

Learning and memory with complex synaptic plasticity

Subhaneil Lahiri

Stanford University, Applied Physics

March 30, 2019

What is a synapse?

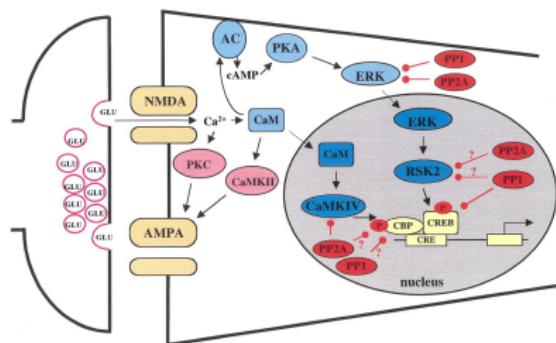
Experimentalists

Theorists

What is a synapse?

Experimentalists

Theorists

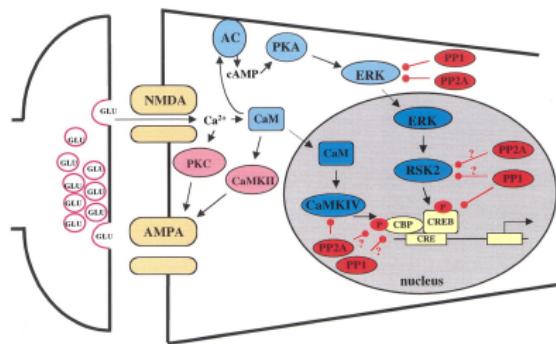


[Klann (2002)]

What is a synapse?

Experimentalists

Theorists



W_{ij}

[Klann (2002)]

Storage capacity of synaptic memory

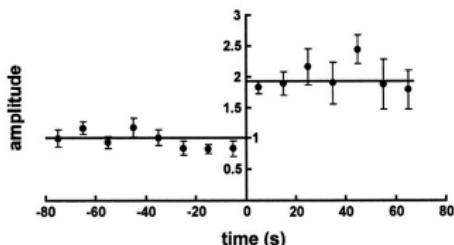
Hopfield, perceptron have capacity $\propto N$, (# synapses).

Assumes unbounded analogue synapses

With discrete, finite synapses:

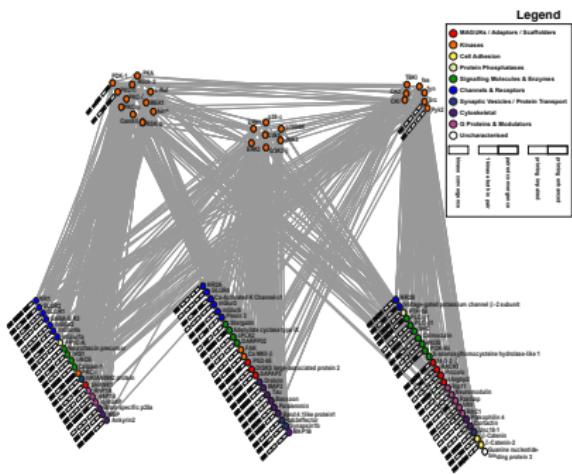
\implies memory capacity $\sim \mathcal{O}(\log N)$.

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

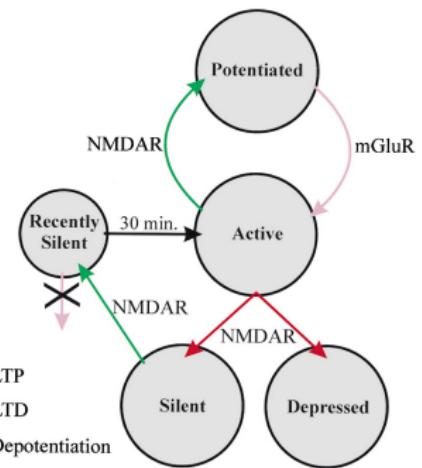


[Petersen et al. (1998), O'Connor et al. (2005)]

Synapses are complex

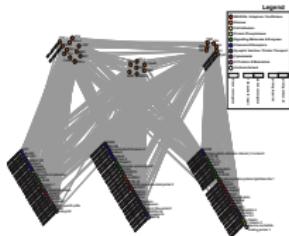


[Coba et al. (2009)]

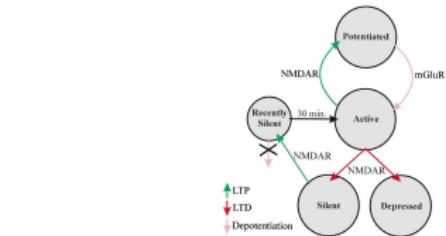


[Montgomery and Madison (2002)]

Synapses are complex

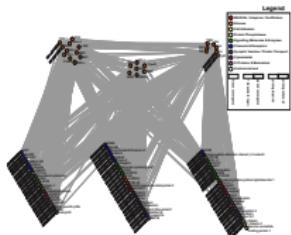


[Coba et al. (2009)]

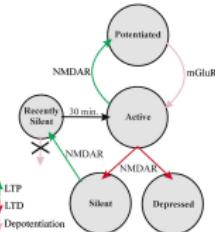


[Montgomery and Madison (2002)]

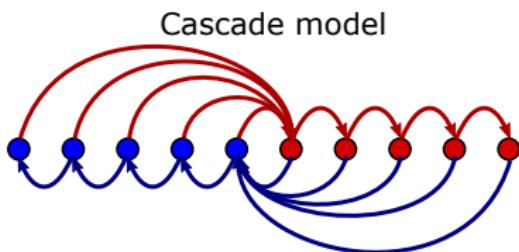
Synapses are complex



[Coba et al. (2009)]



[Montgomery and Madison (2002)]

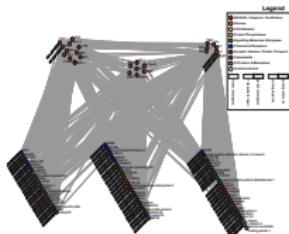


Cascade model

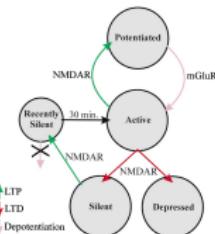
Capacity $\propto N^{2/3}$.

[Fusi et al. (2005)]

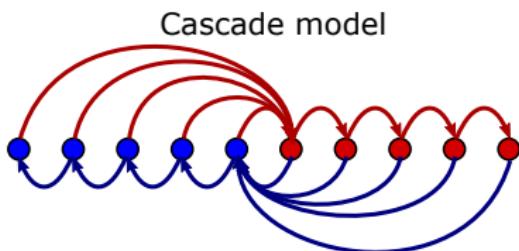
Synapses are complex



[Coba et al. (2009)]



[Montgomery and Madison (2002)]



Cascade model

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

[Fusi et al. (2005)]

Capacity $\propto N$.

[Benna and Fusi (2016)]

Outline

1 Learning with enhanced plasticity

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

2 Memory over different timescales

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

3 Designing experiments

Section 1

Learning with enhanced plasticity

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

Overview

Learning requires synaptic plasticity.

Expect: enhanced plasticity → enhanced learning.

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



Overview

Learning requires synaptic plasticity.

Expect: enhanced plasticity → enhanced learning.

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



But often: enhanced plasticity → 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)]



Overview



Learning requires synaptic plasticity.

Expect: enhanced plasticity → enhanced learning.

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



But often: enhanced plasticity → impaired learning.

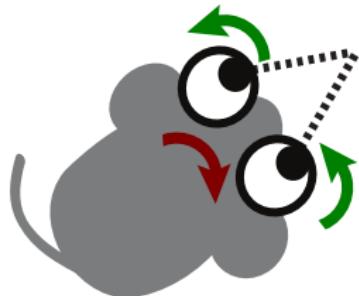
[Migaud et al. (1998), Uetani et al. (2000), Hayashi et al. (2004)]

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

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

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

Vestibulo-Occular Reflex



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

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

Needs to be adjusted as eye muscles age, etc.

Vestibulo-Occular Reflex training

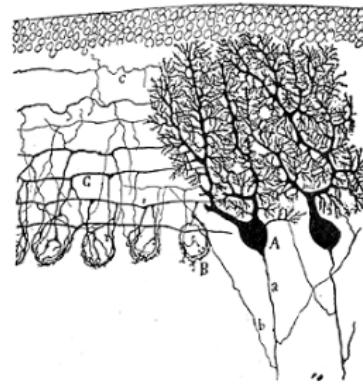
VOR Increase Training



VOR Decrease Training



VOR increase:
VOR decrease:



[Cajal]

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

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

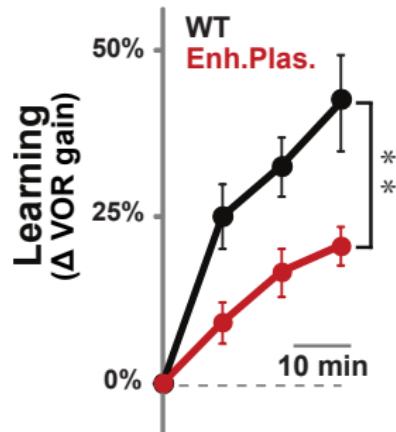
Enhanced plasticity impairs learning

Expectation: enhanced LTD \rightarrow enhanced learning.

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

[McConnell et al. (2009)]

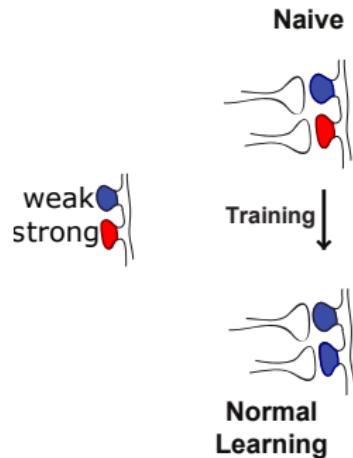
VOR Increase
Training



Experiment: enhanced plasticity \rightarrow impaired learning.

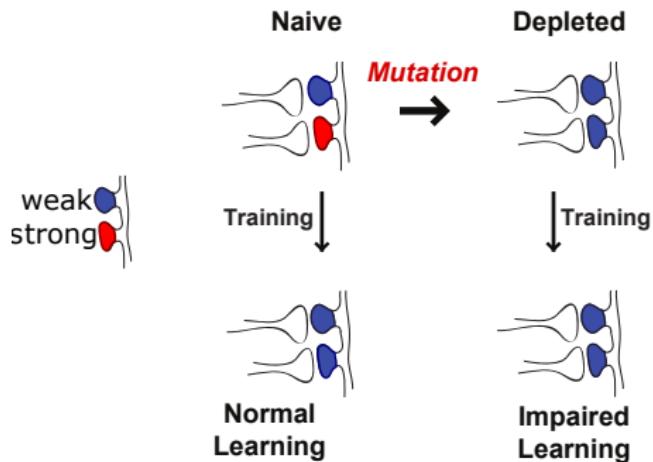
Depletion hypothesis

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



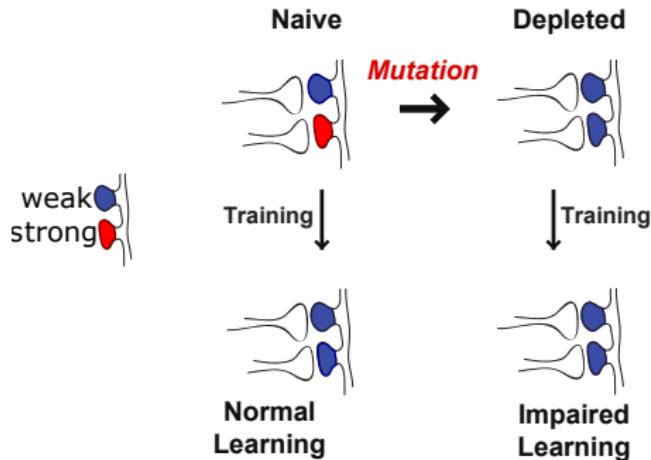
Depletion hypothesis

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



Depletion hypothesis

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

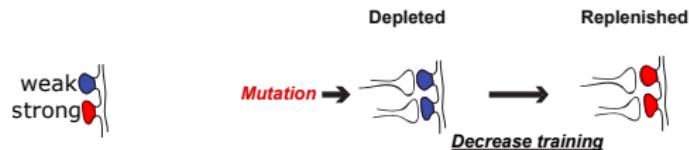


Question 1: depletion effect competes with enhanced intrinsic plasticity.
When is depletion effect stronger?

