# Learning and memory with complex synaptic plasticity

Subhaneil Lahiri

Stanford University, Applied Physics

March 31, 2019

# What is a synapse?

Experimentalists

Theorists

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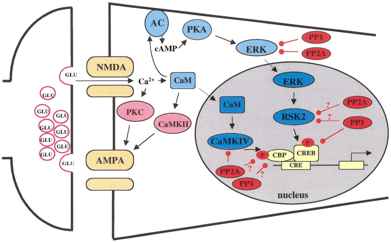
Experimentalists

Theorists

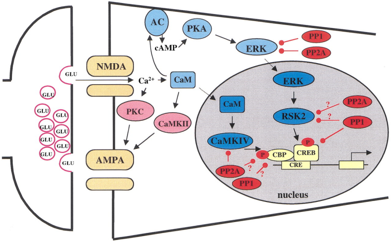



[Klann (2002)]

# What is a synapse?

Experimentalists

Theorists



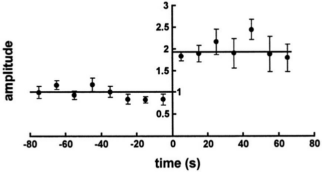

$$W_{ij}$$

[Klann (2002)]

# Storage capacity of synaptic memory

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

Assumes unbounded analogue synapses

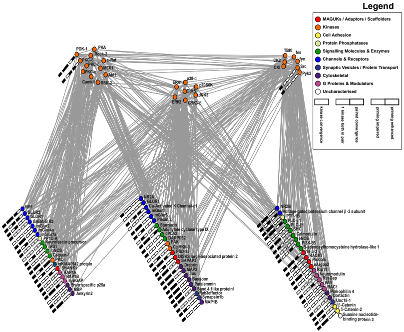



[Petersen et al. (1998), O'Connor et al. (2005)]

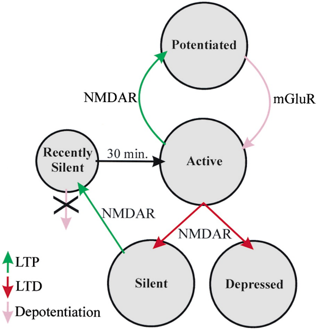
With discrete, finite synapses:
$\implies$ memory capacity $\sim \mathcal{O}(\log N)$.

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

# Synapses are complex




[Coba et al. (2009)]




[Montgomery and Madison (2002)]

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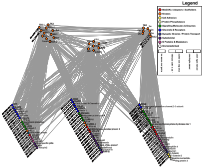

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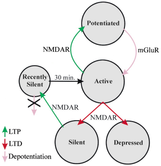


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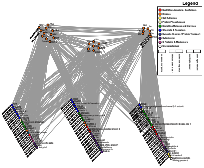


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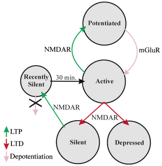


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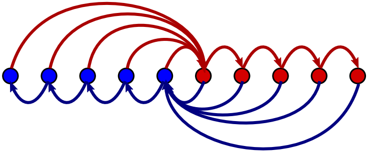
Cascade model



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

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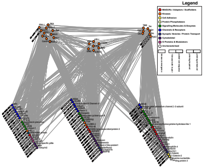


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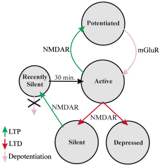


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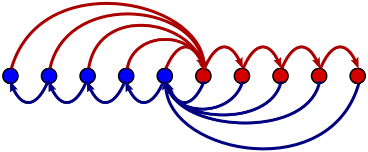


Capacity $\propto N^{2/3}$. [Fusi et al. (2005)]

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

# Outline

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

# Random projections and neural recordings

$\boxed{\text{Relevant neurons}} \to \boxed{\text{Recorded neurons}} \to \boxed{\text{Electrodes}}$.

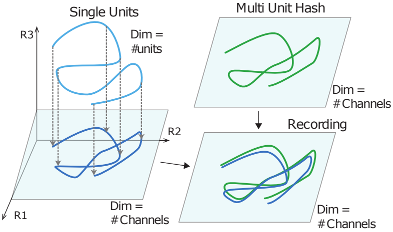
Previous work argued: 1st projection $\implies$ undistorted popn. dynamics.

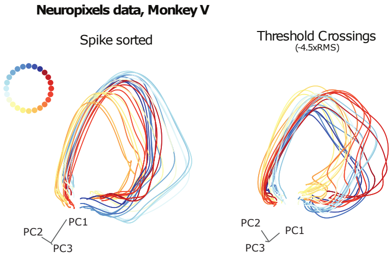
[Gao et al. (2017)]

# Random projections and neural recordings

$\boxed{\text{Relevant neurons}} \rightarrow \boxed{\text{Recorded neurons}} \rightarrow \boxed{\text{Electrodes}}$.

2nd projection (reversed by spike sorting): [Trautmann et al. (2017)]



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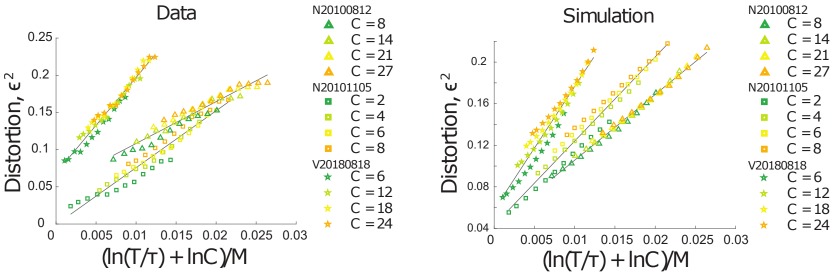
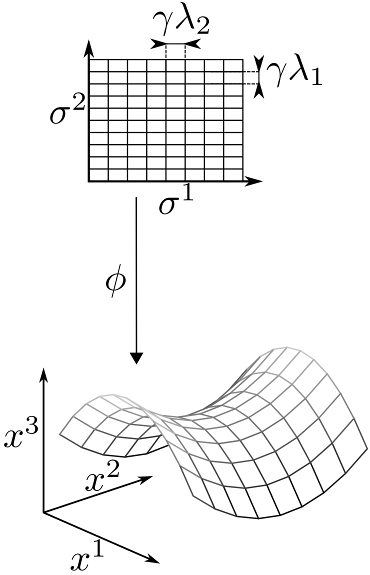
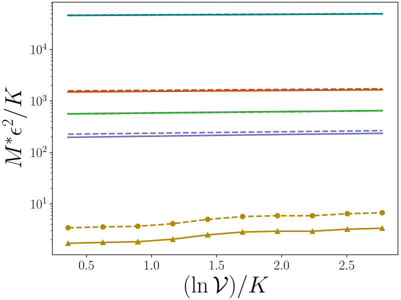


# Random projections of random manifolds

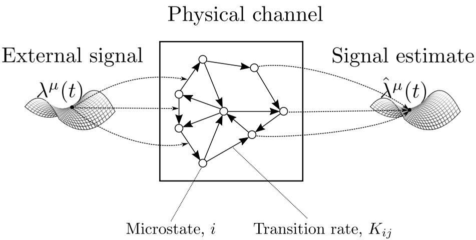


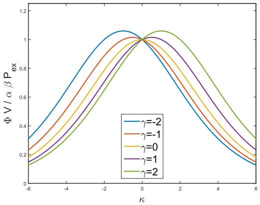
# Energy efficiency of cellular communication

Supercomputer: 1 MW, Brain: 15 W, Human: 100 W.

