

Modelling impaired and enhanced learning with enhanced plasticity

Subhaneil Lahiri

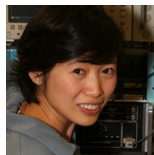
with: Barbara Nguyen-Vu, Grace Zhao, Aparna Suvrathan, Han-Mi Lee, Surya Ganguli, Carla Shatz and Jennifer Raymond

Stanford University

December 3, 2014



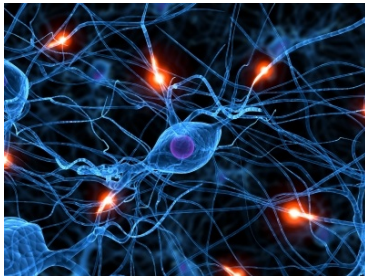
Barbara Nguyen-Vu



Grace Zhao

Introduction

Learning requires synaptic plasticity.

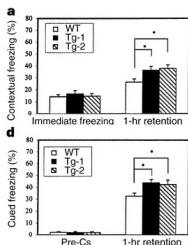


Can we enhance learning by enhancing plasticity?



Enhanced plasticity *can* enhance learning

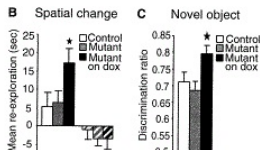
Overexpress NR2B



Fear conditioning

[Tang et al. (1999)]

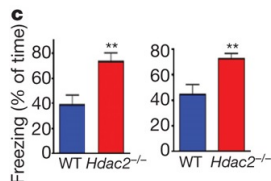
Inhibit CN



Novel object recog.

[Malleret et al. (2001)]

Knockout Hdac2

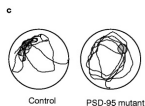


Fear conditioning

[Guan et al. (2009)]

Enhanced plasticity can *impair* learning

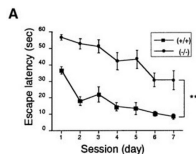
Mutate PSD-95



Water maze

[Migaud et al. (1998)]

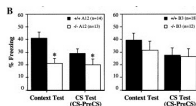
Knockout PTP δ



Water maze

[Uetani et al. (2000)]

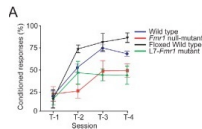
Delete Tmod2



Fear cond.

[Cox et al. (2003)]

Knockout FMR1



Eyeblink

[Koekkoek et al. (2005)]

also: [Hayashi et al. (2004), Rutten et al. (2008)]

Overview

Sometimes enhanced plasticity \rightarrow enhanced learning.
Sometimes enhanced plasticity \rightarrow impaired learning.

Why? How? When?



Overview

Sometimes enhanced plasticity → enhanced learning.
Sometimes enhanced plasticity → impaired learning.

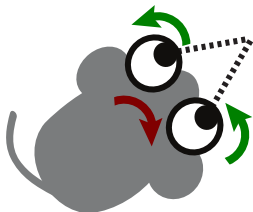


Why? How? When?

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

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

Vestibulo-Occular Reflex



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

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

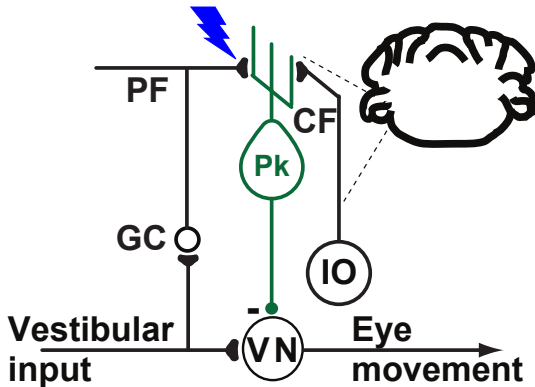
Needs to be adjusted as eye muscles age, etc.

