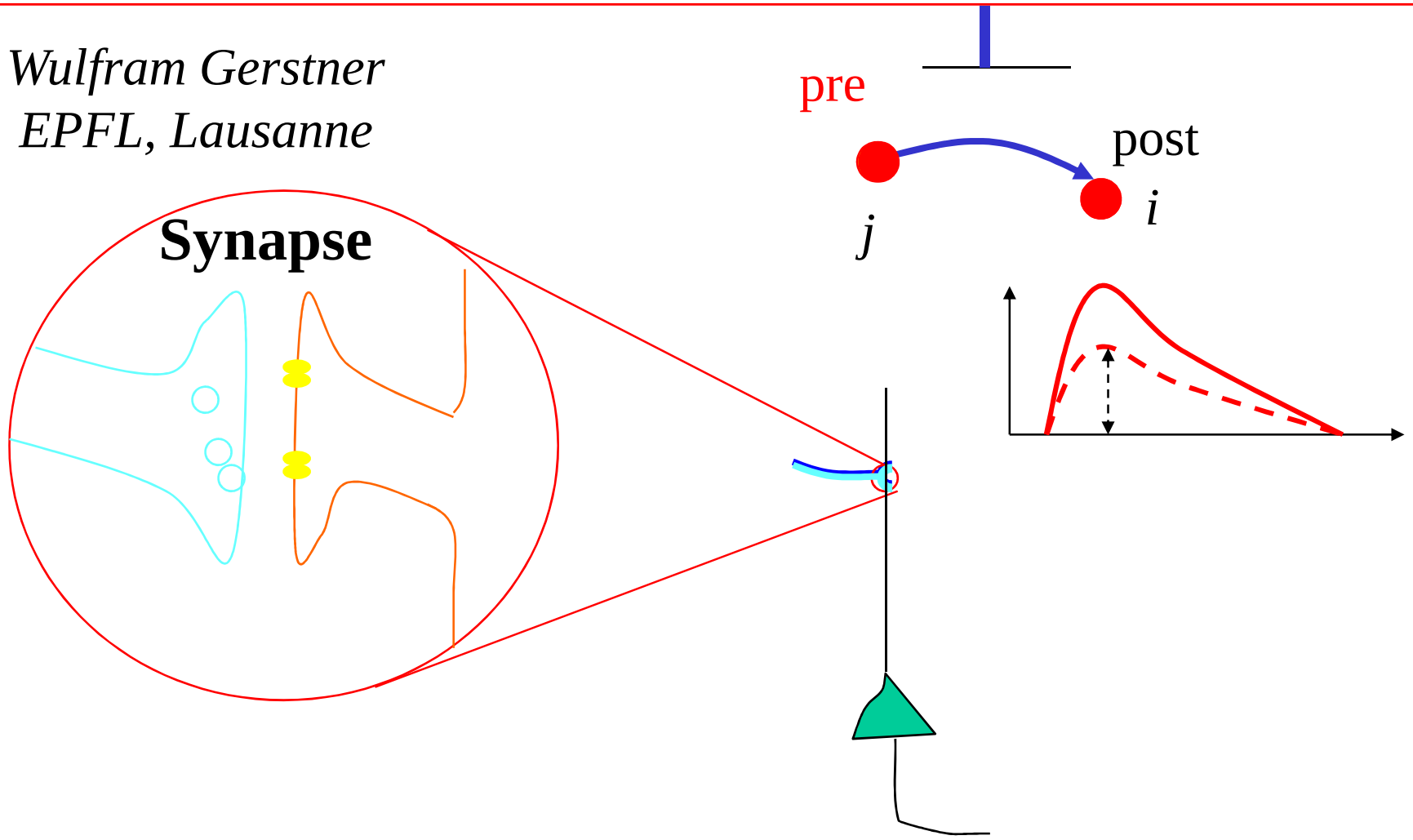
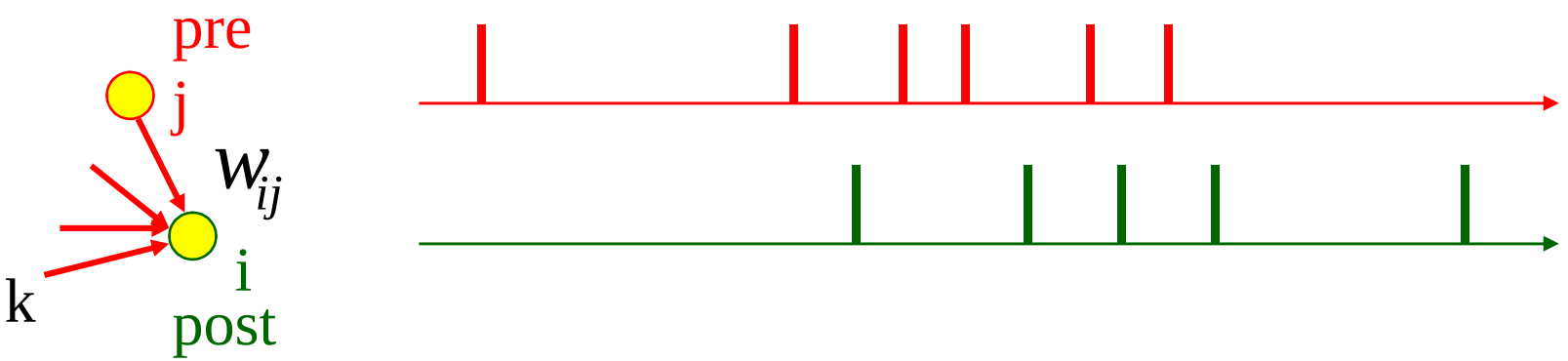
Tag-Trigger-Consolidation:
Modeling synaptic plasticity across different time scales