Sending a signal:




$$\text{Precision}^2\ \text{Speed}^2 \leq \frac{\text{Power}}{\tau k_B T}.$$




[Lahiri et al. (2016)]

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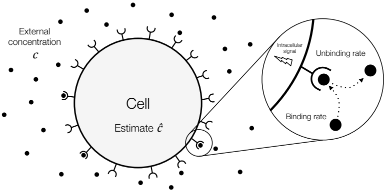
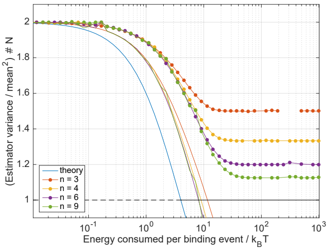
Receiving a signal:




$$\text{Precision}^2 \leq \frac{\text{Energy}}{8 k_B T} + \frac{\#(\text{bindings})}{2}.$$



## 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)*.

# Overview

Learning requires synaptic plasticity.
Expect: enhanced plasticity $\rightarrow$ enhanced learning.

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

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But often: enhanced plasticity $\rightarrow$ impaired learning.

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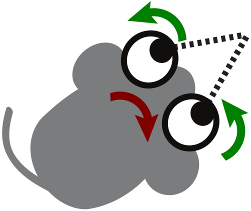
Mice with enhanced cerebellar plasticity can show both impaired and enhanced learning.

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

# Vestibulo-Occular Reflex



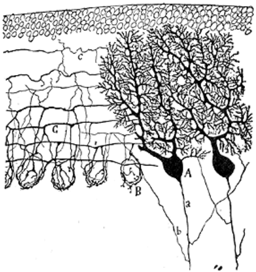
Eye movements compensate for head movements
$\implies$ stabilise image on retina.

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

Needs to be adjusted as eye muscles age, etc.

**VOR Increase Training**

**VOR Decrease Training**



[Cajal]

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

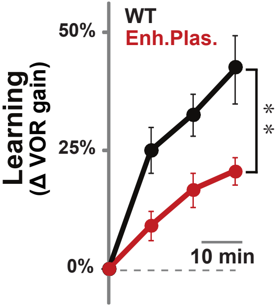
[Marr (1969), Albus (1971), Ito (1972)]

# Enhanced plasticity impairs learning

Expectation: enhanced LTD → enhanced learning.

Knockout of MHC-I $K^bD^b$ molecules in PF-Pk synapses
→ lower threshold for LTD → enhanced learning of Rotarod task.

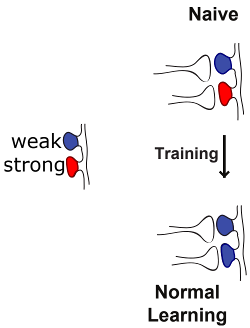
[McConnell et al. (2009)]


Experiment: enhanced plasticity → impaired learning.

# Depletion hypothesis

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



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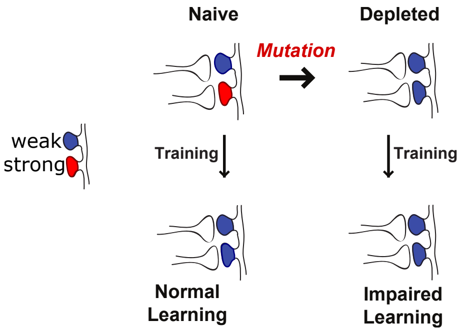

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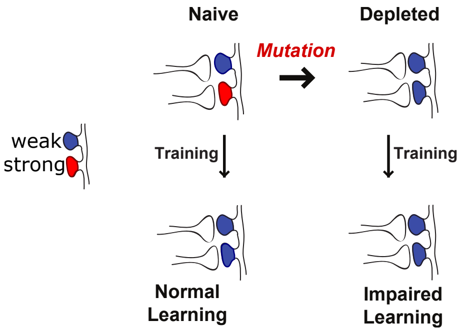


Question 1: depletion effect competes with enhanced intrinsic plasticity.
When is depletion effect stronger?

# Replenishment by reverse-training

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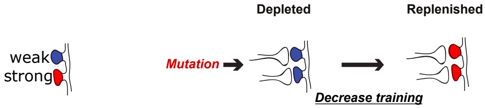

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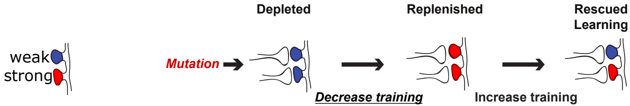

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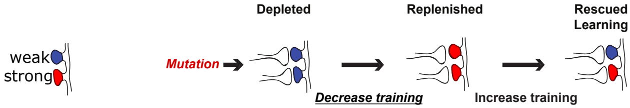


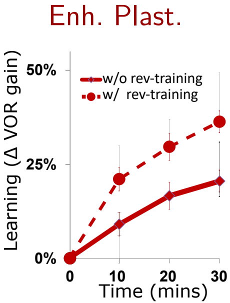


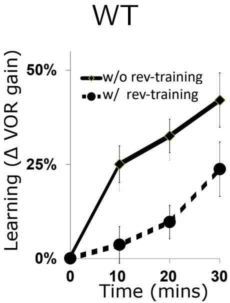

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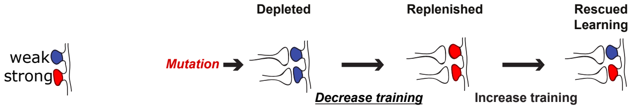
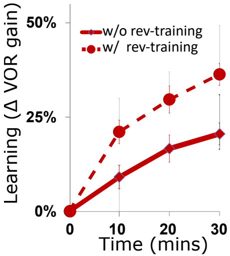
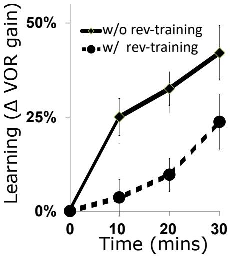



Enh. Plast.

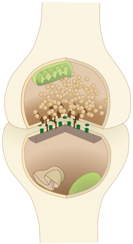



WT



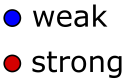

Question 2: How can replenishment *ever* impair learning?

