Modeling impaired and enhanced learning with enhanced plasticity

based on work with: T.D. Barbara Nguyen-Vu, Grace Q. Zhao, Aparna Suvrathan, Han-Mi Lee, Surya Ganguli, Carla J. Shatz, Jennifer L. Raymond

Subhaneil Lahiri

Stanford University, Applied Physics

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1. Acknowledge Barbara and Grace

Introduction

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

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1. It does help in some cases
2. Want to understand when and why
3. Depends on circumstance. Rich pattern of behaviour
4. Develop understanding of when and why learning is enhanced/impaired

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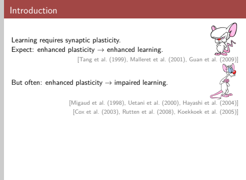
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Mice with enhanced cerebellar plasticity can show both impaired and enhanced learning.

Simple synapses cannot explain behaviour.
→ Necessary & sufficient conditions on complex synapses to replicate it.

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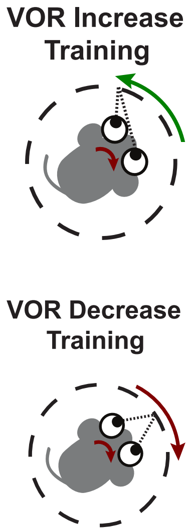
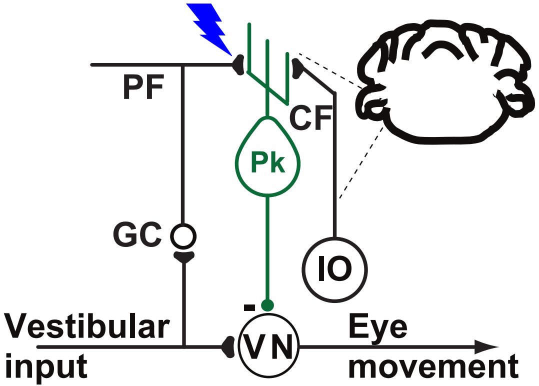
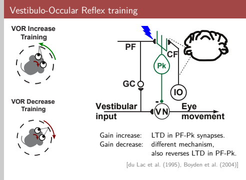
Vestibulo-Occular Reflex training





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)]



1. Explain what VOR gain is
2. trick brain into thinking VOR gain needs adjusting my moving visual stimulu
3. anti-phase → increase gain
4. in phase → decrease gain
5. Gain change involves cerebellum
6. If we enhanced plasticity here: expect enhanced learning

Enhanced plasticity impairs learning

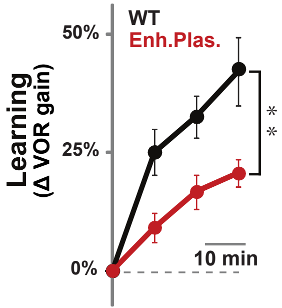
Knockout of MHC-I D^bK^b molecules in PF-Pk synapses

[McConnell et al. (2009)]

$\rightarrow$ lower threshold for LTD $\rightarrow$ enhanced plasticity

$\downarrow$

Hypothesis: enhanced learning.



Experiment: enhanced plasticity $\rightarrow$ impaired learning.

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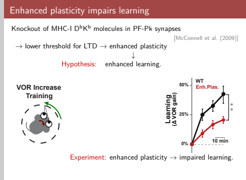
Impaired/enhanced learning w/ enhanced plasticity

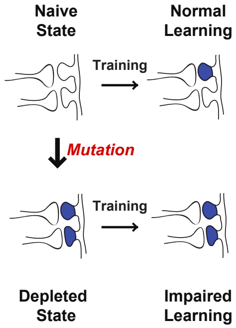
└Enhanced plasticity impairs learning



1. Major Histocompatibility Complex - involved in synaptic plasticity (Carla Shatz lab)
2. Easier LTD $\rightarrow$ expect better learning
3. Impairment of learning
4. Looking at change of VOR gain during gain-up training

Depletion hypothesis

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



Question 1: Can depletion effect overcome enhanced intrinsic plasticity?

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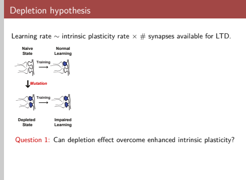
Impaired/enhanced learning w/ enhanced plasticity

└Depletion hypothesis



1. Our model: baseline activity $\to$ saturation $\to$ less depression possible
2. Saturation has to compete with enhanced plsaticity. Which will win?