Wulfram Gerstner
EPFL, Lausanne



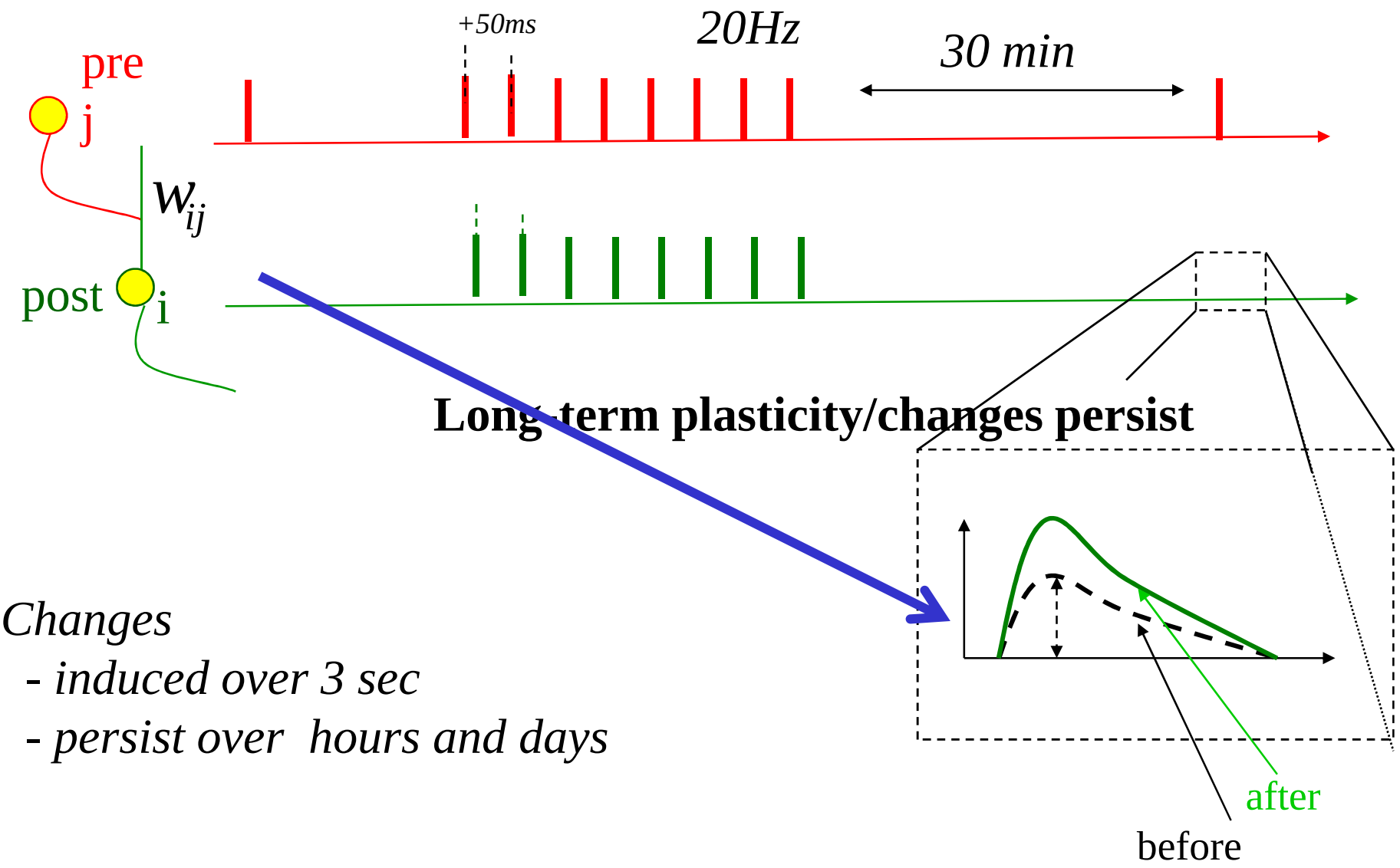
Hebbian Learning



*When an axon of cell **j** repeatedly or persistently takes part in firing cell **i**, then j's efficiency as one of the cells firing i is increased*

Hebb, 1949

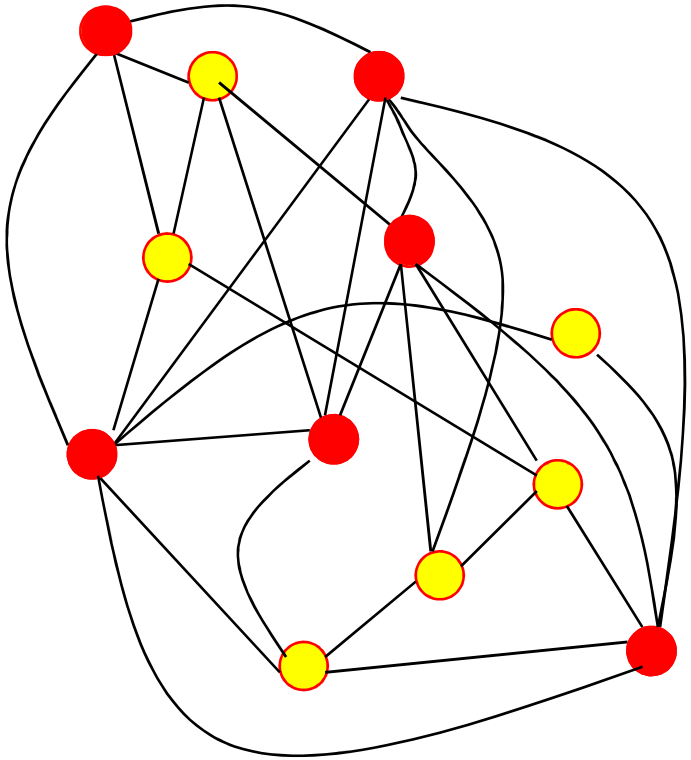
Hebbian learning and LTP



Changes

- *induced over 3 sec*
- *persist over hours and days*

Hebbian Learning



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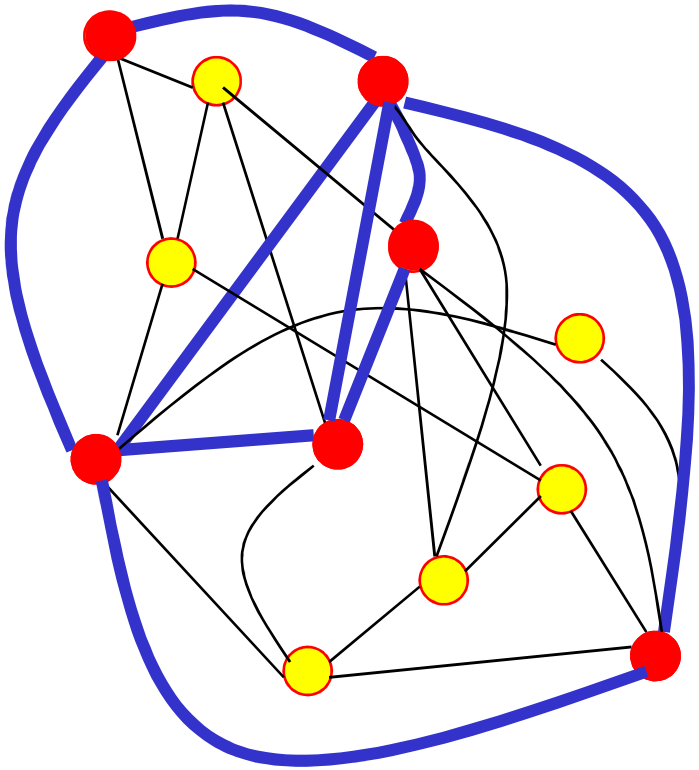
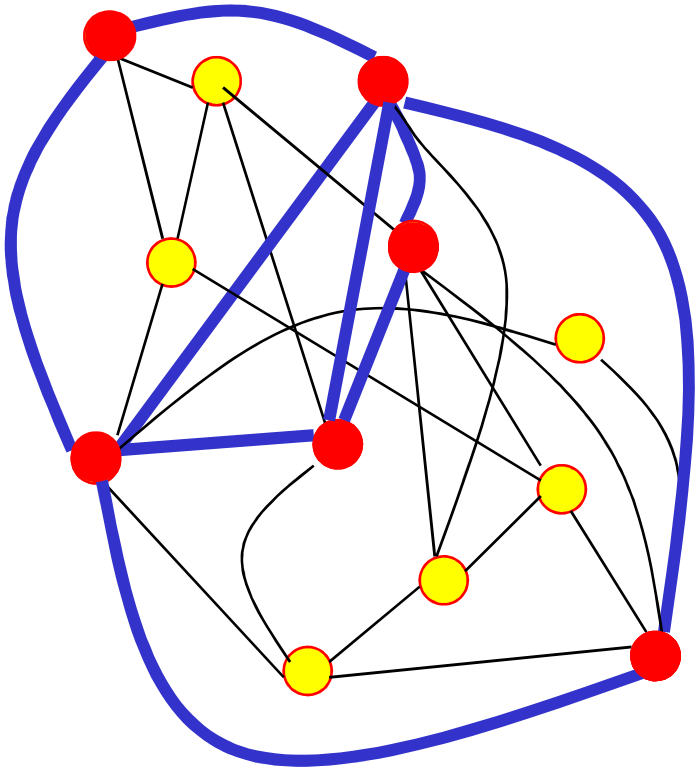


item memorized

Hebbian Learning

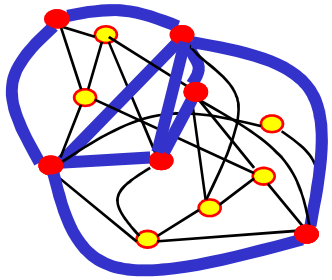
Recall:
Partial info



item recalled

Hebbian Learning: Functional Postulates

1) Useful for memory



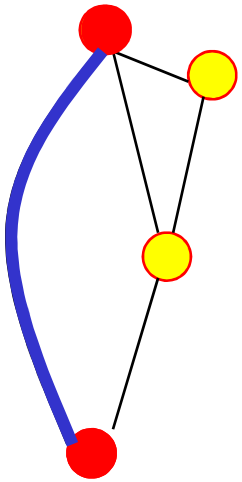
Examples: Hopfield model, associative memory models