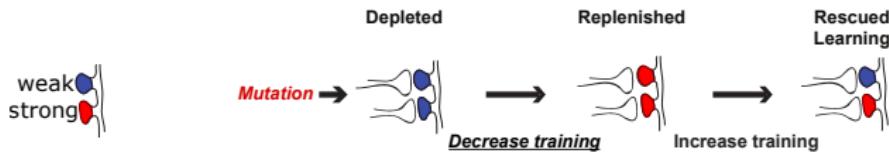
Replenishment by reverse-training



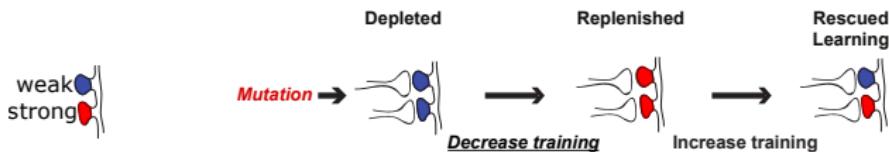
Replenishment by reverse-training



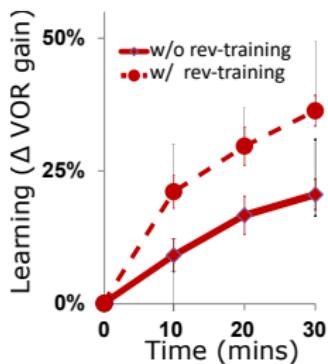
Replenishment by reverse-training



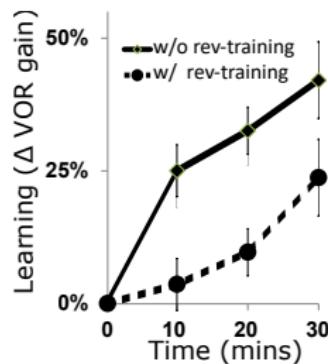
Replenishment by reverse-training



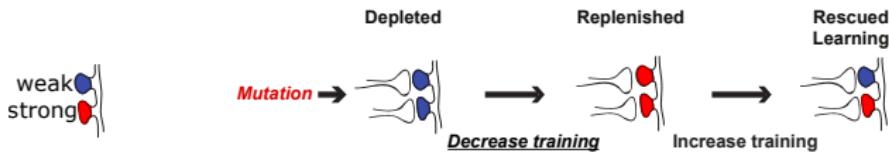
Enh. Plast.



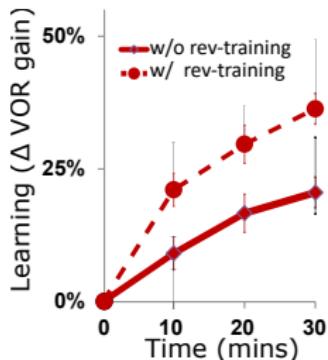
WT



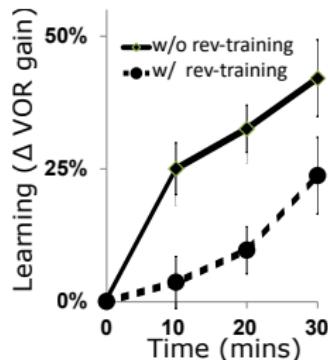
Replenishment by reverse-training



Enh. Plast.



WT



Question 2: How can replenishment ever impair learning?

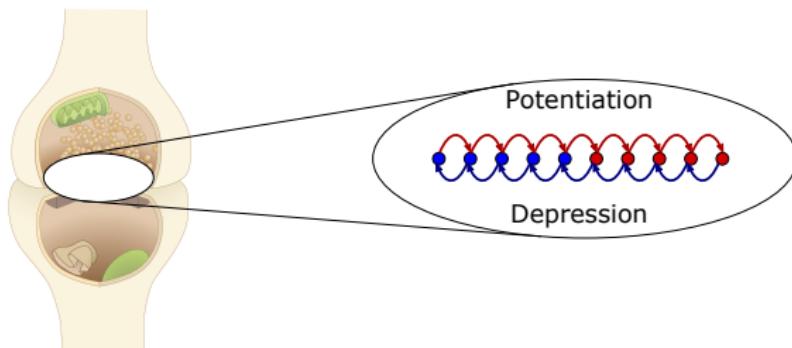
Models of complex synaptic dynamics



Models of complex synaptic dynamics

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

● weak
● strong



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

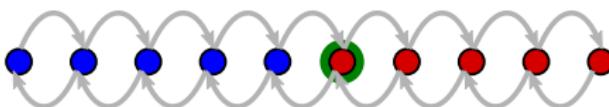
[Fusi et al. (2005), Fusi and Abbott (2007), Barrett and van Rossum (2008)]

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

Models of complex synaptic dynamics

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

Potentiation event

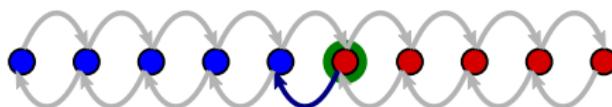


Depression event

Models of complex synaptic dynamics

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

Potentiation event



Depression event

Models of complex synaptic dynamics

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

Potentiation event

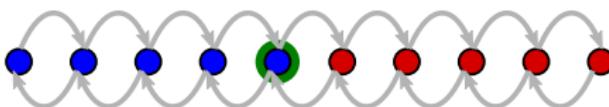


Depression event

Models of complex synaptic dynamics

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

Potentiation event

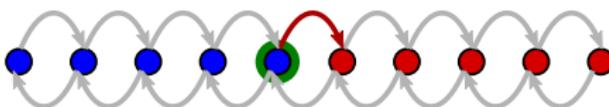


Depression event

Models of complex synaptic dynamics

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

Potentiation event

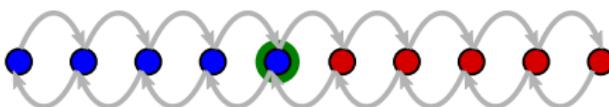


Depression event

Models of complex synaptic dynamics

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

Potentiation event



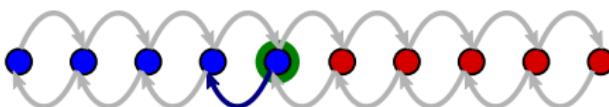
Depression event

Models of complex synaptic dynamics

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

● weak
● strong

Potentiation event



Depression event

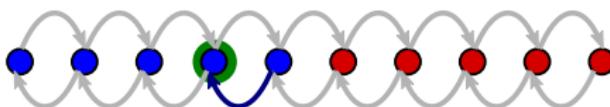
Metaplasticity: change propensity for plasticity
(independent of change in synaptic weight).

Models of complex synaptic dynamics

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

weak
strong

Potentiation event



Depression event

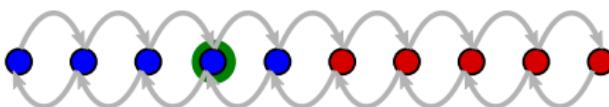
Metaplasticity: change propensity for plasticity
(independent of change in synaptic weight).

Models of complex synaptic dynamics

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

● weak
● strong

Potentiation event



Depression event

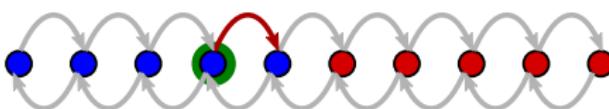
Metaplasticity: change propensity for plasticity
(independent of change in synaptic weight).

Models of complex synaptic dynamics

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

weak
strong

Potentiation event



Depression event

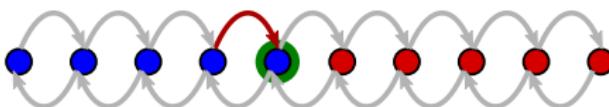
Metaplasticity: change propensity for plasticity
(independent of change in synaptic weight).

Models of complex synaptic dynamics

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

weak
strong

Potentiation event



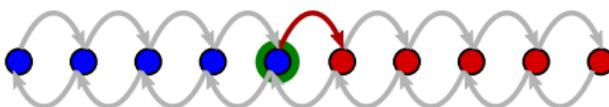
Depression event

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

Models of complex synaptic dynamics

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

Potentiation event



Depression event

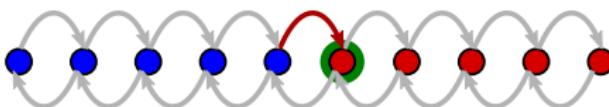
Metaplasticity: change propensity for plasticity
(independent of change in synaptic weight).

Models of complex synaptic dynamics

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

weak
strong

Potentiation event



Depression event

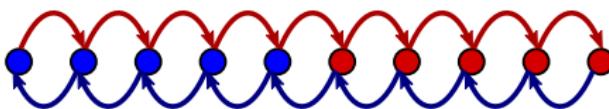
Metaplasticity: change propensity for plasticity
(independent of change in synaptic weight).

