

Learning and memory with complex synaptic plasticity

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What is a synapse?

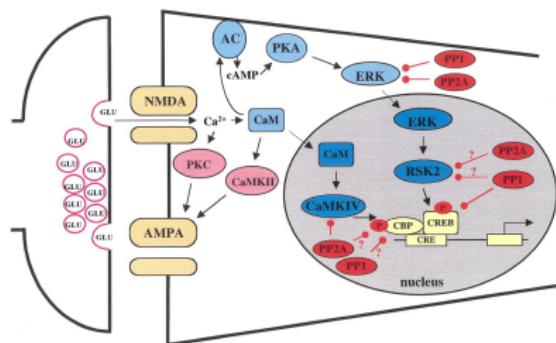
Experimentalists

Theorists

What is a synapse?

Experimentalists

Theorists

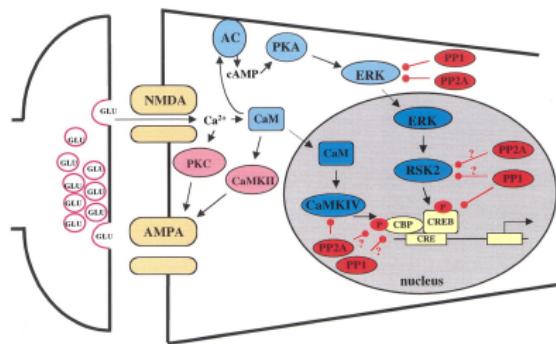


[Klann (2002)]

What is a synapse?

Experimentalists

Theorists



W_{ij}

[Klann (2002)]

Storage capacity of synaptic memory

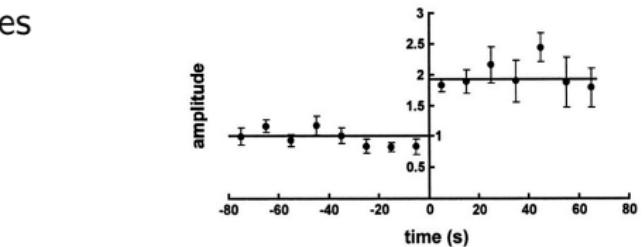
Hopfield, perceptron models have capacity $\propto N$, (# synapses).

Assumes unbounded analogue synapses

With discrete, finite synapses:

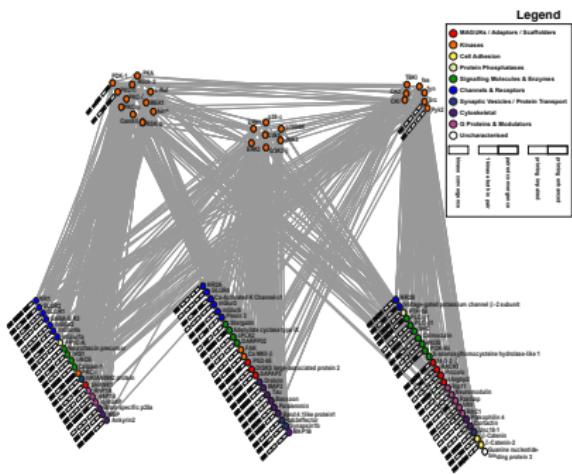
\implies memory capacity $\sim \mathcal{O}(\log N)$.

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

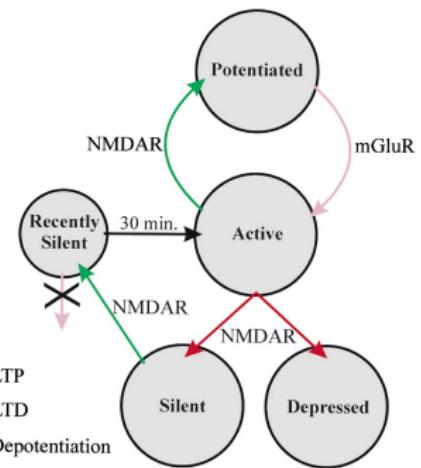


[Petersen et al. (1998), O'Connor et al. (2005)]

Synapses are complex

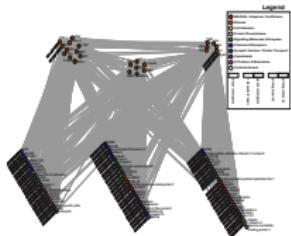


[Coba et al. (2009)]

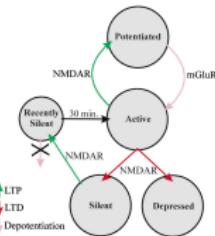


[Montgomery and Madison (2002)]

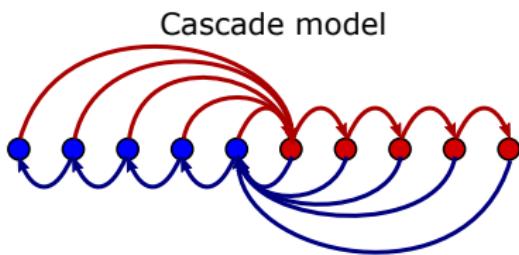
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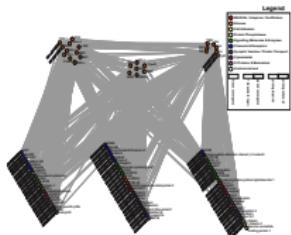


Cascade model

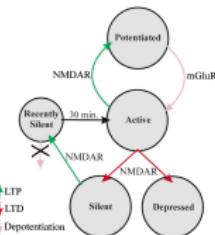
Capacity $\propto N^{2/3}$.

[Fusi et al. (2005)]

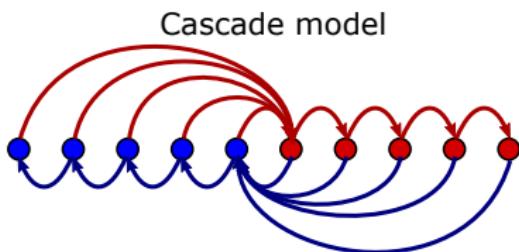
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Cascade model

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

[Fusi et al. (2005)]

Capacity $\propto N$.

[Benna and Fusi (2016)]

Outline

1 Other projects

- Random projections
- Energy consumption in biology

2 Learning with enhanced plasticity

- Effects of enhanced plasticity on cerebellar learning
- Synaptic models of 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

Relevant neurons → Recorded neurons → Electrodes.

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

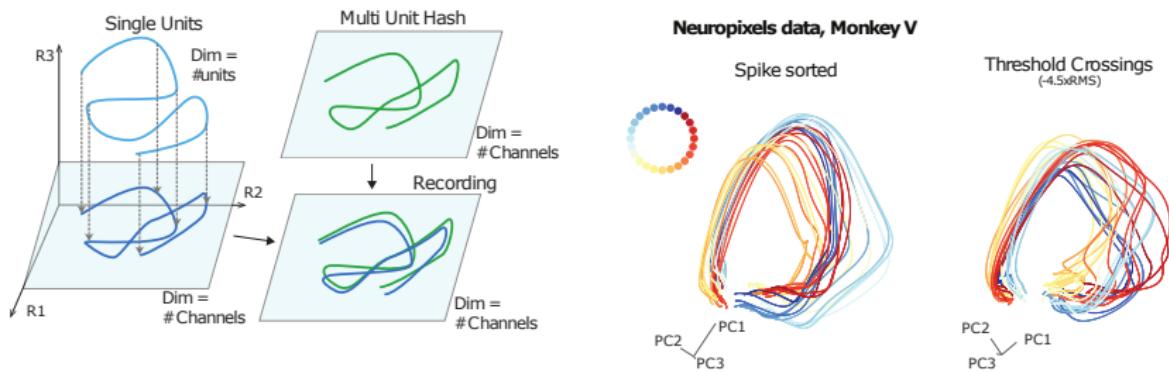
[Gao et al. (2017)]

Random projections and neural recordings

Relevant neurons → Recorded neurons → Electrodes.

2nd projection (reversed by spike sorting):

[Trautmann et al. (2017)]