Vestibulo-Ocular Reflex training

VOR Increase Training



VOR Decrease Training



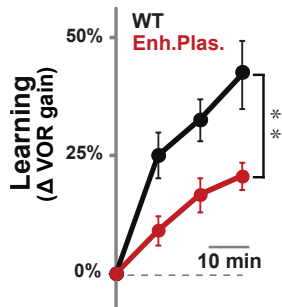
VOR increase: LTD in PF-Pk synapses.
VOR decrease: different mechanism,
also reverses LTD in PF-Pk.

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

Enhanced plasticity impairs learning

Expectation: enhanced LTD → enhanced learning.

VOR Increase Training



Experiment: enhanced plasticity → impaired learning.

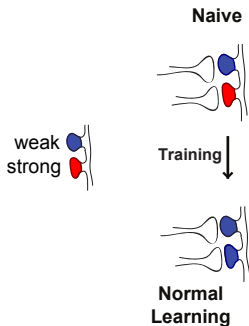
Knockout of MHC-I K^bD^b molecules in PF-Pk synapses

→ lower threshold for LTD

[McConnell et al. (2009)]

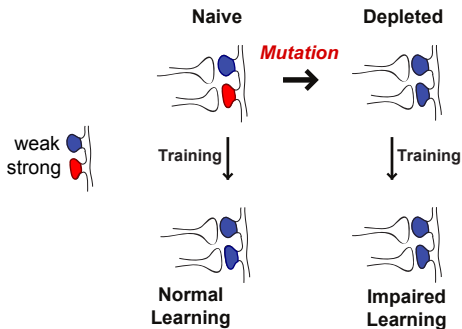
Depletion hypothesis

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



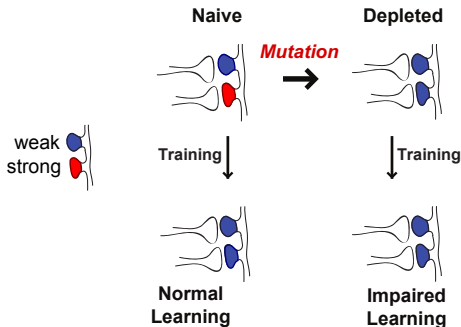
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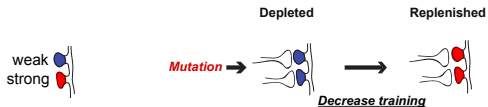


Question 1: depletion effect competes with enhanced intrinsic plasticity.
When is depletion effect stronger?

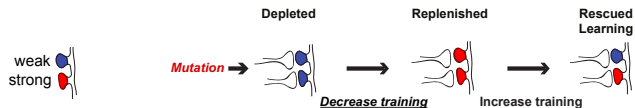
Replenishment by reverse-training



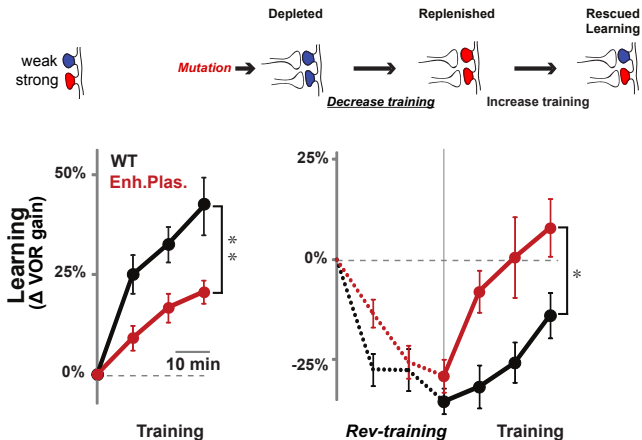
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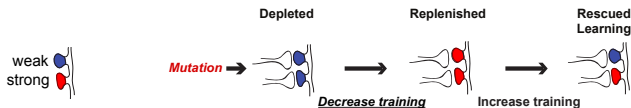
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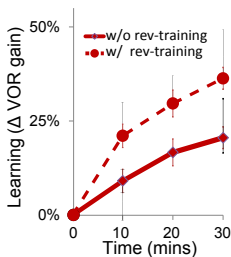
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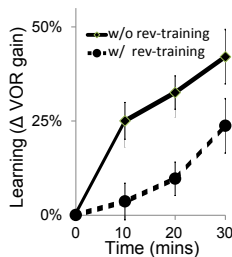
Replenishment by reverse-training



Enh. Plast.