Models of complex synaptic dynamics

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

weak
strong

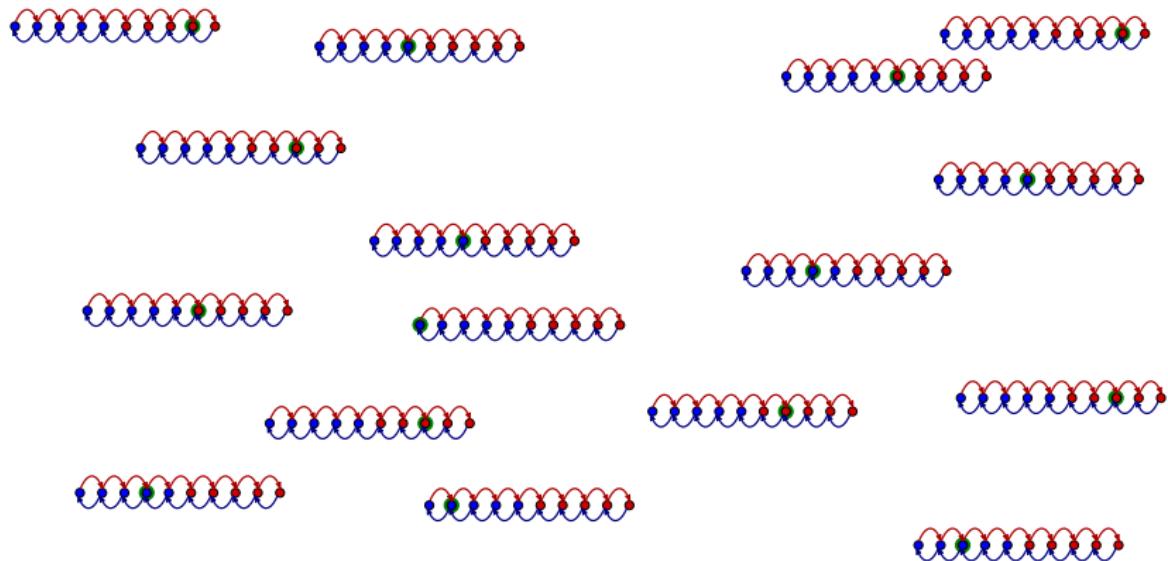
Potentiation



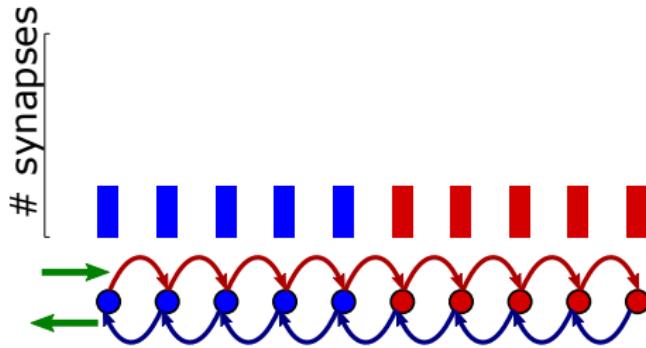
Depression

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

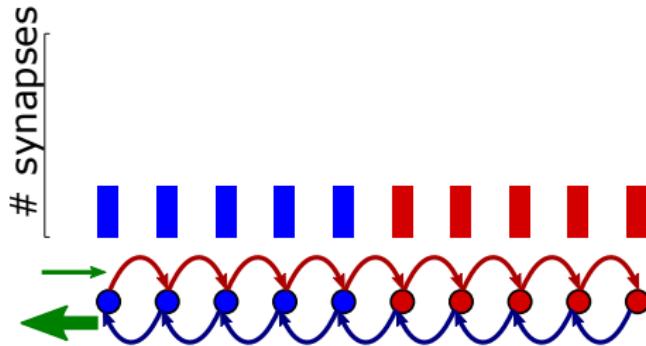
Modelling VOR experiments



Modelling VOR experiments

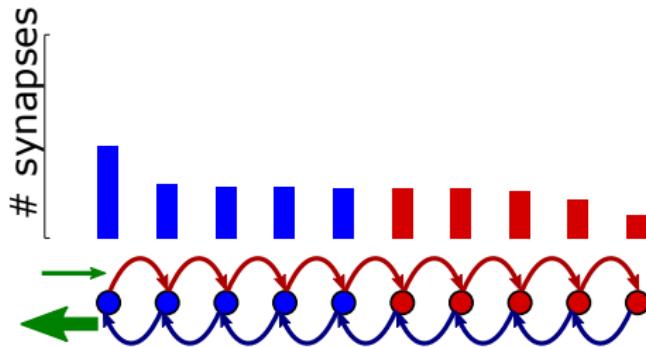


Modelling VOR experiments



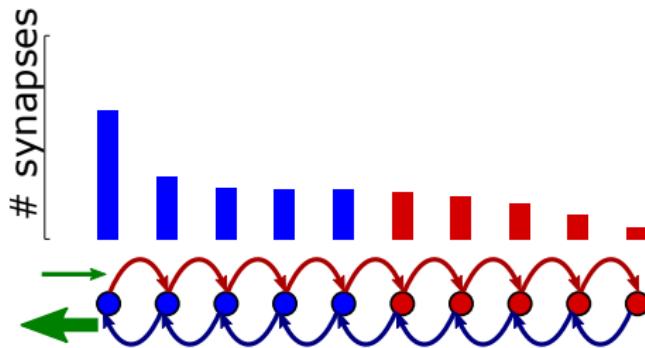
Training: change frequency of pot/dep events.

Modelling VOR experiments



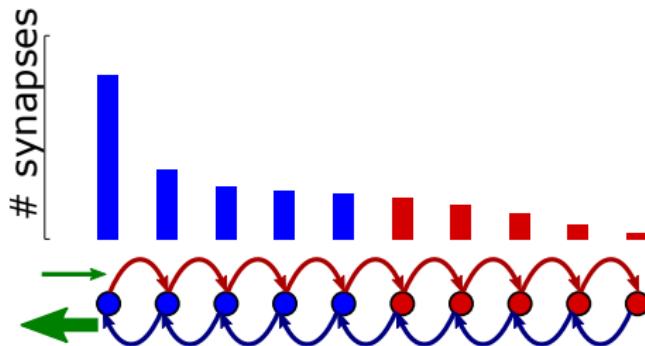
Training: change frequency of pot/dep events.

Modelling VOR experiments



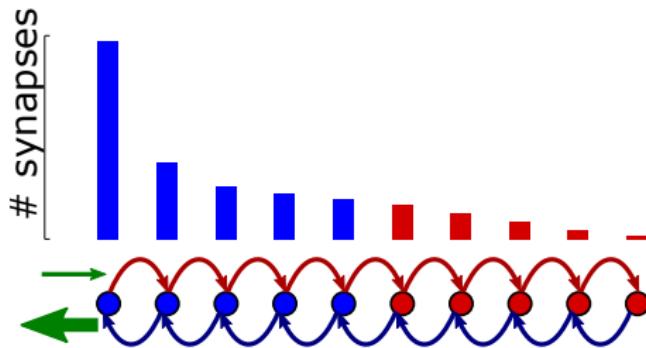
Training: change frequency of pot/dep events.

Modelling VOR experiments



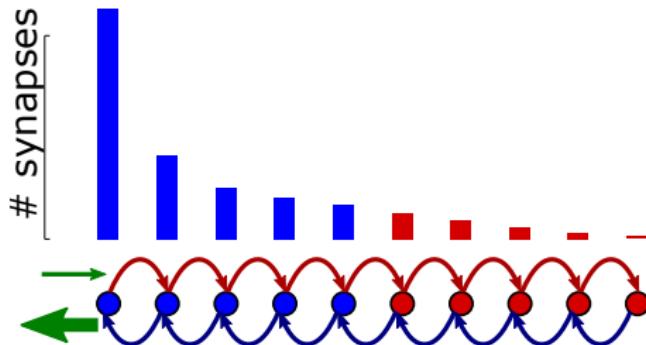
Training: change frequency of pot/dep events.

Modelling VOR experiments



Training: change frequency of pot/dep events.

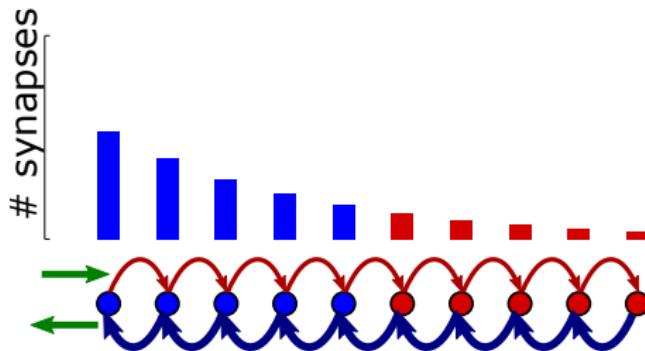
Modelling VOR experiments



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.

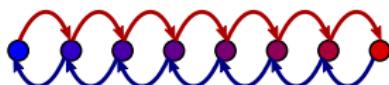
Question 2: How can replenishment ever impair learning?

Enhanced plasticity → enhanced/impaired learning

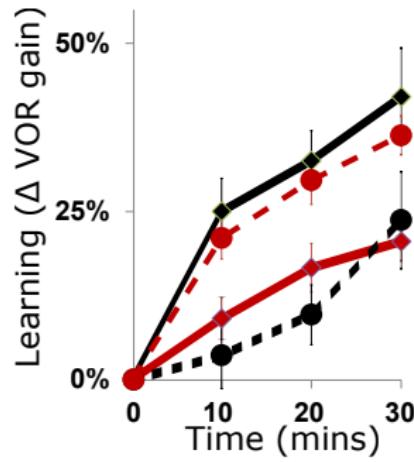
Big question: Why? When?