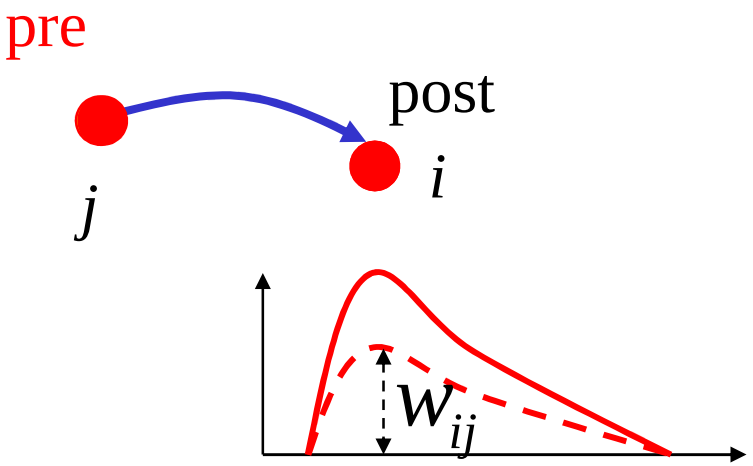
My problem:

Existing models of Hebbian learning and associative memory describe only induction of synaptic changes but not consolidation/maintenance

Examples: Hopfield model, attractor networks –
learning happens in a separate epoch, then synapses fixed
(except Amit and Fusi 1994, Fusi et al. 2000, 2006, Lisman 1989, … 2004)

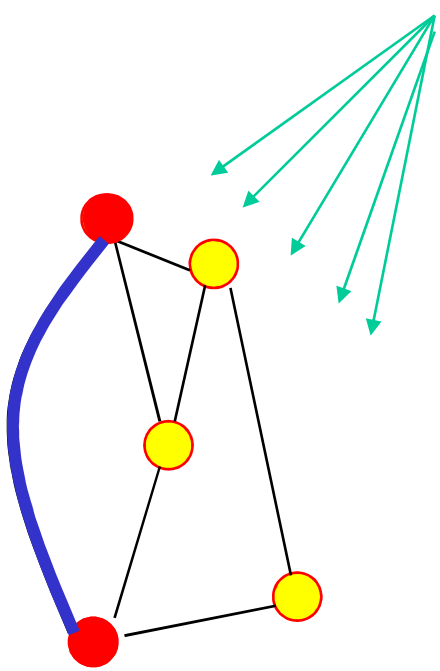
Hebbian Learning
= unsupervised learning





$$\Delta w_{ij} \propto F(pre, post)$$

Reinforcement Learning
= reward + Hebb



$$\Delta w_{ij} \propto F(pre, post, SUCCESS)$$

local global

My problem (2):
Existing models of Hebbian learning and associative memory do not take into account Neuromodulators/cannot describe success

Except: e.g. Schultz et al. 1997, Izhikevich, 2007

Tag-Trigger-Consolidation:
A model of early and late LTP/LTD

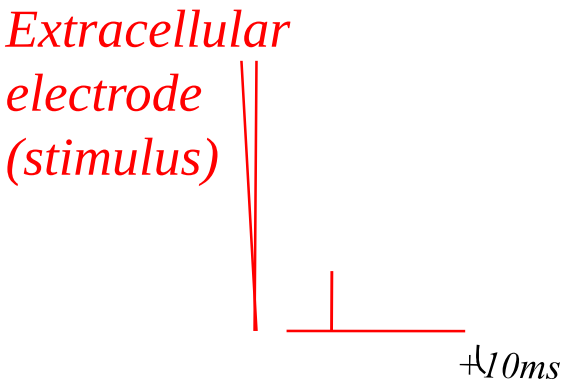
√ *Introduction*

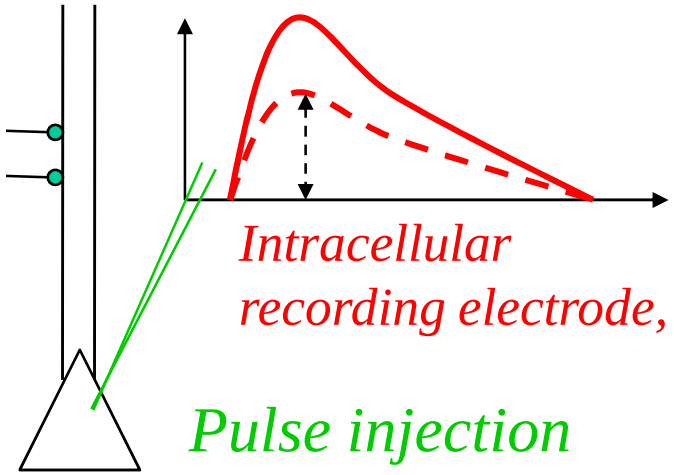
Review of induction protocols

TagTriC model (Tag-Trigger-Consolidation)

- *Model assumptions*
- *Model componenets*
- *Results*

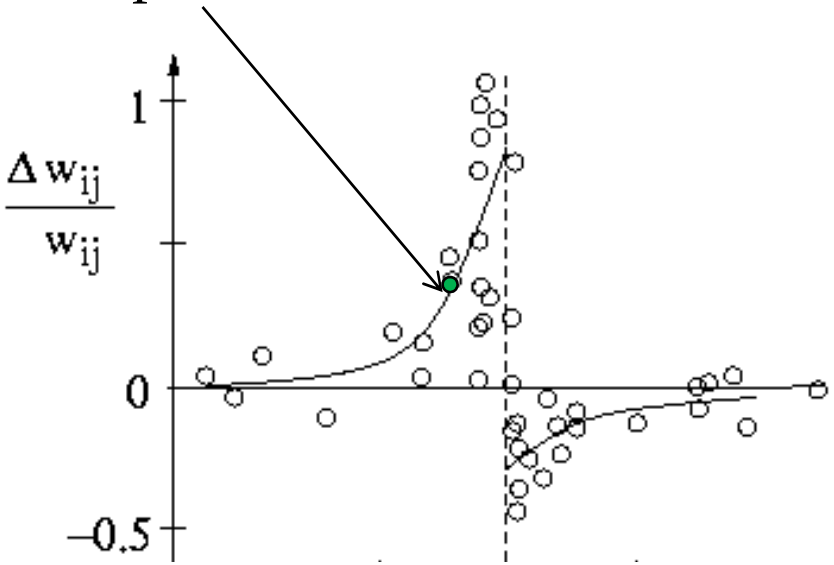
Experimental induction protocols (1)

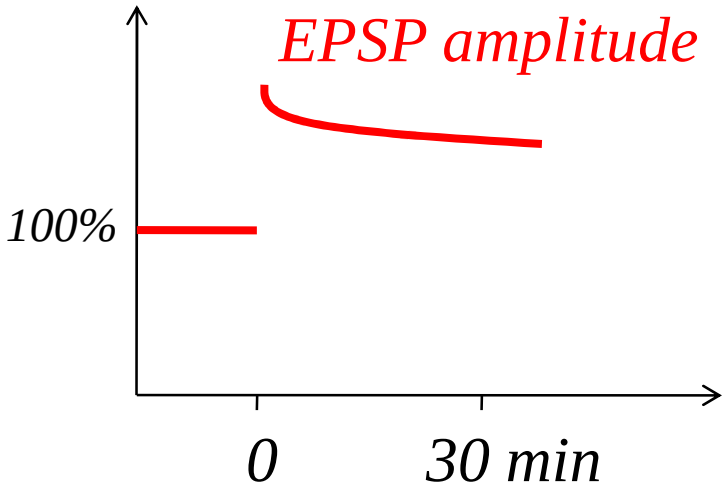




Hebbian interpretation:

Pre-post = causal relation

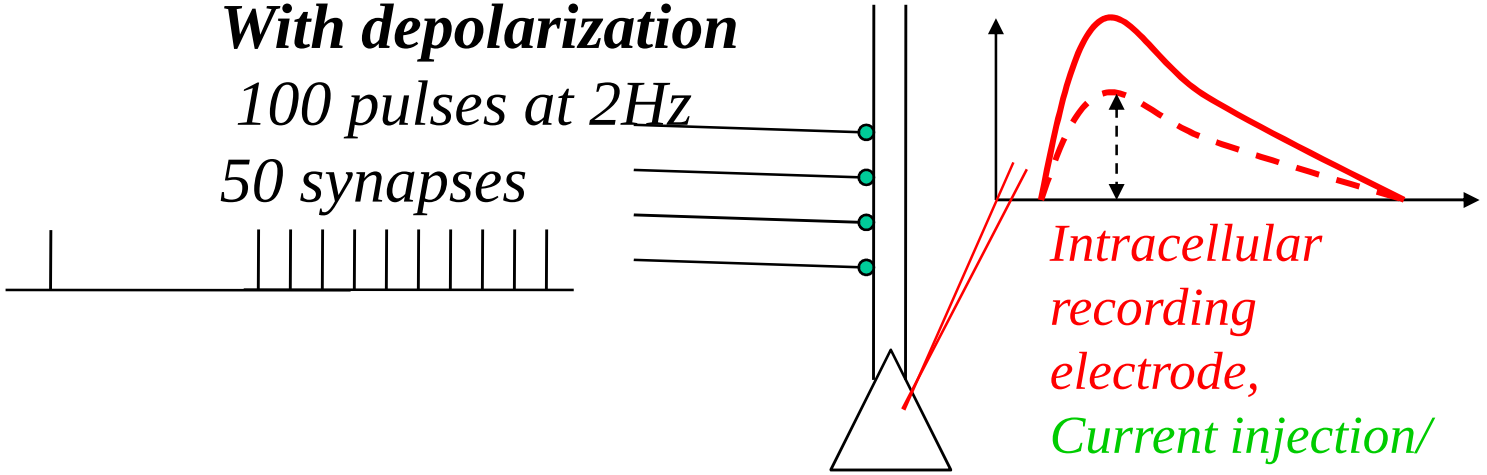




Experimental induction protocols (2)

Low-frequency paired
With depolarization
100 pulses at 2Hz
50 synapses

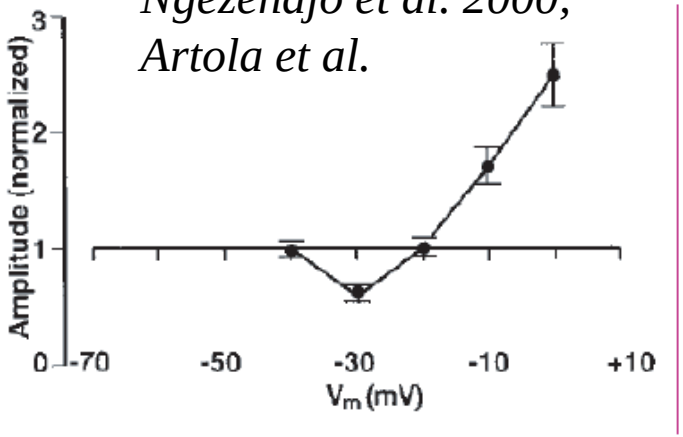
Extracellular electrode (stimulus)

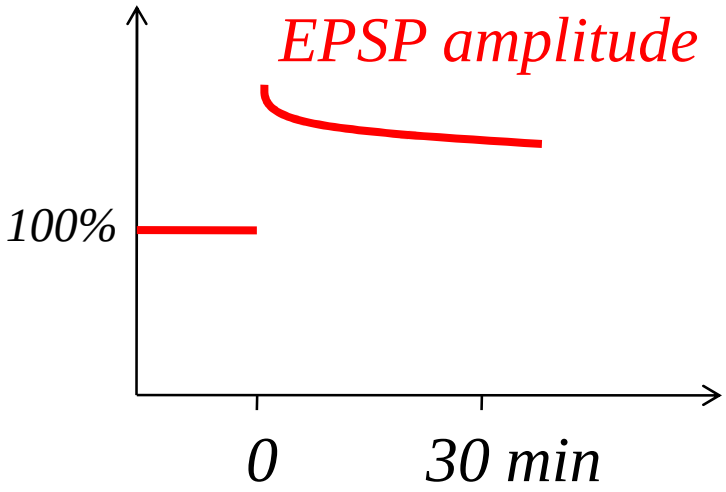


Intracellular recording electrode,
Current injection/ voltage clamp

Voltage dependence

Ngezehajo et al. 2000,
Artola et al.





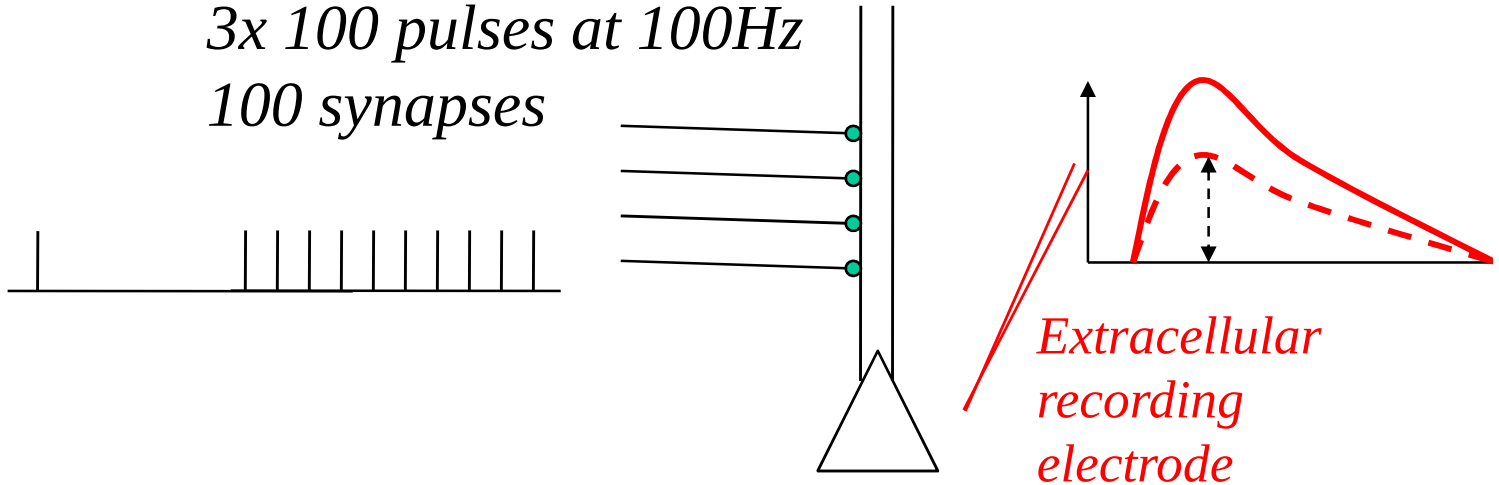
Experimental induction protocols (3)

Strong tetanus

3x 100 pulses at 100Hz

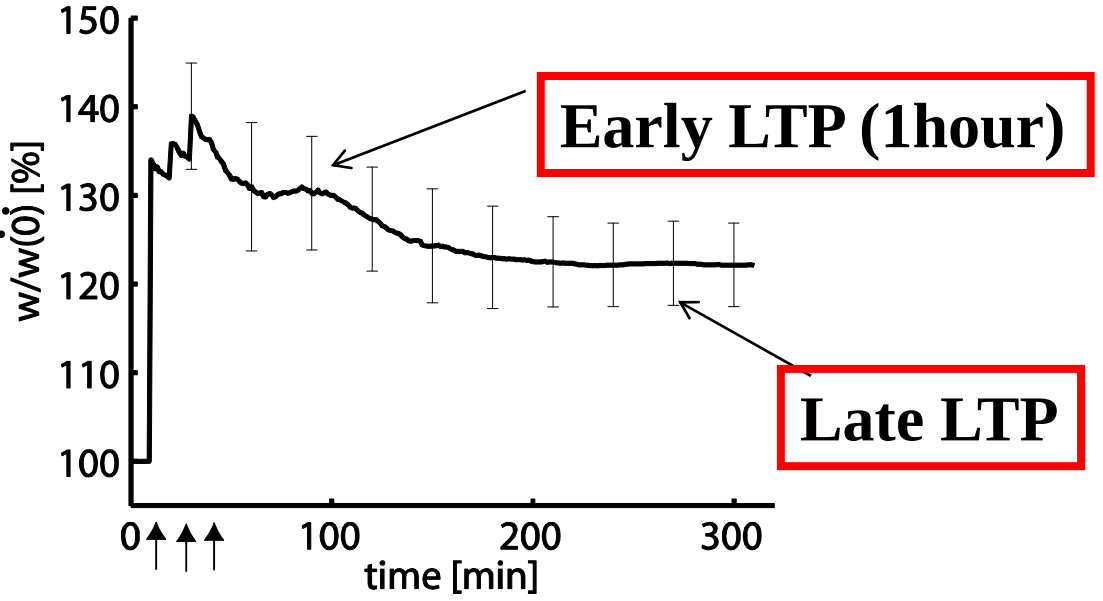
100 synapses

Extracellular electrode (stimulus)