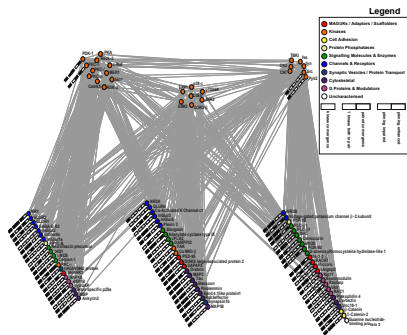


WT

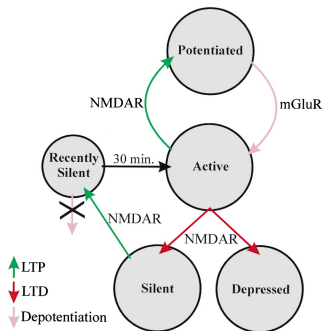


Question 2: How can replenishment ever impair learning?

Synapses are complex



[Coba et al. (2009)]



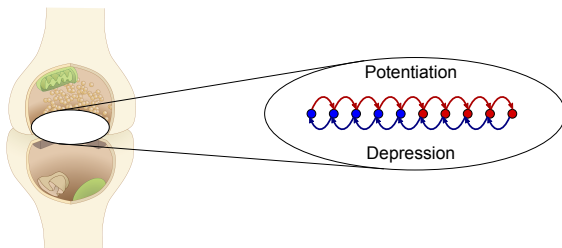
[Montgomery and Madison (2002)]

Models of complex synaptic dynamics



Models of complex synaptic dynamics

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



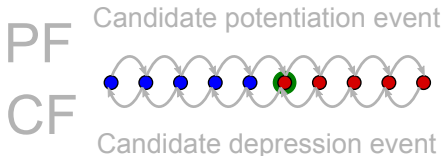
States: NMDAR subunit composition, CaMK II autophosphorylation, activating PKC, p38 MAPK,...

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

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

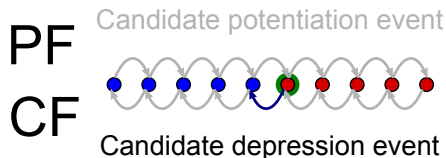
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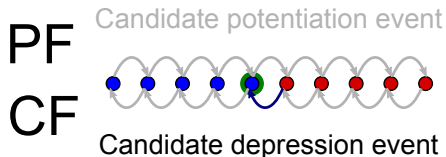
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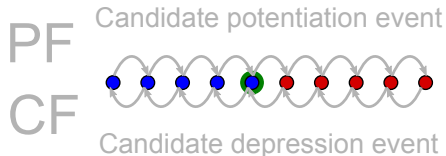
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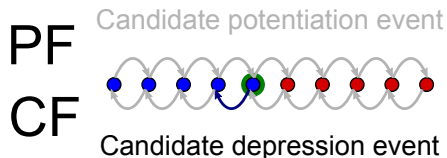
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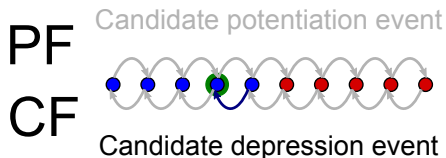
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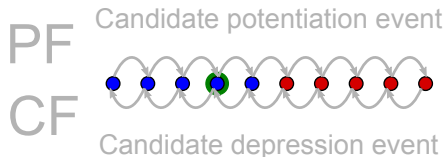
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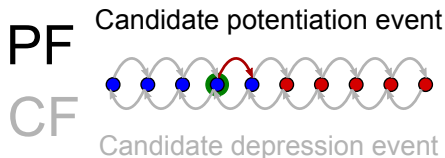
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Metaplasticity: change propensity for plasticity
(independent of change in synaptic weight).