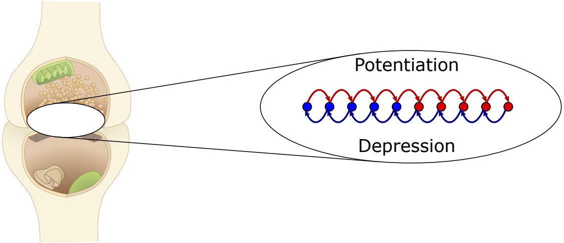
# Models of complex synaptic dynamics



# Models of complex synaptic dynamics

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




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

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

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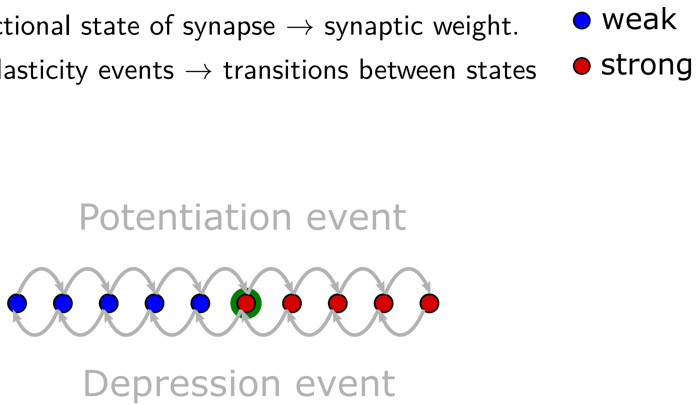

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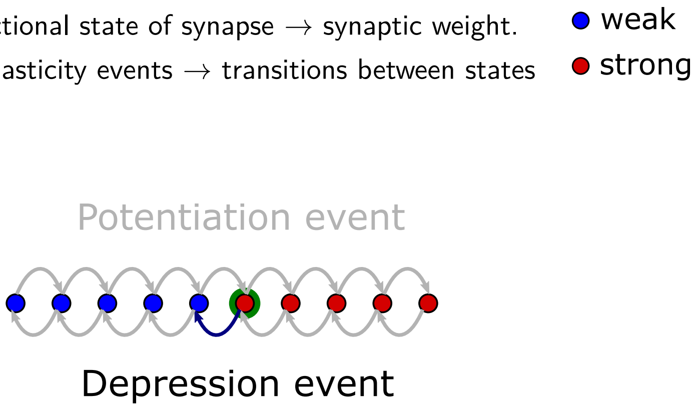

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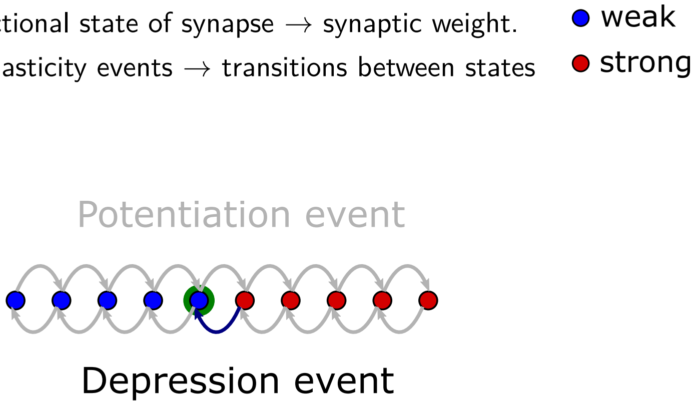

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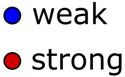


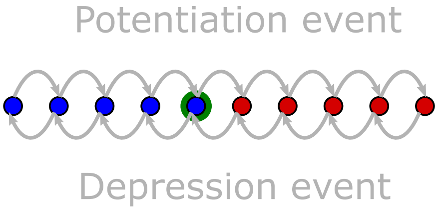

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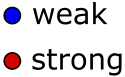


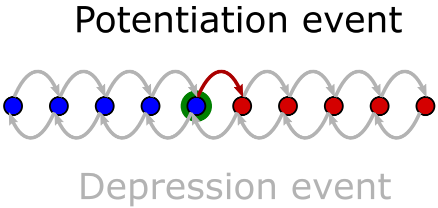

# Models of complex synaptic dynamics

- Internal functional state of synapse → synaptic weight.
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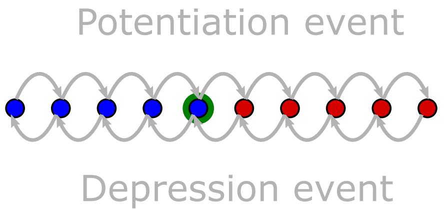
● weak

● strong



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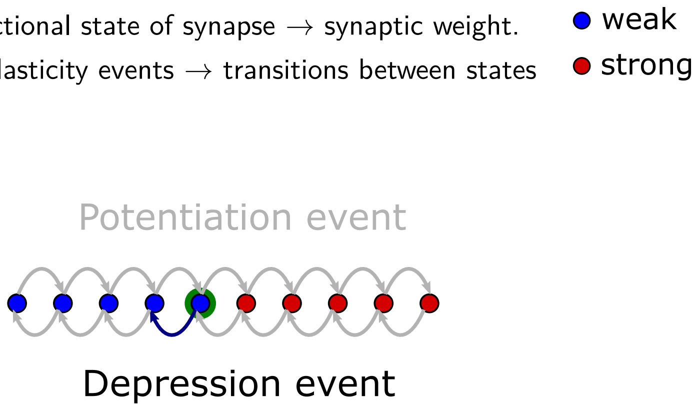


Metaplasticity: change propensity for plasticity
(independent of change in synaptic weight).

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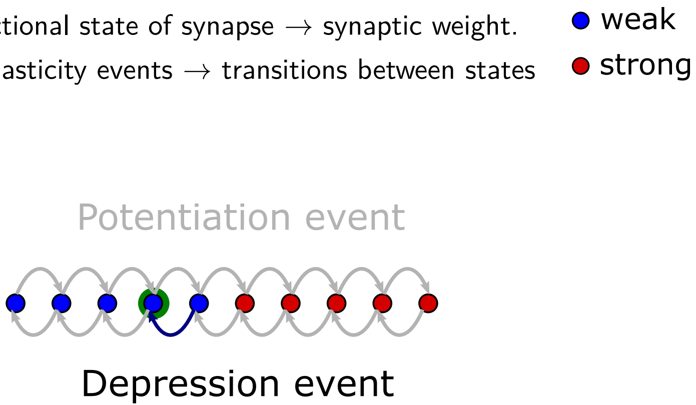


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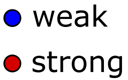


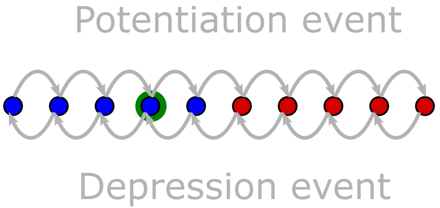


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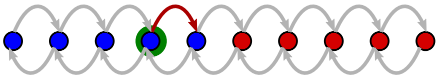


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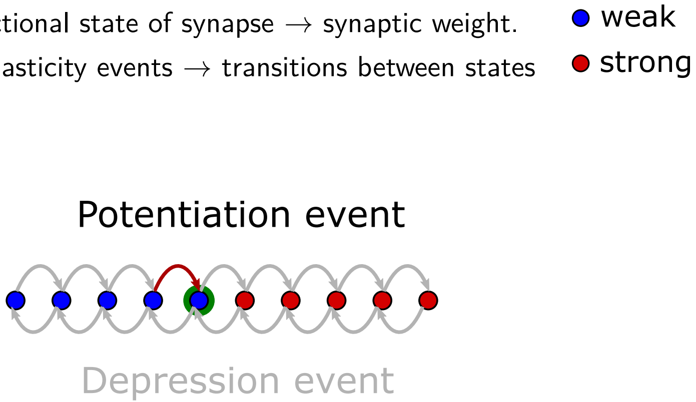


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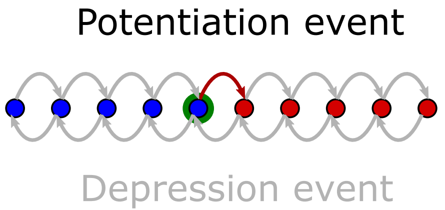