Depletion hypothesis

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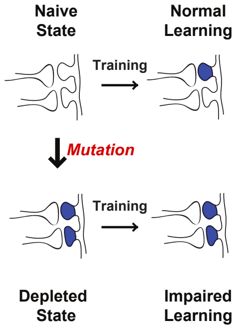
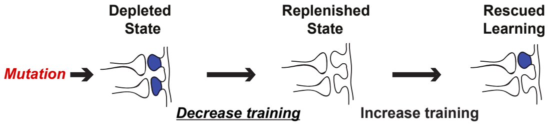


Other tests:

- Mimic depletion with ChR2 stim of CF
- Biochemical marker of LTD



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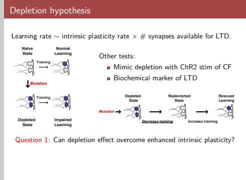
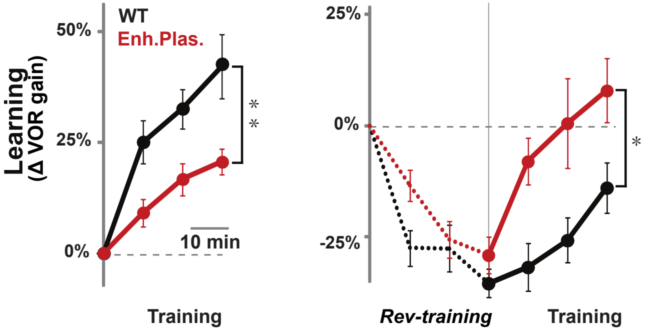


1. Our model: baseline activity $\rightarrow$ saturation $\rightarrow$ less depression possible
2. Saturation has to compete with enhanced plsaticity. Which will win?
3. Prediction: replenish with rev-training $\rightarrow$ rescue

Replenishment by reverse-training



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Impaired/enhanced learning w/ enhanced plasticity

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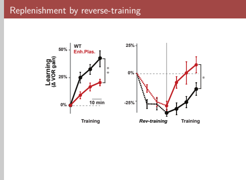
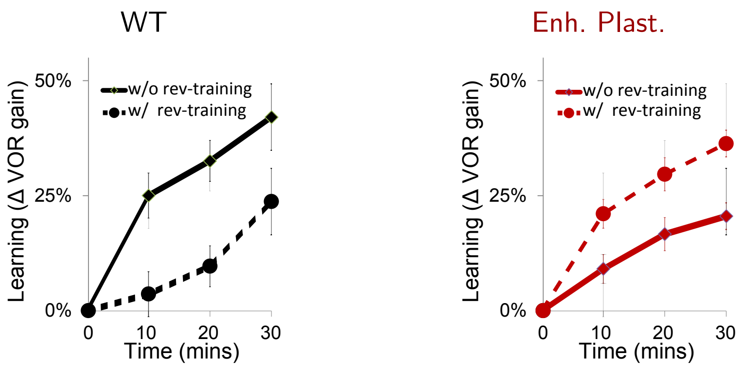


1. precede gain inc training w/ gain dec rev-training: reverses LTD
2. but behaviour from elsewhere → not modelled
3. Focus on gain inc part

Replenishment by reverse-training



Question 2: How can *too much* replenishment impair learning?

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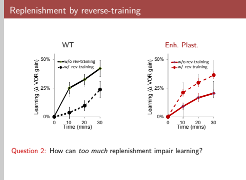
Impaired/enhanced learning w/ enhanced plasticity

└─Replenishment by reverse-training



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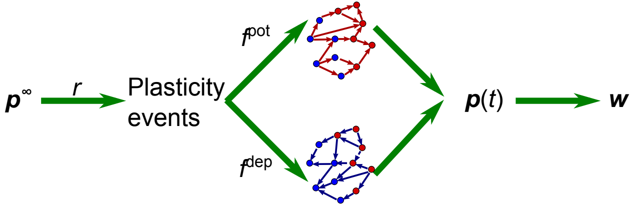
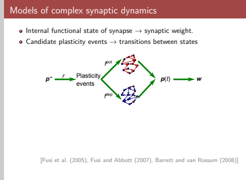
Models of complex synaptic dynamics

- Internal functional state of synapse $\to$ synaptic weight.
- Candidate plasticity events $\to$ transitions between states



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



1. complex synapse: not just synaptic weight. dynamical system
2. important for memory with bounded synapses
3. plasticity events at rate r. indep at each synapse.
4. fraction pot/dep
5. probs changed by Markov matrices, prob $i \to j$
6. Readout: synaptic weight vec when in each state.