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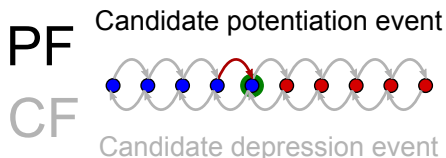
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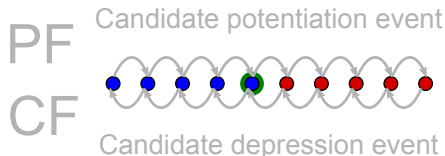


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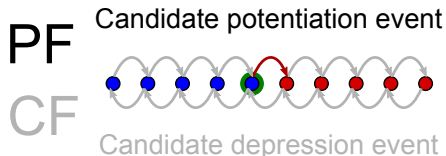
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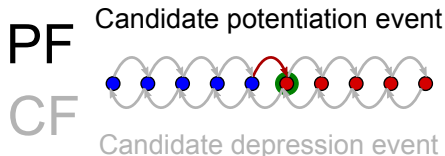


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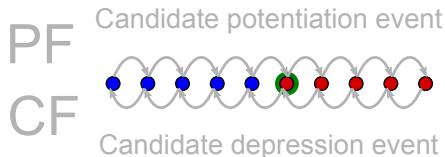


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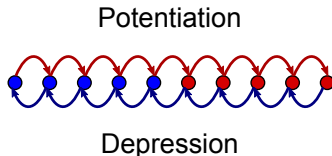


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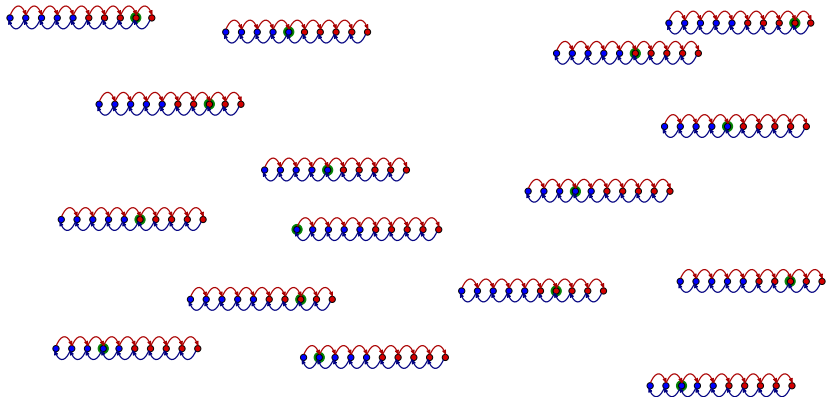
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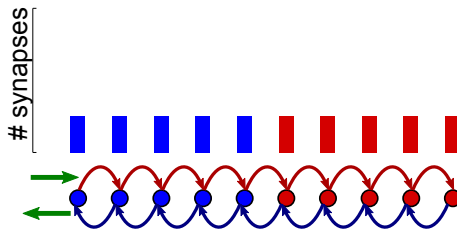


