A saturation model for impaired learning with enhanced plasticity

based on work in preparation by: T.D. Barbara Nguyen-Vu, Grace Q. Zhao, Han-Mi Lee, SL, Surya Ganguli, Carla J. Shatz, Jennifer L. Raymond

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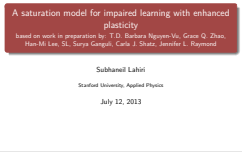
July 12, 2013



1. Acknowledge Barbara and Grace

Introduction

One might expect enhanced plasticity to enhance learning. But often it actually causes impairment.

We argue that this impaired learning is due to basal activity biasing the synapses prior to learning, leaving fewer synapses available for further plasticity.

By analysing several models of complex synapses, we see that the behaviour of enhanced LTD mice in a motor learning task can constrain the synaptic structure.

1. It does help in some cases

Introduction

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Outline

1. VOR learning and the cerebellum
2. The effects of enhanced plasticity and saturation
3. Modelling approach
4. Modelling results

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VOR learning and the cerebellum
The effects of enhanced plasticity and saturation
Modelling approach
Modelling results

Section 1

VOR learning and the cerebellum

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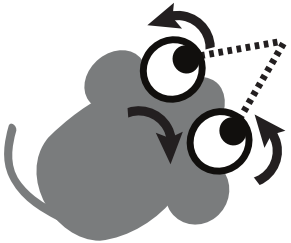
VOR learning and the cerebellum

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.

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

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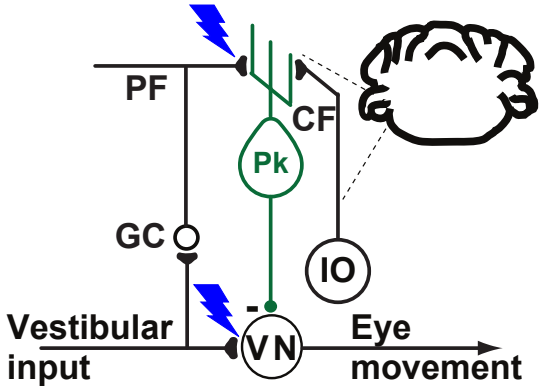
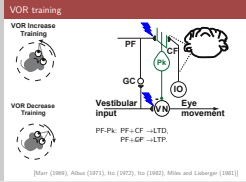
VOR training



PF-Pk: PF+CF →LTD,
PF+~~CF~~ →LTP.

[Marr (1969), Albus (1971), Ito (1972), Ito (1982), Miles and Lisberger (1981)]



1. trick brain into thinking VOR gain needs adjusting my moving visual stimulu
2. anti-phase →increase gain
3. in phase →decrease gain
4. Gain change involves cerebellum
5. Marr-Albus-Ito: Pf-Pk synapses
6. Lisberger-Miles: Vestibular input-VN synapses
7. Different mechs for different freq, head angle, gain up/down.
8. Different Pk cells have different tunings.
9. Gain up in case of interest: LTD in Pf-Pk in flocculus
10. Gain down: uses different mech for behaviour, but does reverse LTD in Pf-Pk in flocculus

Section 2

The effects of enhanced plasticity and saturation

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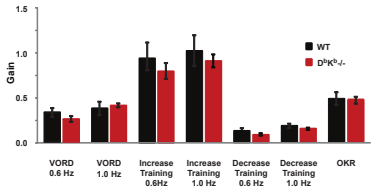
The effects of enhanced plasticity and saturation

MHC-I D^bK^b – /– knockout

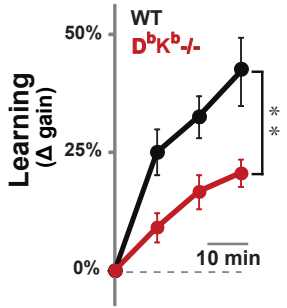
Knockout of molecules lowers threshold for LTD in PF-Pk synapses.

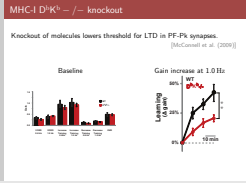
[McConnell et al. (2009)]

Baseline



Gain increase at 1.0 Hz

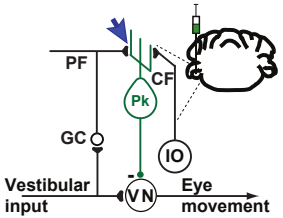


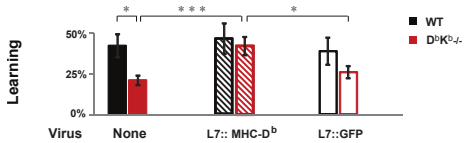


1. Easier LTD →expect better learning
2. No difference at baseline
3. Impairment of learning

Viral rescue removes defect

Local injection of Pk specific virus used to restore the knocked-out molecules.