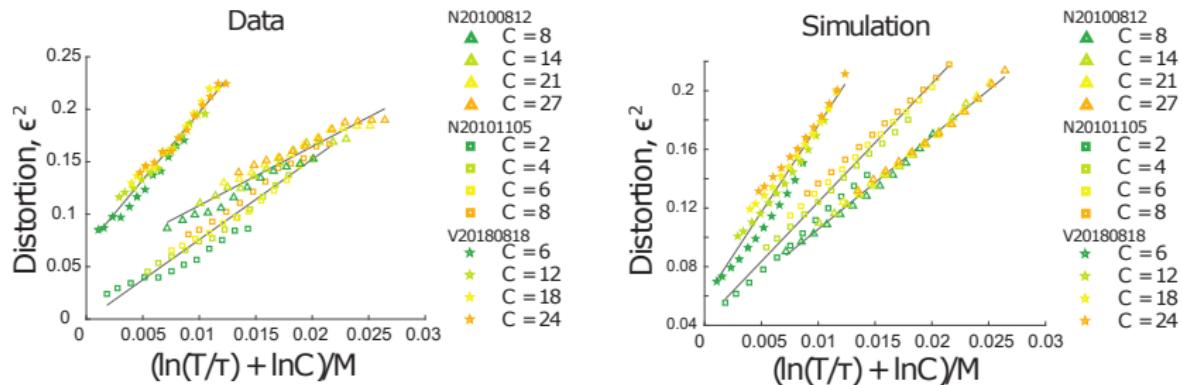


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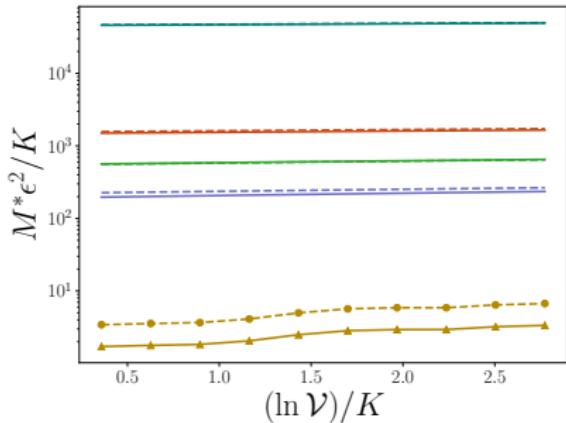
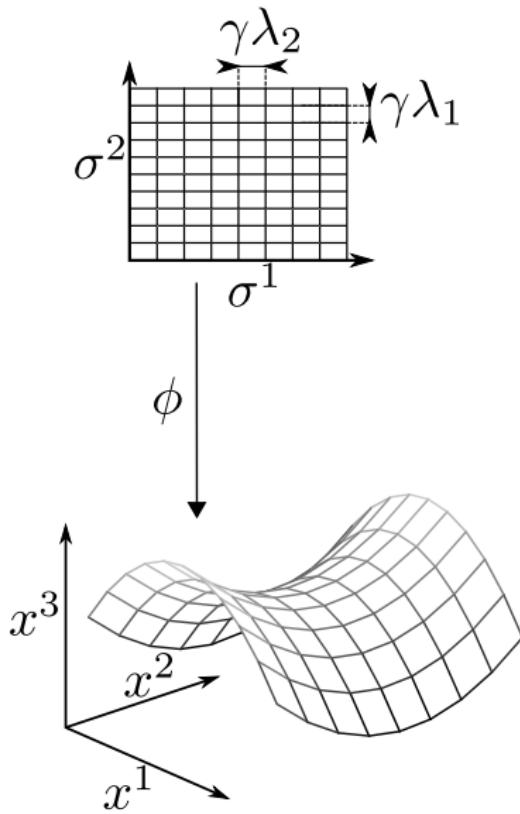
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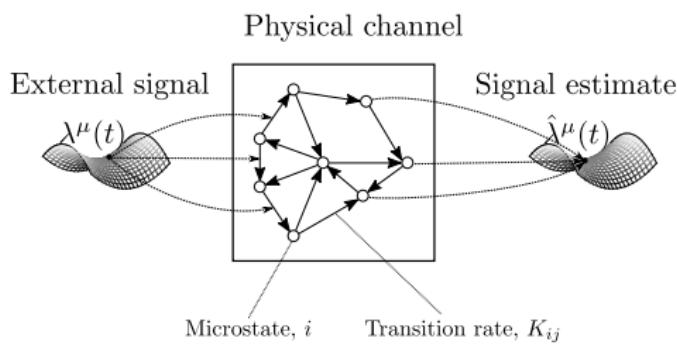
Random projections of random manifolds



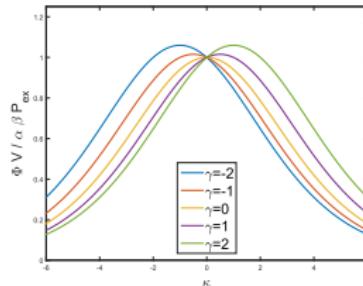
Energy efficiency of cellular communication

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)]

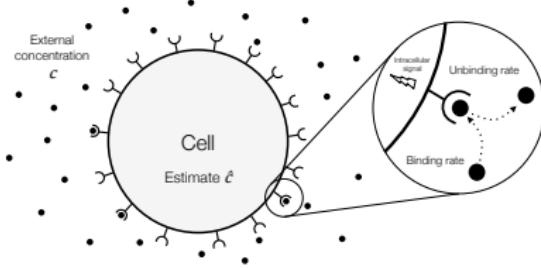
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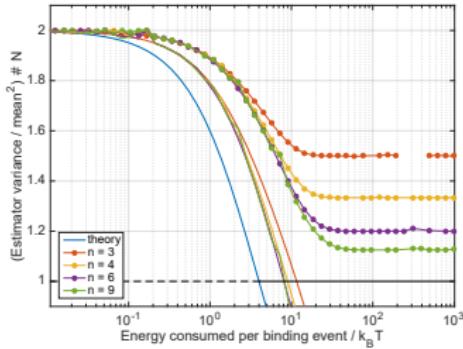
Brain: 15 W,

Human: 100 W.

Receiving a signal:



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



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 → enhanced learning.

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



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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)]



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

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

Vestibulo-Occular Reflex training

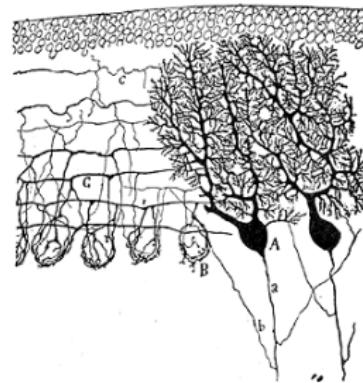
VOR Increase Training



VOR Decrease Training



VOR increase:
VOR decrease:



[Cajal]

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

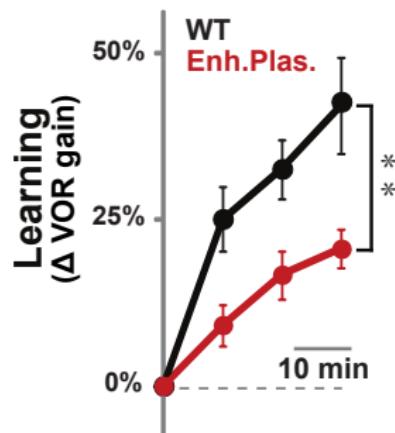
[Marr (1969), Albus (1971), Ito (1972)]

Depletion hypothesis

Knockout of MHC-I K^bD^b molecules in PF-Pk synapses

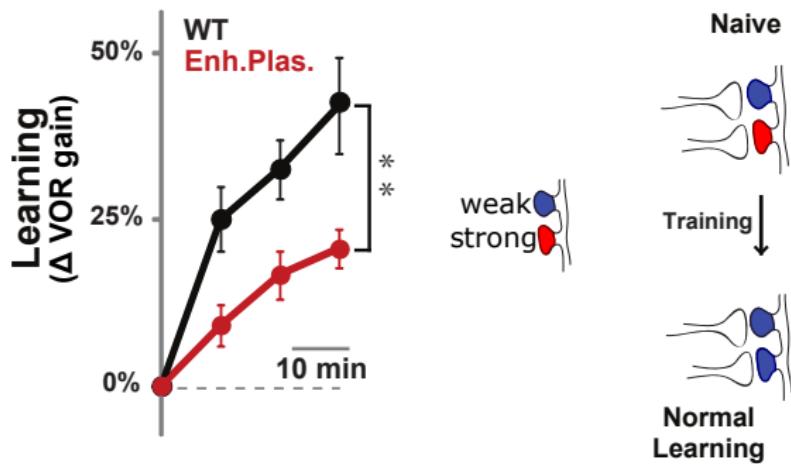
→ lower threshold for LTD → enhanced learning of Rotarod task.

[McConnell et al. (2009)]



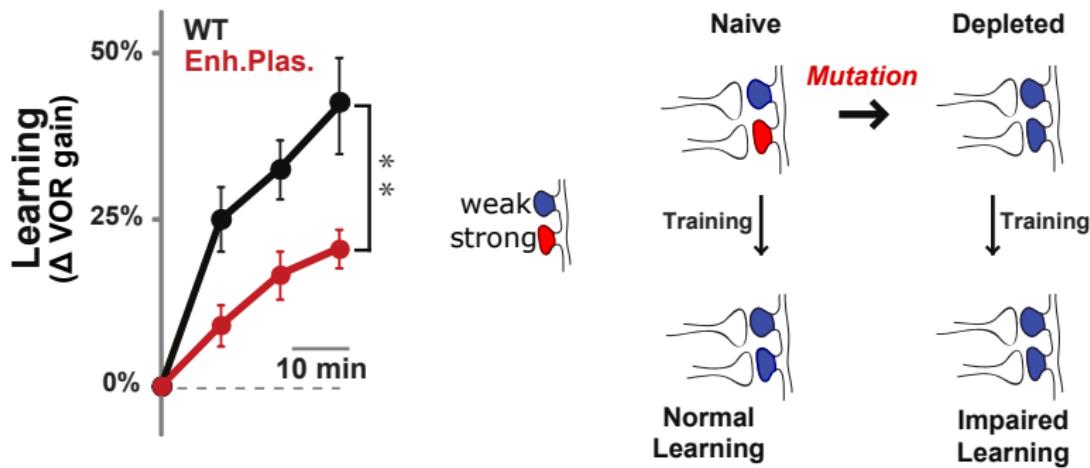
Depletion hypothesis

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



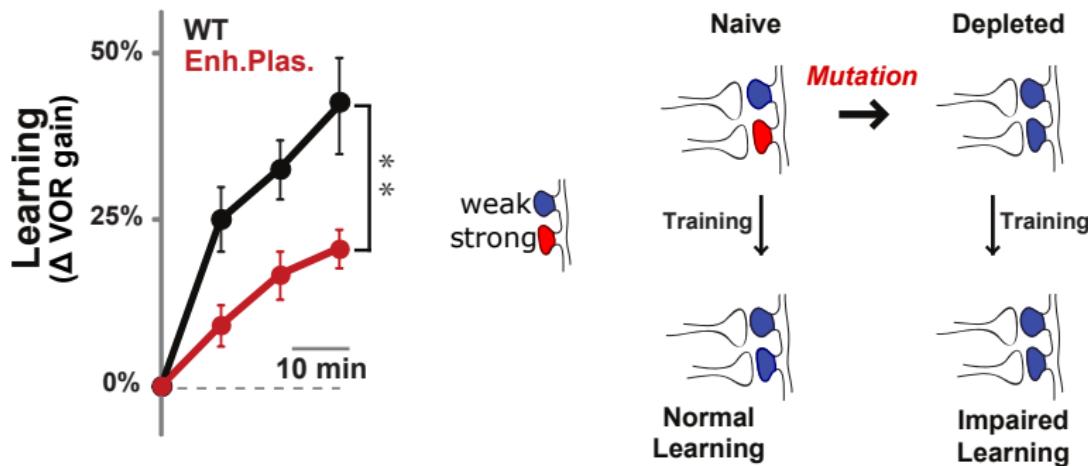
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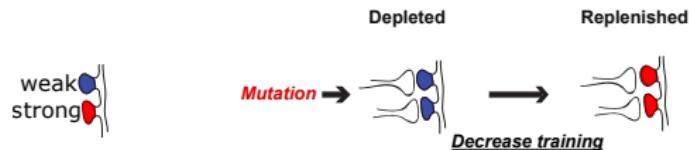


Question 1: depletion effect competes with enhanced intrinsic plasticity.
When is depletion effect stronger?