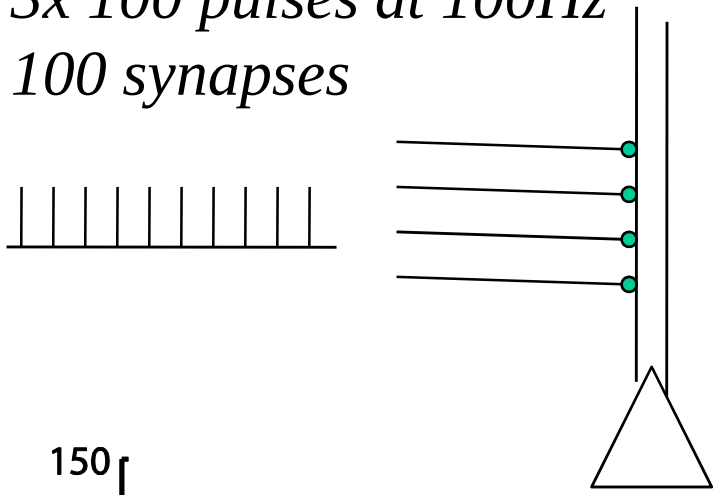
Extracellular recording electrode

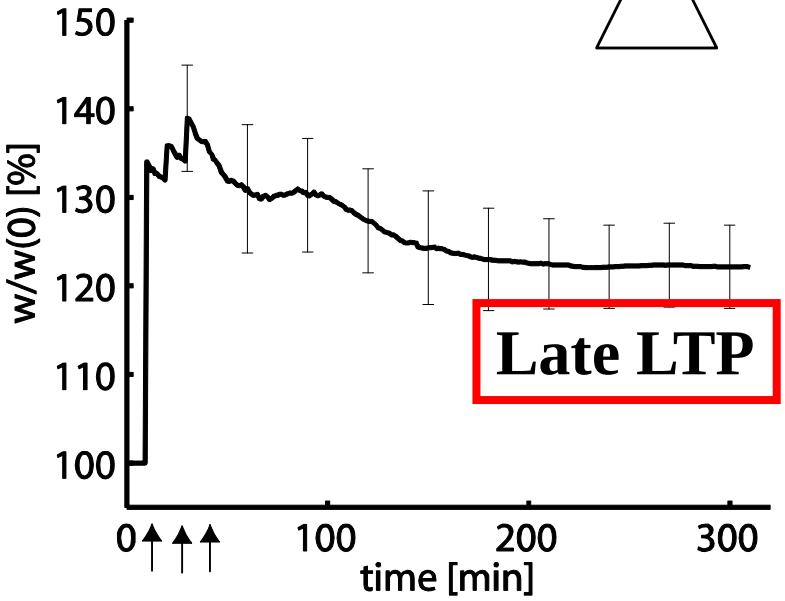
Hebbian interpretation:
postsynaptic neuron fires together with presyn. spike arrival



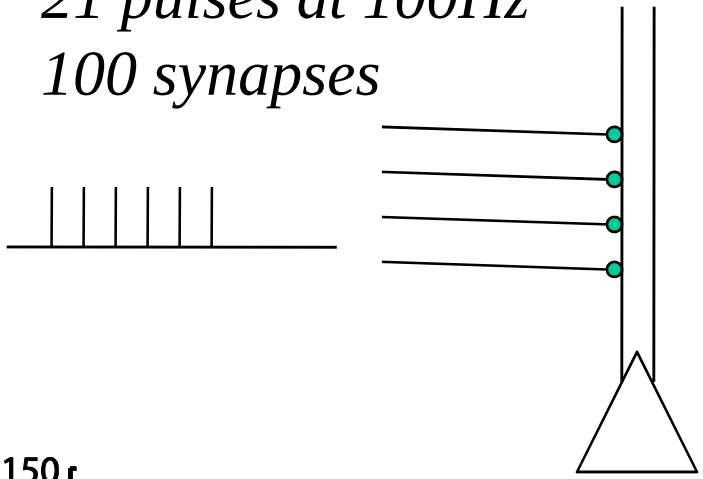
Strong and weak Tetanus

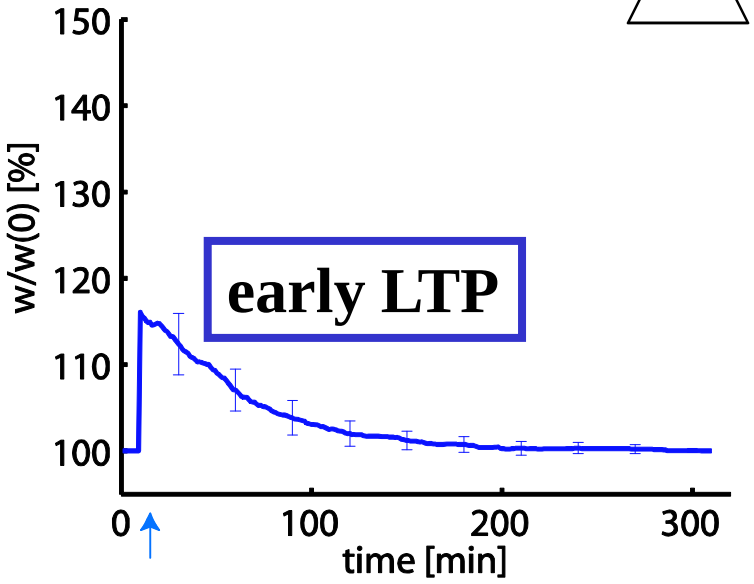
3x 100 pulses at 100Hz
100 synapses





21 pulses at 100Hz
100 synapses

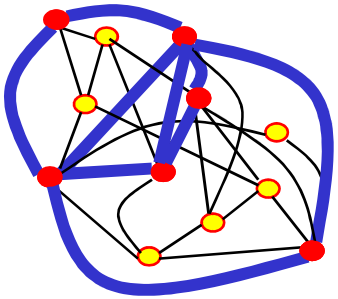




Experiments: Frey and Morris 1997

Hebbian Learning: Functional Desiderata

1) memory, must persist
2) success/reward must modulate learning



Hebbian Learning: experimental aspects

1) Can be triggered by ‘strong’ tetanic stimulation
2) Depends on spike timing
3) Depends on postsynaptic voltage
4) Happens on different time scales (early and late LTP)

My problem (3): one and the same model must account for:
- different induction protocols
- different time scales

Tag-Trigger-Consolidation:
Modeling synaptic learning across time scales

√ *Introduction*

√ *Review of Hebbian Induction protocols*

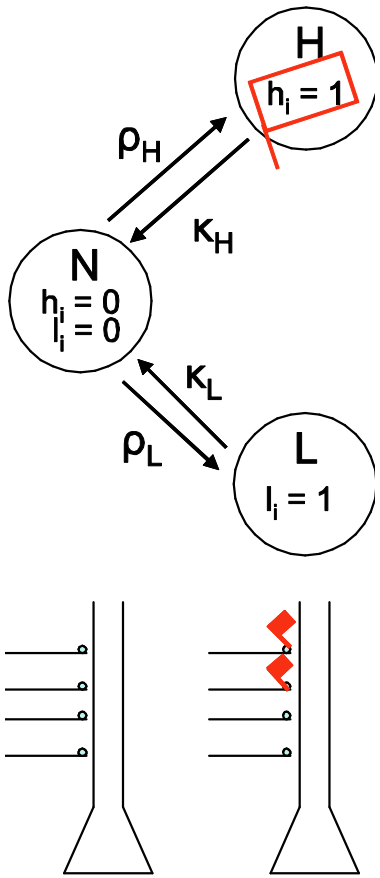
→ *TagTriC model (Tag-Trigger-Consolidation)*

