

# Understanding impaired learning with enhanced plasticity

based on work in preparation with: T.D. Barbara Nguyen-Vu, Grace Q. Zhao,  
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# Introduction

Learning requires synaptic plasticity.

Expect enhanced plasticity → enhance learning.

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



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But often: → impairment.



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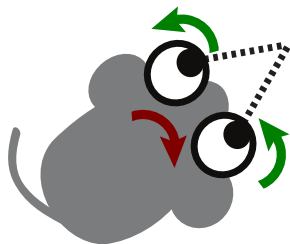
Mice with enhanced cerebellar plasticity can show both impaired and enhanced learning.

Simple synapses cannot explain behaviour.

→ Necessary & sufficient conditions on complex synapses to replicate this.

- Motor learning
  - Cerebellar learning of mice with enhanced plasticity
  - Complex synaptic models
- (Memory capacity of complex synapses)

# Vestibulo-Occular Reflex



Eye movements compensate for head movements to maintain fixation.

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

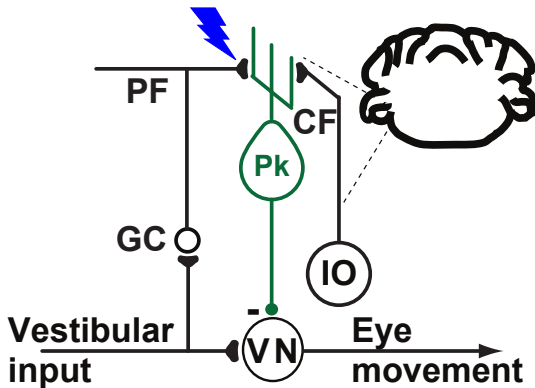
Needs to be adjusted as eye muscles age, etc.

# VOR training

## VOR Increase Training



## VOR Decrease Training



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

[du Lac et al. (1995), Boyden et al. (2004)]

# Enhanced plasticity impairs learning

Knockout of MHC-I  $D^bK^b$  molecules in PF-Pk synapses

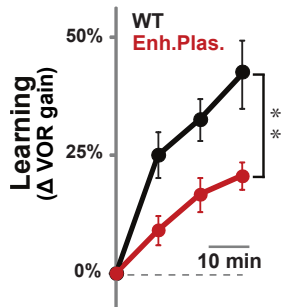
[McConnell et al. (2009)]

