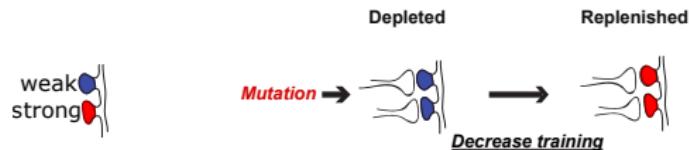


Question 1: depletion effect competes with enhanced intrinsic plasticity.  
When is depletion effect stronger?

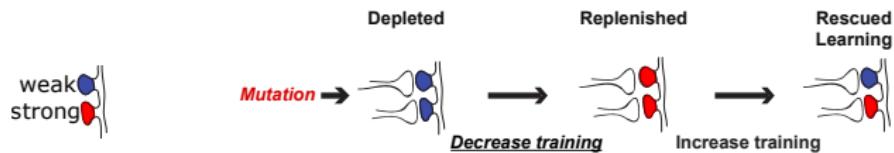
# Replenishment by reverse-training



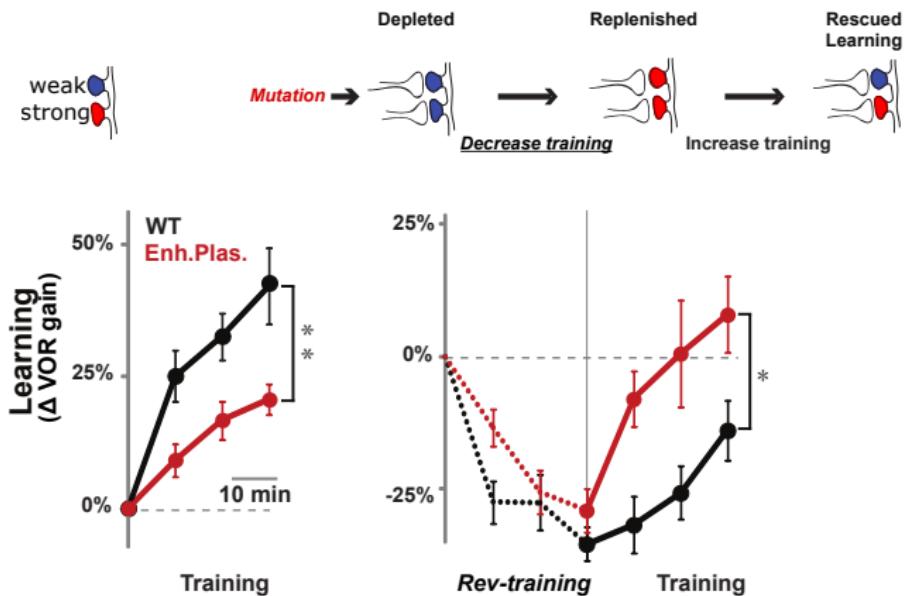
# Replenishment by reverse-training



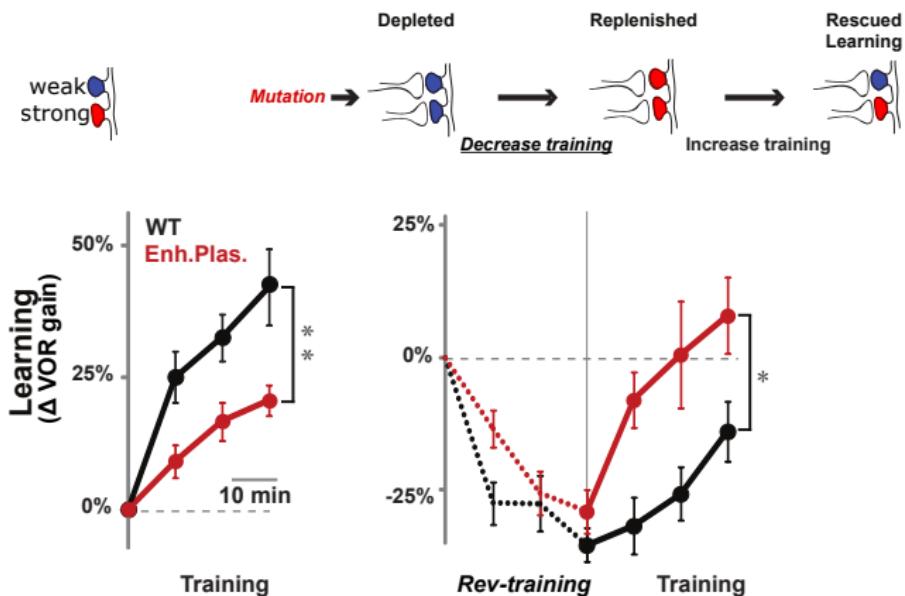
# Replenishment by reverse-training



# Replenishment by reverse-training



# Replenishment by reverse-training

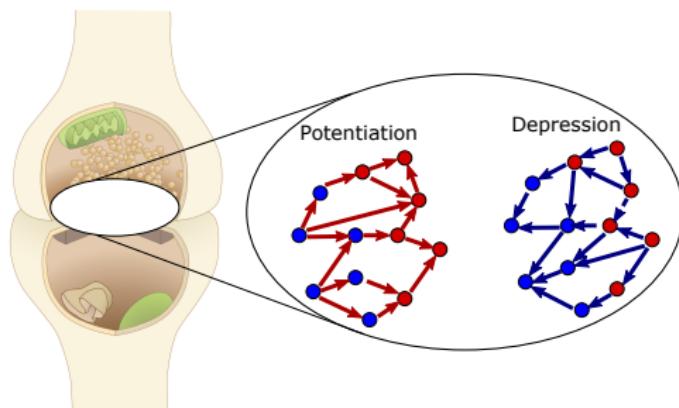


Question 2: When does enhanced plasticity impair learning?

# Models of complex synaptic dynamics

There are  $N$  identical synapses with  $M$  internal functional states.