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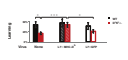
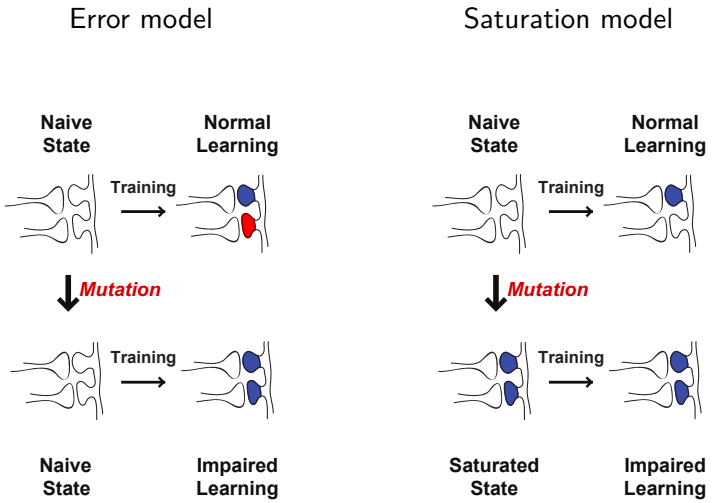
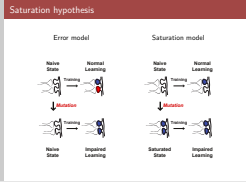


1. removes defect
2. tells us that it is these PF-Pk synapses that are important
3. But what mechanism?

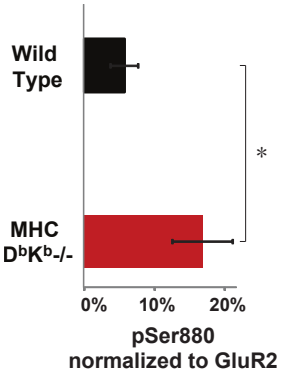
Saturation hypothesis





1. Older explanation: error model
2. Our model: baseline activity →saturation →less depression possible
3. Saturation has to compete with enhanced plsaticity. Which will win?

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.

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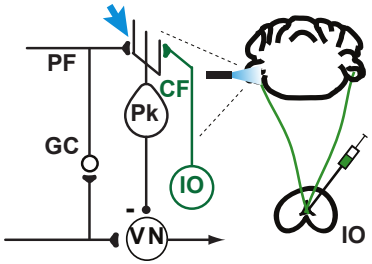
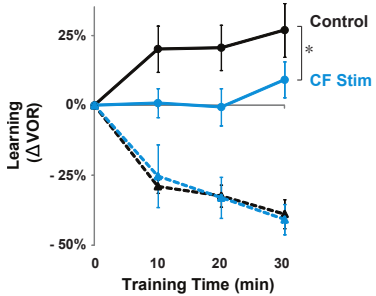
1. Predicted by saturation hypothesis

Evidence: saturation by CF stimulation

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





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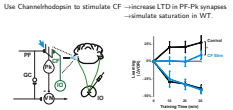
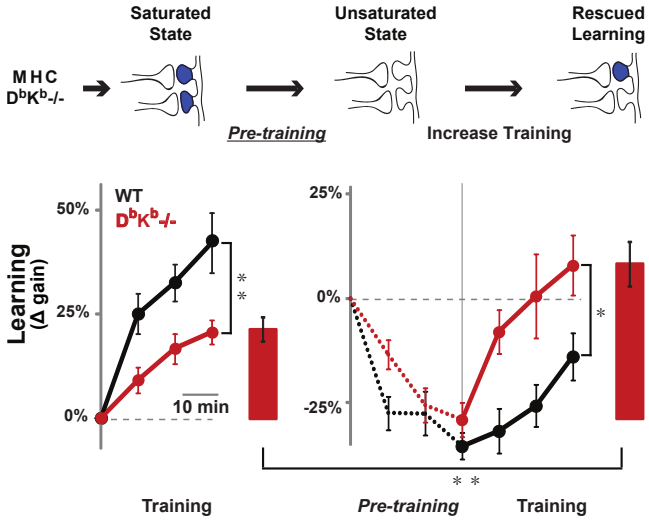
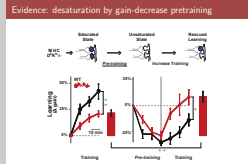