→ lower threshold for LTD → enhanced plasticity



**Hypothesis:** enhanced learning.

**VOR Increase  
Training**

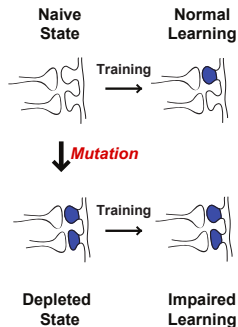


**Experiment:** enhanced plasticity → impaired learning.



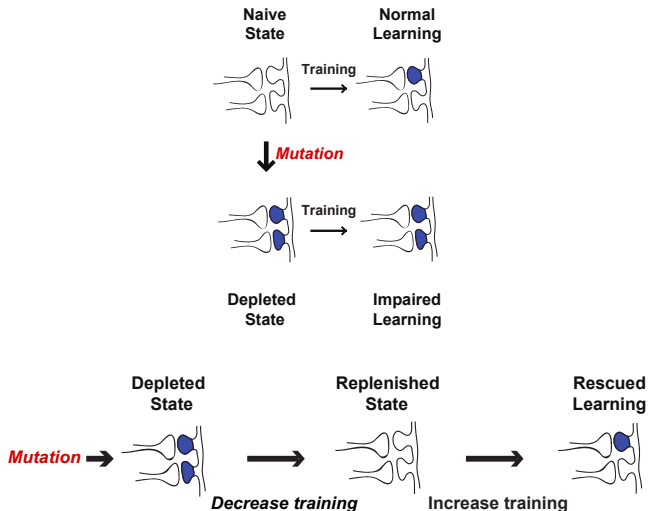
# Depletion hypothesis

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

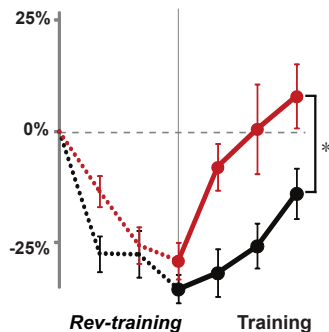
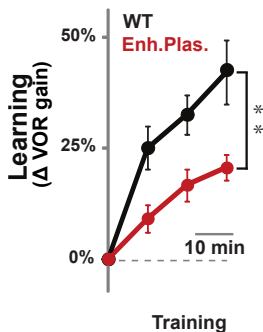
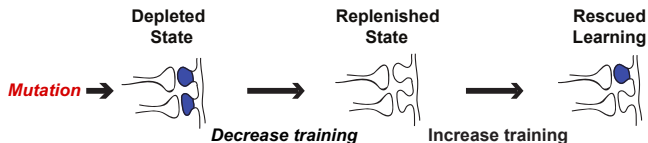


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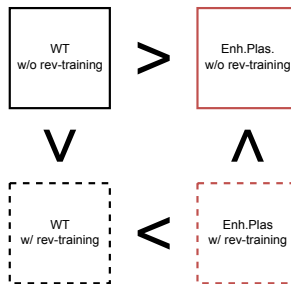
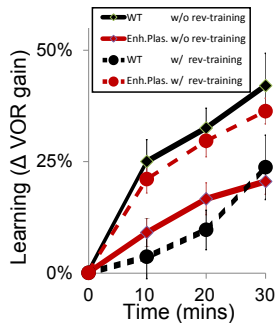
Learning rate  $\sim$  intrinsic plasticity rate  $\times$  # synapses available for LTD.



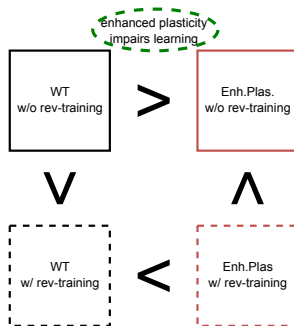
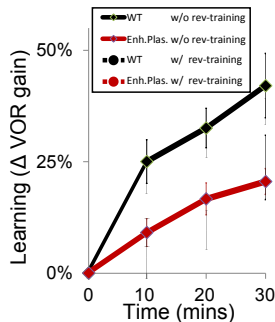
# Replenishment by reverse-training



# Summary of training results



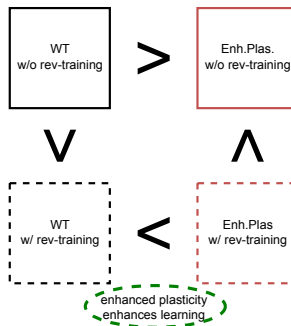
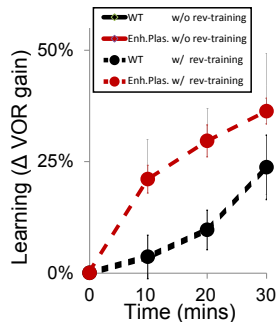
# Summary of training results



Questions:

- Can the depletion effect overcome intrinsic plasticity?