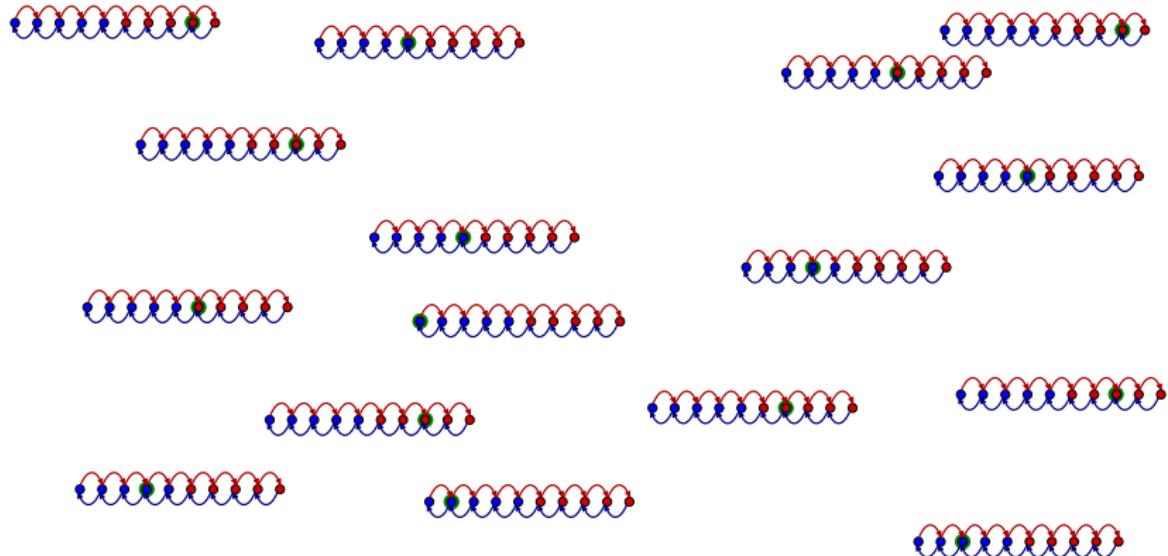
- Internal functional state of synapse → synaptic weight.  
● weak
- Candidate plasticity events → transitions between states  
● strong



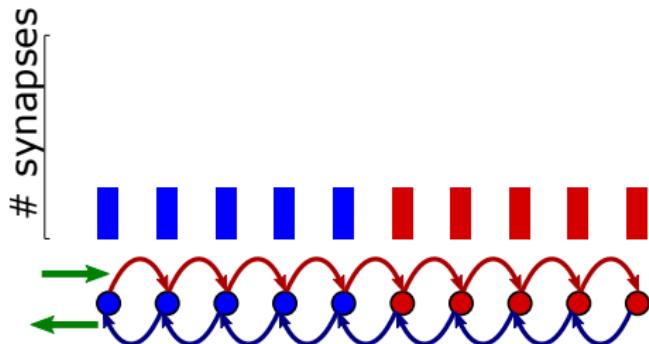
States: #AMPAR, #NMDAR, NMDAR subunit composition,  
CaMK II autophosphorylation, activating PKC, p38 MAPK,...

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

# Modelling VOR experiments

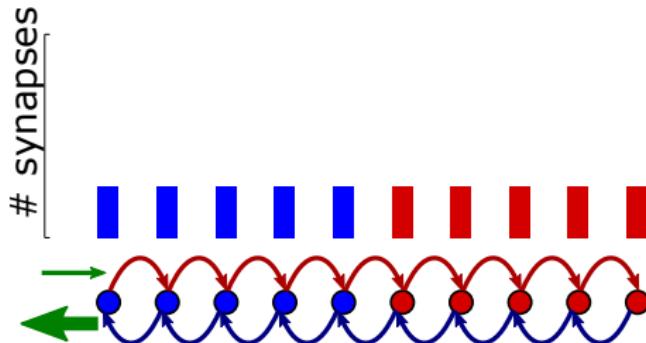


# Modelling VOR experiments



# Modelling VOR experiments

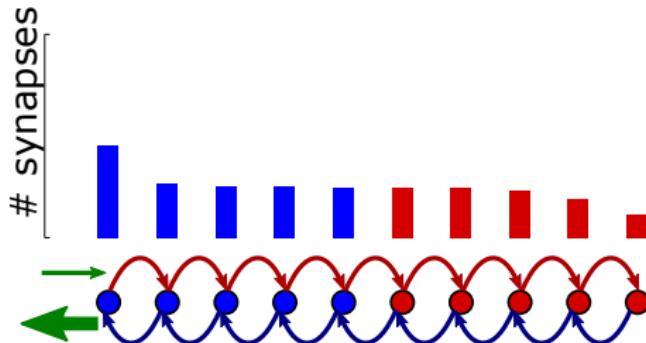
PF-Pk LTD → VOR increase



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

# Modelling VOR experiments

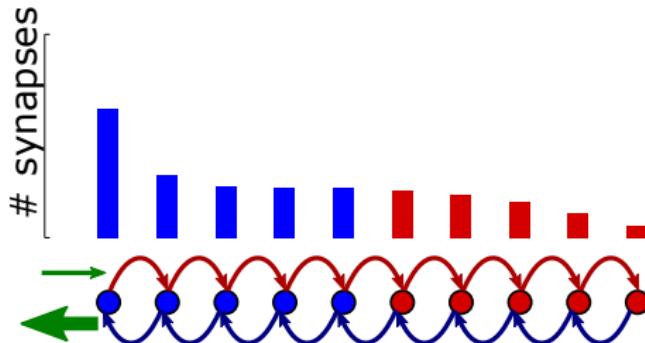
PF-Pk LTD → VOR increase



Training: different CF activity  $\Rightarrow$   
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# Modelling VOR experiments

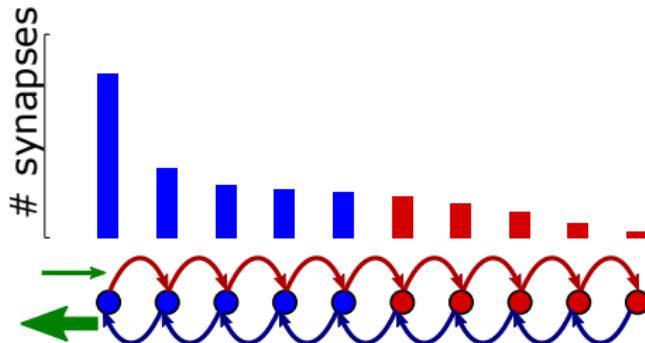
PF-Pk LTD → VOR increase



Training: different CF activity  $\Rightarrow$   
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# Modelling VOR experiments