1. should result in similar behaviour to KO

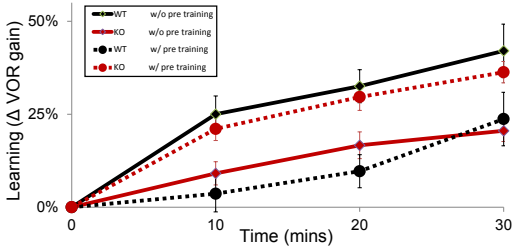
Evidence: desaturation by gain-decrease pretraining

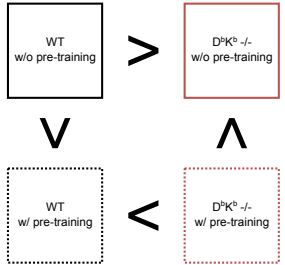




1. gain dec reverses LTD
2. but behaviour from elsewhere

Summary of training results





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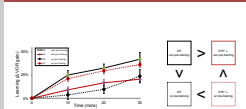

1. Restricted to gain inc for comparison
2. Black: WT. Red: KO
3. Solid: no pre. Dashed: with pre
4. Horz and vert comparisons: conceptual
5. Diagonal comparisons: paramter fitting. Depend on size of KO vs. pretraining
6. KO hurts w/o, but helps w/
7. pre helps KO but hurts WT
8. top and left most restrictive
9. Pay attention to solid: black above red
10. Pay attention to black: solid above dashed
11. Concentrate on initial slope

Questions

- Can the saturation effect overcome the enhanced plasticity?
- How can a little reverse bias help, but too much hurt?
- Can we find a purely synaptic explanation of these results?

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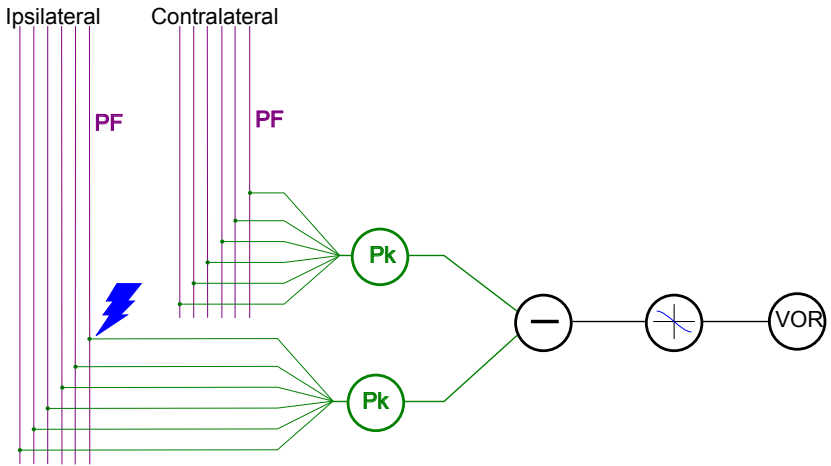
- Can we find a purely synaptic explanation of these results?

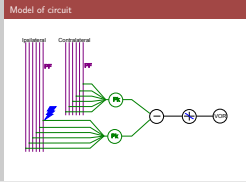
1. in competition
2. first makes sense, but second?
3. This is a question about synaptic populations after all.

Section 3

Modelling approach

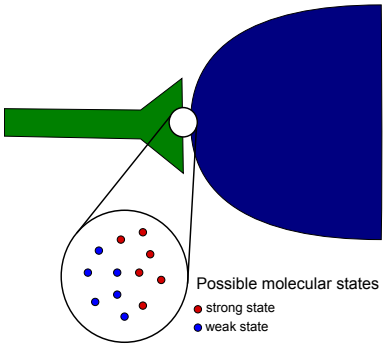
Model of circuit

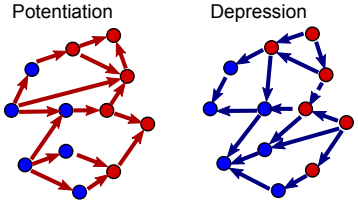


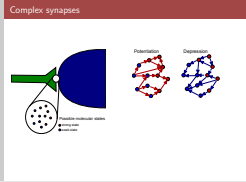


1. Contralateral baseline shift compensates for Our baseline shift
2. Gain increase due to LTD at lightning
3. Gain decease due to plasticity elsewhere, but also reverses LTD at lightning
4. Nonlinearity here won't affect our questions, as long as it doesn't change
5. Nonlinearity before compensation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

Complex synapses







1. functional states, not molecules
2. synaptic weight depends on state
3. many states can have same weight
4. stochastic transitions

Simplifying assumptions

- No spatial/temporal correlations in plasticity events.
- Potentiating/depressing plasticity events $\sim$ Poisson processes.
- Potentiation and depression are described by Markov processes.