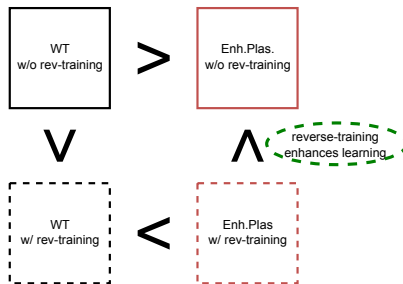
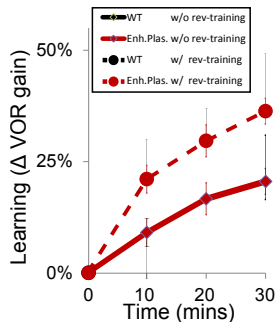
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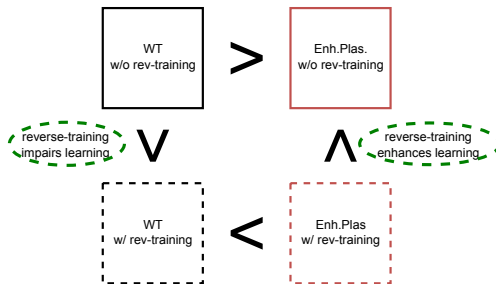
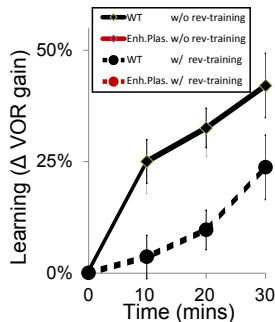
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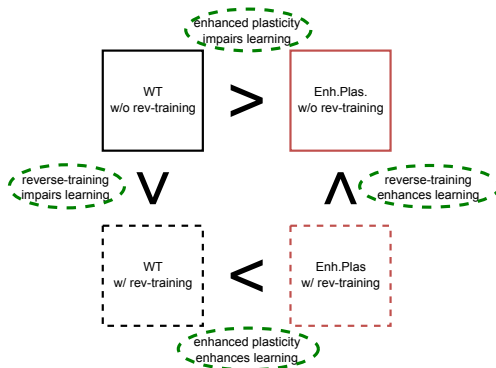
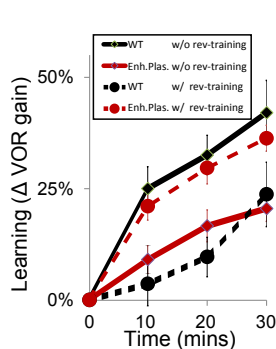


Questions:

- Can the depletion effect overcome intrinsic plasticity?
- How can a little replenishment help, but too much hurt?



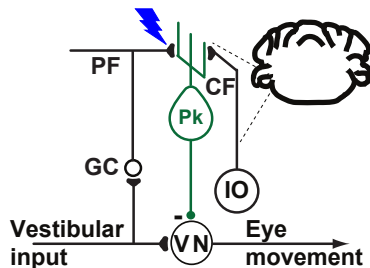
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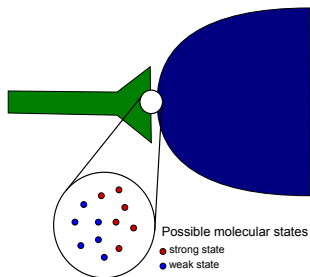
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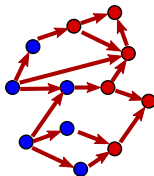
## VOR Increase Training



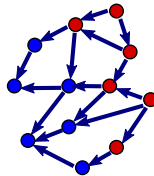
# Complex synapses



Potential



Depression

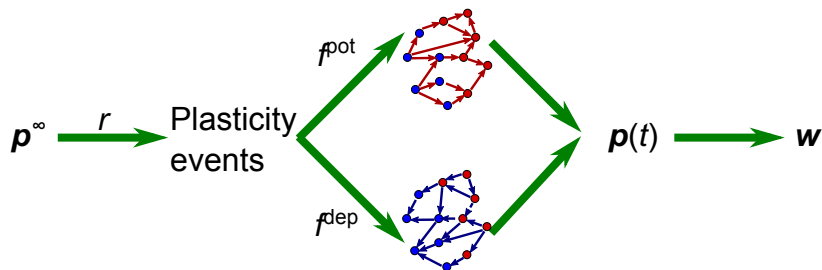


Simplifying assumptions:

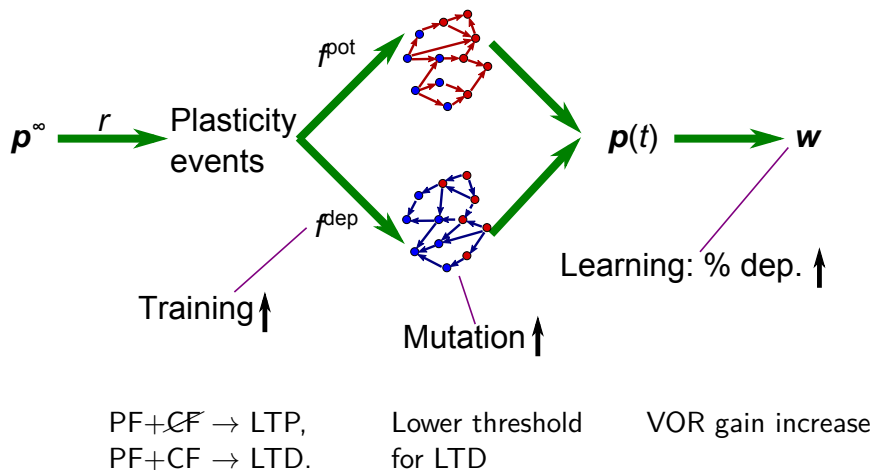
- Candidate plasticity events occur independently at each synapse,
- Each synapse responds with the same state-dependent rules,
- Keep track of distribution of synapses across states.

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

# Synaptic dynamics

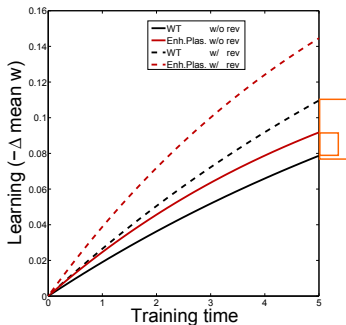
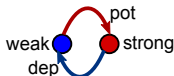


# Synaptic dynamics

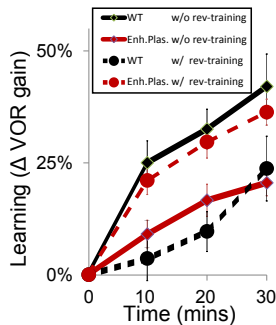


# Simple synapses cannot explain the data

## Binary synapse

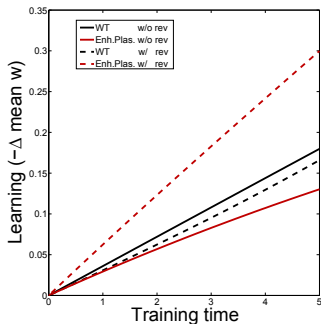
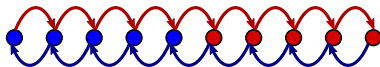


## VOR Increase Training

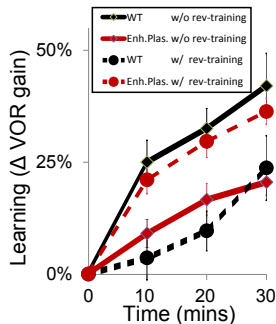


# Complex synapses can explain the data

## Serial synapse

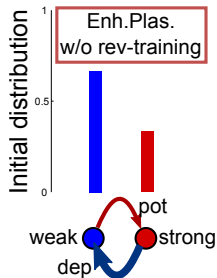


## VOR Increase Training



[Leibold and Kempter (2008)]

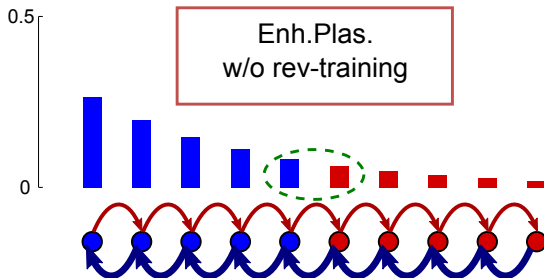
# Enhanced plasticity can enhance or impair learning



Intrinsic plasticity  
dominates depletion



enhanced plasticity  
enhances learning



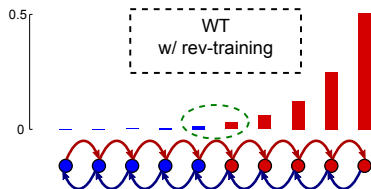
Depletion dominates  
intrinsic plasticity