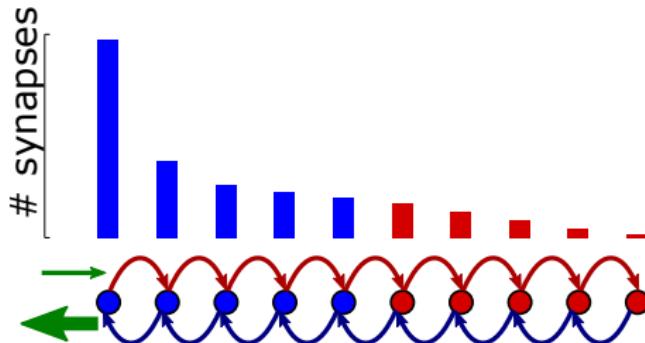
PF-Pk LTD → VOR increase



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

# Modelling VOR experiments

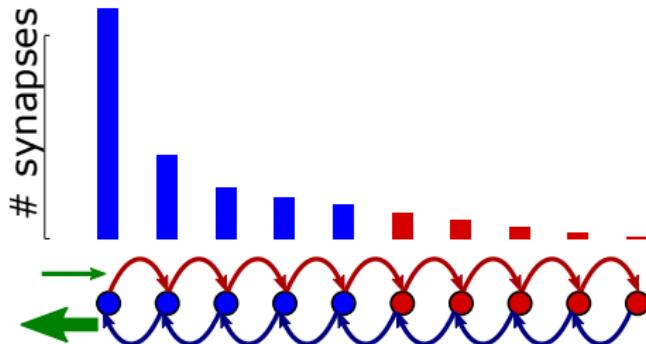
PF-Pk LTD → VOR increase



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

# Modelling VOR experiments

PF-Pk LTD → VOR increase

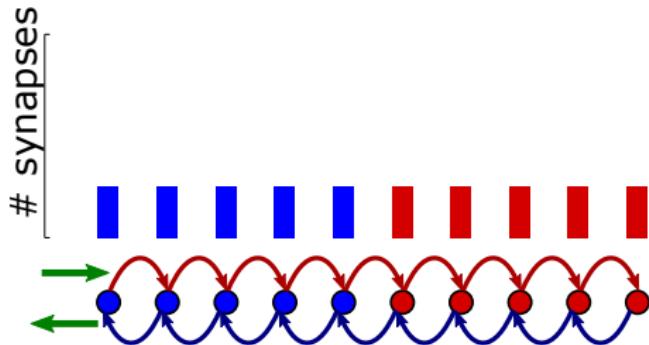


Training: different CF activity  $\implies$   
change frequency of pot/dep events.

Learning: decrease in average synaptic weight.

# Modelling VOR experiments

PF-Pk LTD → VOR increase



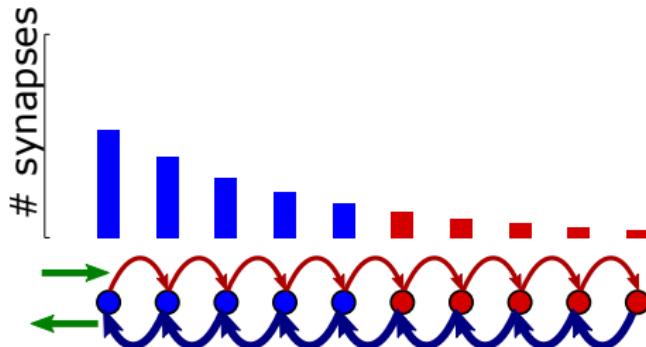
Training: different CF activity  $\Rightarrow$   
change frequency of pot/dep events.

Learning: decrease in average synaptic weight.

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

# Modelling VOR experiments

PF-Pk LTD → VOR increase



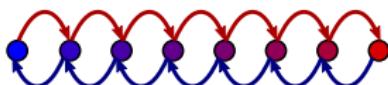
Training: different CF activity  $\Rightarrow$   
change frequency of pot/dep events.

Learning: decrease in average synaptic weight.

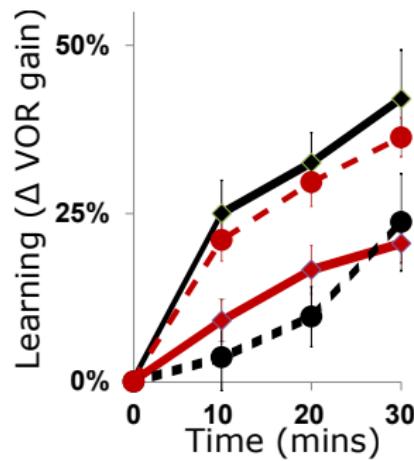
Mutation: lower threshold for LTD  $\Rightarrow$   
increase transition probability for depression events.