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

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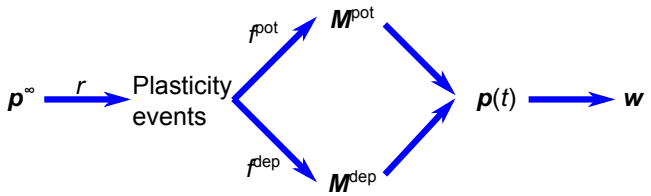
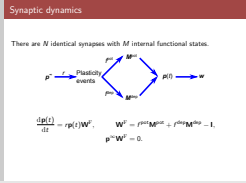
1. allows us to concentrate on synapse, not neuron/network
2. No filing system
3. don't care if STDP...

Synaptic dynamics

There are N identical synapses with M internal functional states.



$$\frac{\mathrm{d}\mathbf{p}(t)}{\mathrm{d}t} = r\mathbf{p}(t)\mathbf{W}^{\mathrm{F}}, \qquad \mathbf{W}^{\mathrm{F}} = f^{\mathrm{pot}}\mathbf{M}^{\mathrm{pot}} + f^{\mathrm{dep}}\mathbf{M}^{\mathrm{dep}} - \mathbf{I},$$
$$\mathbf{p}^{\infty}\mathbf{W}^{\mathrm{F}} = 0.$$



1. stoch process has steady state.
2. Prior activity puts it in this state. row vec.
3. plasticity events at rate r
4. fraction pot/dep
5. probs changed by Markov matrices, prob $i \to j$
6. Readout: synaptic weight vec when in each state.
7. Memory at $t = 0$, keep track of pot/dep
8. subsequent: average over pot/dep

Modelling VOR learning

Mutation: Changes mechanism of LTD $\Longrightarrow$ change $\mathbf{M}^{\text{dep}}$.

Training: Changes statistics of LTP/LTD $\Longrightarrow$ change $r, f^{\text{pot}}, f^{\text{dep}}$.

Learning: Change in VOR gain $\Longrightarrow$ fn. of decrease in $\langle \mathbf{w} \rangle$.

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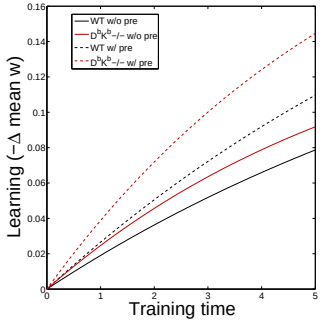
Mutation: Changes mechanism of LTD $\Longrightarrow$ change $\mathbf{M}^{\text{dep}}$.
Training: Changes statistics of LTP/LTD $\Longrightarrow$ change $r, f^{\text{pot}}, f^{\text{dep}}$.
Learning: Change in VOR gain $\Longrightarrow$ fn. of decrease in $\langle \mathbf{w} \rangle$.

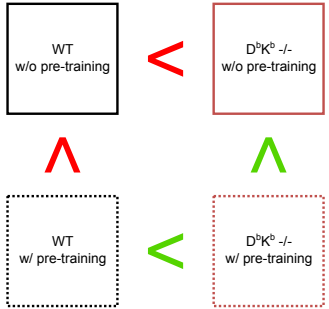
1. lower threshold $\rightarrow$increase off-diagonal elements.
2. Only parameters we have. Don't care about r.
3. Same PF+CF input $\rightarrow$same $r, f^{\text{pot}}, f^{\text{dep}}$ in each case.
4. Only output we have. Don't keep track of synaptic identity.
5. Input to Pk, some linear combination of $\mathbf{w}$'s.