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- Internal functional state of synapse → synaptic weight.
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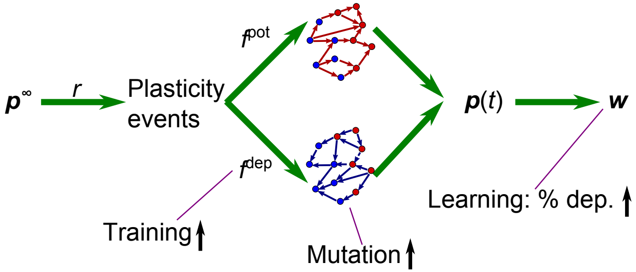
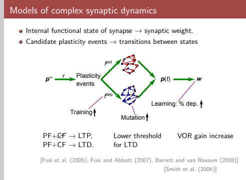


PF+~~CF~~ → LTP, PF+CF → LTD. Lower threshold for LTD VOR gain increase

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



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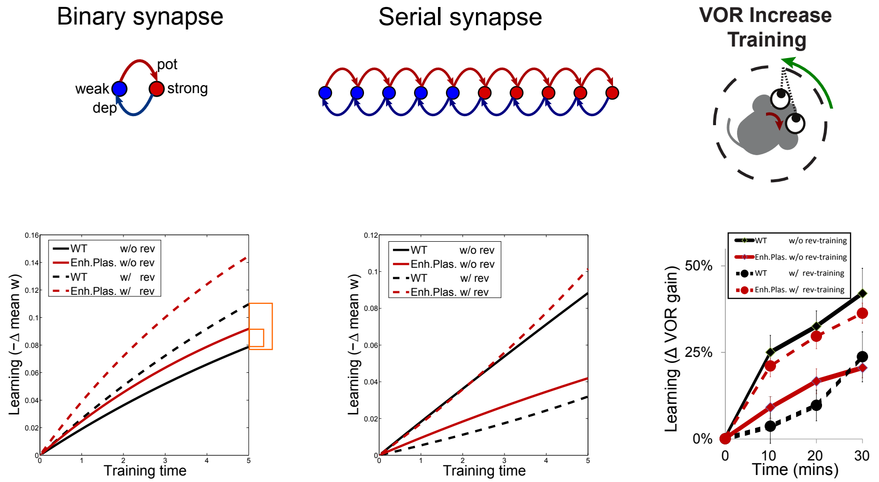
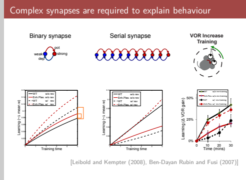
7. Mutation: lower threshold → increase transition probs
8. Training: Changes statistics of LTP/LTD. Only parameters we have. Don't care about r.
9. Learning: Only output we have. Don't keep track of synaptic identity.

Complex synapses are required to explain behaviour

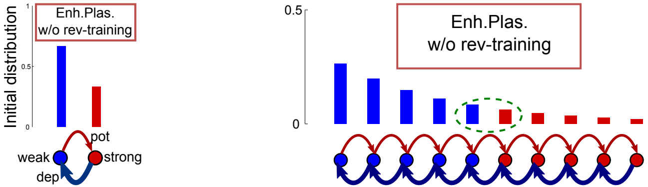


[Leibold and Kempter (2008), Ben-Dayan Rubin and Fusi (2007)]



1. Binary fails – mathematical proof for any params
2. Enh.Plas: faster depression wins over bias
3. pre: reduces/reverses bias. always helps.
4. Serial: still only two weights. Works.
5. Understand by looking at distributions before training

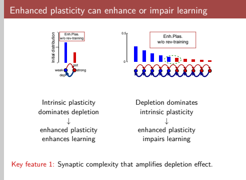
Enhanced plasticity can enhance or impair learning



Intrinsic plasticity dominates depletion
↓
enhanced plasticity enhances learning

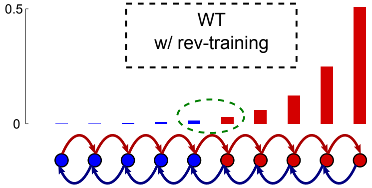
Depletion dominates intrinsic plasticity
↓
enhanced plasticity impairs learning

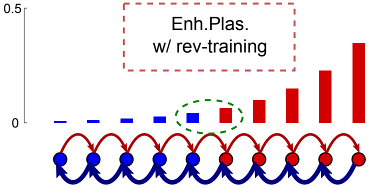
Key feature 1: Synaptic complexity that amplifies depletion effect.



1. Binary: enhanced plasticity $\to$ bias
2. Not enough to overcome faster depression
3. Serial: Only get signal from boundary
4. Exponential decay depopulates boundary, enhances effect of bias
5. borne out by other models

Reverse-training can impair or enhance learning





reverse-training
depopulates boundary
↓
impaired learning

reverse-training
repopulates boundary
↓
enhanced learning

Key feature 2: "Stubborn" metaplasticity.