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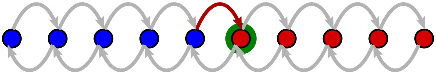
● weak
● strong

Potentiation event



Depression event

Metaplasticity: change propensity for plasticity
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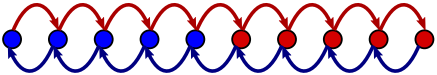
# Models of complex synaptic dynamics

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

weak

strong

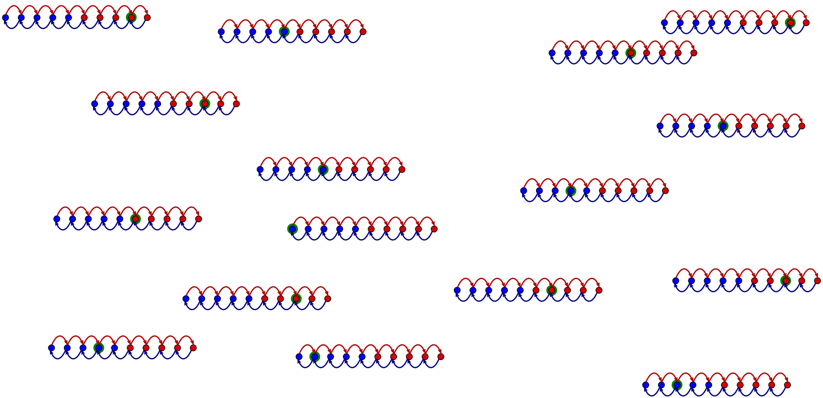
Potentiation



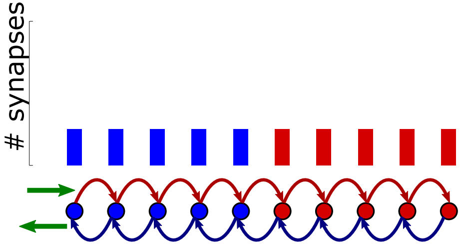
Depression

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

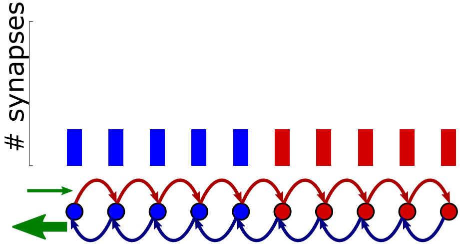
# Modelling VOR experiments



# Modelling VOR experiments

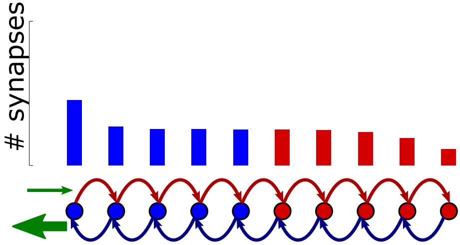


# Modelling VOR experiments



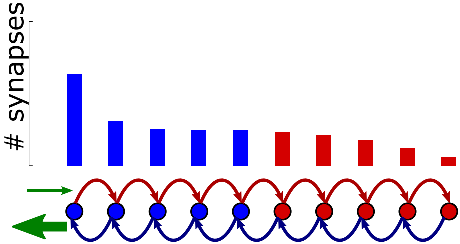

Training: change frequency of pot/dep events.

# Modelling VOR experiments



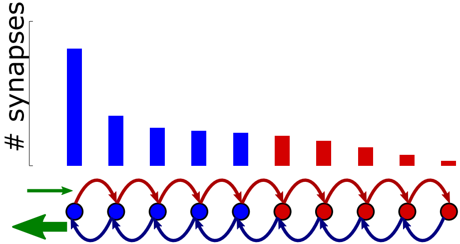

Training: change frequency of pot/dep events.

# Modelling VOR experiments



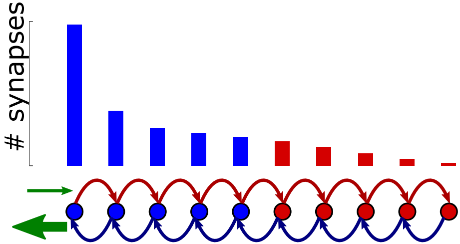

Training: change frequency of pot/dep events.

# Modelling VOR experiments



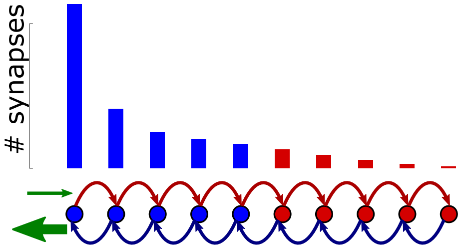

Training: change frequency of pot/dep events.

# Modelling VOR experiments




Training: change frequency of pot/dep events.

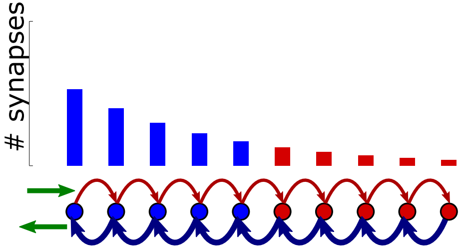
# Modelling VOR experiments




Training: change frequency of pot/dep events.

Learning: decrease in average synaptic weight.

# Modelling VOR experiments




Training: change frequency of pot/dep events.

Learning: decrease in average synaptic weight.

Mutation: increase transition probability for depression events.

# Questions

Depletion effect competes with enhanced intrinsic plasticity.

Question 1: When is the depletion effect stronger?

Reverse training impairs learning in wild-type.

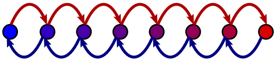
Question 2: How can replenishment *ever* impair learning?

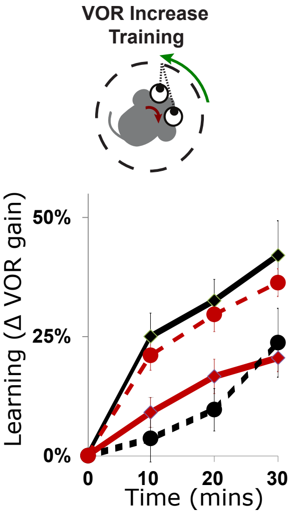
Enhanced plasticity $\rightarrow$ enhanced/impaired learning

Big question: Why? When?