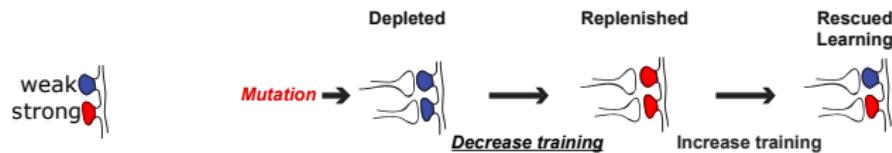
Replenishment by reverse-training



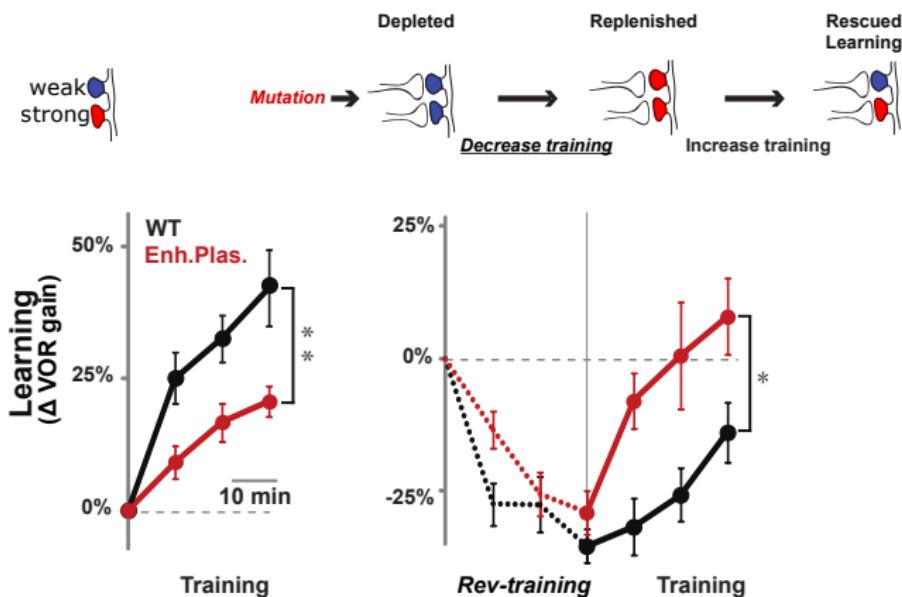
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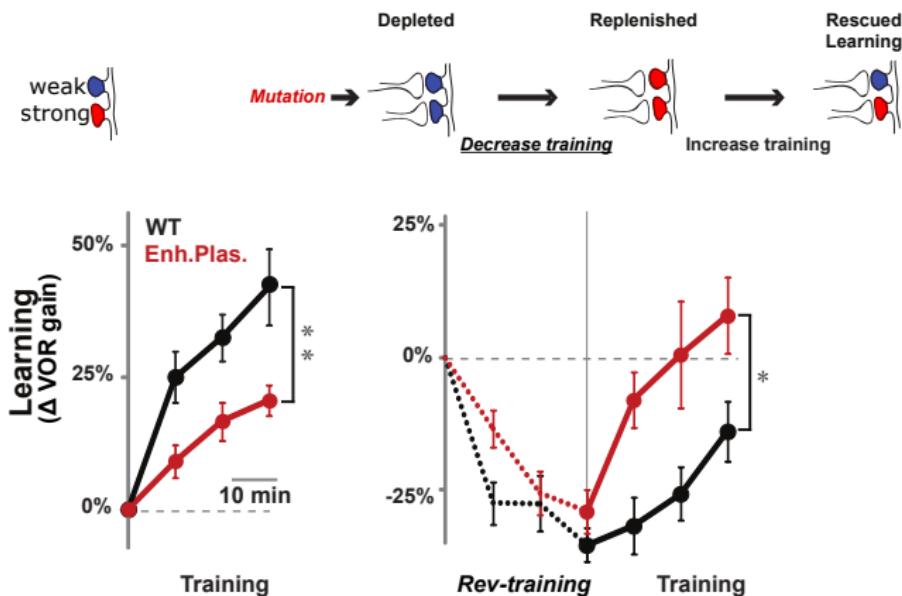
Replenishment by reverse-training



Replenishment by reverse-training



Replenishment by reverse-training



Question 2: When does enhanced plasticity impair learning?

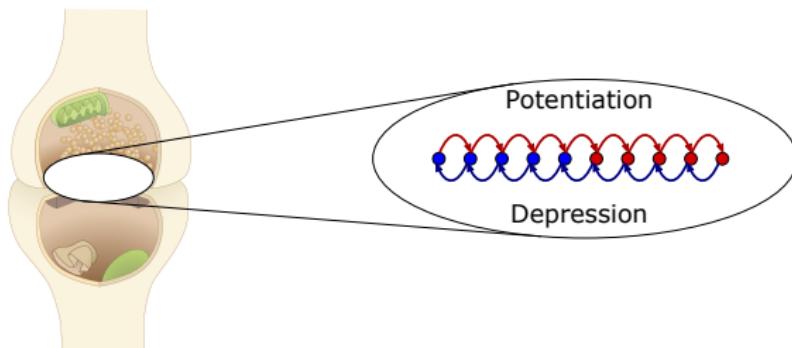
Models of complex synaptic dynamics



Models of complex synaptic dynamics

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

weak
strong



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

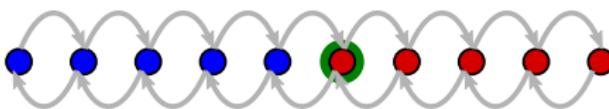
[Fusi et al. (2005), Fusi and Abbott (2007), Barrett and van Rossum (2008)]

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

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Potentiation event

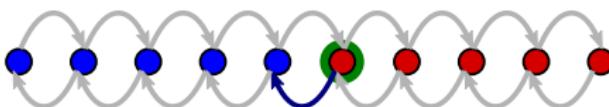


Depression event

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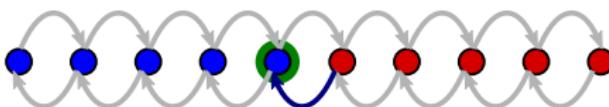


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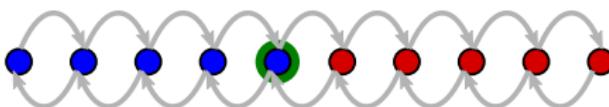


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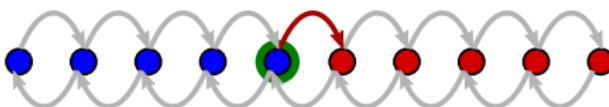


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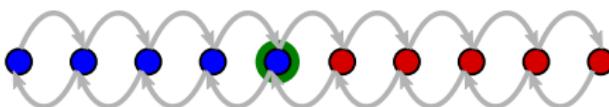


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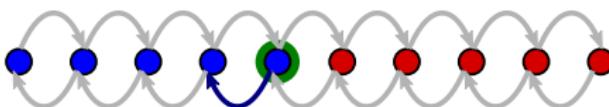
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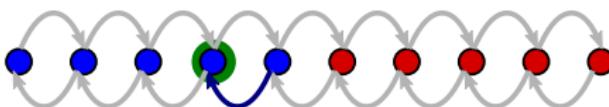
Metaplasticity: change propensity for plasticity
(independent of change in synaptic weight).

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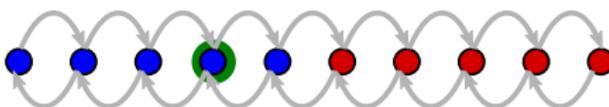
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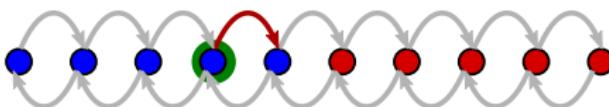
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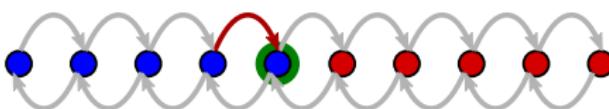
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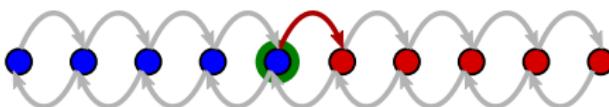
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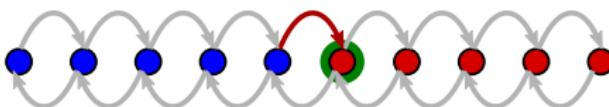
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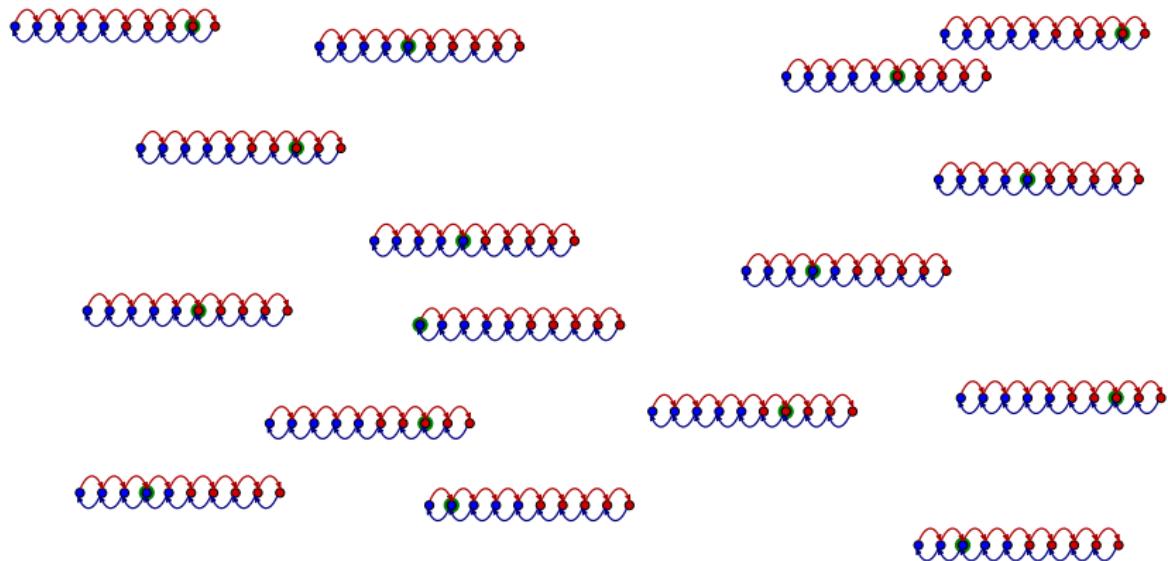
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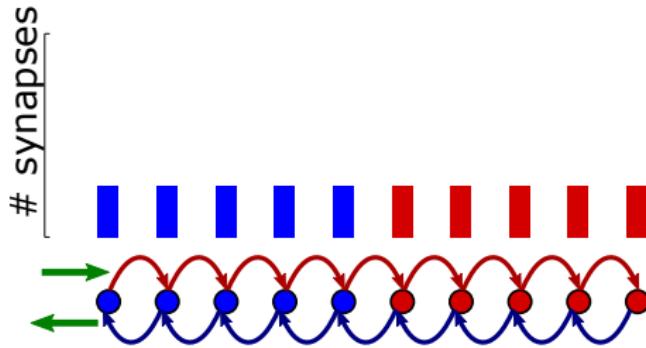
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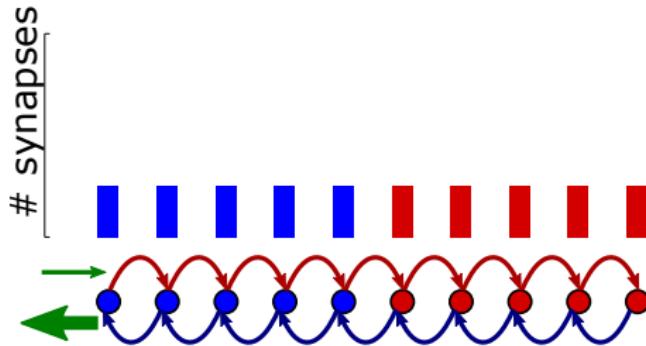
Modelling VOR experiments