Simple synapses cannot explain the data

Multistate synapse

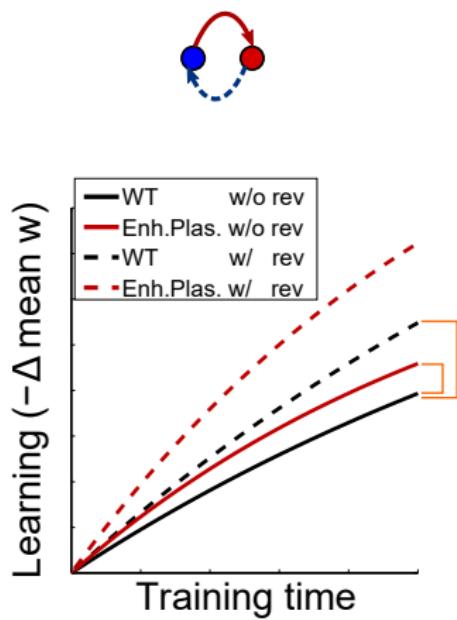


VOR Increase
Training

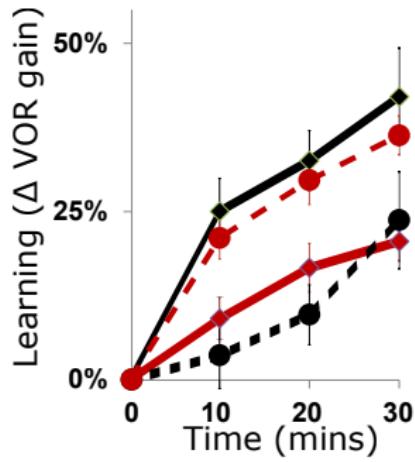


Simple synapses cannot explain the data

Two-state model

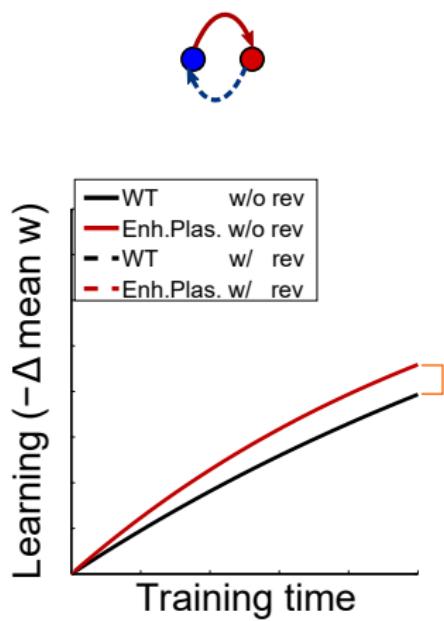


VOR Increase
Training

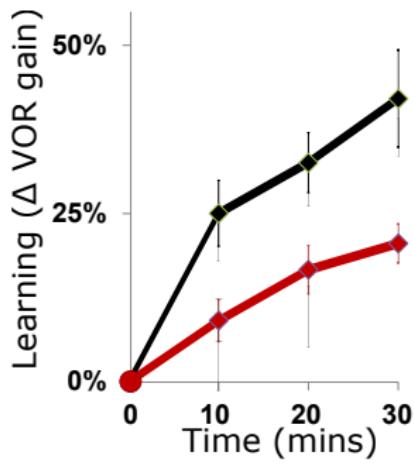


Simple synapses cannot explain the data

Two-state model



VOR Increase
Training

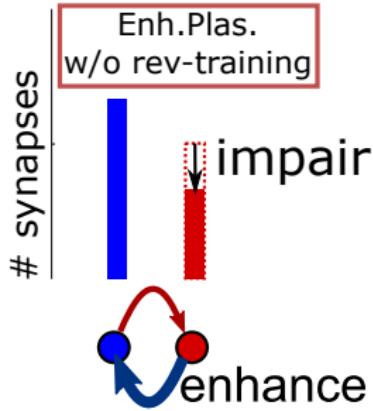


Simple synapses cannot explain the data

Two-state model



Initial distribution

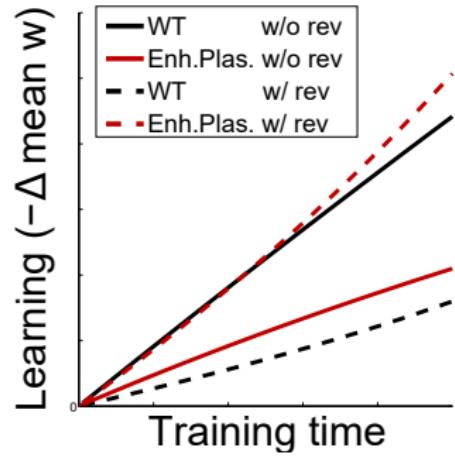
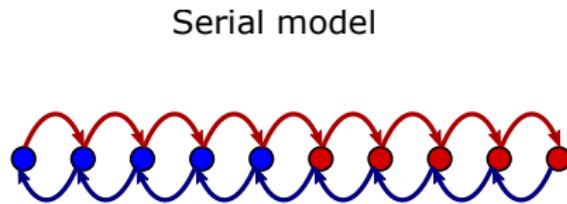


depletion effect

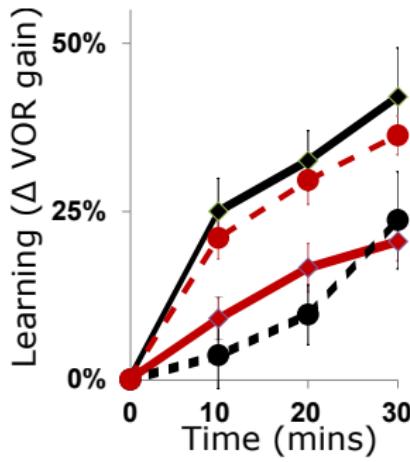
<
enhanced plasticity

⇒ enhanced learning

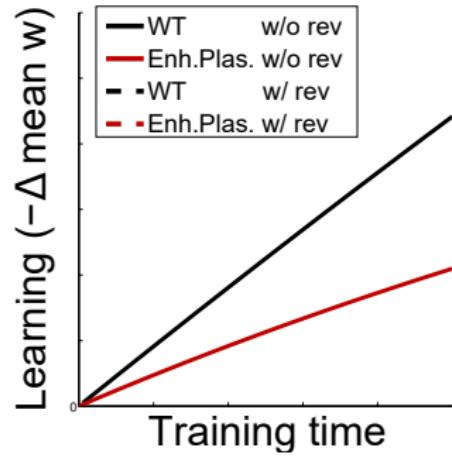
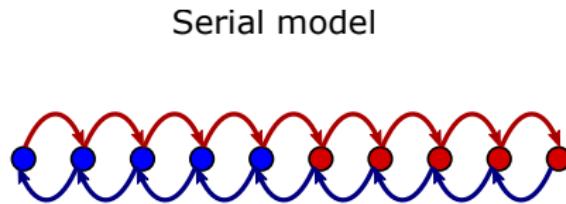
Complex metaplastic synapses can explain the data



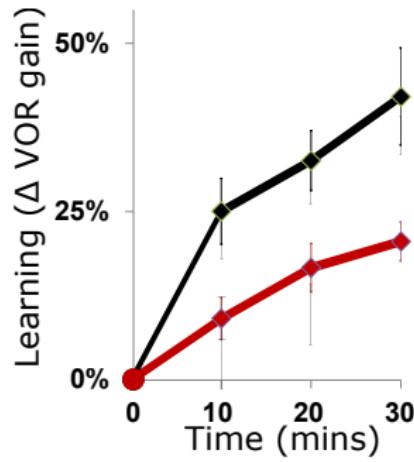
VOR Increase
Training



Complex metaplastic synapses can explain the data

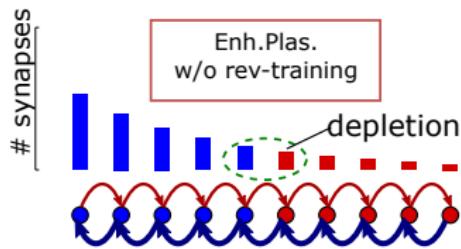
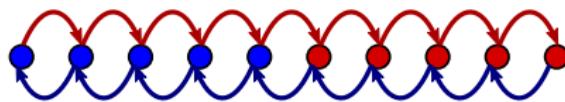


VOR Increase
Training



Complex metaplastic synapses can explain the data

Serial model



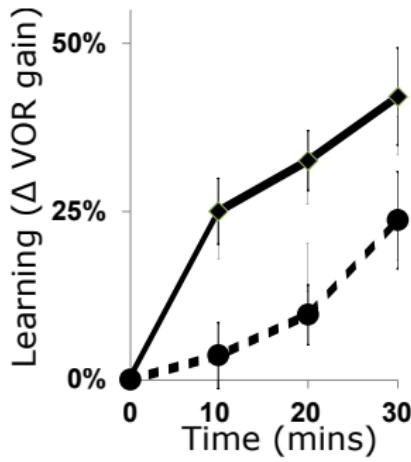
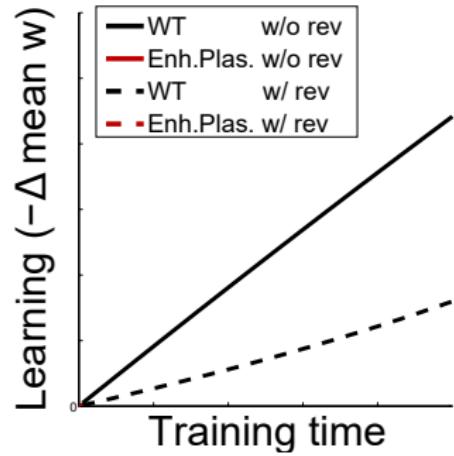
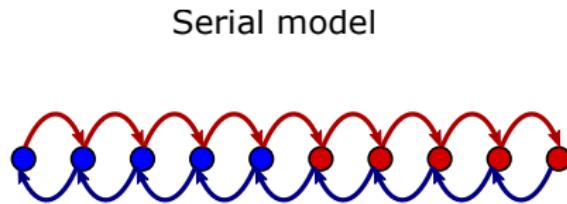
amplified depletion

>

enhanced plasticity

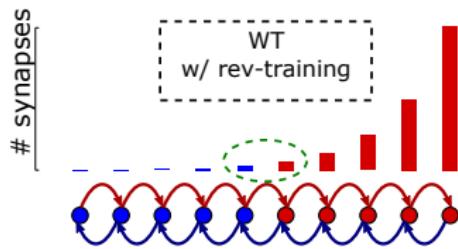
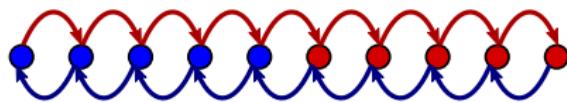
⇒ impaired learning

Complex metaplastic synapses can explain the data



Complex metaplastic synapses can explain the data

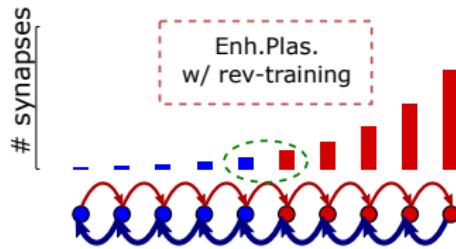
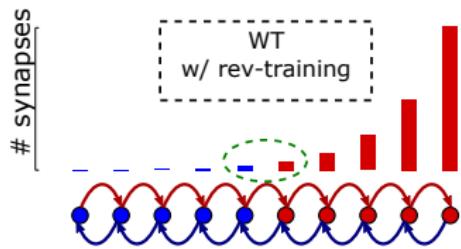
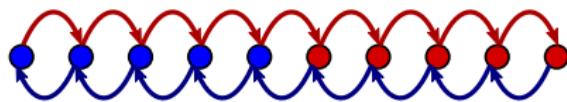
Serial model



reverse training
+
“stubborn” metaplasticity
⇒ impaired learning

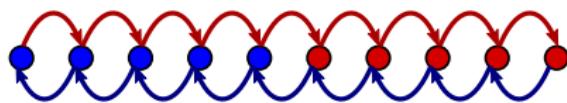
Complex metaplastic synapses can explain the data

Serial model



Complex metaplastic synapses can explain the data

Serial model



starting point:
labile states



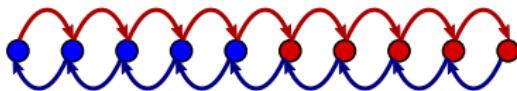
enhanced plasticity
⇒ impaired learning

starting point:
stubborn states



enhanced plasticity
⇒ enhanced learning

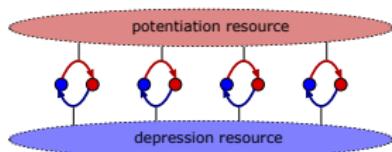
Essential features



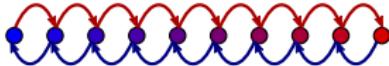
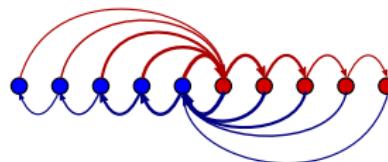
The success of the serial model relies on two features:

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

Fail:



Succeed:



Section 2

Memory over different timescales

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

Storage capacity of synaptic memory

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

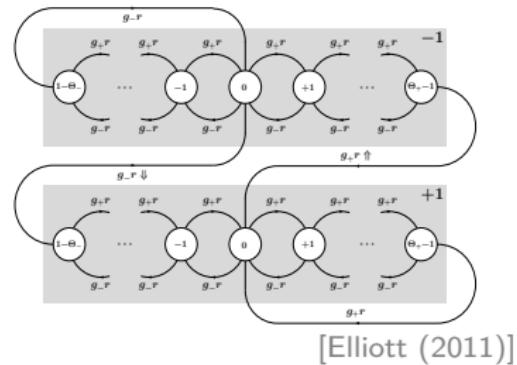
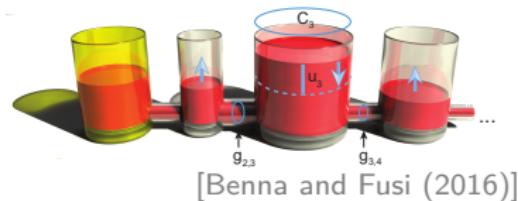
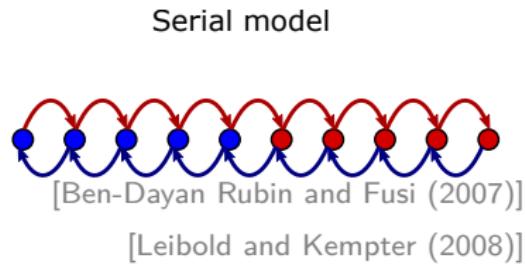
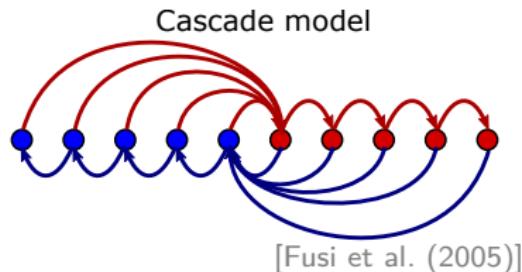
Assumes unbounded analogue synapses

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

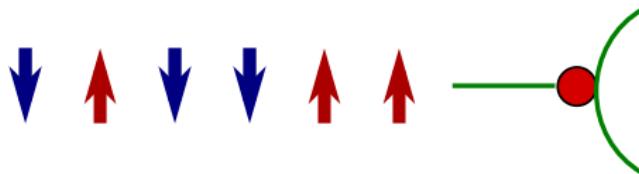
[Amit and Fusi (1992), Amit and Fusi (1994)]

New memories overwrite old \implies stability-plasticity dilemma.