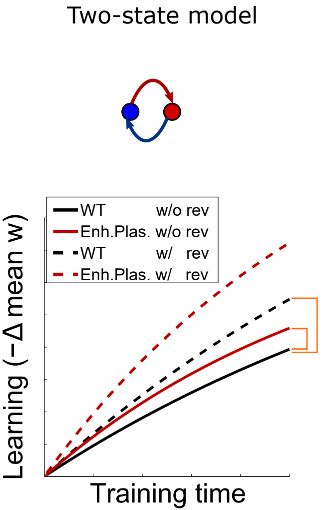
# Simple synapses cannot explain the data

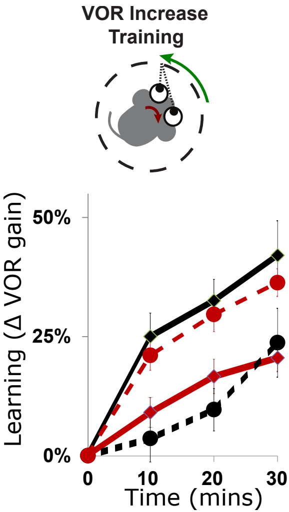
Multistate synapse





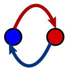
# Simple synapses cannot explain the data

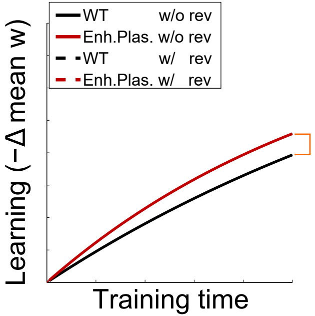


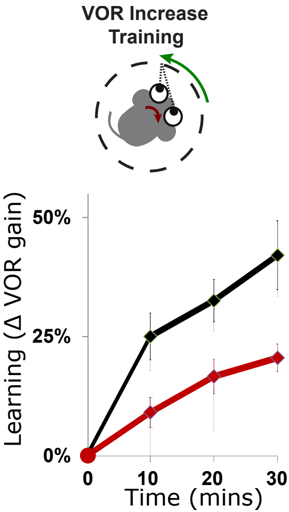



# Simple synapses cannot explain the data

Two-state model





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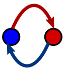
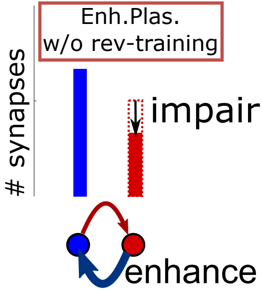


Initial distribution



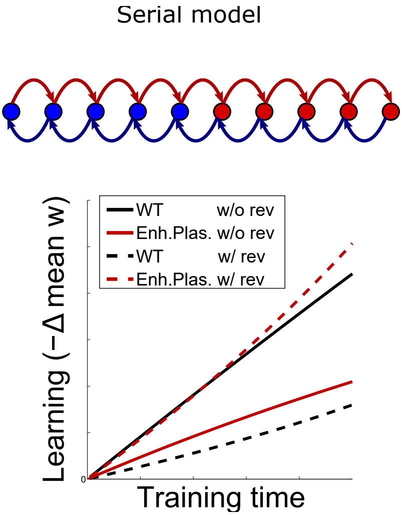

depletion effect

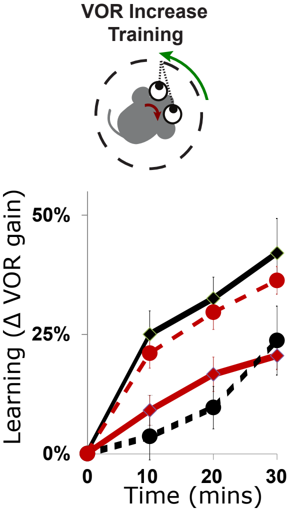
$<$

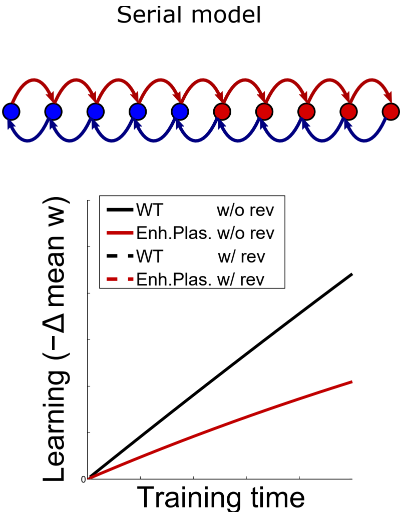
enhanced plasticity

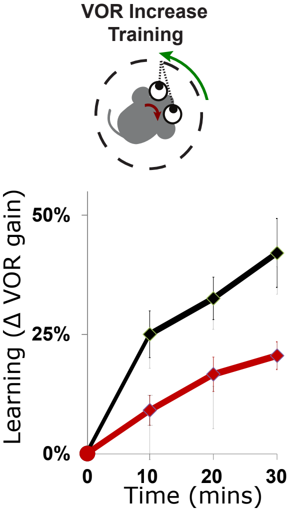
$\Longrightarrow$ enhanced learning

# Complex metaplastic synapses can explain the data

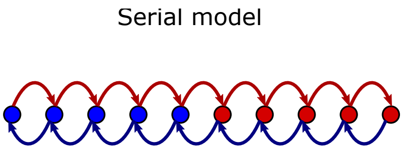


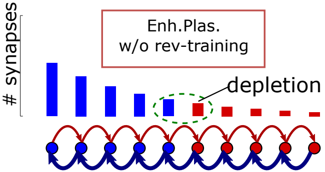




Serial model
WT w/o rev
Enh.Plas. w/o rev
WT w/ rev
Enh.Plas. w/ rev
Learning (−Δ mean w)
0
Training time


VOR Increase Training
50%
25%
0%
Learning (Δ VOR gain)
0
10
20
30
Time (mins)

# Complex metaplastic synapses can explain the data

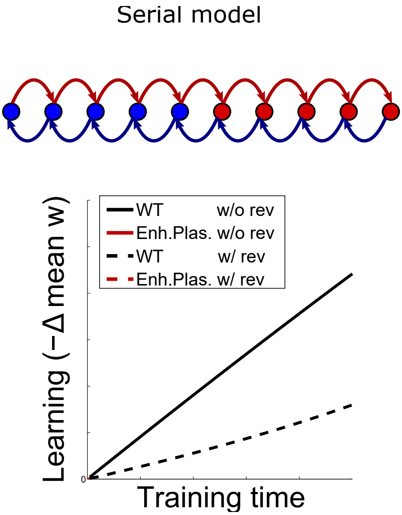


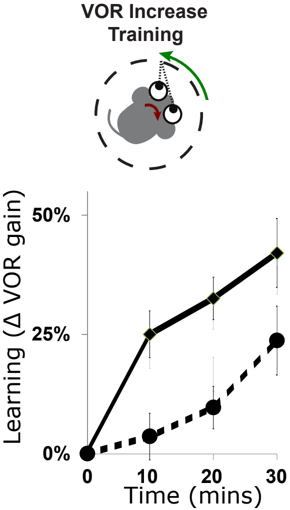




amplified depletion
$>$
enhanced plasticity

$\Longrightarrow$ impaired learning

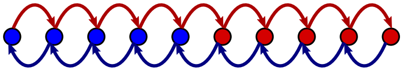
# Complex metaplastic synapses can explain the data

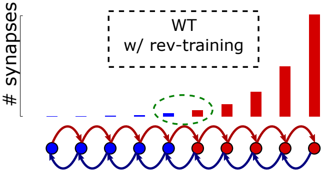


# Complex metaplastic synapses can explain the data

Serial model



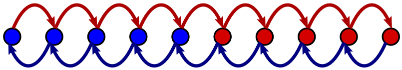


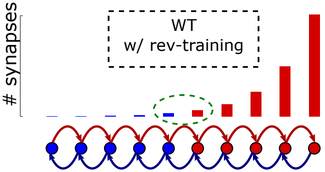

reverse training
$+$
“stubborn” metaplasticity

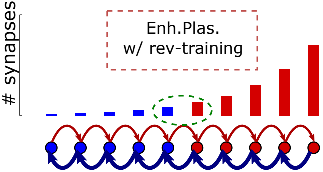
$\Longrightarrow$ impaired learning

# Complex metaplastic synapses can explain the data

Serial model

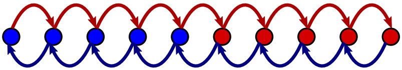




# Complex metaplastic synapses can explain the data

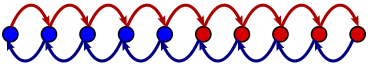
Serial model



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

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

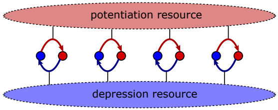
# Essential features

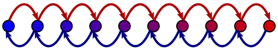


The success of the serial model relies on two features:

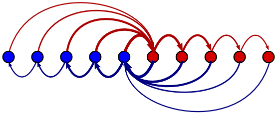
- Complexity - needed for depletion to dominate enhanced plasticity,
- Stubbornness - repeated potentiation impairs subsequent depression.