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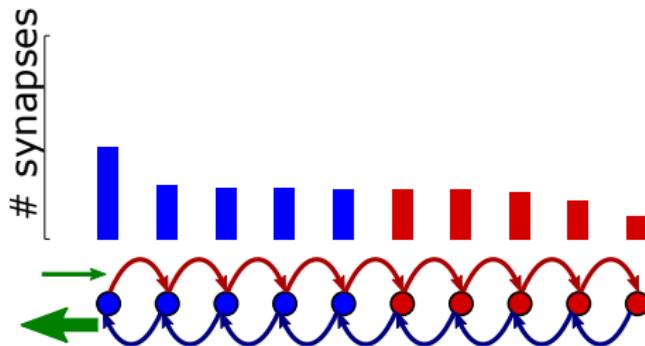


Modelling VOR experiments



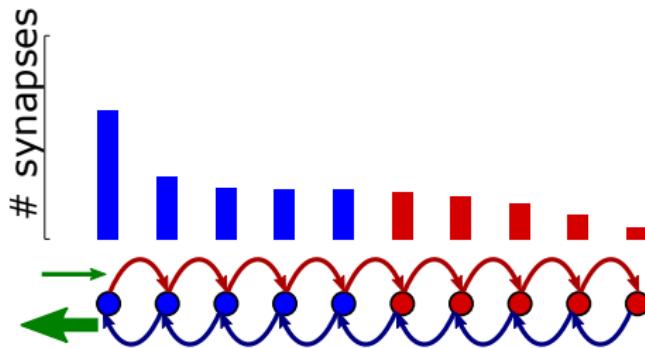
Training: change frequency of pot/dep events.

Modelling VOR experiments



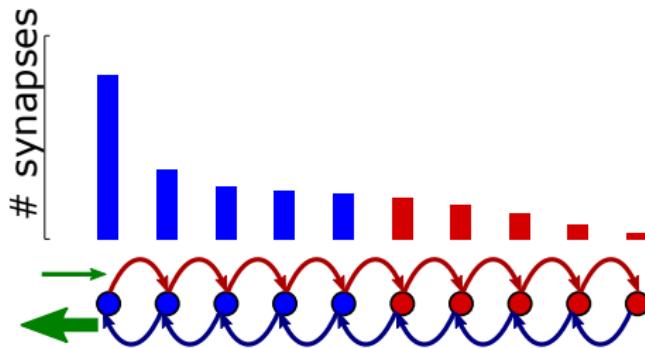
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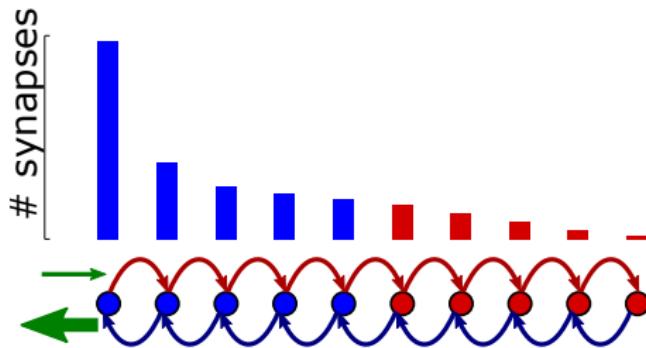
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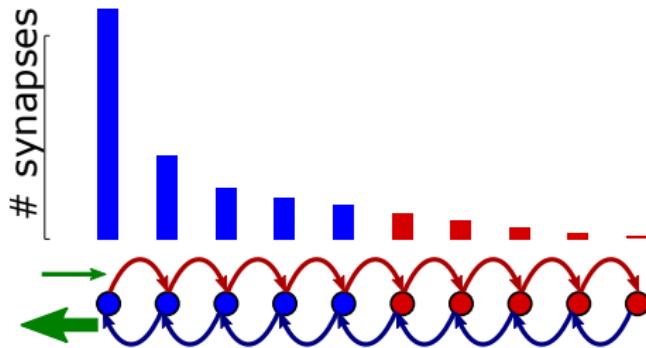
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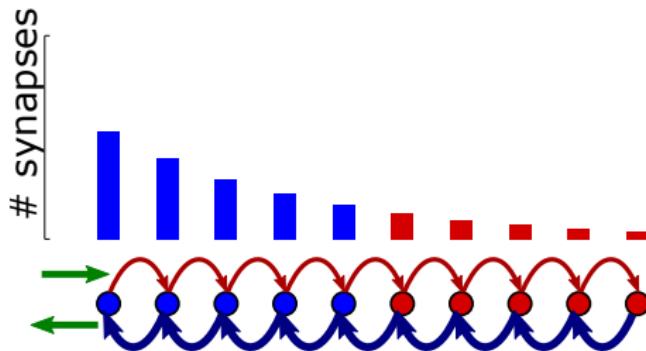
Modelling VOR experiments



Training: change frequency of pot/dep events.

Learning: decrease in average synaptic weight.

Modelling VOR experiments



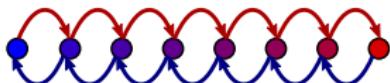
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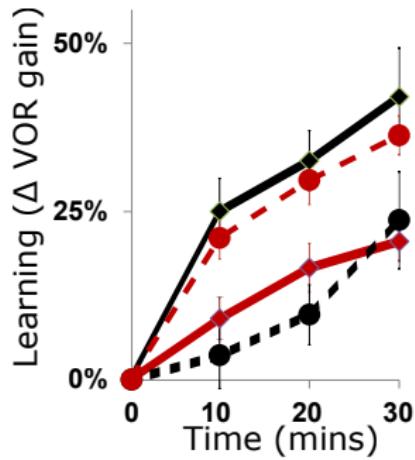
Mutation: increase transition probability for depression events.

Simple synapses cannot explain the data

Multistate synapse

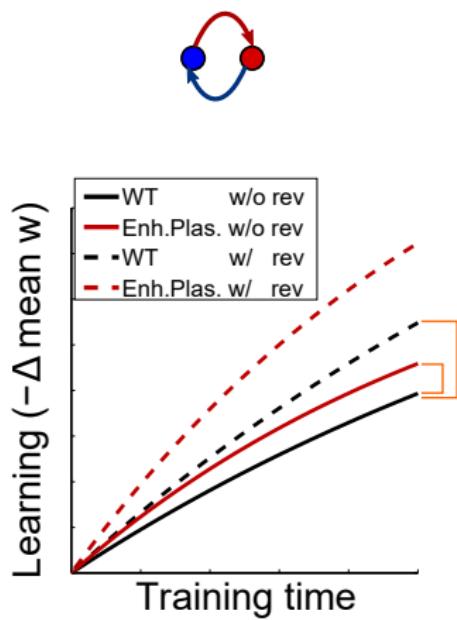


VOR Increase
Training

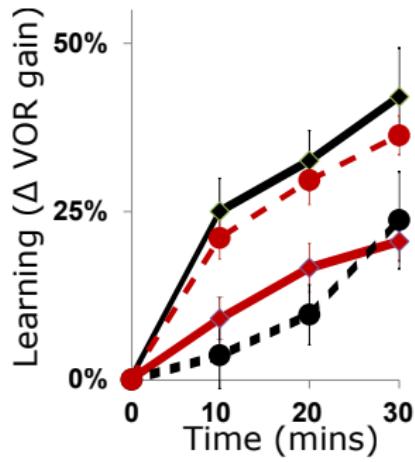


Simple synapses cannot explain the data

Two-state model

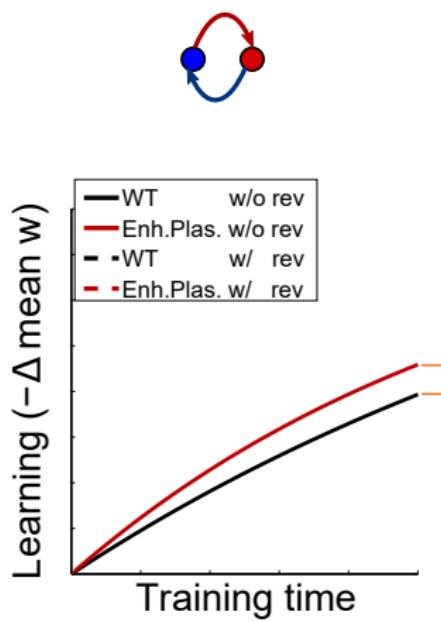


VOR Increase
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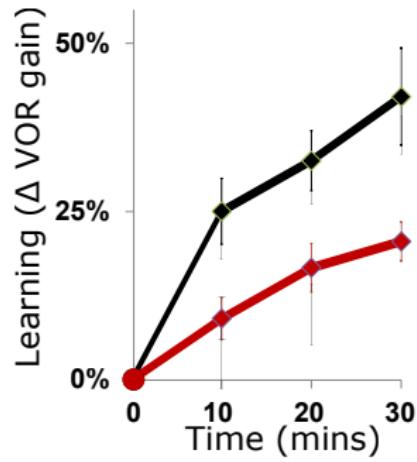


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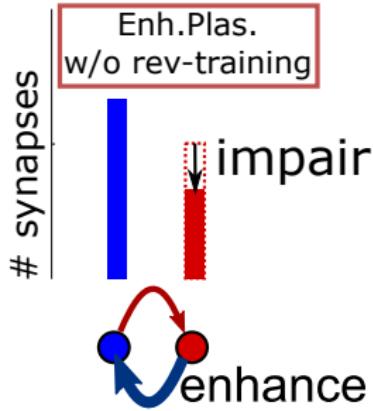