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Modelling VOR experiments

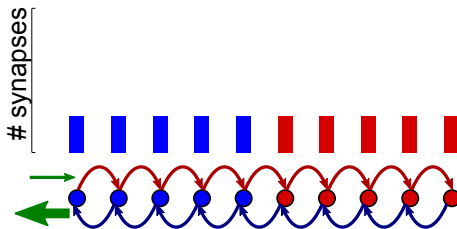


Modelling VOR experiments



Modelling VOR experiments

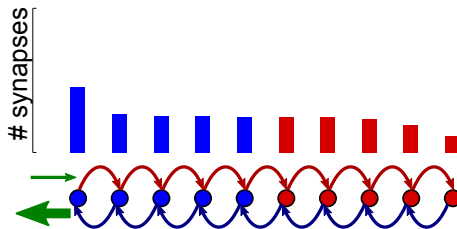
PF-Pk LTD \rightarrow VOR increase



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

Modelling VOR experiments

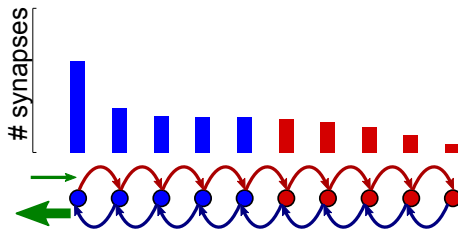
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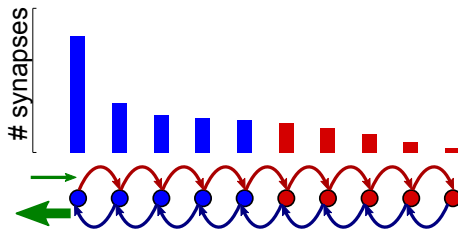
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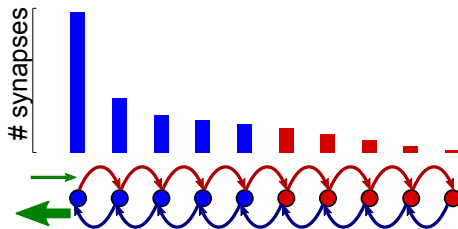
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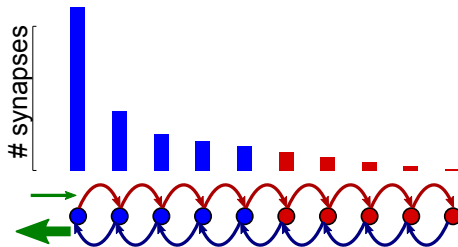
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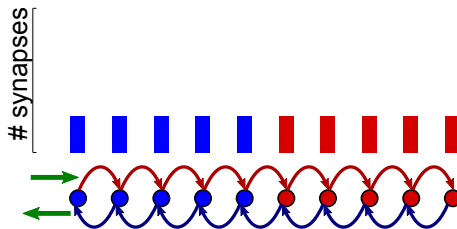


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Modelling VOR experiments

PF-Pk LTD \rightarrow VOR increase



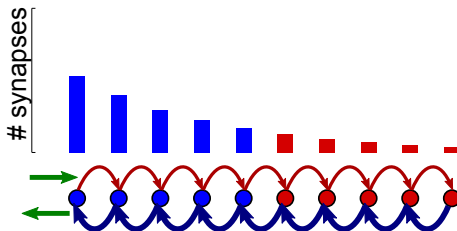
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Mutation: lower threshold for LTD \Rightarrow
increase transition probability for depression events.

Modelling VOR experiments

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change frequency of pot/dep events.

Learning: decrease in average synaptic weight.

Mutation: lower threshold for LTD \Rightarrow
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

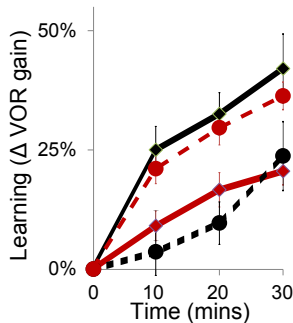
Big question: Why?