# Simple synapses cannot explain the behaviour

Multistate synapse

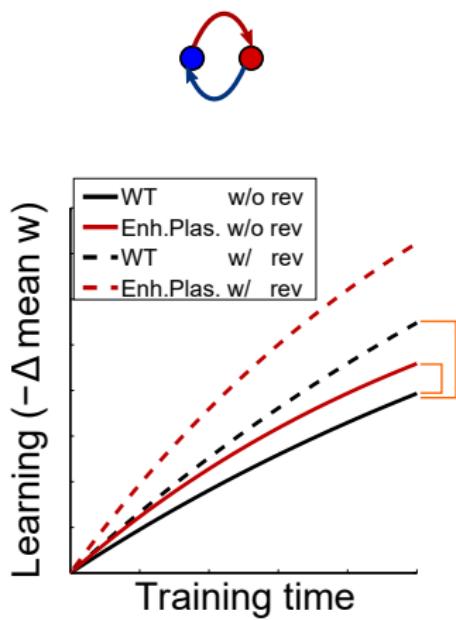


VOR Increase  
Training

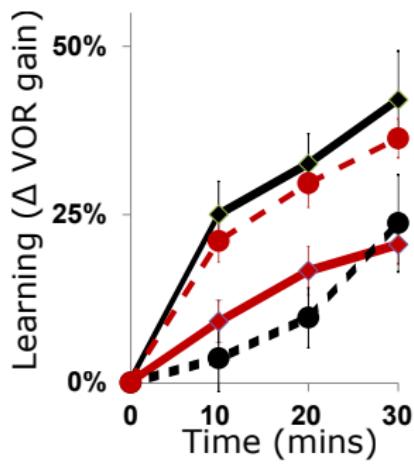


# Simple synapses cannot explain the behaviour

Two-state model

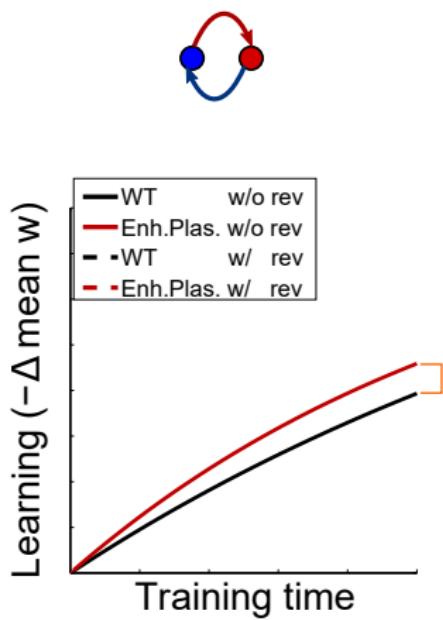


VOR Increase  
Training

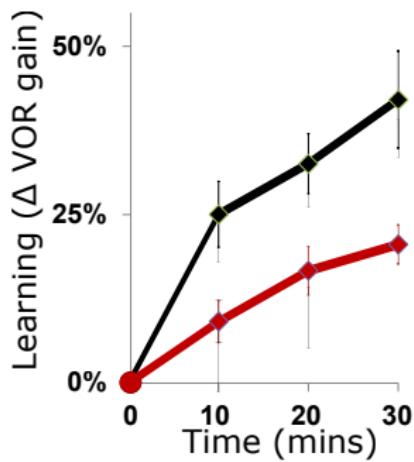


# Simple synapses cannot explain the behaviour

Two-state model



VOR Increase  
Training

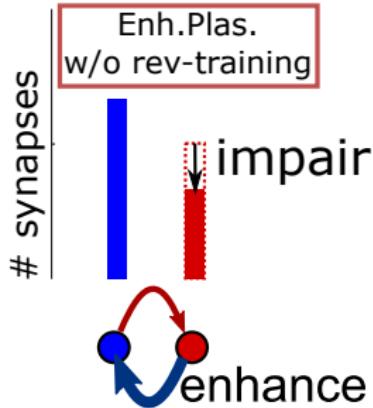


# Simple synapses cannot explain the behaviour

Two-state model



Initial distribution



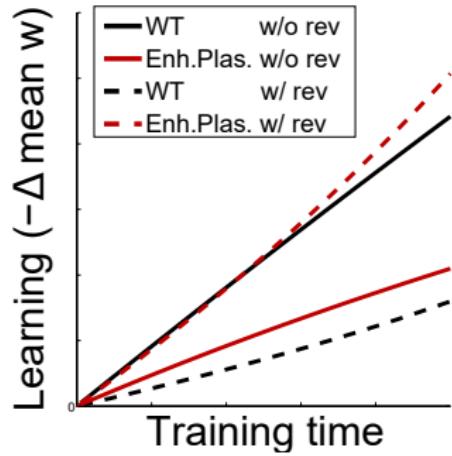
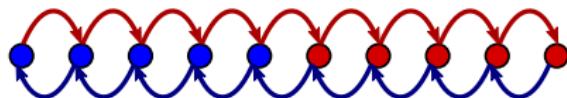
depletion effect

<  
enhanced plasticity

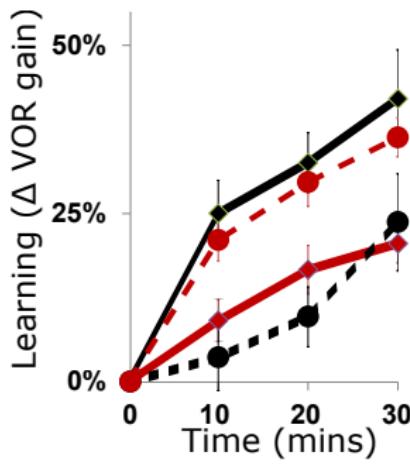
⇒ enhanced learning

# Complex metaplastic synapses can explain the behaviour

Serial model

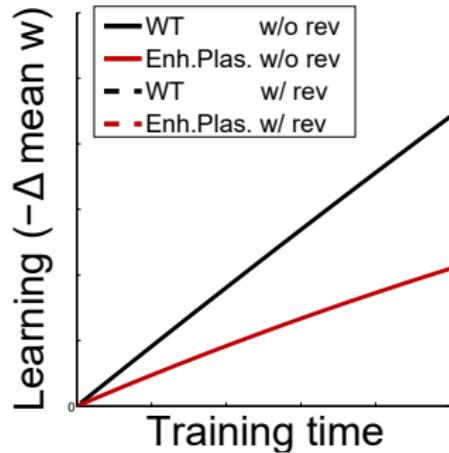
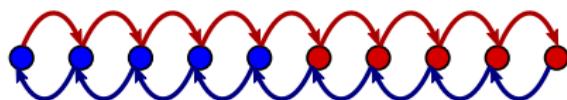


VOR Increase  
Training

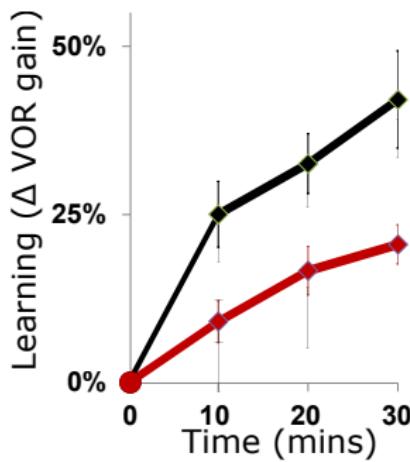


# Complex metaplastic synapses can explain the behaviour

Serial model

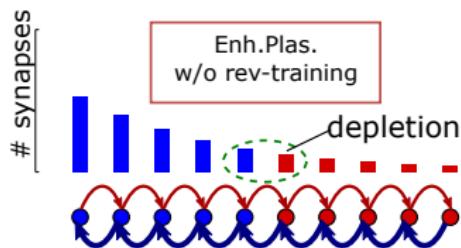
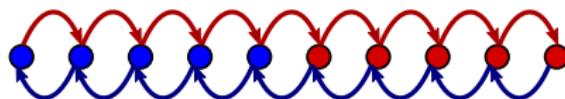