Simple synapses cannot explain the data

Two-state model



Initial distribution

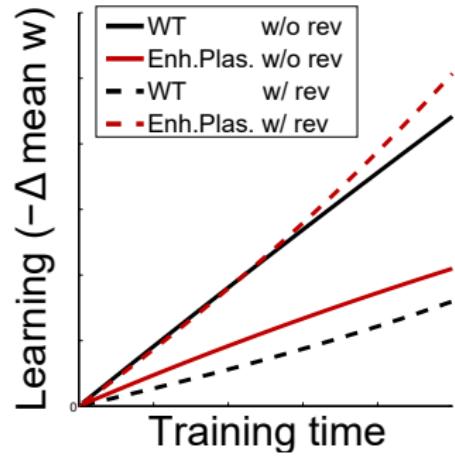
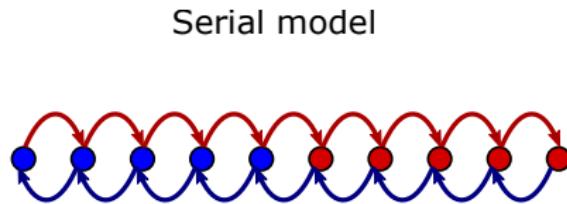


depletion effect

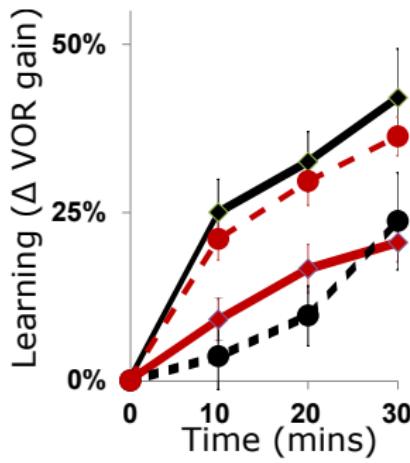
<
enhanced plasticity

⇒ enhanced learning

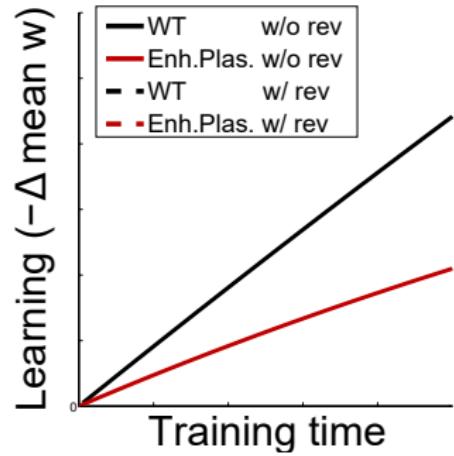
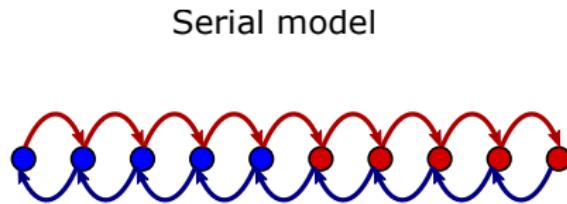
Complex metaplastic synapses can explain the data



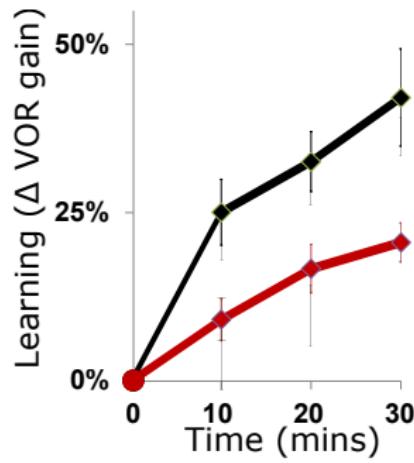
VOR Increase
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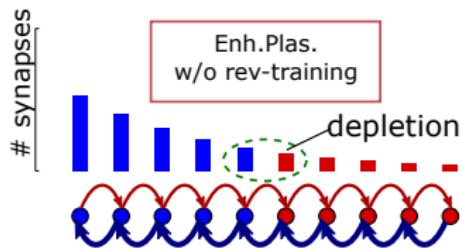
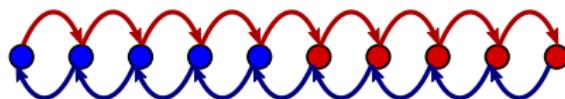


VOR Increase
Training



Complex metaplastic synapses can explain the data

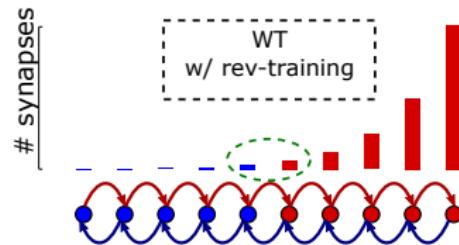
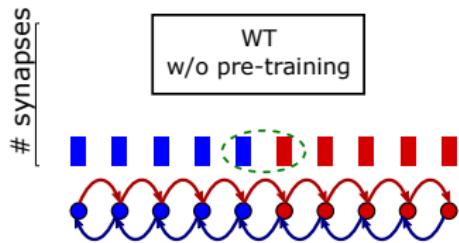
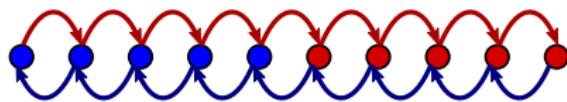
Serial model



amplified depletion
>
enhanced plasticity
⇒ impaired learning

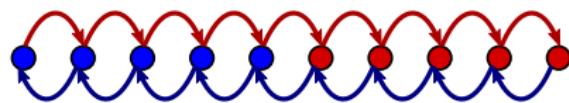
Complex metaplastic synapses can explain the data

Serial model



Complex metaplastic synapses can explain the data

Serial model



starting point:
labile states



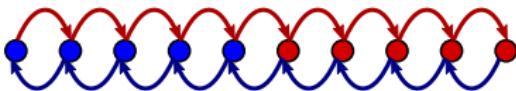
enhanced plasticity
⇒ impaired learning

starting point:
stubborn states



enhanced plasticity
⇒ enhanced learning

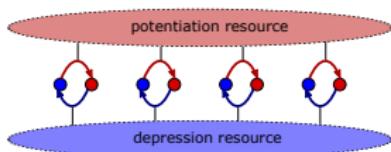
Essential features



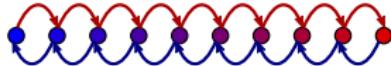
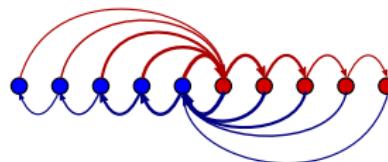
The success of the serial model relies on two features:

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

Fail:



Succeed:



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

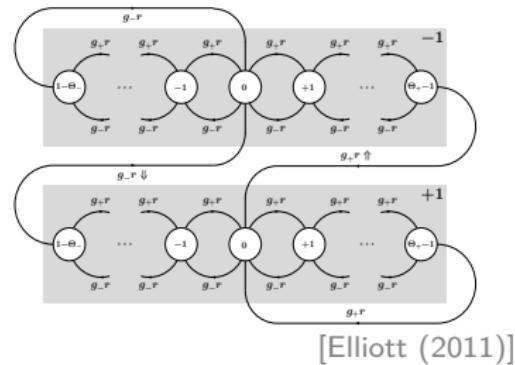
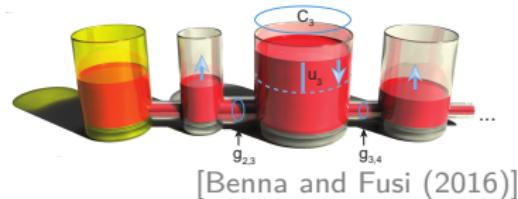
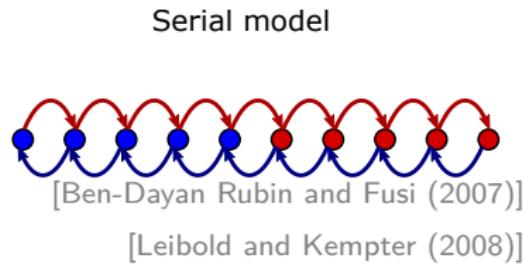
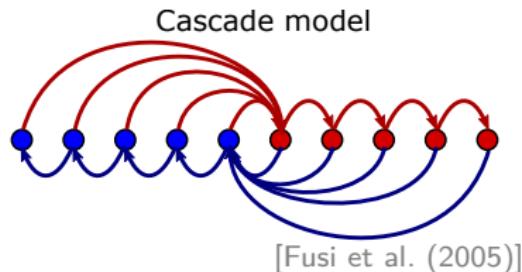
Assumes unbounded analogue synapses

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

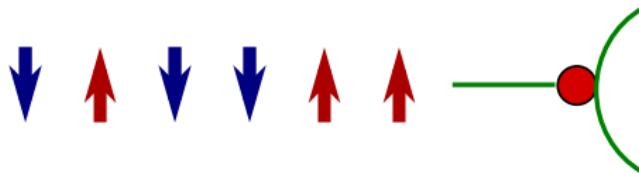
[Amit and Fusi (1992), Amit and Fusi (1994)]

New memories overwrite old \implies stability-plasticity dilemma.

Specific models of complex synaptic dynamics

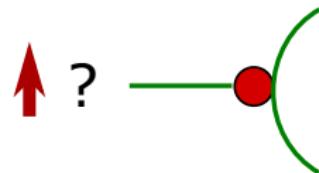


Synaptic memory curves



Synapses store a sequence of memories.

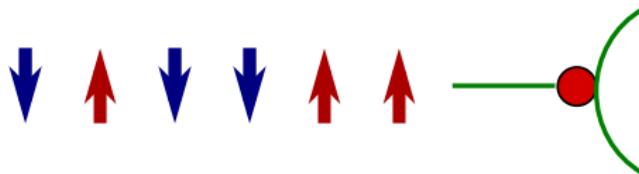
Synaptic memory curves



Synapses store a sequence of memories.

Recognition memory: has this pattern been seen before?

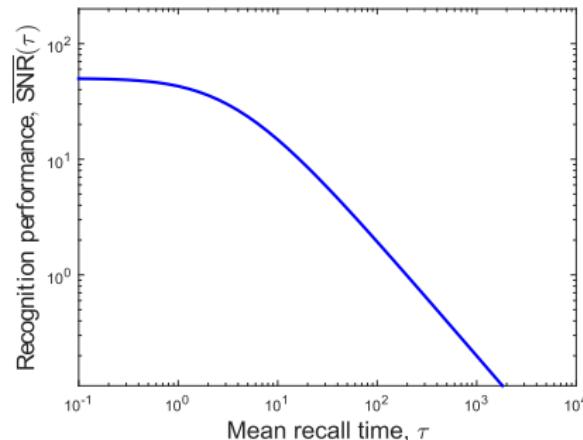
Synaptic memory curves



Synapses store a sequence of memories.