Simple synapses cannot explain the data

Multistate synapse

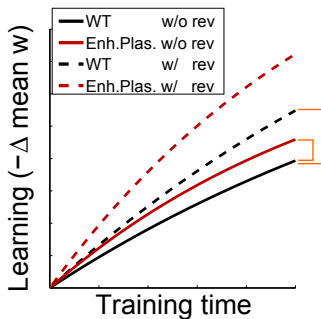


VOR Increase Training

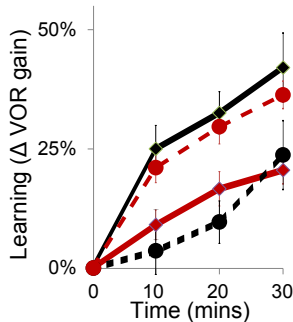


Simple synapses cannot explain the data

Binary synapse

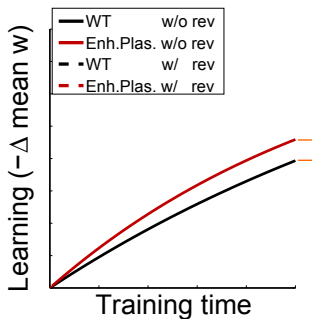
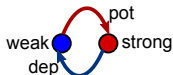


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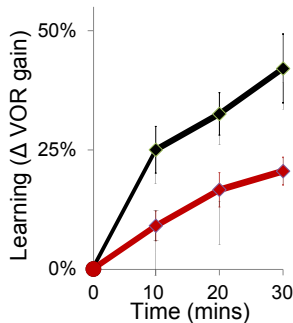


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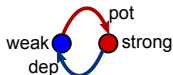


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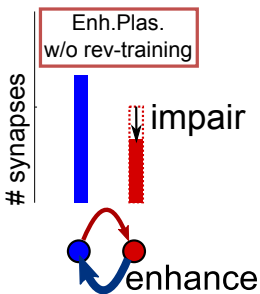


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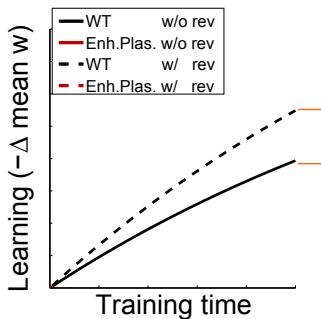
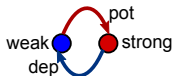
Initial distribution



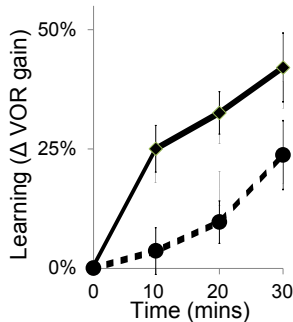
depletion effect
<
enhanced plasticity
 \Rightarrow enhanced learning

Simple synapses cannot explain the data

Binary synapse

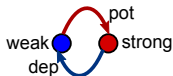


VOR Increase Training

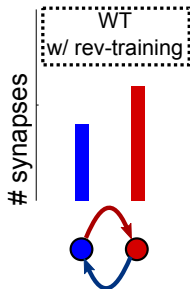


Simple synapses cannot explain the data

Binary synapse



Initial distribution



reverse training



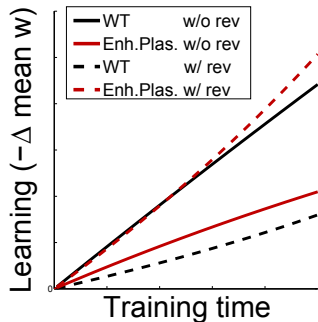
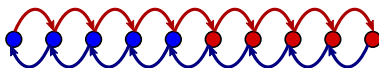
replenishment



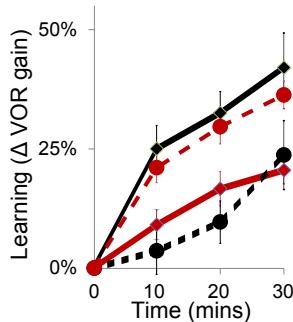
enhanced learning

Complex metaplastic synapses can explain the data

Serial synapse

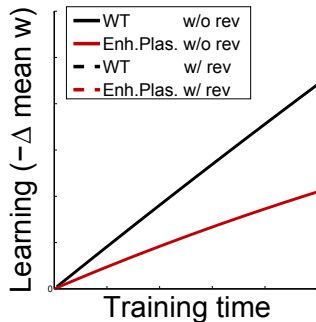
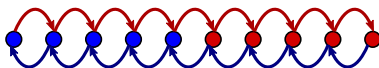