Section 4

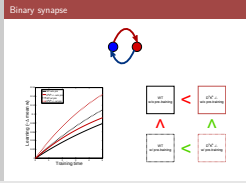
Modelling results

Binary synapse





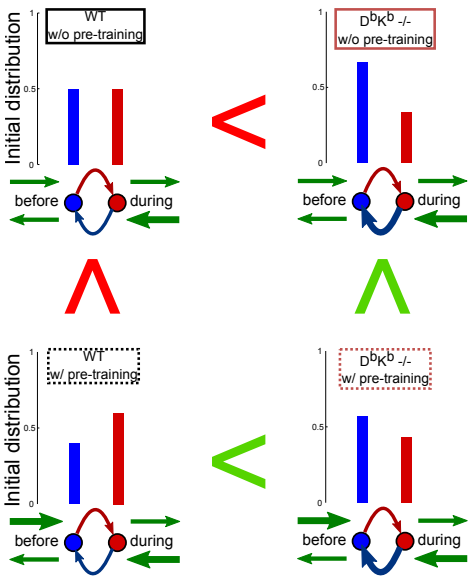
Binary synapse

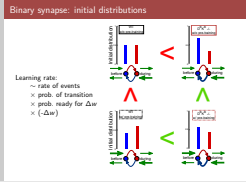


1. Compare solid curves
2. Compare black curves
3. understand why next slide

Binary synapse: initial distributions

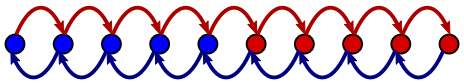
Learning rate:
- $\sim$ rate of events
- $\times$ prob. of transition
- $\times$ prob. ready for Δw
- $\times$ ($-\Delta w$)



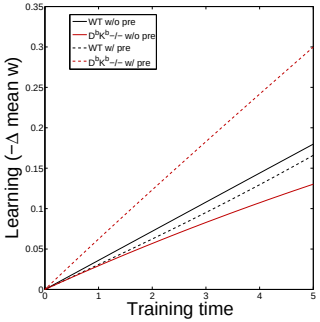


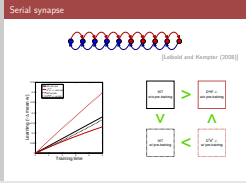
1. WT: start with everything equal – just for illustration, not essential
2. WT: during training, increase f^{dep} (green arrow) $\rightarrow$ weakening.
3. KO: inc $q^{\text{pot}} \rightarrow$ bias
4. KO: competition between inc prob trans & dec prob ready
5. KO: first one wins. see why after next model
6. pre: reduces/reverses bias. always helps.

Serial synapse



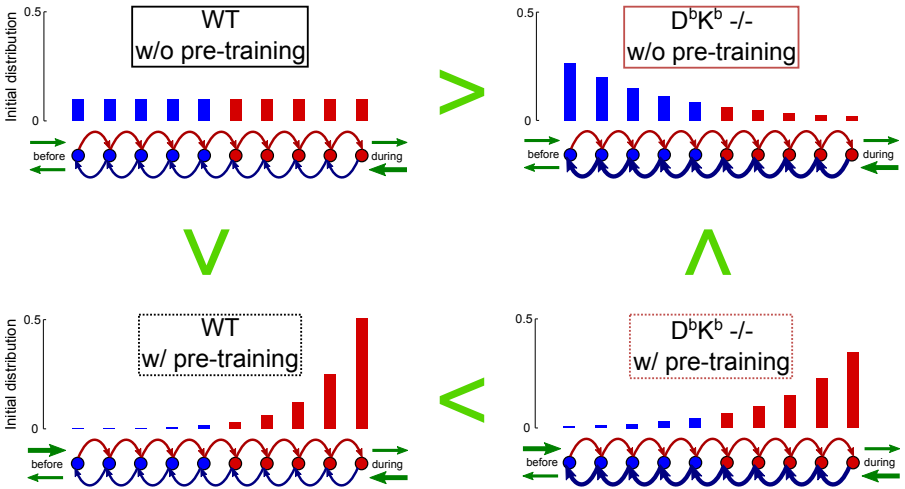
[Leibold and Kempter (2008)]

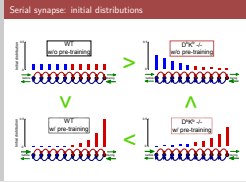




1. Still looks binary from outside. Hidden states (not essential).
2. Only see Δw at boundary.
3. understand why next slide

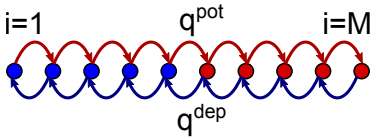
Serial synapse: initial distributions





1. Now only get signal from crossing boundary
2. KO: inc $q^{\text{pot}} \rightarrow$ bias, now exponential
3. KO: prob ready wins over prob trans, now exponential
4. pre: reduces/reverses bias.
5. pre: little reverse bias repopulates bndry, helps.
6. pre: too much reverse bias moves away from bndry, hurts.
7. maths next slide

Mathematical explanation



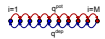
Serial synapse: $\mathbf{p}_i^\infty \sim \mathcal{N}\left(\frac{q^{pot}}{q^{dep}}\right)^i$.