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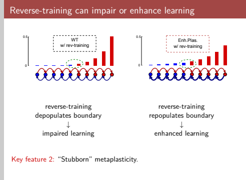
Impaired/enhanced learning w/ enhanced plasticity

└Reverse-training can impair or enhance learning



1. rev-training: little repopulates boundary
2. Too much pushes to other side, depopulates boundary
3. this effect is absent in any simple synapse
4. repeated potentiation makes subsequent depression harder
5. borne out by other models

Conclusions

- We find diverse behavioural patterns in these mutant mice:
  Enhanced plasticity $\rightarrow$ enhance/impair learning depending on prior experience.
  Reverse-training $\rightarrow$ 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

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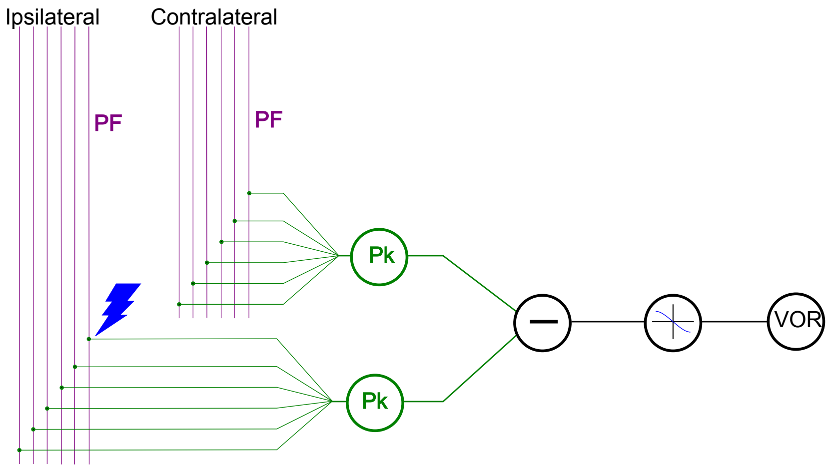
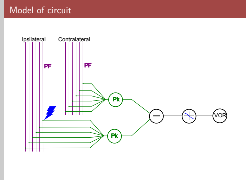
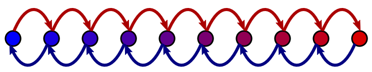
Model of circuit

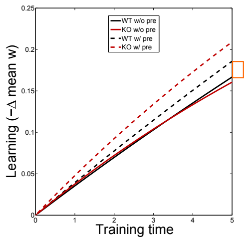




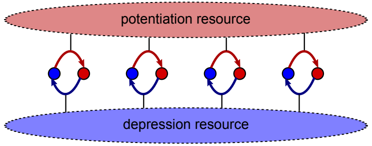
1. Contralateral baseline shift compensates for Our baseline shift
2. Gain increase due to LTD at lightning
3. Gain decease due to plasticity elsewhere, but also reverses LTD at lightning
4. Nonlinearity here won't affect our questions, as long as it doesn't change
5. Nonlinearity before compensation could change things

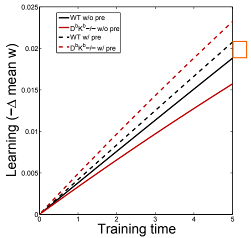
Multistate model



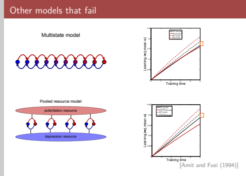


Pooled resource model





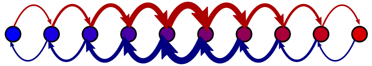
[Amit and Fusi (1994)]

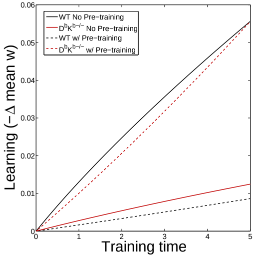


1. MS: linear weights, unlike serial.
2. like bunch of binary synapses in series.
3. solid curves: fails early on , but catches up quickly
4. black curves: fails badly
5. No real enhancement of saturation, no metaplasticity.
6. All transitions contribute: pushing to end has little effect.
7. Pooled: resource depleted by pot/dep. replenished by reverse.
8. solid curves succeed: enhanced saturation
9. black curves fail: opposite metaplasticity, pot makes dep easier

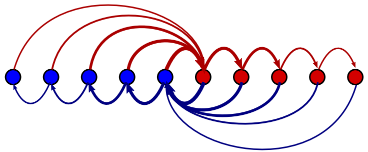
Other models that work

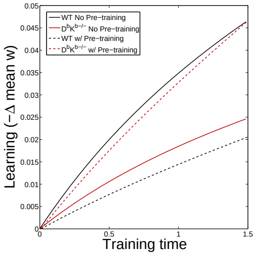
Non-uniform multistate model



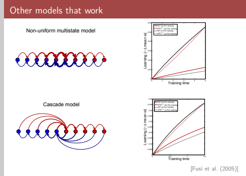


Cascade model





[Fusi et al. (2005)]



1. Both models, trans probs decay exponentially from centre.
2. Nonuni: linear weights. Cascade: binary weights.
3. Enhanced saturation and metaplasticity
4. Pushing to end makes pot and dep harder
5. Note: hidden states not necessary