Specific models of complex synaptic dynamics

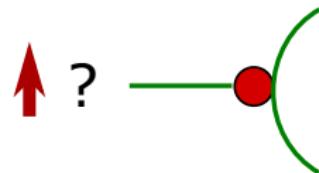


Synaptic memory curves



Synapses store a sequence of memories.

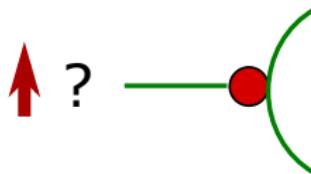
Synaptic memory curves



Synapses store a sequence of memories.

Recognition memory: has this pattern been seen before?

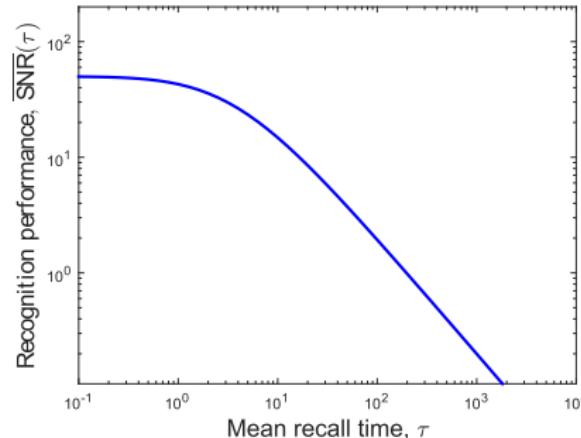
Synaptic memory curves



Synapses store a sequence of memories.

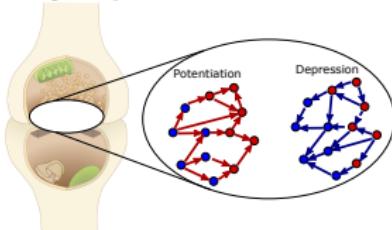
Recognition memory: has this pattern been seen before?

Performance described by SNR.

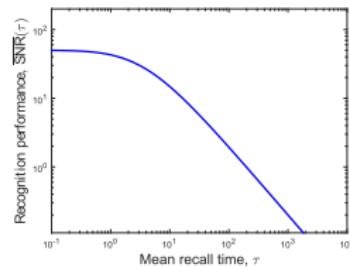


General principles relating structure and function?

Synaptic structure



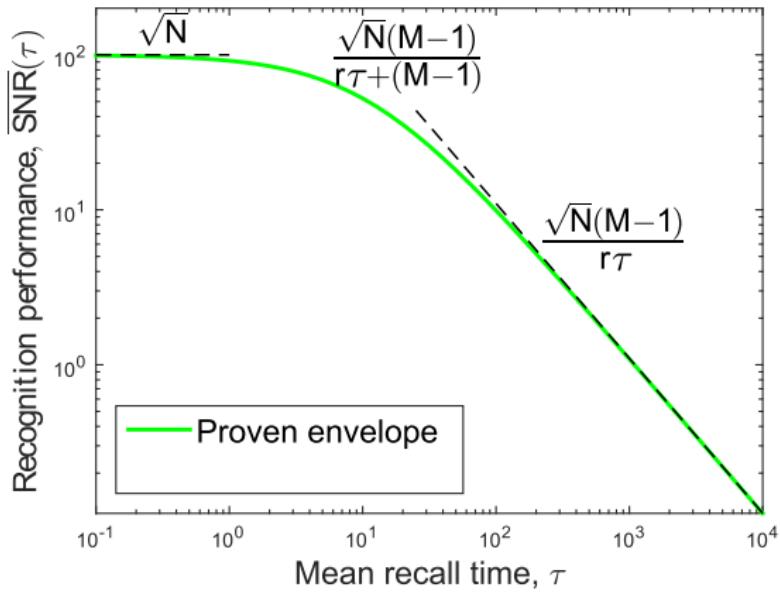
Synaptic function



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

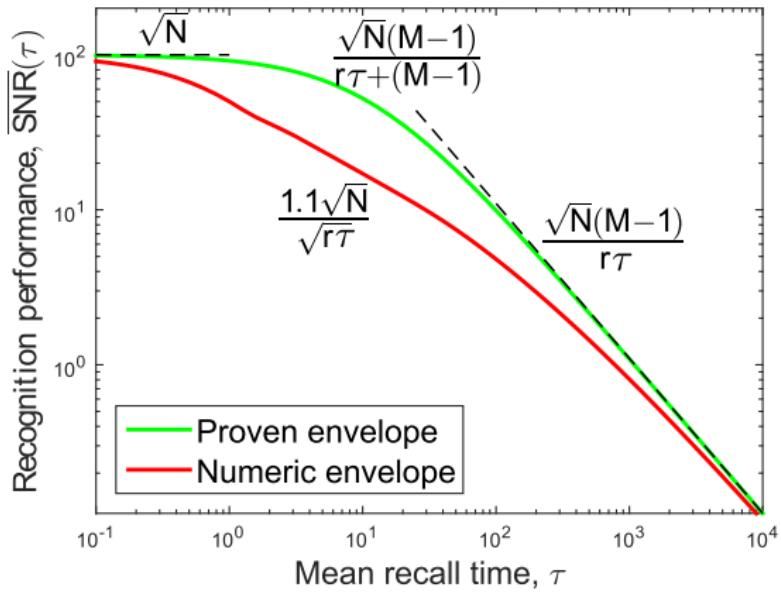
Proven envelope: memory frontier

Upper bound on memory curve at *any* timescale.

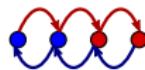
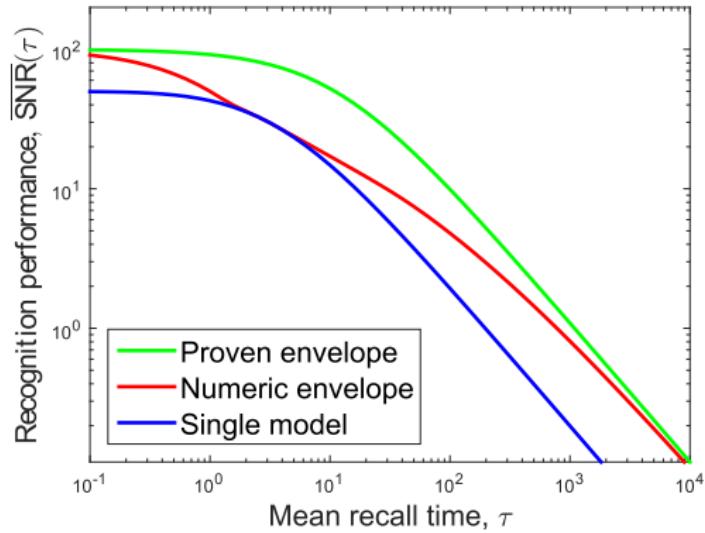


Proven envelope: memory frontier

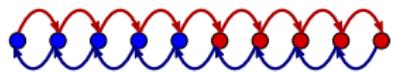
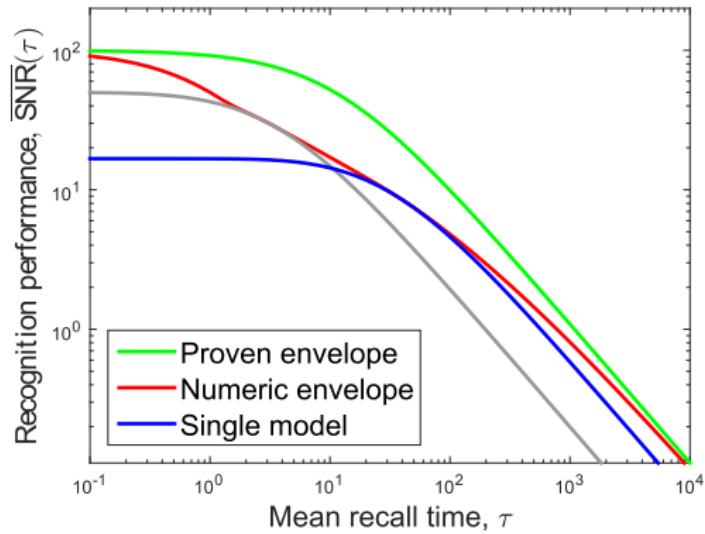
Upper bound on memory curve at *any* timescale.



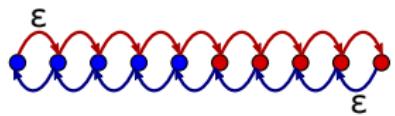
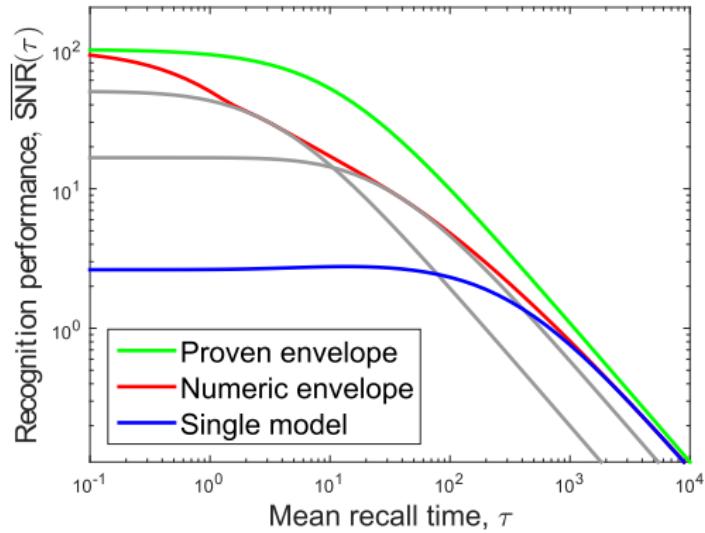
Models that maximize memory for one timescale



Models that maximize memory for one timescale

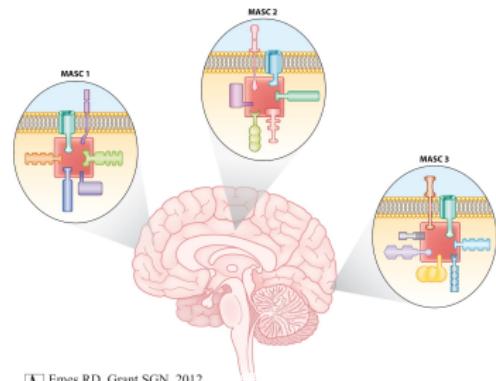


Models that maximize memory for one timescale



Synaptic diversity and timescales of memory

Different synapses have different molecular structures.