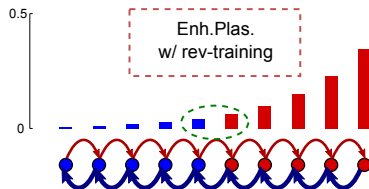
enhanced plasticity  
impairs learning



# Reverse-training can impair or enhance learning

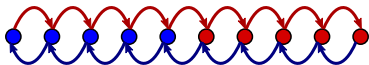


reverse-training  
depopulates boundary  
↓  
impaired learning



reverse-training  
repopulates boundary  
↓  
enhanced learning

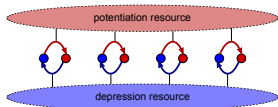
# Essential features



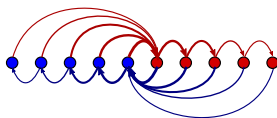
The success of the serial model relies on two features:

- Complexity - needed to amplify the effect of depletion,
- Metaplasticity – repeated potentiation makes subsequent depression harder.

Fail:



Succeed:



[Amit and Fusi (1994), Fusi et al. (2005)]

- We find diverse behavioural patterns:  
**Enhanced plasticity** → **enhance/impair** learning depending on prior experience.  
**Reverse-training** → **enhance/impair** learning depending on plasticity rates.
- We can explain these behavioural patterns using synaptic models.
- Key required synaptic properties are:  
**Synaptic complexity**: necessary to amplify depletion.  
**Synaptic stubbornness**: repeated potentiation makes subsequent depression harder.
- We used behaviour to constrain the dynamics of synaptic plasticity

# Tradeoff: learning vs. remembering

## What about memory?

- Simple synapses have poor memory storage capacity.  
Synaptic complexity is needed for rescue.

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

- Trade-off between learning and remembering:  
Too rigid → difficult to learn new memories.  
Too plastic → new memories quickly overwrite old.
- Exploring the *entire* space of complex synaptic models  
→ upper bounds on their storage ability  
& the models that saturate them.

[Lahiri and Ganguli (submitted)]

# The frontiers of complex synaptic memory

We have  $N$  synapses with  $M$  internal states each.

We study the decay of one memory over time due to corruption by subsequent memories.

We prove that, no matter what the structure, no synaptic model can have:

- initial fidelity (SNR) greater than  $\sqrt{N}$ .
- memory lifetime greater than  $\sim \sqrt{NM}$ .
- fidelity decay slower than  $\sim \sqrt{NM}/t$ .

At late times, fidelity is maximised by a model with a simple chain structure.

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Han-Mi Lee

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# References I



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) .

2

3

4



Gaël Malleret, Ursula Haditsch, David Genoux, Matthew W. Jones, Tim V.P. Bliss, Amanda M. Vanhose, 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) .

2

3

4

# References II



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) .

2

3

4



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, (Dec, 1998) .

2

3

4



# References III



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, (Jun, 2000) .

2

3

4



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) .

2

3

4

# References IV



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) .

2 3 4



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) .

2 3 4

# References V



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) .

2

3

4



S du Lac, J L Raymond, T J Sejnowski, and S G Lisberger.

“Learning and Memory in the Vestibulo-Ocular Reflex”.

*Annual Review of Neuroscience*, 18(1):409–441, (1995) .

7

# References VI



Edward S. Boyden, Akira Katoh, and Jennifer L. Raymond.

“CEREBELLUM-DEPENDENT LEARNING: The Role of Multiple Plasticity Mechanisms”.

*Annual Review of Neuroscience*, 27(1):581–609, (2004) .

7



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) .

8

# References VII



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

“Cascade models of synaptically stored memories”.

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

19

26



S. Fusi and L. F. Abbott.

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

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

19



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

“Optimal learning rules for discrete synapses”.

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

19

# References VIII



Christian Leibold and Richard Kempter.

“Sparseness Constrains the Prolongation of Memory Lifetime via Synaptic Metaplasticity”.

*Cerebral Cortex*, 18(1):67–77, (2008) .

23



D. J. Amit and S. Fusi.

“Learning in neural networks with material synapses”.

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

26

28



D. J. Amit and S. Fusi.

“Constraints on learning in dynamic synapses”.

*Network: Computation in Neural Systems*, 3(4):443–464, (1992) .

28