VOR Increase  
Training



# Complex metaplastic synapses can explain the behaviour

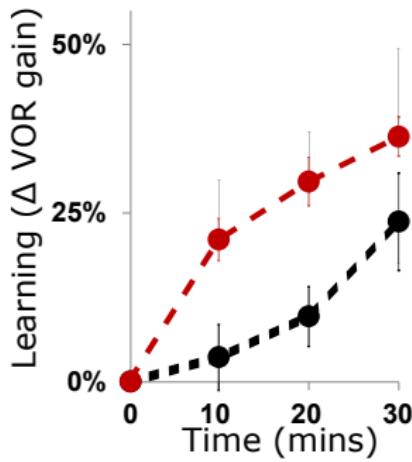
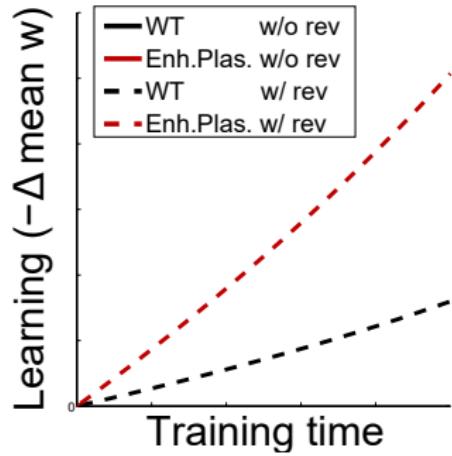
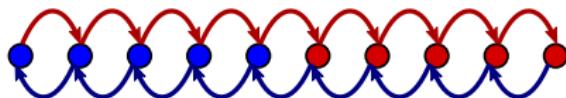
Serial model



amplified depletion  
>  
enhanced plasticity  
⇒ impaired learning

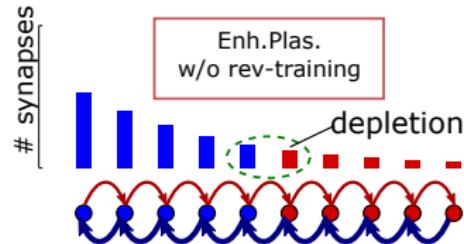
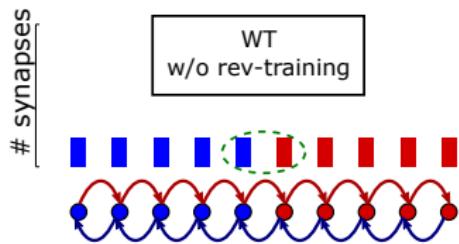
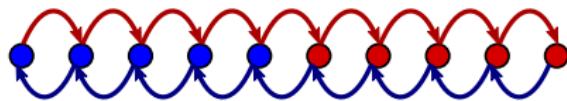
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Serial model



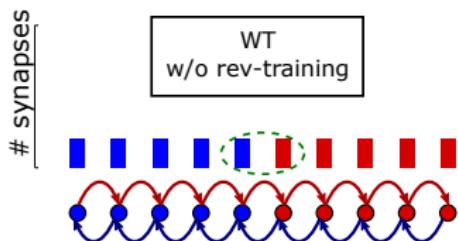
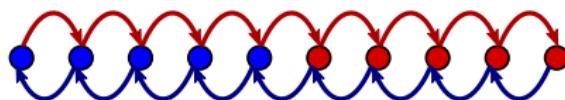
# Complex metaplastic synapses can explain the behaviour

Serial model



# Complex metaplastic synapses can explain the behaviour

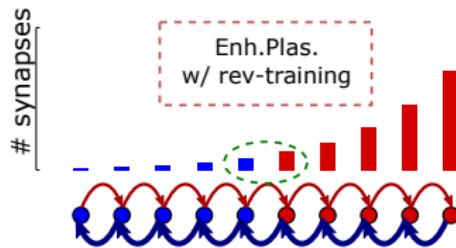
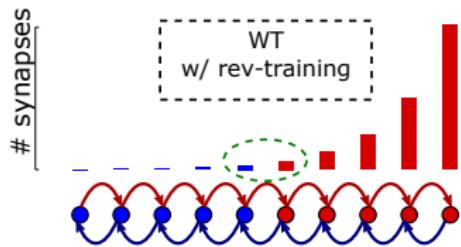
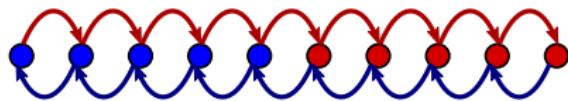
Serial model



start in: labile states  
↓  
enhanced plasticity  
⇒ impaired learning

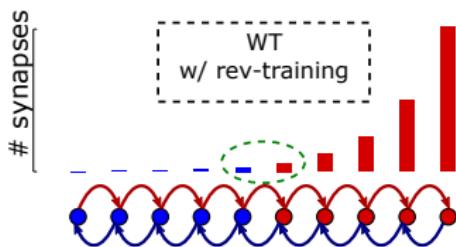
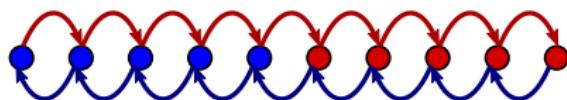
# Complex metaplastic synapses can explain the behaviour

Serial model



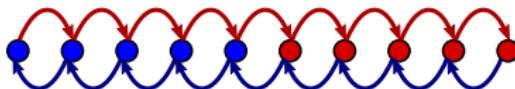
# Complex metaplastic synapses can explain the behaviour

Serial model



start in: stubborn states  
↓  
enhanced plasticity  
⇒ enhanced learning

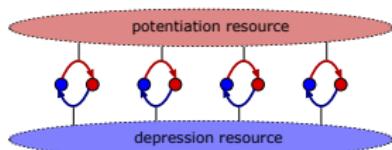
# Essential features of successful models



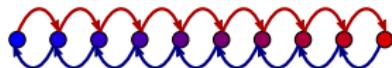
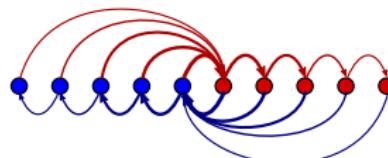
The serial model is successful in reproducing the data due to two features:

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

Fail:



Succeed:



# Conclusions

- In VOR learning, depending on prior experience:  
**Enhanced plasticity → enhance/impair learning.**
- **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.