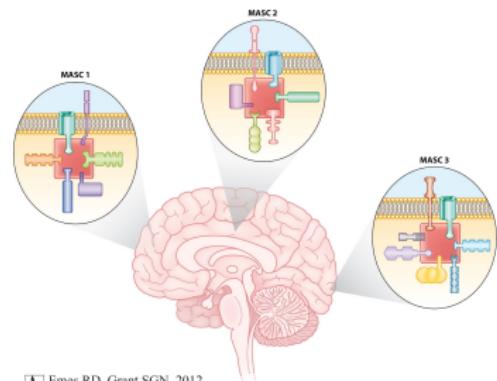


[A] Emes RD, Grant SGN. 2012.
Annu. Rev. Neurosci. 35:111–31

[Emes and Grant (2012)]

Synaptic diversity and timescales of memory

Different synapses have different molecular structures.



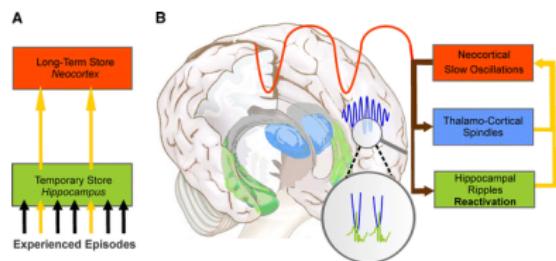
[Emes RD, Grant SGN. 2012.
Annu. Rev. Neurosci. 35:111–31]

[Emes and Grant (2012)]

Memories stored in different places for different timescales

[Squire and Alvarez (1995)]

[McClelland et al. (1995)]



[Born and Wilhelm (2012)]

Also: Cerebellar cortex → nuclei.

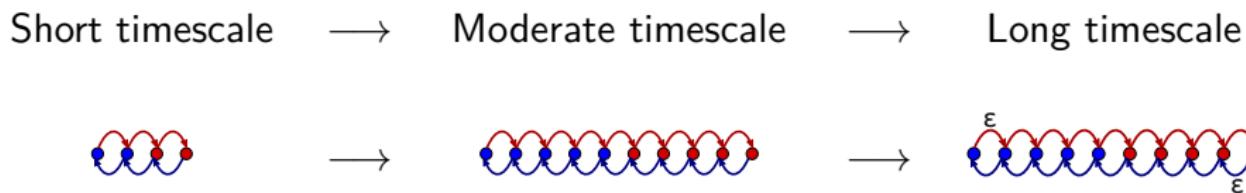
[Attwell et al. (2002)]

[Cooke et al. (2004)]

Synaptic structure and function: general principles

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

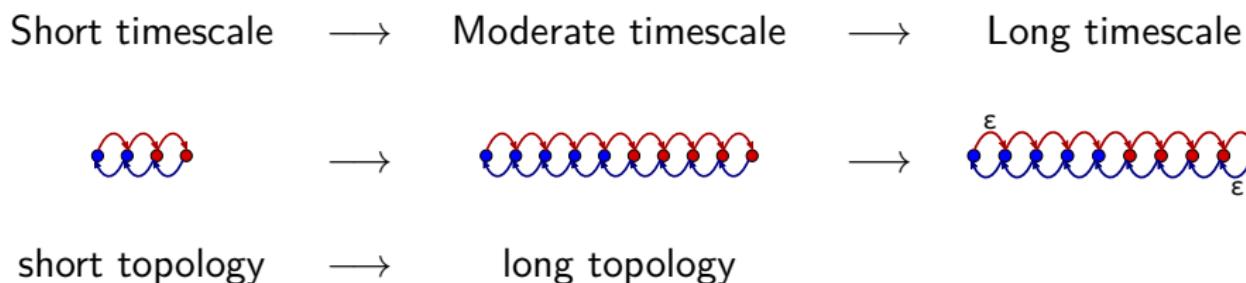
What can we conclude?



Synaptic structure and function: general principles

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

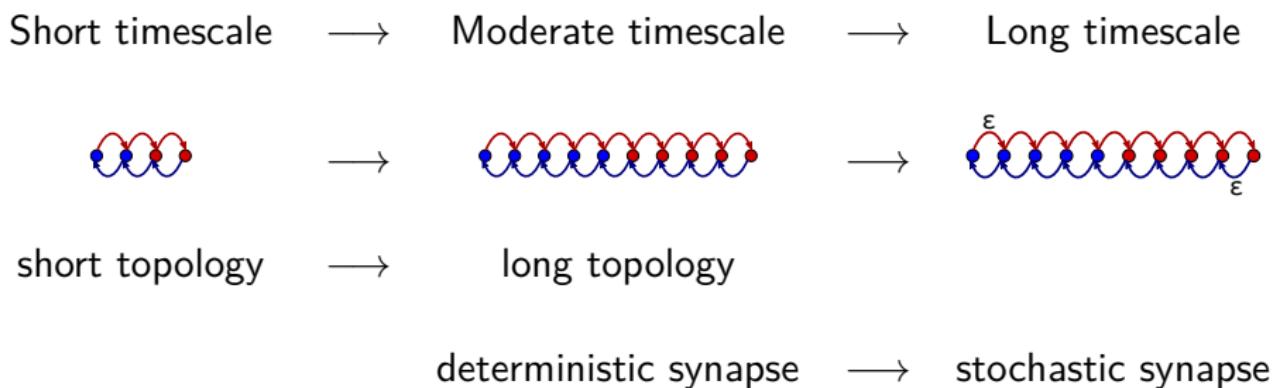
What can we conclude?



Synaptic structure and function: general principles

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

What can we conclude?



Experimental tests?

Traditional experiments:



Experimental tests?

Traditional experiments:

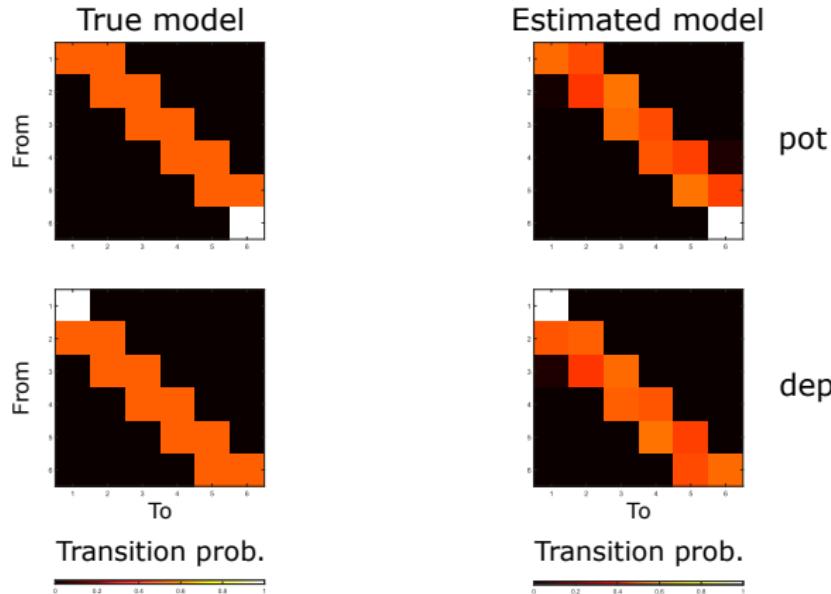


To fit a model: long sequence of small plasticity events.

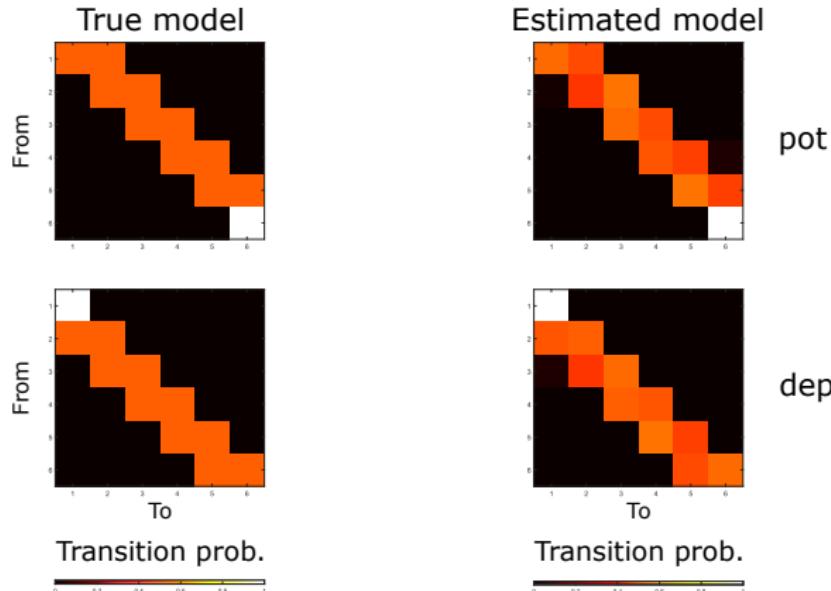
Observe the changes in synaptic efficacy.



Simulated experiment



Simulated experiment



Problem: need *long* sequences.

Whole cell patch of postsynaptic neuron → Ca washout.