VOR Increase Training

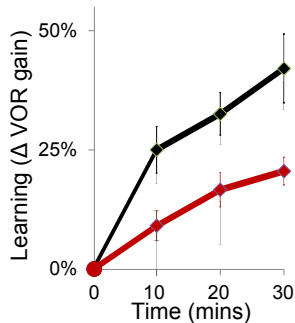


Complex metaplastic synapses can explain the data

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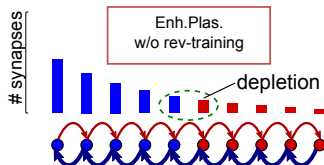
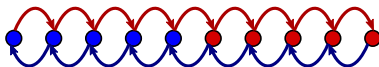


VOR Increase Training



Complex metaplastic synapses can explain the data

Serial synapse



amplified depletion

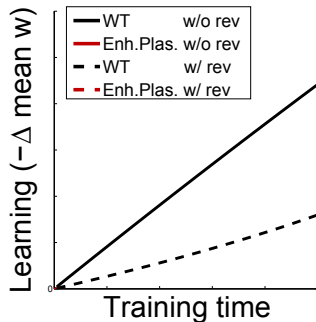
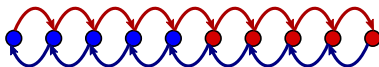
>

enhanced plasticity

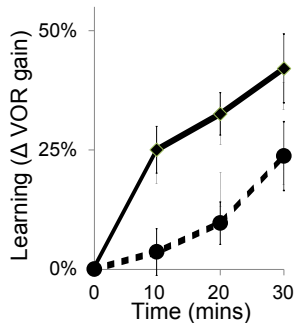
⇒ impaired learning

Complex metaplastic synapses can explain the data

Serial synapse

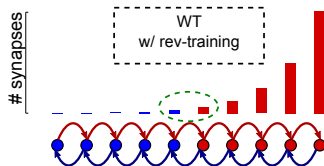
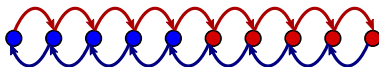


VOR Increase Training



Complex metaplastic synapses can explain the data

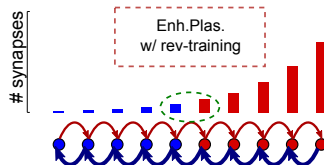
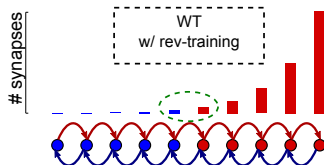
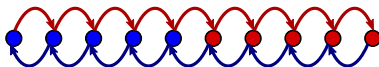
Serial synapse



reverse training
+
“stubborn” metaplasticity
⇒ impaired learning

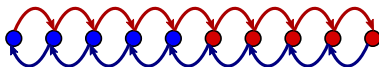
Complex metaplastic synapses can explain the data

Serial synapse



Complex metaplastic synapses can explain the data

Serial synapse



starting point:
labile states



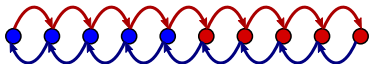
enhanced plasticity
 \Rightarrow impaired learning

starting point:
stubborn states



enhanced plasticity
 \Rightarrow enhanced learning

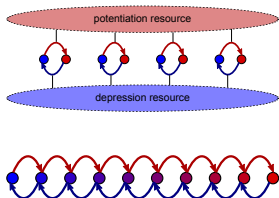
Essential features



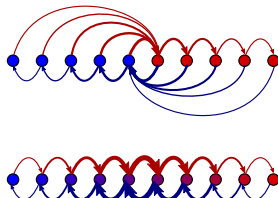
The success of the serial model relies on two features:

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

Fail:



Succeed:



Conclusions

- Diverse behavioural patterns:
Enhanced plasticity → enhance/impair learning (prior experience).
Reverse-training → enhance/impair learning (plasticity rates).
- enhanced LTD vs. depletion → learning outcome.
- Predictions for synaptic physiology:
Complexity: necessary to amplify depletion.
Stubbornness: repeated potentiation impairs subsequent depression.
- We used behaviour to constrain the dynamics of synaptic plasticity.



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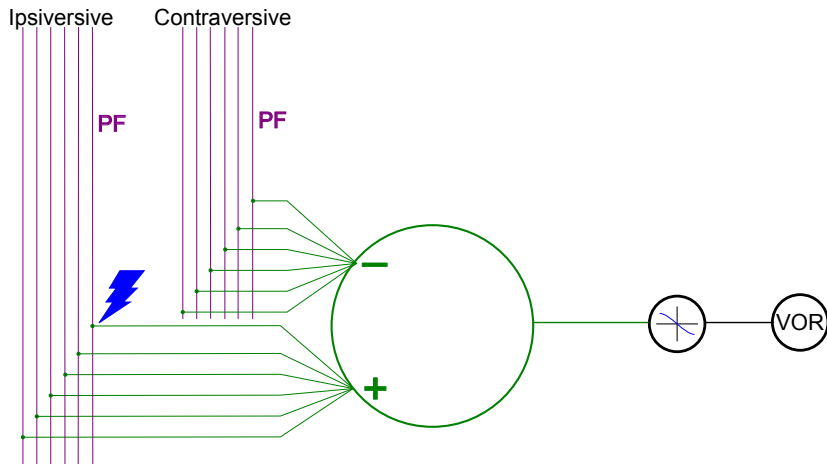
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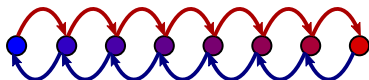
Funding: Swartz Foundation, Stanford Bio-X Genentech fellowship.

Model of circuit

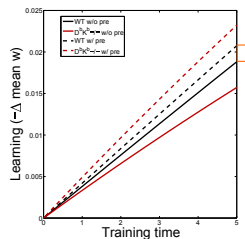
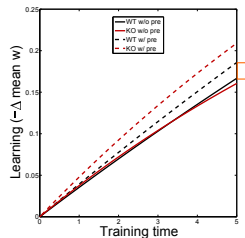
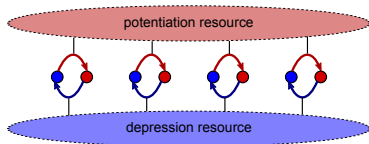


Other models that fail

Multistate synapse



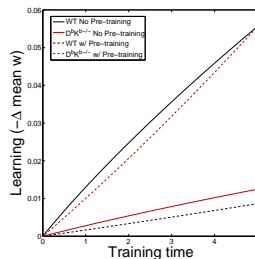
Pooled resource model



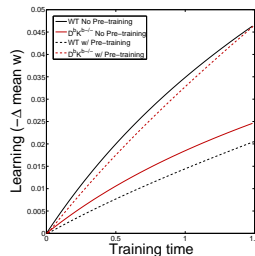
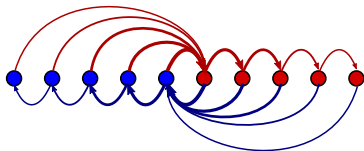
[Amit and Fusi (1994)]

Other models that work

Non-uniform multistate model

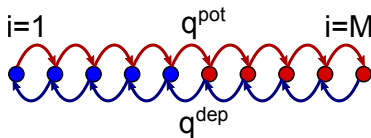


Cascade model



[Fusi et al. (2005)]

Mathematical explanation



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

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

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

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

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