- *Model assumptions*
- *Model componenets*
- *Results*

TagTriC Model

Early LTP *Protein synthesis* *Late LTP*

Tag



Basic ideas from synaptic tagging and capture

Frey and Morris 1997

*-Induction of LTP/LTD sets **tags** at individual synapses*

*-Consolidation of weights requires **protein synthesis***

*-Consolidation happens if tagged synapses **capture** protein*

additional hypothesis of the TagTriC Model

➡ *-LTP/LTD induction is equivalent to setting the tags*
→ identify tag and E-LTP or E-LTD

➡ *-LTP/LTD induction is possible by different protocols*
→ connect to Hebbian learning

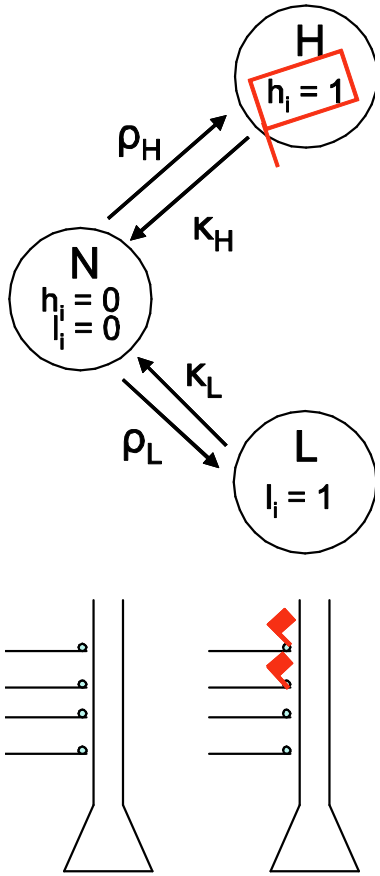
-protein synthesis requires sufficient number of tags=E-LTP/D
→ trigger threshold

-long-term stability requires that synapse has 2 stable states
→ synaptic weight can be maintained over weeks

TagTriC Model

Early LTP

Tag



-LTP/LTD induction = setting the tags

→ identify tag and E-LTP or E-LTD

Tags are set by

Hebbian

induction protocol

⟶ E-LTP/E-LTD

TagTriC Model

E-LTP

$$w_j = w_0[1+h_j]$$

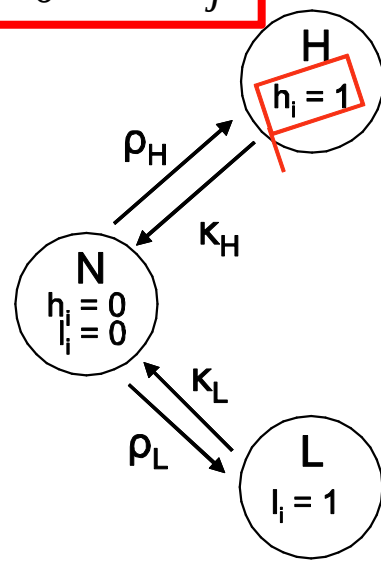
Tag

Tags are set by

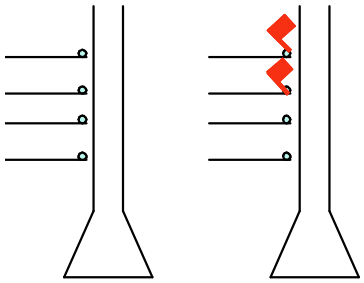
Hebbian

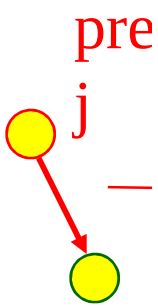
induction protocol

$\longrightarrow$ *E-LTP/E-LTD*



ρ_H





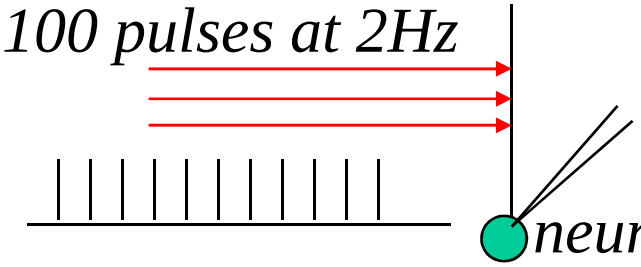
Setting the tag= changing the weight

Voltage dependence of LTP/LTD induction

E-LTP/E-LTD

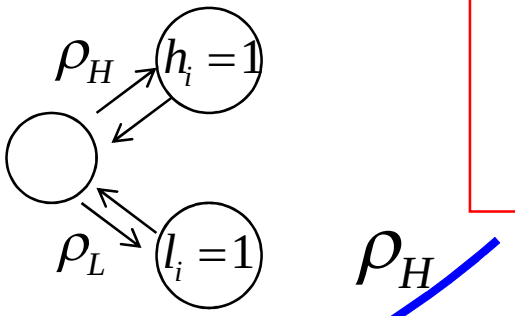
$$w_i = w_0[1 + h_i - l_i]$$

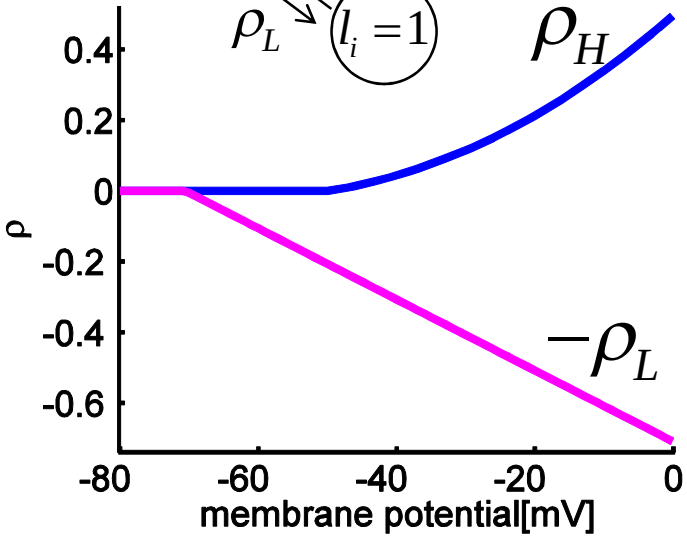
LTP induction: 100 synapses, 100 pulses at 2Hz



Ngezehayo et al. 2000
Artola et al. 1990

neuron depolarized



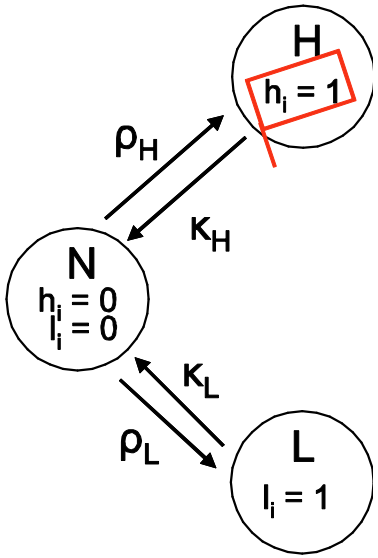


$$\rho_H = A_{LTP}\,\bar{x}\,\bar{u}\,(u - \vartheta_{LTP})$$

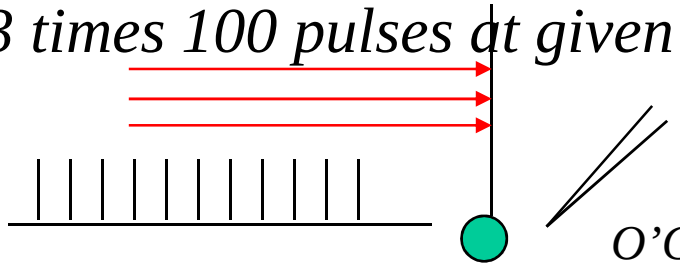
$$\rho_L = A_{LTD}\,x(t)\,(\bar{u} - \vartheta_{LTD})$$

presyn.