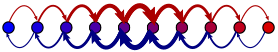
Fail:



Succeed:





Section 3

## Memory over different timescales

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

# Storage capacity of synaptic memory

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

Assumes unbounded analogue synapses

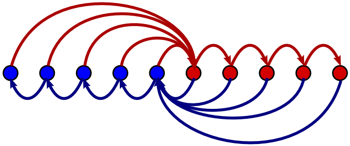
With discrete, *finite* synapses: $\implies$ memory capacity $\sim \mathcal{O}(\log N)$.

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

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

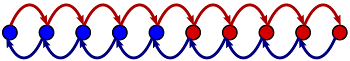
# Specific models of complex synaptic dynamics

Cascade model



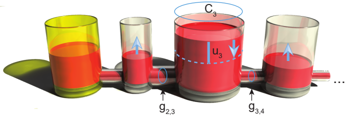
[Fusi et al. (2005)]

Serial model

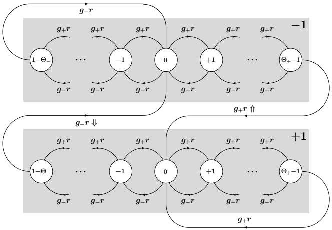


[Ben-Dayan Rubin and Fusi (2007)]

[Leibold and Kempter (2008)]

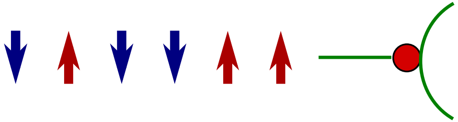



[Benna and Fusi (2016)]



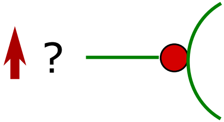

[Elliott (2011)]

# Synaptic memory curves



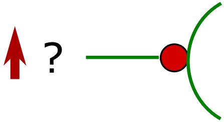
Synapses store a sequence of memories.

# Synaptic memory curves

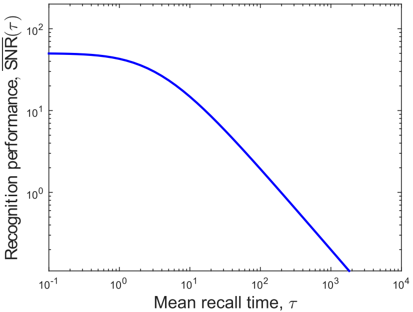



Synapses store a sequence of memories.
Recognition memory: has this pattern been seen before?

# Synaptic memory curves

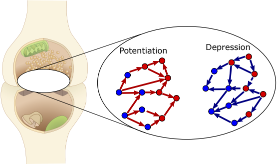



Synapses store a sequence of memories.
Recognition memory: has this pattern been seen before?
Performance described by SNR.

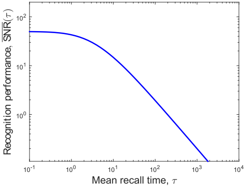


# General principles relating structure and function?

Synaptic structure



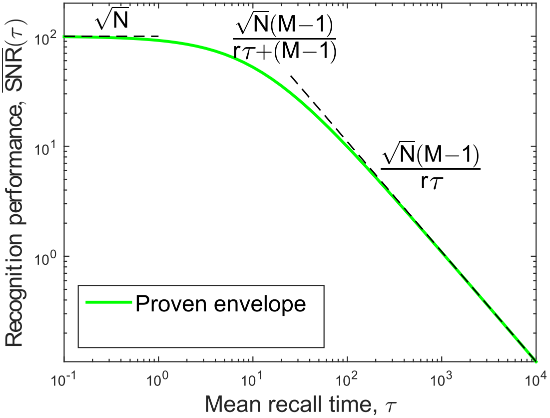

Synaptic function




- 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.



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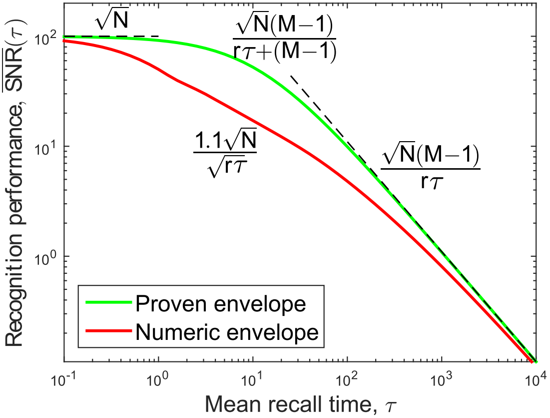
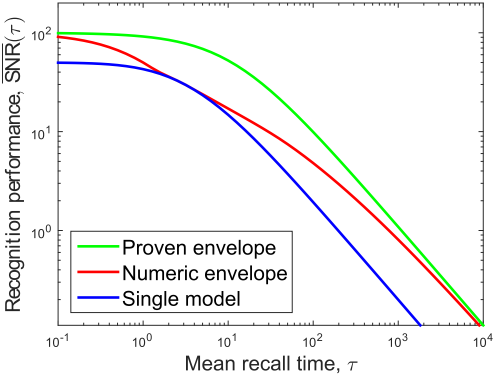
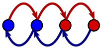
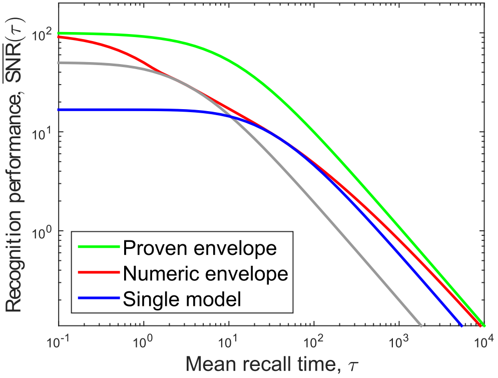


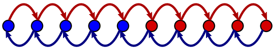
# Models that maximize memory for one timescale



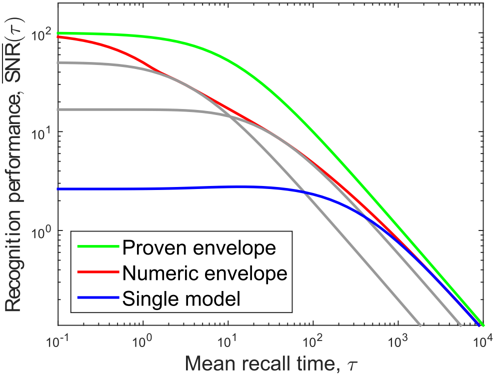



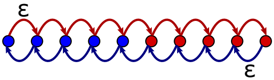
# Models that maximize memory for one timescale



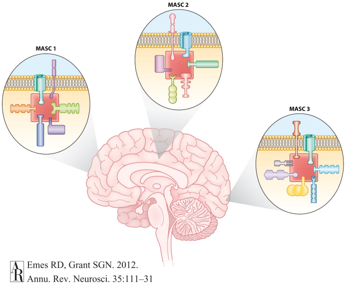
# Models that maximize memory for one timescale



# Synaptic diversity and timescales of memory

Different synapses have different molecular structures.