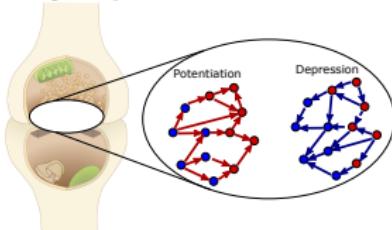
Recognition memory: has this pattern been seen before?

Performance described by SNR.

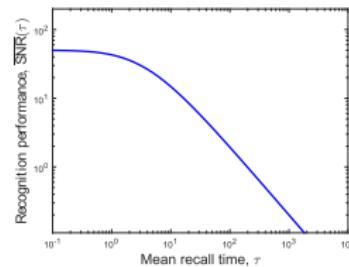


General principles relating structure and function?

Synaptic structure



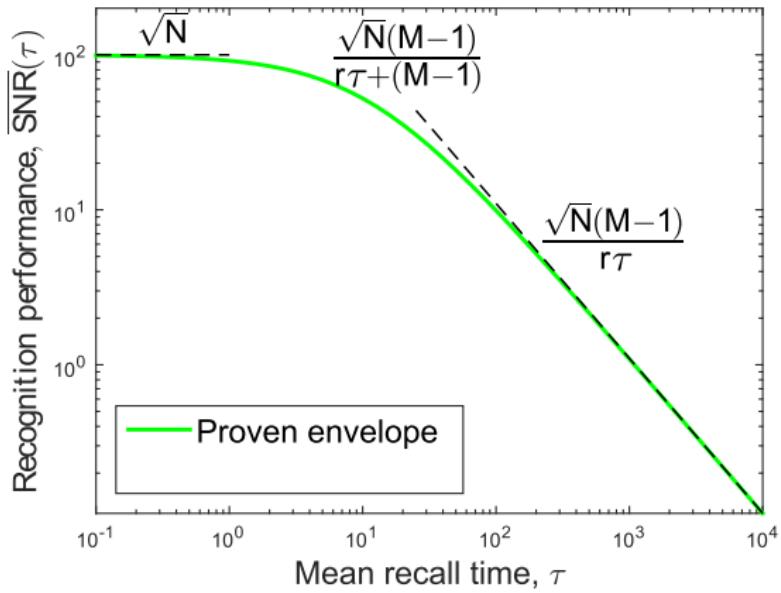
Synaptic function



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

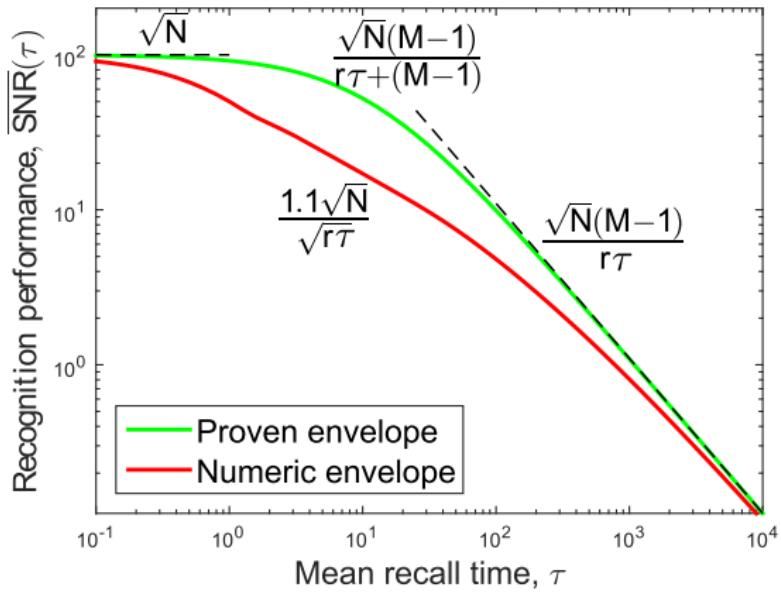
Proven envelope: memory frontier

Upper bound on memory curve at *any* timescale.

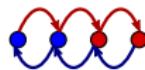
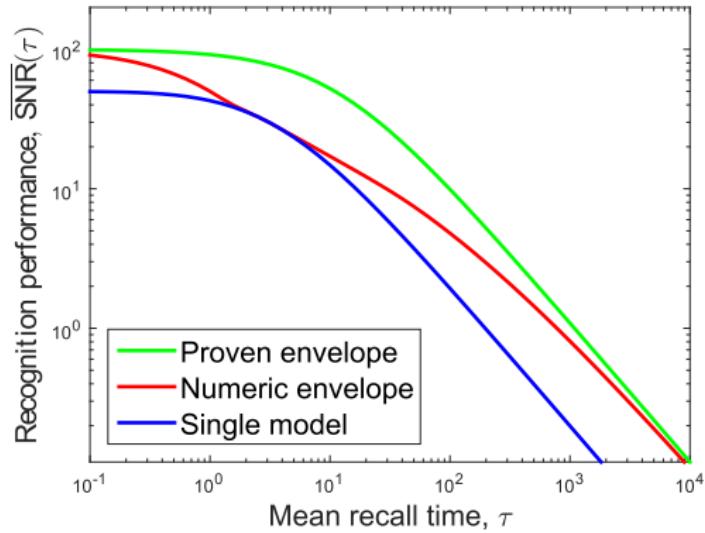


Proven envelope: memory frontier

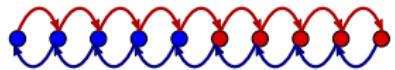
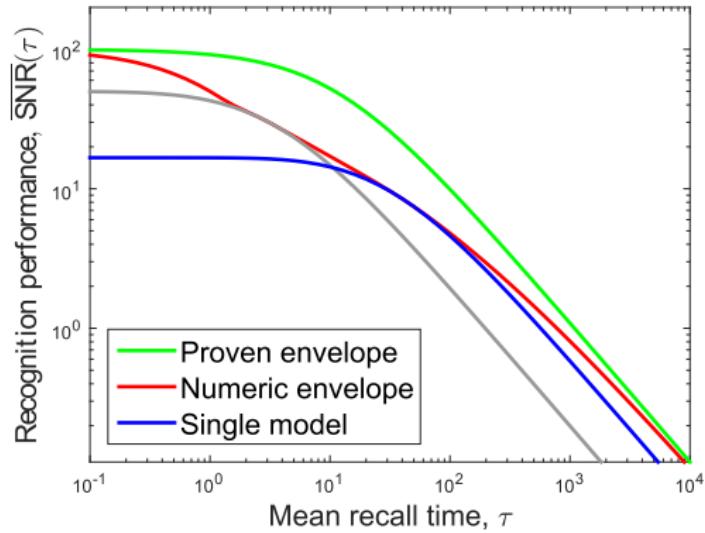
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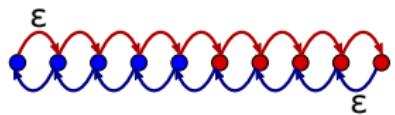
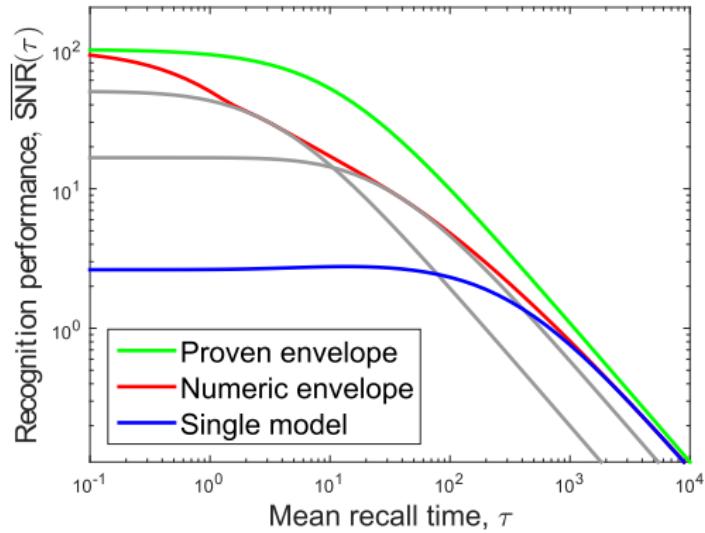
Models that maximize memory for one timescale



Models that maximize memory for one timescale

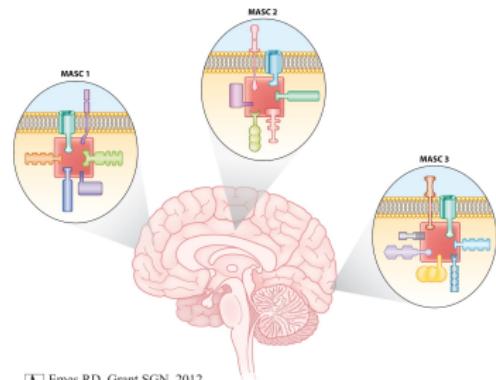


Models that maximize memory for one timescale



Synaptic diversity and timescales of memory

Different synapses have different molecular structures.

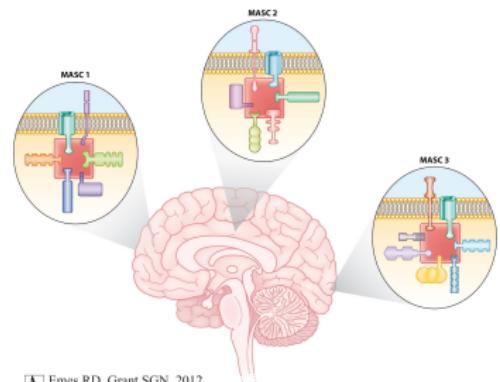


[A] Emes RD, Grant SGN. 2012.
Annu. Rev. Neurosci. 35:111–31

[Emes and Grant (2012)]

Synaptic diversity and timescales of memory

Different synapses have different molecular structures.



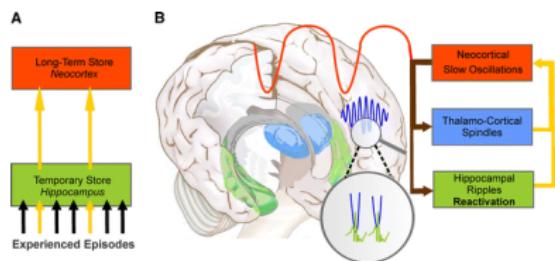
[Emes RD, Grant SGN. 2012.
Annu. Rev. Neurosci. 35:111–31]

[Emes and Grant (2012)]

Memories stored in different places for different timescales

[Squire and Alvarez (1995)]

[McClelland et al. (1995)]



[Born and Wilhelm (2012)]

Also: Cerebellar cortex → nuclei.