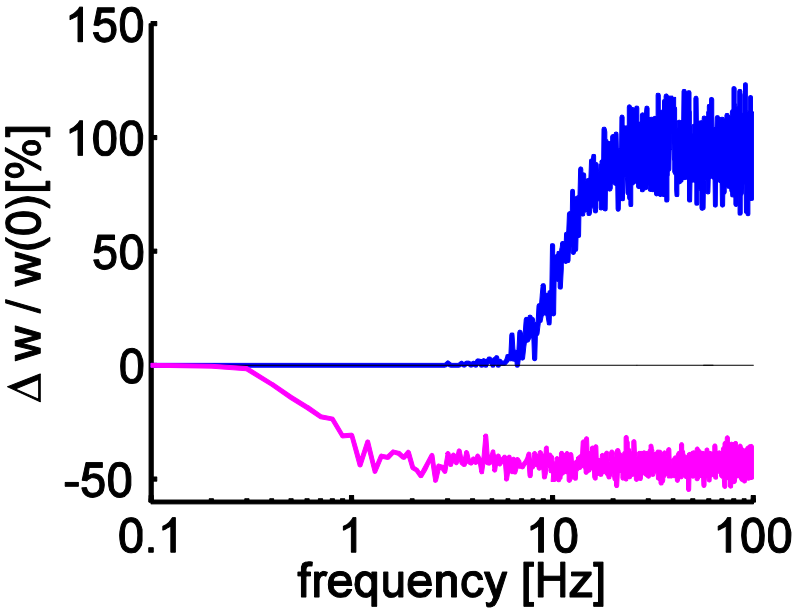
Setting the tag=changing the weight frequency dependence of LTP/LTD

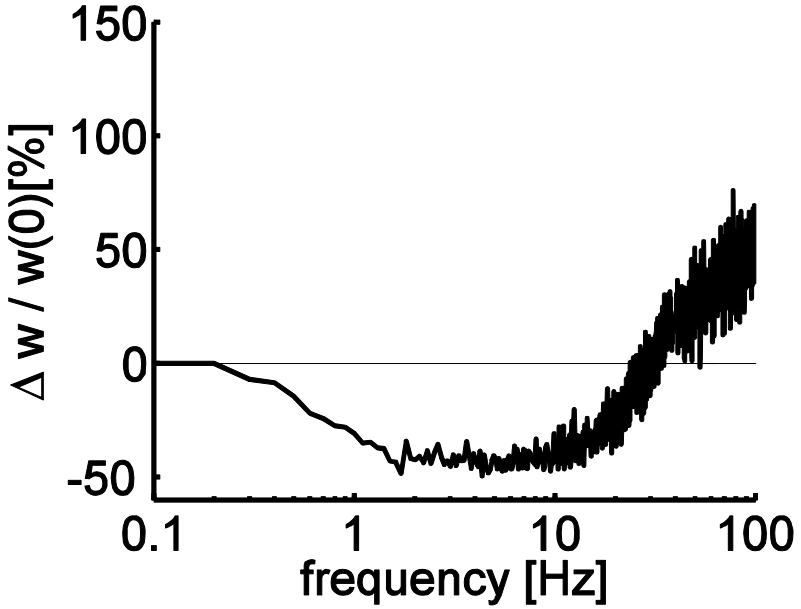


LTP/LTD induction: 100 synapses, 3 times 100 pulses at given frequency



O'Connor et al. 2005





Basic ideas from synaptic tagging and capture

*-Induction of LTP/LTD sets **tags** at individual synapses*

*-Consolidation of weights requires **protein synthesis***

*-Consolidation happens if tagged synapses **capture** protein*

additional hypothesis of the TagTriC Model

⋁ *-LTP/LTD induction is possible by different protocols*
→ connect to Hebbian learning

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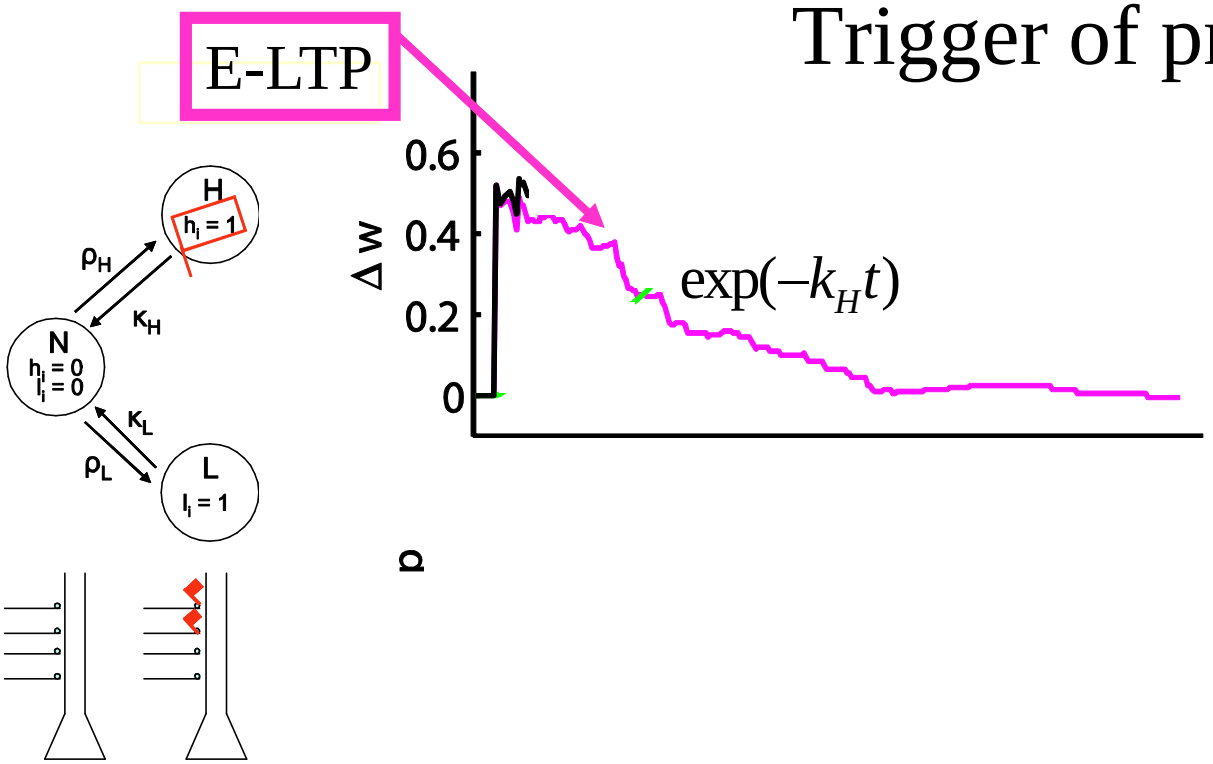
→ identify tag and E-LTP or E-LTD

→ *-protein synthesis requires sufficient number of tags=E-LTP/D*
→ trigger threshold

-long-term stability requires that synapse has 2 stable states
→ synaptic weight can be maintained over weeks

Trigger of protein synthesis



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hypothesis of the TagTriC Model

-long-term stability requires that synapse has 2 stable states

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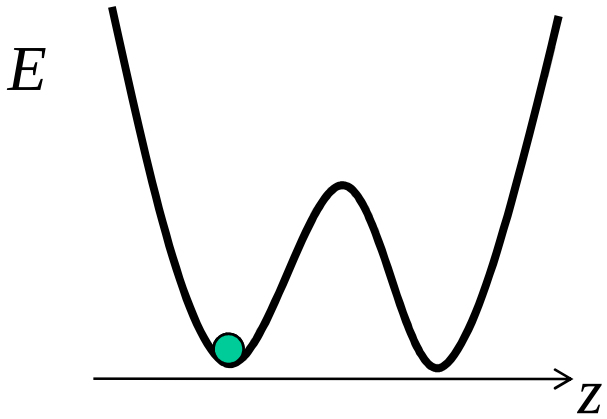
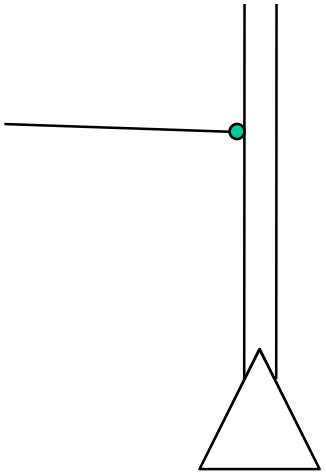
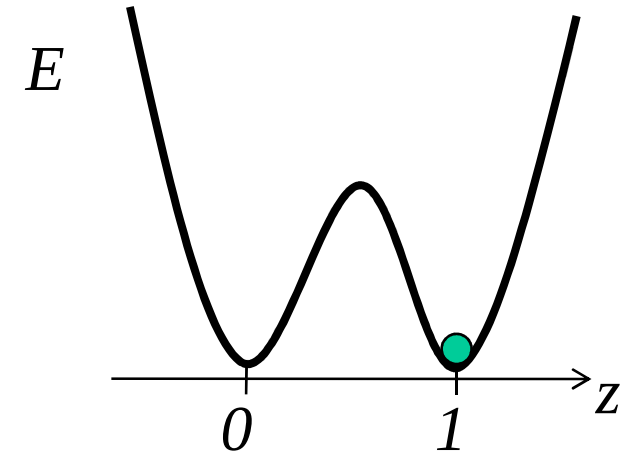