# Experimental tests?

Traditional experiments:



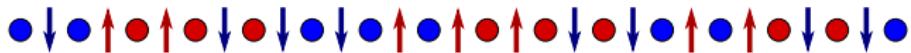
# Experimental tests?

Traditional experiments:

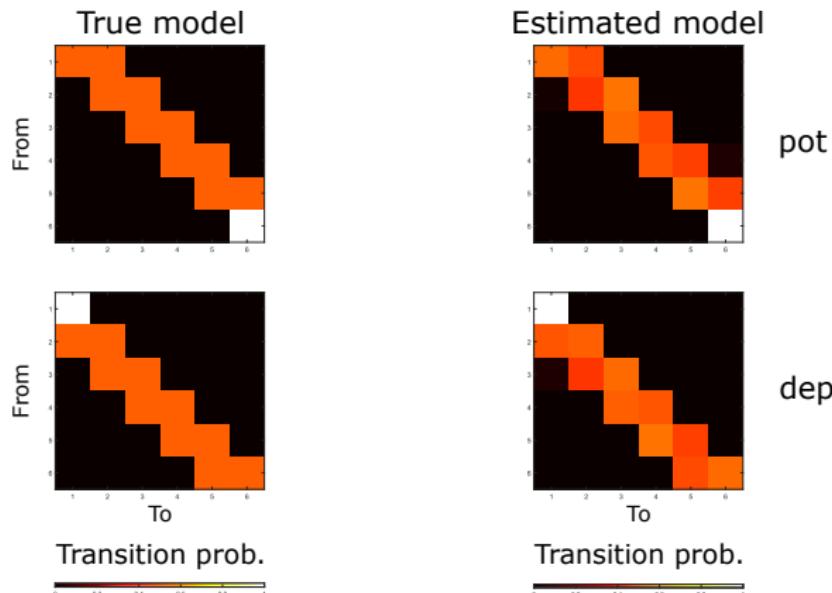


To fit a model: long sequence of small plasticity events.

Observe the changes in synaptic efficacy.



# Simulated experiment



Problem: need *long* sequences.

Whole cell patch of postsynaptic neuron → Ca washout.

# Future directions

## Learning and memory

- Multiple presentations.
- Correlations.
- More realistic tasks.
- Relation to molecular structure?

## Energy use in living systems

- Include space as well as time.
- Coarse graining: molecules → cells → systems.

## High dimensional statistics

- Theory of noisy random projections.

# Acknowledgements

## **Surya Ganguli**

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Rhea Kimpo

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Hanmi Lee

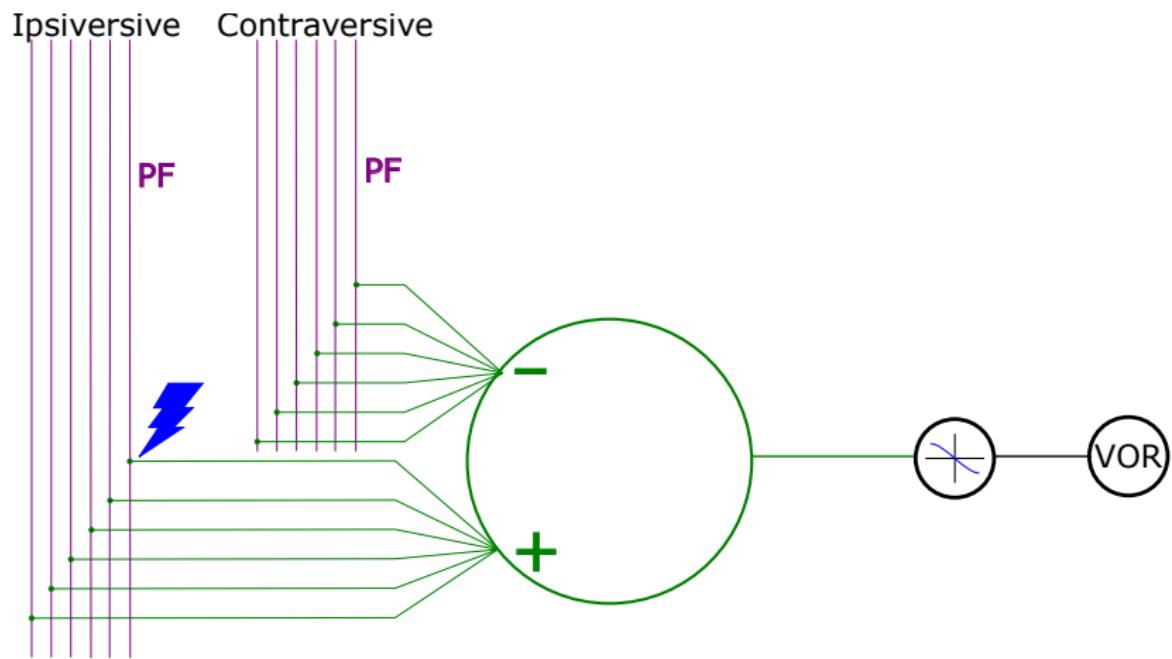
Marcus Benna

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

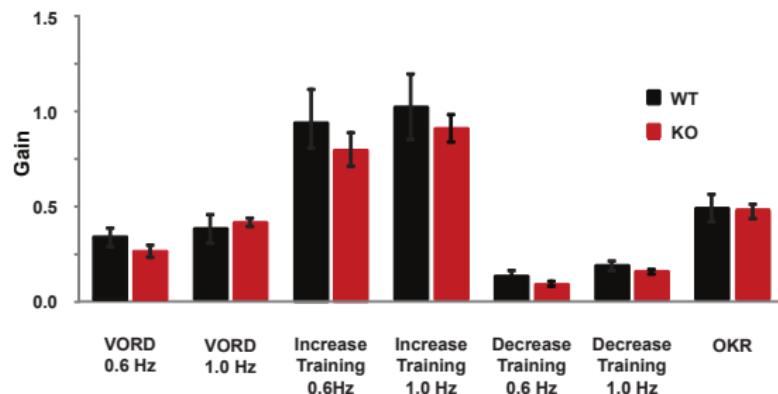
# Summary

- 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.