[Emes and Grant (2012)]

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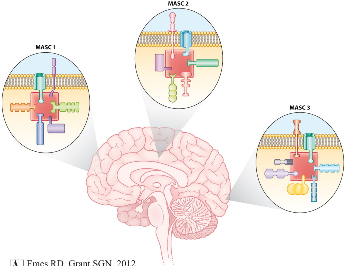


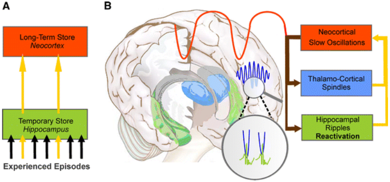

Emes RD, Grant SGN. 2012.
Annu. Rev. Neurosci. 35:111–31

[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 $\rightarrow$ nuclei.

[Attwell et al. (2002)]

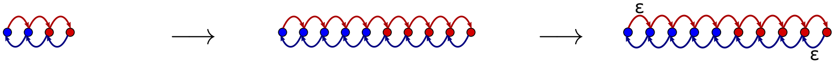
[Cooke et al. (2004)]

# Synaptic structure and function: general principles

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

What can we conclude?

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



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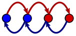
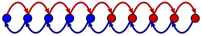
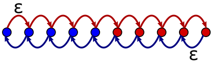
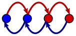
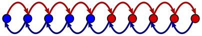
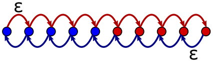

$\longrightarrow$

$\longrightarrow$



short topology $\longrightarrow$ long topology

# Synaptic structure and function: general principles

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

What can we conclude?

| | | | | |
|---|---|---|---|---|
| Short timescale | ⟶ | Moderate timescale | ⟶ | Long timescale |
|  | ⟶ |  | ⟶ |   |
| short topology | ⟶ | long topology | | |
| | | deterministic synapse | ⟶ | stochastic synapse |

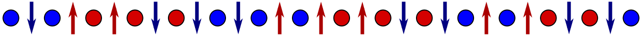
# Experimental tests?

Traditional experiments:

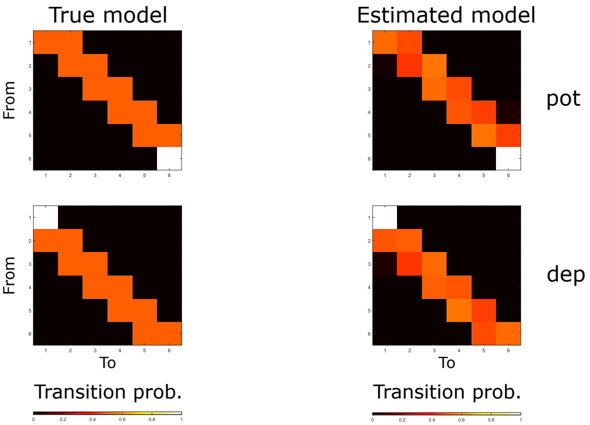
# Experimental tests?

Traditional experiments:

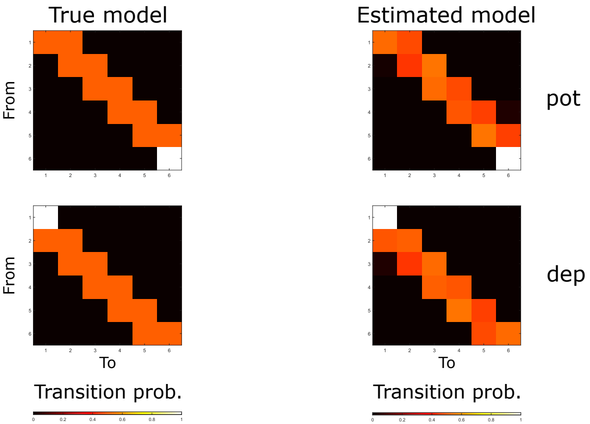
To fit a model: long sequence of small plasticity events.
Observe the changes in synaptic efficacy.



# Simulated experiment



# Simulated experiment




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

# Summary

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

# Acknowledgements


**Surya Ganguli**
Jascha Sohl-Dickstein
Friedemann Zenke
Sam Ocko
Stephane Deny
Jonathan Kadmon
Madhu Advani
Peiran Gao

David Sussillo

Niru Maheswaranathan
Ben Poole
Kiah Hardcastle
Lane McIntosh
Alex Williams
Christopher Stock
Sarah Harvey
Aran Nayebi

Stefano Fusi

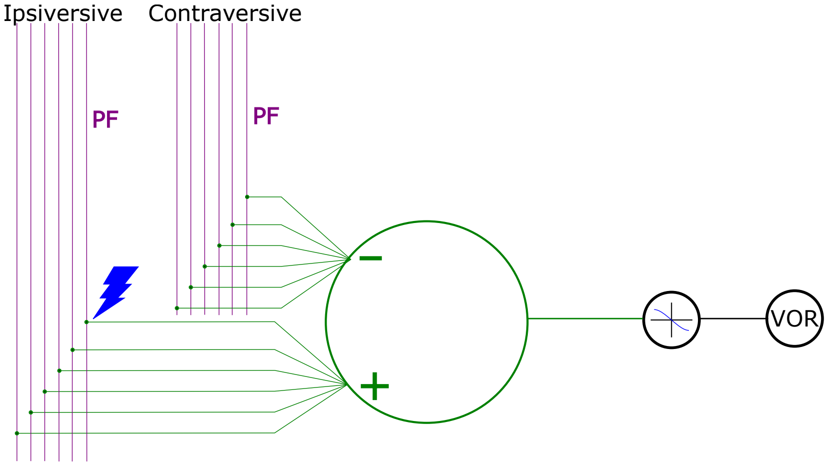
**Jennifer Raymond**
Barbara Nguyen-Vu
Grace Zhao
Aparna Suvrathan
Rhea Kimpo

**Carla Shatz**
Hanmi Lee

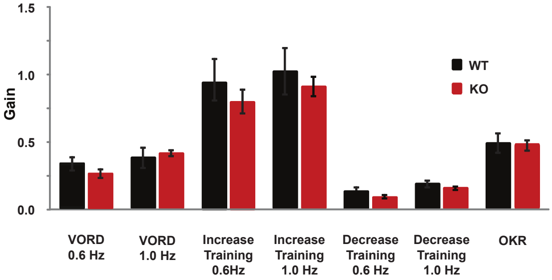
Marcus Benna

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

# Model of circuit

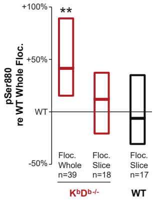


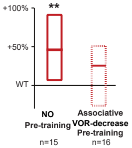
# Baseline



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

# Evidence: level of depression



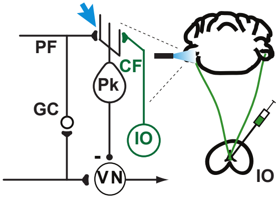

Basal level of GluR2 phosphorylation at serine 880 in AMPA receptor.