Summary

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

Acknowledgements

Surya Ganguli

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

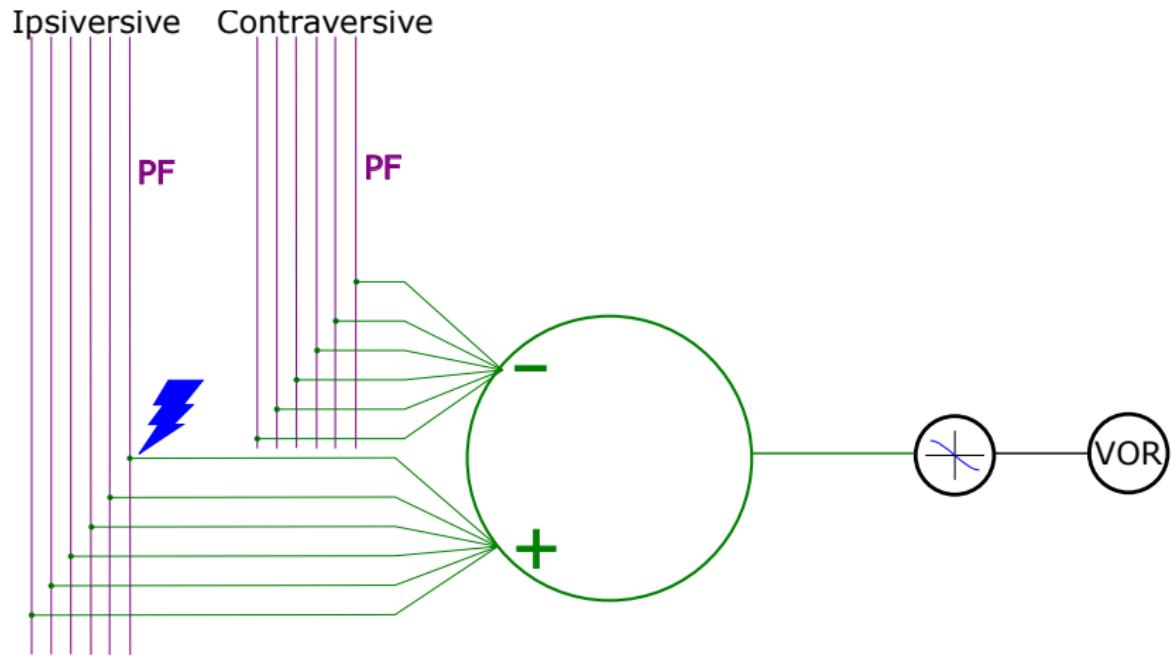
Carla Shatz

Hanmi Lee

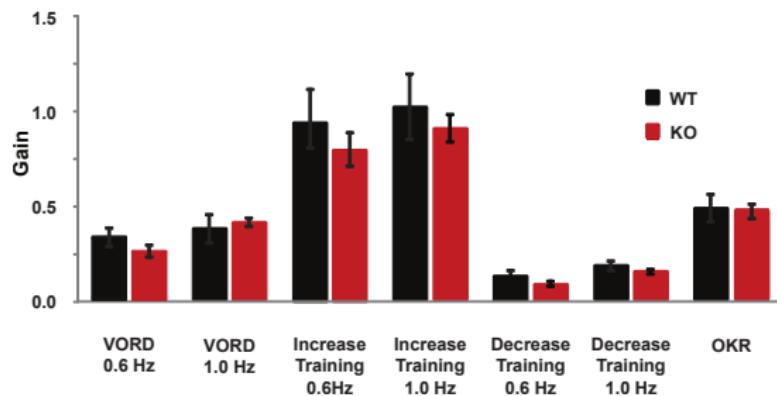
Marcus Benna

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

Model of circuit

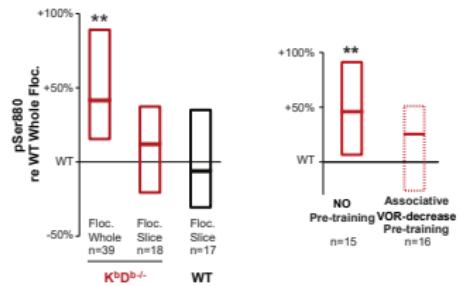


Baseline



Evidence: level of depression

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

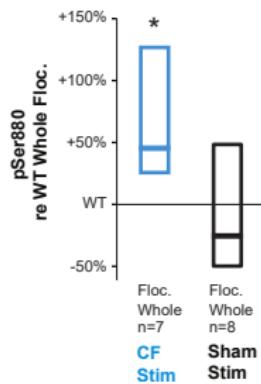
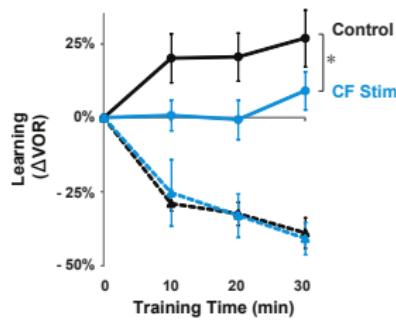
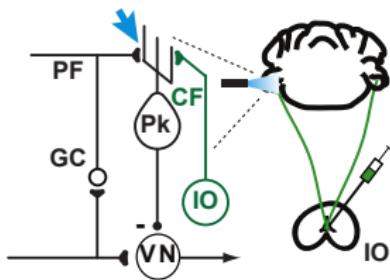


Biochemical signature of PF-Pk LTD.

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

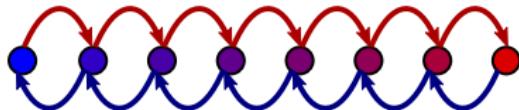
Evidence: saturation by CF stimulation

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

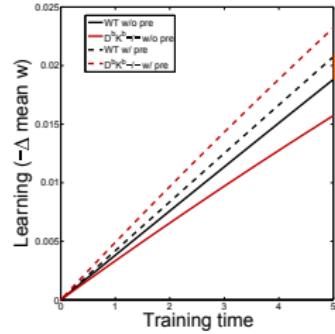
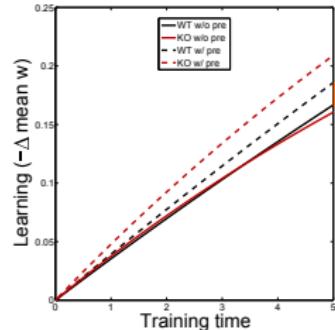
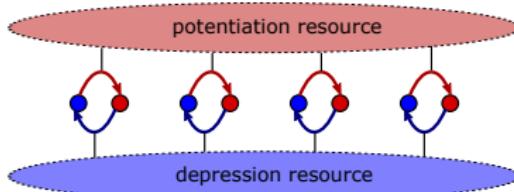


Other models that fail

Multistate synapse



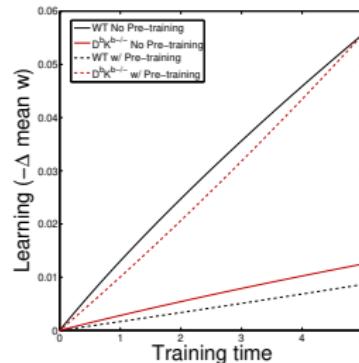
Pooled resource model



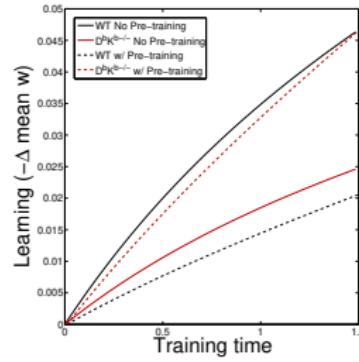
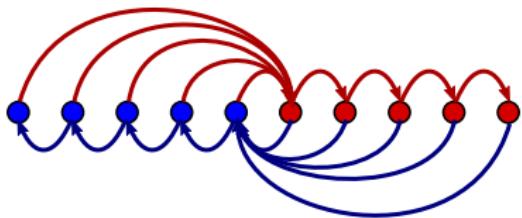
[Amit and Fusi (1994)]

Other models that work

Non-uniform multistate model

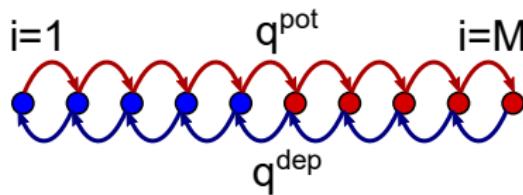


Cascade model



[Fusi et al. (2005)]

Mathematical explanation



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

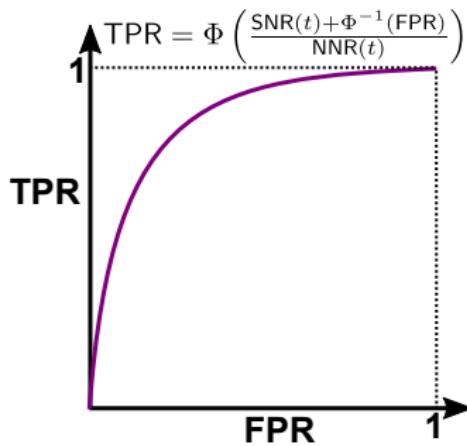
Learning rate $\sim \pi_{M/2} \left(\frac{q^{\text{dep}}}{q^{\text{pot}}} \right) = \mathcal{N} \left(\frac{q^{\text{pot}}}{q^{\text{dep}}} \right)^{\frac{M}{2}-1}$.

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

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

Quantifying memory quality

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



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

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

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

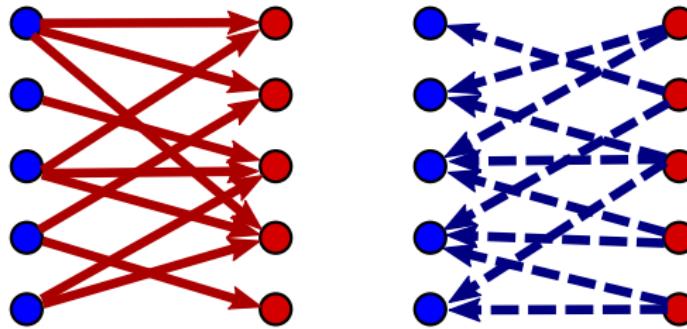
Also: KL divergence, Chernoff distance, . . .

Initial SNR as flux

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

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

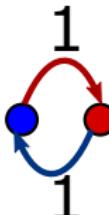
Max when potentiation guarantees $\mathbf{w} \rightarrow +1$,
depression guarantees $\mathbf{w} \rightarrow -1$.



Two-state model

Two-state model equivalent to previous slide:

Transitions:


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

Maximal initial SNR:

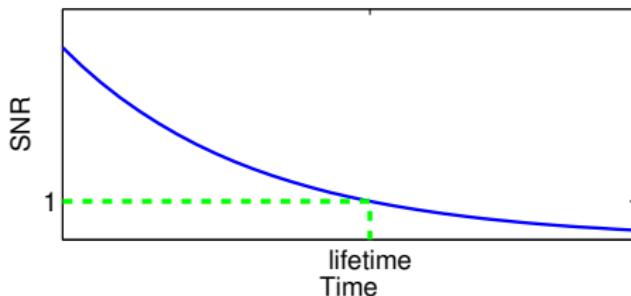
$$\text{SNR}(0) \leq \sqrt{N}.$$

Area under memory curve

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

Area bounds memory lifetime:

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



This area has an upper bound:

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

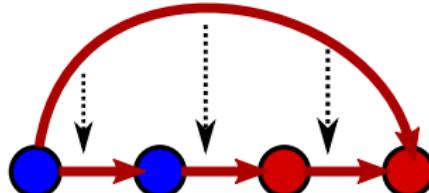
Saturated by a model with linear chain topology.

Proof of area bound

For any model, we can construct perturbations that

- preserve equilibrium distribution,
- increase area.

details



e.g. decrease “shortcut” transitions, increase bypassed “direct” ones.
Endpoint: linear chain

The area of this model is

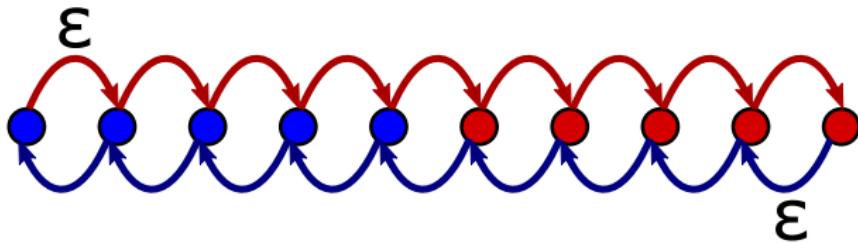
$$A = \frac{2\sqrt{N}}{r} \sum_k \pi_k |k - \langle k \rangle|.$$

Max: equilibrium probability distribution concentrated at both ends.