# Model of circuit

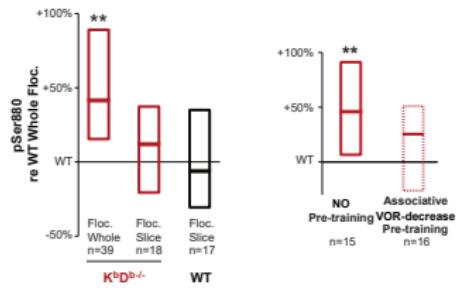


# Baseline



# Evidence: level of depression

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

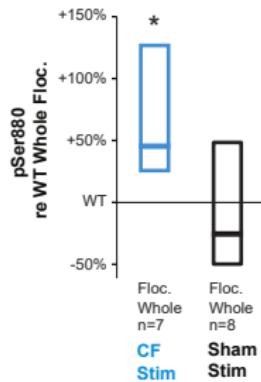
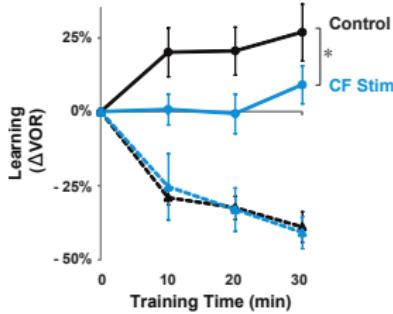
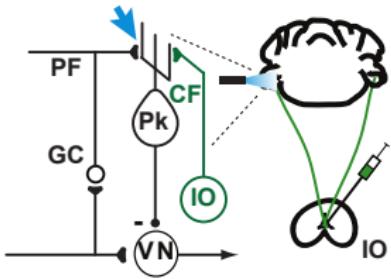


Biochemical signature of PF-Pk LTD.

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

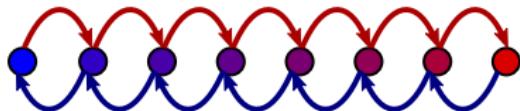
# Evidence: saturation by CF stimulation

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

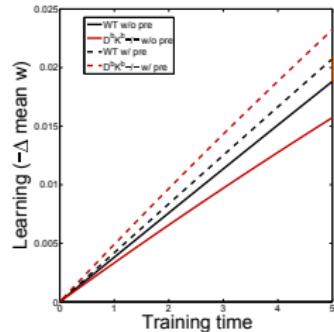
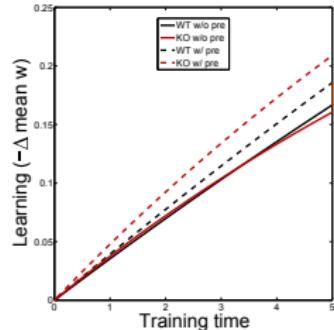
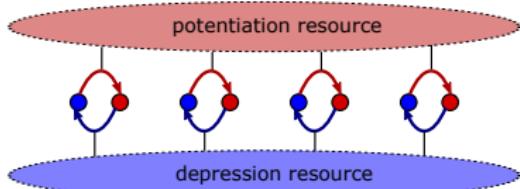


# Other models that fail

## Multistate synapse



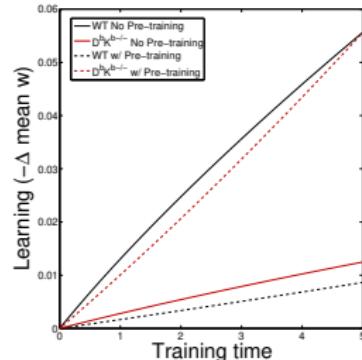
Pooled resource model



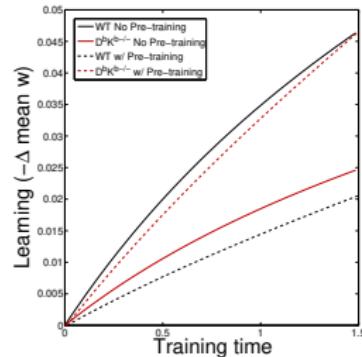
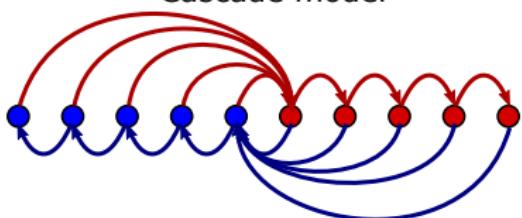
[Amit and Fusi (1994)]

# Other models that work

Non-uniform multistate model

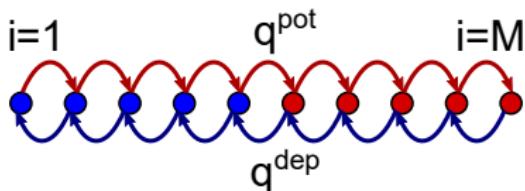


Cascade model



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

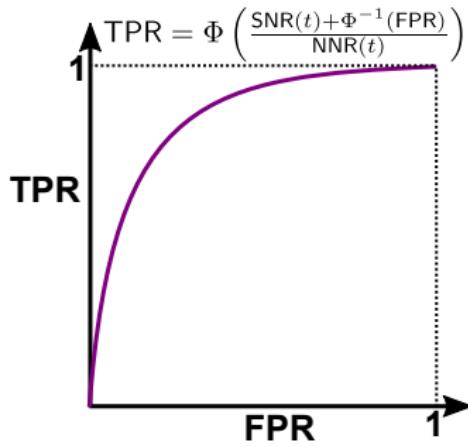
For  $M > 2$ : larger  $q^{\text{dep}}$   $\implies$  slower learning.