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

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

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

Mathematical explanation



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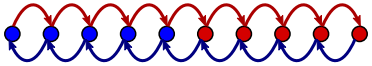
For $M = 2$: larger $q^{dep} \implies$ larger $\mathcal{N} \implies$ faster learning.

1. Detailed balance. Exponential decay.
2. for large enough M, q^{pot}, overcome $\mathcal{N}$
3. Other factor in $\mathbf{p}^\infty$ smaller $\implies$ $\mathcal{N}$ larger.

Essential features



The success of the serial model relies on two features:

- Enhancing the effect of saturation,
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Essential features
The success of the serial model relies on two features:
- Enhancing the effect of saturation,
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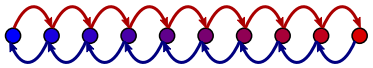
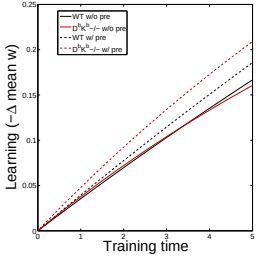
1. due to exponential decay
2. push away from boundary where signal generated
3. borne out by other models that fail/succeed

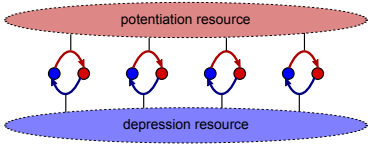
Other models that fail

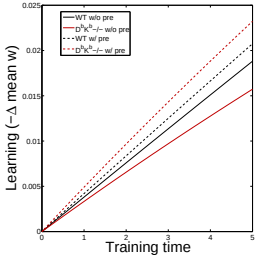
Multistate model



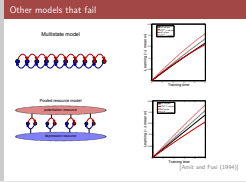


Pooled resource model





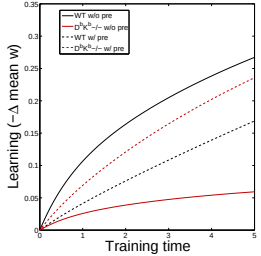
[Amit and Fusi (1994)]



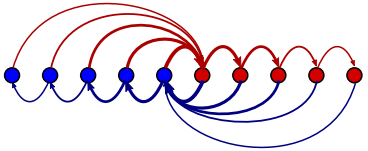
1. MS: linear weights, unlike serial.
2. like bunch of binary synapses in series.
3. solid curves: fails early on , but catches up quickly
4. black curves: fails badly
5. No real enhancement of saturation, no metaplasticity.
6. All transitions contribute: pushing to end has little effect.
7. Pooled: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

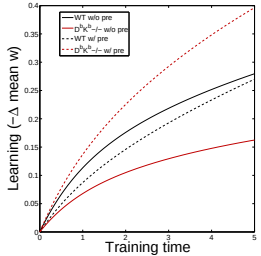
Other models that work

Non-uniform multistate model

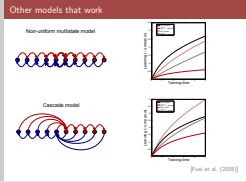


Cascade model





[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

Conclusions and further questions

- The saturation effect overcome the enhanced plasticity, if it is enhanced. Requires complexity
- A little reverse bias can help, but too much hurts, if repeated potentiation makes depression harder. Requires metaplasticity
- We can find a purely synaptic explanation of VOR behaviour, iff the synapses have these features.
- We used behaviour to constrain molecular structure of synapses!
- Can we constrain it further with more experiments?

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- The saturation effect overcome the enhanced plasticity, if it is enhanced. Requires complexity
- A little reverse bias can help, but too much hurts, if repeated potentiation makes depression harder. Requires metaplasticity
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- We used behaviour to constrain molecular structure of synapses!
- Can we constrain it further with more experiments?

1. e.g. exponential deacy, resource depletion,...
2. e.g. moving away from weight boundary, or weaker transitions.
3. Other explanations? Non-linearity in PK cell?

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