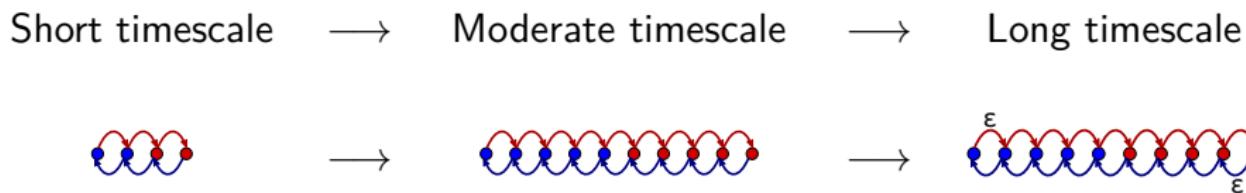
[Attwell et al. (2002)]

[Cooke et al. (2004)]

Synaptic structure and function: general principles

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

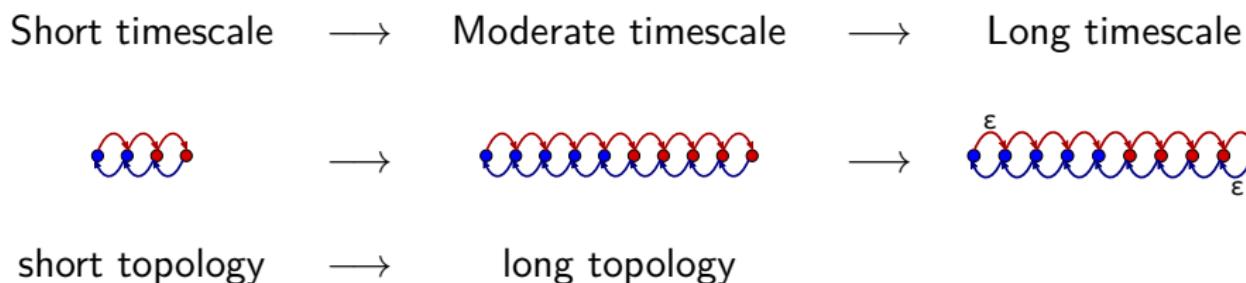
What can we conclude?



Synaptic structure and function: general principles

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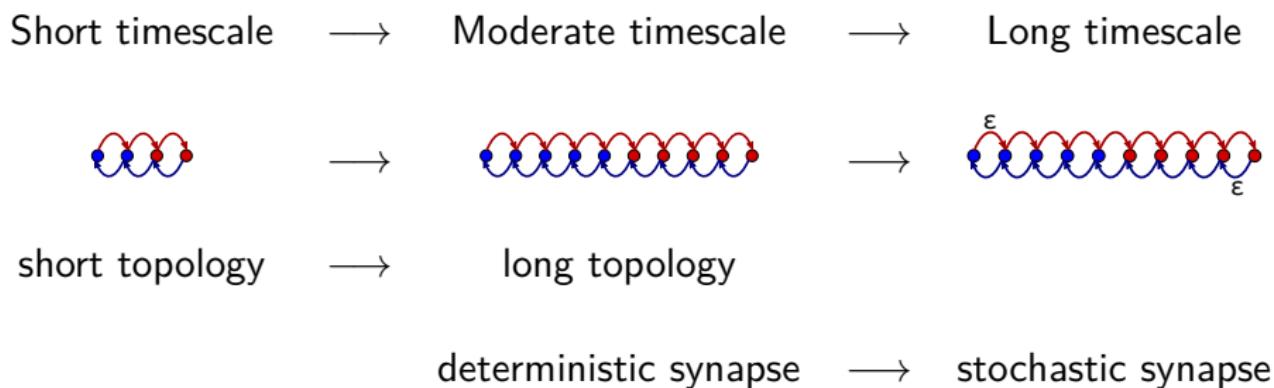
What can we conclude?



Synaptic structure and function: general principles

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

What can we conclude?



Experimental tests?

Traditional experiments:



Experimental tests?

Traditional experiments:

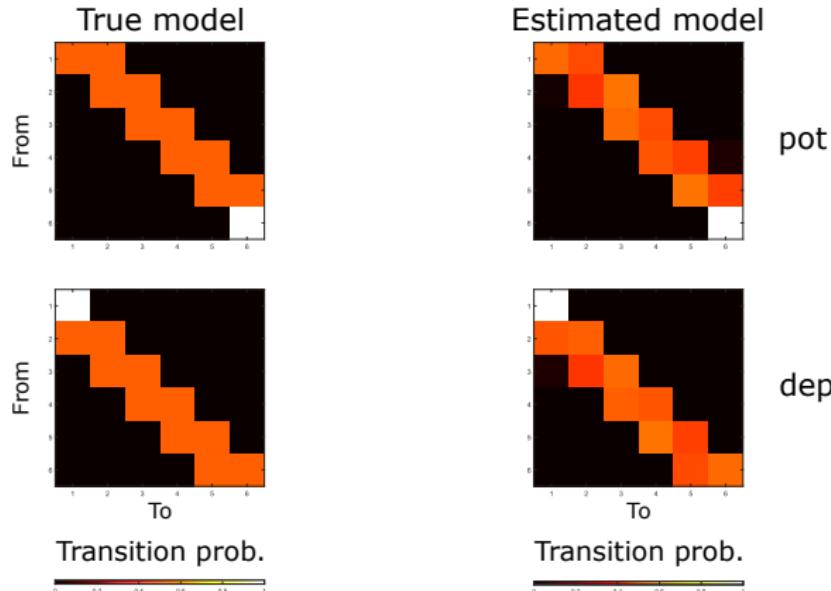


To fit a model: long sequence of small plasticity events.

Observe the changes in synaptic efficacy.



Simulated experiment



Problem: need *long* sequences.

Whole cell patch of postsynaptic neuron → Ca washout.

Summary

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

Acknowledgements

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Lane McIntosh
Alex Williams
Christopher Stock
Sarah Harvey
Aran Nayebi

Stefano Fusi

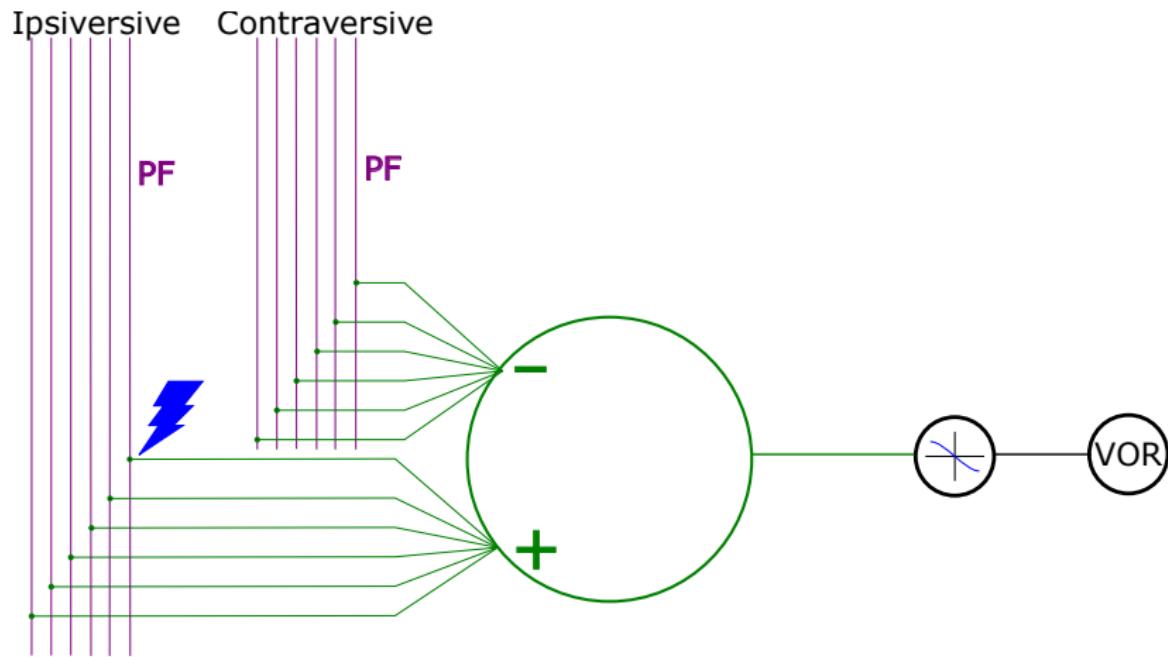
Jennifer Raymond

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Aparna Suvrathan
Rhea Kimpo
Carla Shatz
Hanmi Lee

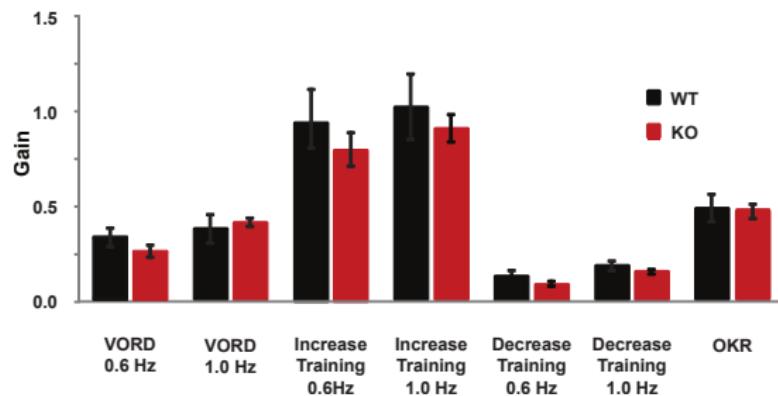
Marcus Benna

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

Model of circuit

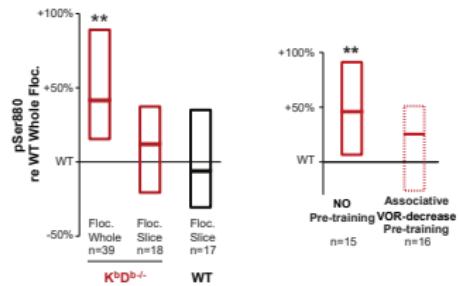


Baseline



Evidence: level of depression

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

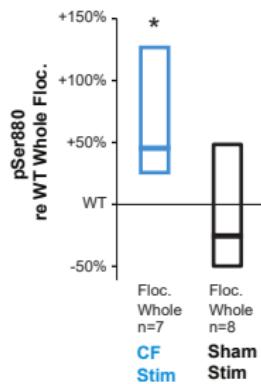
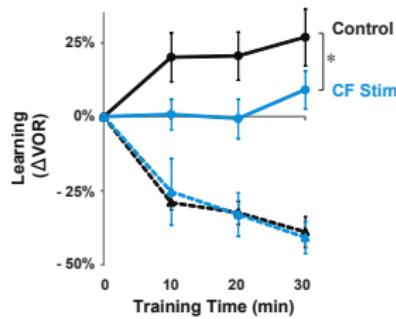
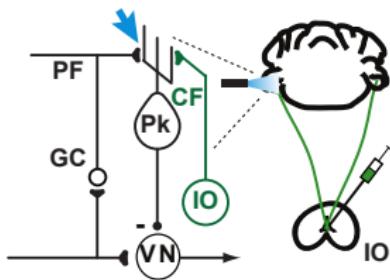


Biochemical signature of PF-Pk LTD.