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

# Quantifying memory quality

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

[Sommer and Dayan (1998)]



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

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

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

Also: KL divergence, Chernoff distance, . . .

# Parameters for synaptic dynamics

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

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

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

Constraints:

$$f^{\text{pot/dep}}, M_{ij}^{\text{pot/dep}} \in [0, 1], \quad f^{\text{pot}} + f^{\text{dep}} = \sum_j M_{ij}^{\text{pot/dep}} = 1.$$

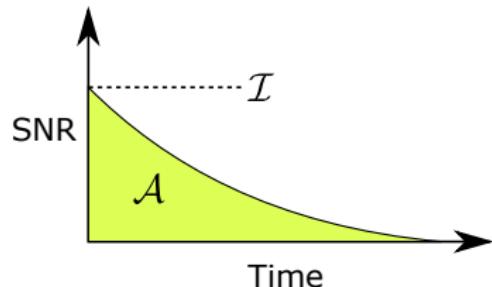
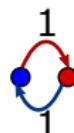
Memory curve given by

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

# Upper bounds on measures of memory

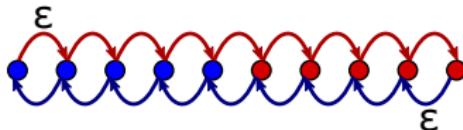
Initial SNR:

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



Area under curve:

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



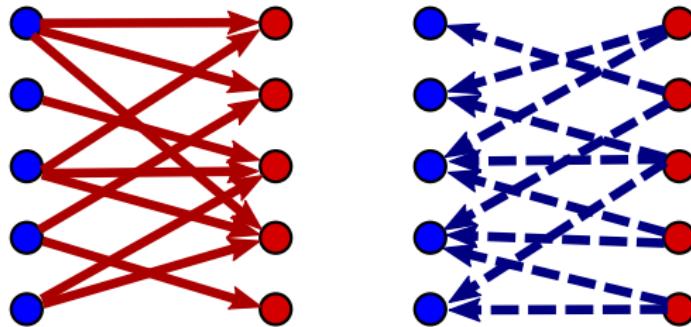
[Lahiri and Ganguli (2013)]

## Initial SNR as flux

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

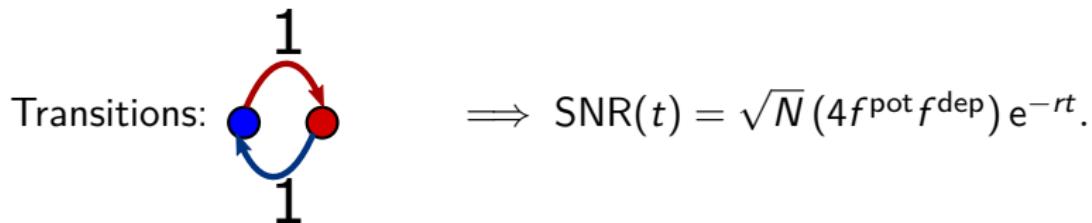
$$\text{SNR}(0) \leq \frac{4\sqrt{N}}{r} \Phi_{-+}.$$

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:

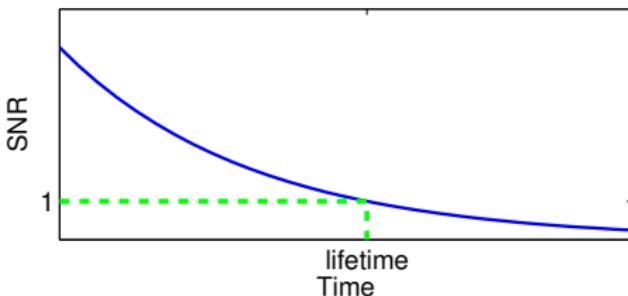
$$\text{SNR}(0) \leq \sqrt{N}.$$

## 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:

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

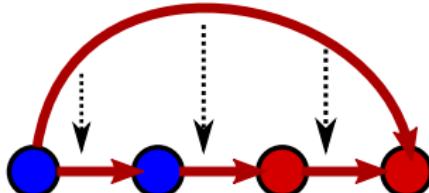
Saturated by a model with linear chain topology.

## 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

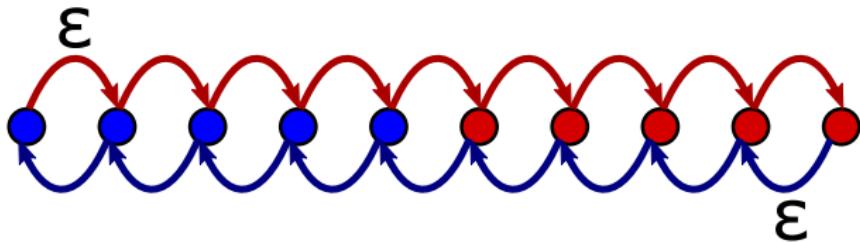
$$A = \frac{2\sqrt{N}}{r} \sum_k \pi_k |k - \langle k \rangle|.$$

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)]

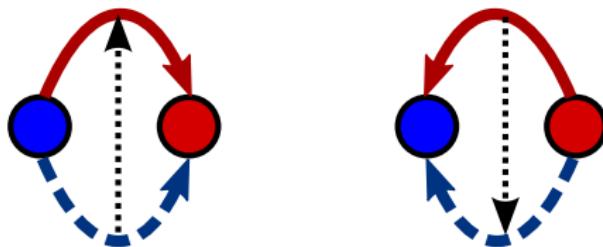
We define:

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

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

## Technical detail: upper/lower triangular

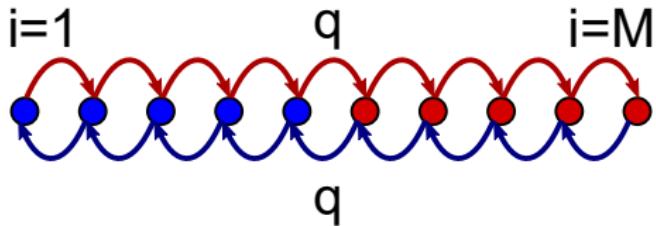
With states in order:



Endpoint: potentiation goes right, depression goes left.

back

## Intuition for using topology



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

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