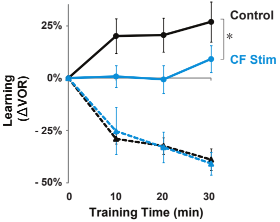
Biochemical signature of PF-Pk LTD.

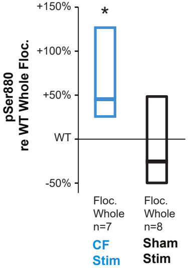
Shows that # depressed synapses in flocculus is larger in KO than WT.

# Evidence: saturation by CF stimulation

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

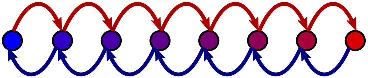


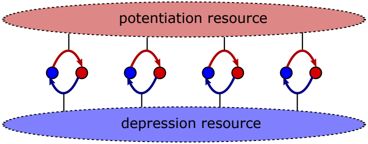



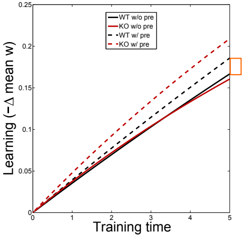
# Other models that fail

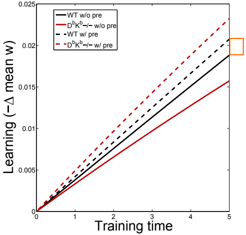
Multistate synapse



Pooled resource model



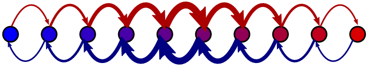



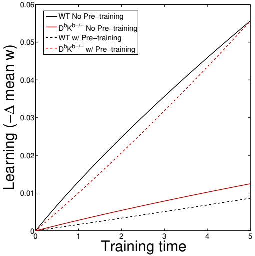




[Amit and Fusi (1994)]

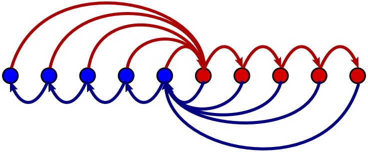
# Other models that work

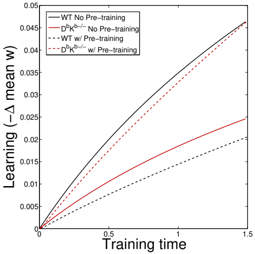
Non-uniform multistate model





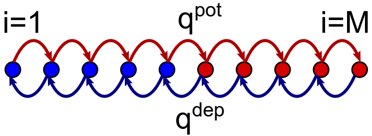

Cascade model






[Fusi et al. (2005)]

# Mathematical explanation




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

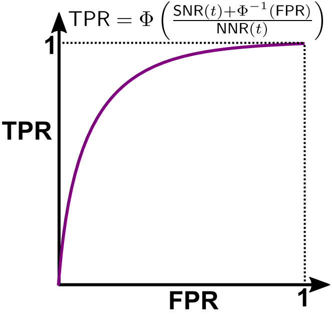
Learning rate $\sim \boldsymbol{\pi}_{M/2}\left(\frac{q^{\text{dep}}}{q^{\text{pot}}}\right) = \mathcal{N}\left(\frac{q^{\text{pot}}}{q^{\text{dep}}}\right)^{\frac{M}{2}-1}$.

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

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

# Quantifying memory quality

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




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

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

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

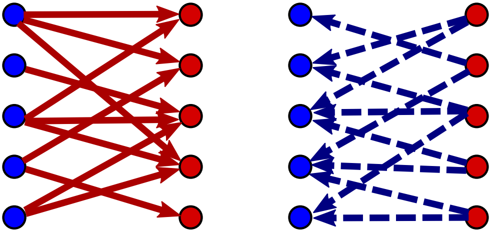
Also: KL divergence, Chernoff distance, . . .

# Initial SNR as flux

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

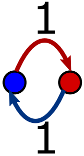
$$\mathrm{SNR}(0) \leq \frac{4\sqrt{N}}{r}\,\mathbf{\Phi}_{-+}.$$

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



# Two-state model

Two-state model equivalent to previous slide:

Transitions: 


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

Maximal initial SNR:

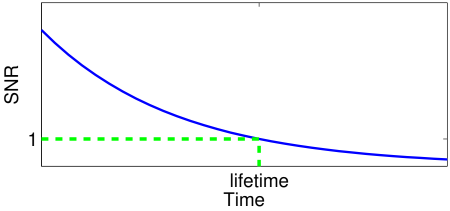
$$\mathrm{SNR}(0) \leq \sqrt{N}.$$

# Area under memory curve

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

Area bounds memory lifetime:

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




This area has an upper bound:

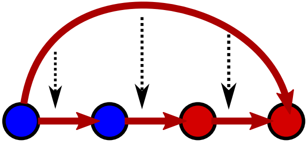
$$\mathcal{A} \leq \sqrt{N}(M-1)/r.$$

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

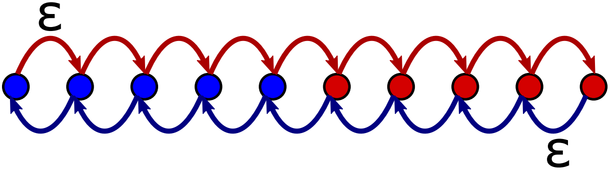
$$A = \frac{2\sqrt{N}}{r} \sum_k \pi_k \left| k - \langle k \rangle \right| .$$

Max: equilibrium probability distribution concentrated at both ends.

[Barrett and van Rossum (2008)]

# Saturating model

Make end states "sticky"




Has long decay time, but terrible initial SNR.

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

# Technical detail: ordering states

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

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

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

[Kemeny and Snell (1960)]

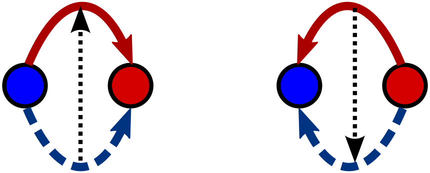
We define:

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

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

# Technical detail: upper/lower triangular

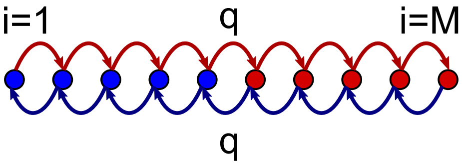
With states in order:



Endpoint: potentiation goes right, depression goes left.

back

# Intuition for using topology




$$\mathcal{I} \propto q, \qquad \max_a \tau_a \propto \frac{1}{q}, \qquad \Longrightarrow \qquad \text{Stochasticity:} \quad \mathcal{I} \propto \frac{1}{\tau_{\text{max}}},$$

$$\mathcal{I} \propto \frac{1}{M}, \qquad \max_a \tau_a \propto M^2, \qquad \qquad \text{Topology:} \quad \mathcal{I} \propto \frac{1}{\sqrt{\tau_{\text{max}}}}.$$

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