[Barrett and van Rossum (2008)]

Saturating model

Make end states “sticky”



Has long decay time, but terrible initial SNR.

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

Technical detail: ordering states

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

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

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

[Kemeny and Snell (1960)]

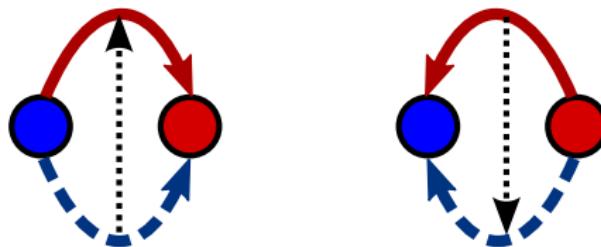
We define:

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

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

Technical detail: upper/lower triangular

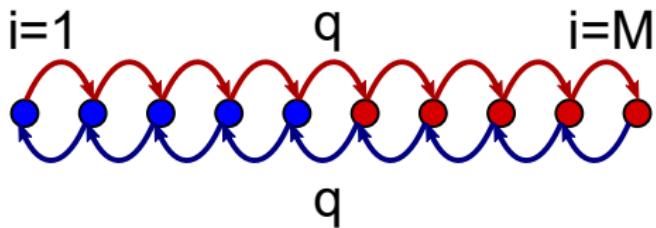
With states in order:



Endpoint: potentiation goes right, depression goes left.

[back](#)

Intuition for using topology



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

References I



Eric Klann.

“Metaplastic Protein Phosphatases”.

Learning and Memory, 9(4):153–155, (2002) ,

<http://learnmem.cshlp.org/content/9/4/153.full.pdf+html>.

2 3 4



D. J. Amit and S. Fusi.

“Constraints on learning in dynamic synapses”.

Network: Comp. Neural, 3(4):443–464, (1992) .

5 65



D. J. Amit and S. Fusi.

“Learning in neural networks with material synapses”.

Neural Comput., 6(5):957–982, (1994) .

5 65 91

References II



Carl C. H. Petersen, Robert C. Malenka, Roger A. Nicoll, and John J. Hopfield.

“All-or-none potentiation at CA3-CA1 synapses”.

Proc. Natl. Acad. Sci. U.S.A., 95(8):4732–4737, (1998) .

5



Daniel H. O'Connor, Gayle M. Wittenberg, and Samuel S.-H. Wang.

“Graded bidirectional synaptic plasticity is composed of switch-like unitary events”.

Proc. Natl. Acad. Sci. U.S.A., 102(27):9679–9684, (2005) .

5

References III



M. P. Coba, A. J. Pocklington, M. O. Collins, M. V. Kopanitsa, R. T. Uren, S. Swamy, M. D. Croning, J. S. Choudhary, and S. G. Grant.

“Neurotransmitters drive combinatorial multistate postsynaptic density networks”.

Sci Signal, 2(68):ra19, (2009) .

6 7 8 9



Johanna M. Montgomery and Daniel V. Madison.

“State-Dependent Heterogeneity in Synaptic Depression between Pyramidal Cell Pairs”.

Neuron, 33(5):765 – 777, (2002) .

6 7 8 9

References IV



S. Fusi, P. J. Drew, and L. F. Abbott.

“Cascade models of synaptically stored memories”.

Neuron, 45(4):599–611, (February, 2005) .

7 8 9 27 66 92



Marcus K. Benna and Stefano Fusi.

“Computational principles of synaptic memory consolidation”.

Nature Neuroscience, 19(12):1697–1706, (July, 2016) , arXiv:1507.07580 [q-bio.NC].

7 8 9 66



Y. P. Tang, E. Shimizu, G. R. Dube, C. Rampon, G. A. Kerchner, M. Zhuo, G. Liu, and J. Z. Tsien.

“Genetic enhancement of learning and memory in mice”.

Nature, 401(6748):63–69, (Sep, 1999) .

12 13 14

References V



Gaël Malleret, Ursula Haditsch, David Genoux, Matthew W. Jones, Tim V.P. Bliss, Amanda M. Vanhoose, Carl Weitlauf, Eric R. Kandel, Danny G. Winder, and Isabelle M. Mansuy.

“Inducible and Reversible Enhancement of Learning, Memory, and Long-Term Potentiation by Genetic Inhibition of Calcineurin”.

Cell, 104(5):675 – 686, (2001) .

12

13

14



J. S. Guan, S. J. Haggarty, E. Giacometti, J. H. Dannenberg, N. Joseph, J. Gao, T. J. Nieland, Y. Zhou, X. Wang, R. Mazitschek, J. E. Bradner, R. A. DePinho, R. Jaenisch, and L. H. Tsai.

“HDAC2 negatively regulates memory formation and synaptic plasticity”.

Nature, 459(7243):55–60, (May, 2009) .

12

13

14

References VI



M. Migaud, P. Charlesworth, M. Dempster, L. C. Webster, A. M. Watabe, M. Makhinson, Y. He, M. F. Ramsay, R. G. Morris, J. H. Morrison, T. J. O'Dell, and S. G. Grant.

"Enhanced long-term potentiation and impaired learning in mice with mutant postsynaptic density-95 protein".

Nature, 396(6710):433–439, (December, 1998) .

12

13

14



N. Uetani, K. Kato, H. Ogura, K. Mizuno, K. Kawano, K. Mikoshiba, H. Yakura, M. Asano, and Y. Iwakura.

"Impaired learning with enhanced hippocampal long-term potentiation in PTPdelta-deficient mice".

EMBO J., 19(12):2775–2785, (June, 2000) .

12

13

14

References VII



Mansuo L Hayashi, Se-Young Choi, B.S.Shankaranarayana Rao, Hae-Yoon Jung, Hey-Kyoung Lee, Dawei Zhang, Sumantra Chattarji, Alfredo Kirkwood, and Susumu Tonegawa.

"Altered Cortical Synaptic Morphology and Impaired Memory Consolidation in Forebrain- Specific Dominant-Negative {PAK} Transgenic Mice".

Neuron, 42(5):773 – 787, (2004) .

12

13

14



Patrick R Cox, Velia Fowler, Bisong Xu, J.David Sweatt, Richard Paylor, and Huda Y Zoghbi.

"Mice lacking tropomodulin-2 show enhanced long-term potentiation, hyperactivity, and deficits in learning and memory".

Molecular and Cellular Neuroscience, 23(1):1 – 12, (2003) .

12

13

14

References VIII



Kris Rutten, Dinah L. Misner, Melissa Works, Arjan Blokland, Thomas J. Novak, Luca Santarelli, and Tanya L. Wallace.

“Enhanced long-term potentiation and impaired learning in phosphodiesterase 4D-knockout (PDE4D-/-) mice”.

European Journal of Neuroscience, 28(3):625–632, (2008) .

12

13

14



S.K.E. Koekkoek, K. Yamaguchi, B.A. Milojkovic, B.R. Dortland, T.J.H. Ruigrok, R. Maex, W. De Graaf, A.E. Smit, F. VanderWerf, C.E. Bakker, R. Willemsen, T. Ikeda, S. Kakizawa, K. Onodera, D.L. Nelson, E. Mientjes, M. Joosten, E. De Schutter, B.A. Oostra, M. Ito, and C.I. De Zeeuw.

“Deletion of *FMR1* in Purkinje Cells Enhances Parallel Fiber LTD, Enlarges Spines, and Attenuates Cerebellar Eyelid Conditioning in Fragile X Syndrome”.

Neuron, 47(3):339 – 352, (2005) .

12

13

14

References IX



David Marr.

“A theory of cerebellar cortex”.

The Journal of Physiology, 202(2):437–470, (1969) .

16



James S. Albus.

“A theory of cerebellar function”.

Mathematical Biosciences, 10(1):25 – 61, (1971) .

16



Masao Ito.

“Neural design of the cerebellar motor control system”.

Brain research, 40(1):81–84, (1972) .

16

References X



Michael J. McConnell, Yanhua H. Huang, Akash Datwani, and Carla J. Shatz.

"H2-Kb and H2-Db regulate cerebellar long-term depression and limit motor learning".

Proc. Natl. Acad. Sci. U.S.A., 106(16):6784–6789, (2009) .

17



S. Fusi and L. F. Abbott.

"Limits on the memory storage capacity of bounded synapses".

Nat. Neurosci., 10(4):485–493, (Apr, 2007) .

27



A. B. Barrett and M. C. van Rossum.

"Optimal learning rules for discrete synapses".

PLoS Comput. Biol., 4(11):e1000230, (November, 2008) .

27

98

References XI



Maurice A Smith, Ali Ghazizadeh, and Reza Shadmehr.

“Interacting Adaptive Processes with Different Timescales Underlie Short-Term Motor Learning”.

PLoS Biol., 4(6):e179, (May, 2006) .

27



Subhaneil Lahiri and Surya Ganguli.

“A memory frontier for complex synapses”.

In C.J.C. Burges, L. Bottou, M. Welling, Z. Ghahramani, and K.Q. Weinberger, editors, *Adv. Neural Inf. Process. Syst. 26*, pages 1034–1042. NIPS, 2013.

URL <https://papers.nips.cc/paper/4872-a-memory-frontier-for-complex-synapses>.

27

References XII

 Daniel D Ben-Dayan Rubin and Stefano Fusi.

“Long memory lifetimes require complex synapses and limited sparseness”.
Front. Comput. Neurosci., 1:1–14, (November, 2007) .

66

 Christian Leibold and Richard Kempter.

“Sparseness Constrains the Prolongation of Memory Lifetime via Synaptic Metaplasticity”.
Cereb. Cortex, 18(1):67–77, (2008) .

66

References XIII



Terry Elliott.

"The mean time to express synaptic plasticity in integrate-and-express, stochastic models of synaptic plasticity induction", jan 2011.

ISSN 08997667.

URL

http://www.mitpressjournals.org/doi/10.1162/NECO_a_00061.

66



Richard D. Emes and Seth G.N. Grant.

"Evolution of Synapse Complexity and Diversity".

Annual Review of Neuroscience, 35(1):111–131, (2012) .

76

77

References XIV



Larry R Squire and Pablo Alvarez.

“Retrograde amnesia and memory consolidation: a neurobiological perspective”.

Current Opinion in Neurobiology, 5(2):169–177, (April, 1995) .

76

77



James L McClelland, Bruce L McNaughton, and Randall C O'Reilly.

“Why there are complementary learning systems in the hippocampus and neocortex: Insights from the successes and failures of connectionist models of learning and memory.”, 1995.

76

77



Jan Born and Ines Wilhelm.

“System consolidation of memory during sleep.”.

Psychological research, 76(2):192–203, (mar, 2012) .

76

77

References XV

 Phillip J.E. Attwell, Samuel F. Cooke, and Christopher H. Yeo.
“Cerebellar Function in Consolidation of a Motor Memory”.
Neuron, 34(6):1011–1020, (jun, 2002) .

76 77

 Samuel F Cooke, Phillip J E Attwell, and Christopher H Yeo.
“Temporal properties of cerebellar-dependent memory consolidation.”.
J. Neurosci., 24(12):2934–41, (mar, 2004) .

76 77

 J.G. Kemeny and J.L. Snell.
Finite markov chains.
Springer, 1960.

100