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

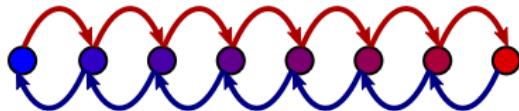
Evidence: saturation by CF stimulation

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

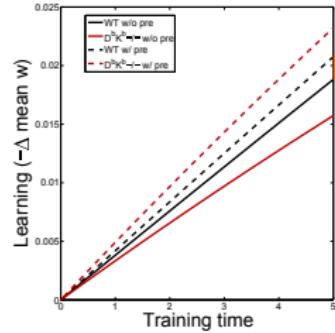
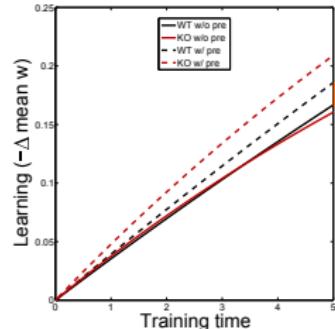
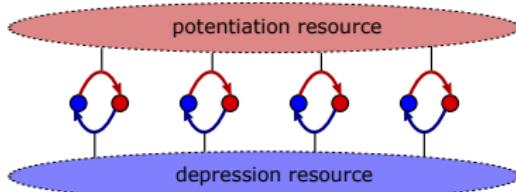


Other models that fail

Multistate synapse



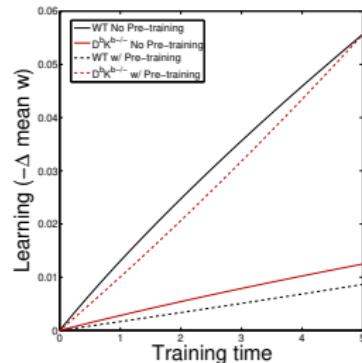
Pooled resource model



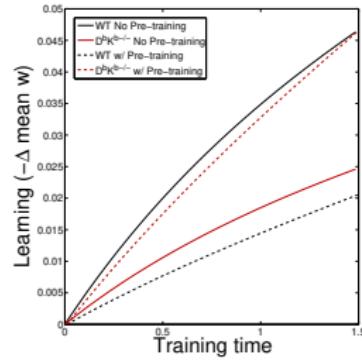
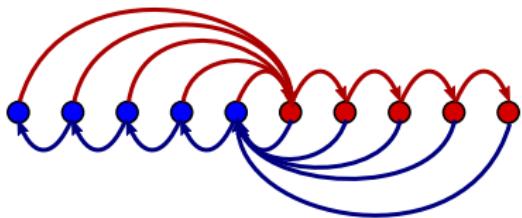
[Amit and Fusi (1994)]

Other models that work

Non-uniform multistate model

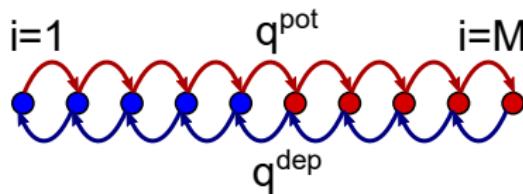


Cascade model



[Fusi et al. (2005)]

Mathematical explanation



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

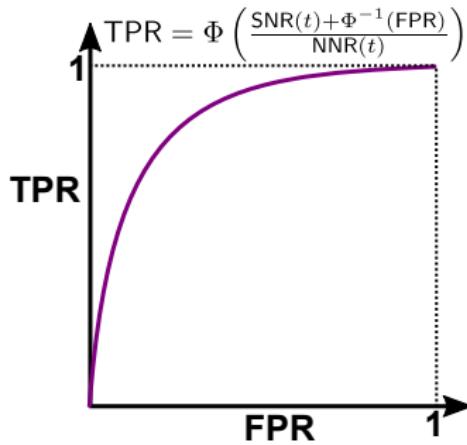
Learning rate $\sim \pi_{M/2} \left(\frac{q^{dep}}{q^{pot}} \right) = \mathcal{N} \left(\frac{q^{pot}}{q^{dep}} \right)^{\frac{M}{2}-1}$.

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

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

Quantifying memory quality

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



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

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

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

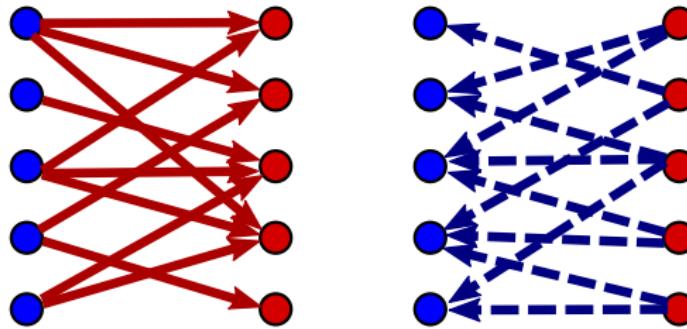
Also: KL divergence, Chernoff distance, . . .

Initial SNR as flux

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

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

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



Two-state model

Two-state model equivalent to previous slide:

Transitions:


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

Maximal initial SNR:

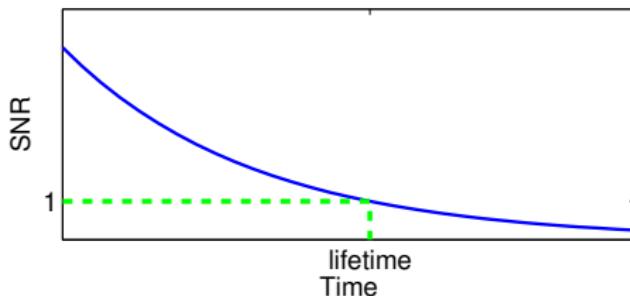
$$\text{SNR}(0) \leq \sqrt{N}.$$

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:

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

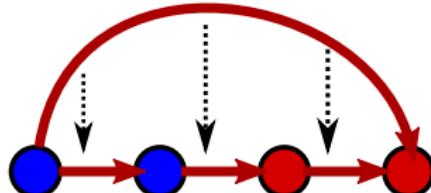
Saturated by a model with linear chain topology.

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

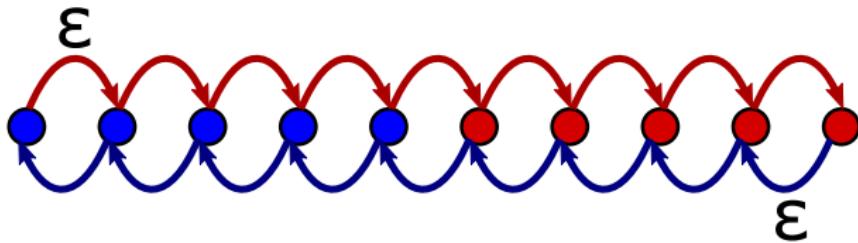
$$A = \frac{2\sqrt{N}}{r} \sum_k \pi_k |k - \langle k \rangle|.$$

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)]

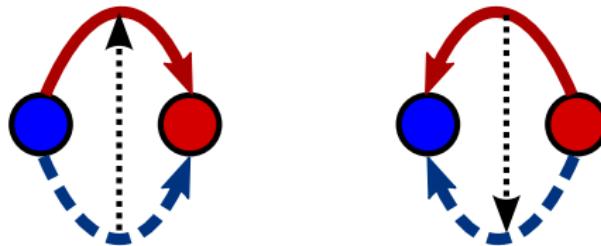
We define:

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

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

Technical detail: upper/lower triangular

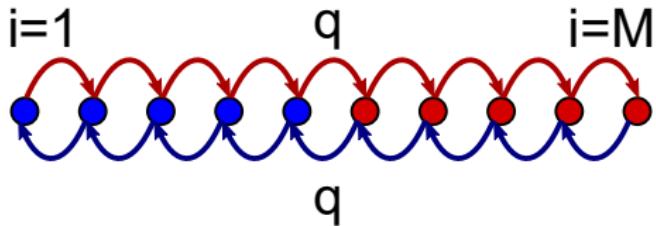
With states in order:



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 90

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



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

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 31 66 91

 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 66

 Peiran Gao, Eric Trautmann, Byron M. Yu, Gopal Santhanam, Stephen Ryu,
Krishna Shenoy, and Surya Ganguli.
“A theory of multineuronal dimensionality, dynamics and measurement”.
(November, 2017) , BioRxiv:214262.

10

References V



Eric Trautmann, Sergey Stavisky, Subhaneil Lahiri, Katherine Ames, Matthew Kaufman, Stephen Ryu, Surya Ganguli, and Krishna Shenoy.

“Accurate estimation of neural population dynamics without spike sorting”.
(December, 2017) , bioRxiv:229252.

11

12



Subhaneil Lahiri, Jascha Sohl-Dickstein, and Surya Ganguli.

“A universal tradeoff between power, precision and speed in physical communication”.

(2016) , arXiv:1603.07758 [cond-mat.stat-mech].

14

References VI



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) .

17

18

19



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) .

17

18

19

References VII



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) .

17

18

19



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) .

17

18

19

References VIII



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) .

17

18

19



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) .

17

18

19

References IX



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) .

17

18

19



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) .

17

18

19

References X



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) .

17

18

19



David Marr.

“A theory of cerebellar cortex”.

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

20

References XI



James S. Albus.

“A theory of cerebellar function”.

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

20



Masao Ito.

“Neural design of the cerebellar motor control system”.

Brain research, 40(1):81–84, (1972) .

20



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) .

21

References XII



S. Fusi and L. F. Abbott.

“Limits on the memory storage capacity of bounded synapses”.

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

31



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

“Optimal learning rules for discrete synapses”.

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

31

97



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) .

31

References XIII



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>.

31



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

References XIV



Christian Leibold and Richard Kempter.

"Sparseness Constrains the Prolongation of Memory Lifetime via Synaptic Metaplasticity".

Cereb. Cortex, 18(1):67–77, (2008) .

66



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

References XV



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



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

References XVI



Jan Born and Ines Wilhelm.

“System consolidation of memory during sleep.”.

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

76

77



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

References XVII



J.G. Kemeny and J.L. Snell.

Finite markov chains.

Springer, 1960.

99