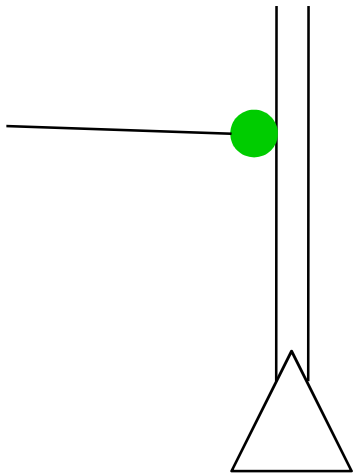


hypothesis of the TagTriC Model

-long-term stability requires that synapse has 2 stable states

→ synaptic weight can be maintained over weeks





Problem: Molecular turnover:
-AMPA receptor recycling
-scaffolding proteins recycled

Generic form of bistability

-e.g. some autocatalytic process (Lisman 1985, Crick 1984)

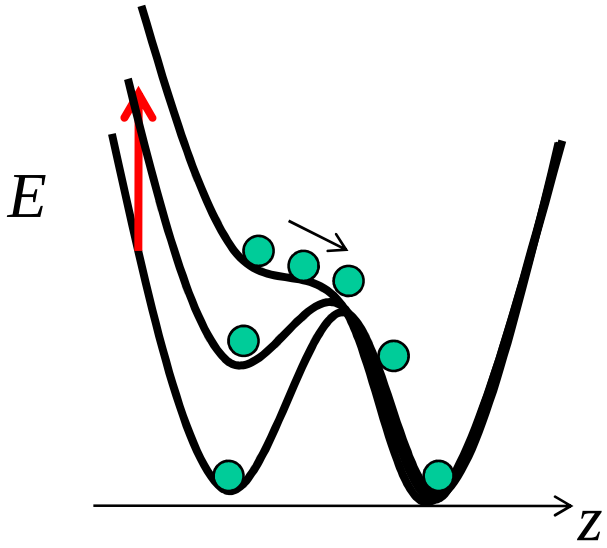
-e.g. clustering of AMPA receptors

-e.g. …

See talk of Paul Bressloff

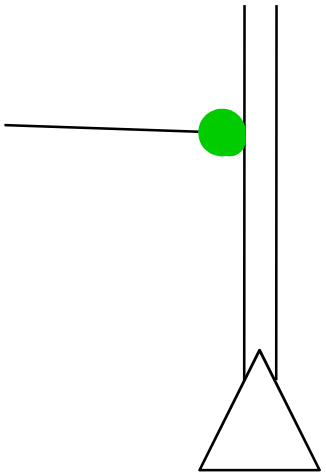
hypothesis of the TagTriC Model

-How does it get from one well to the other?



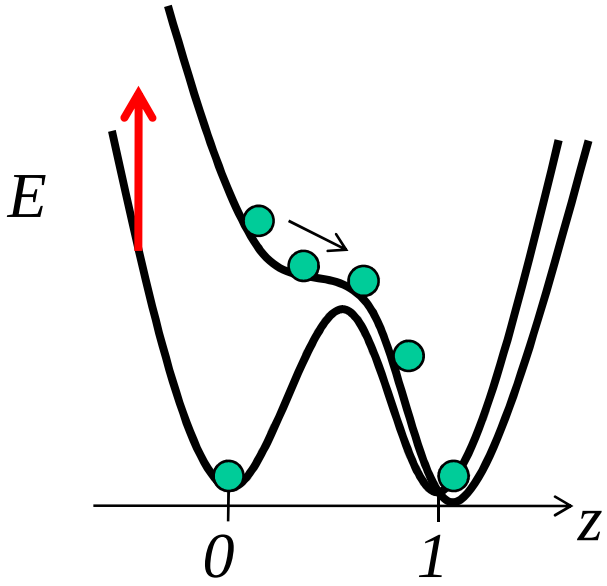
For this to happen we need:

- *LTP tag (h=1)*
- *protein (p>0.5)*



hypothesis of the TagTriC Model

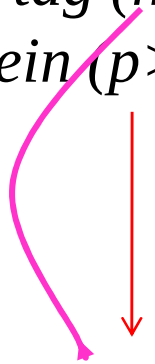
-How does it get from one well to the other?



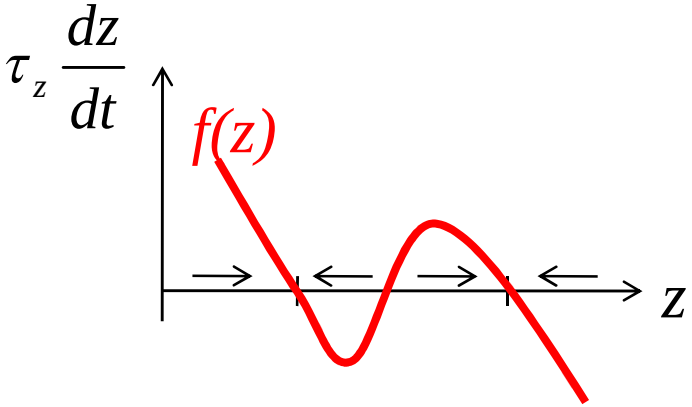
For a change we need:

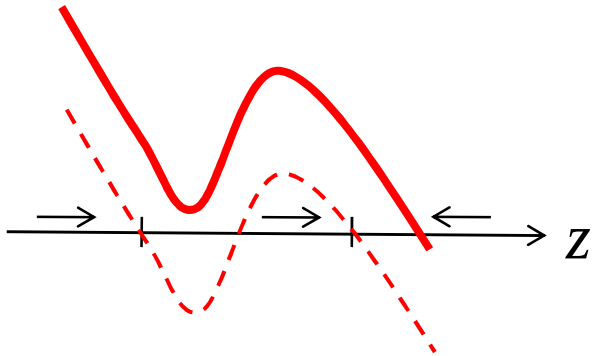
- LTP tag (h=1)

- protein (p>0.5)



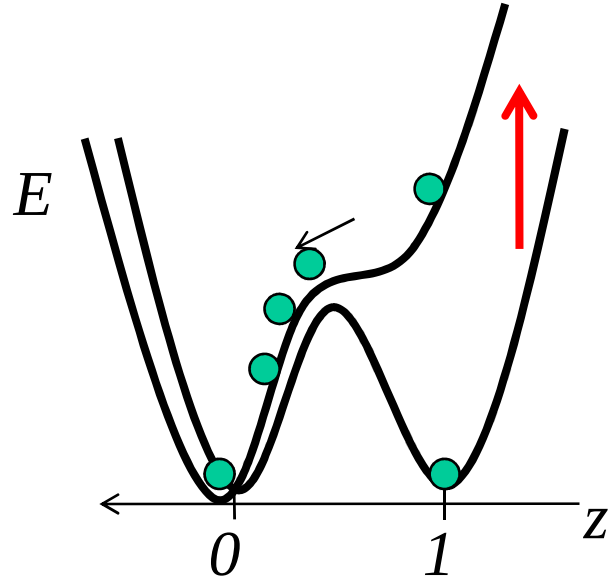
$$\tau_z \frac{dz}{dt} = f(z)$$





hypothesis of the TagTriC Model

-How does it get from one well to the other?

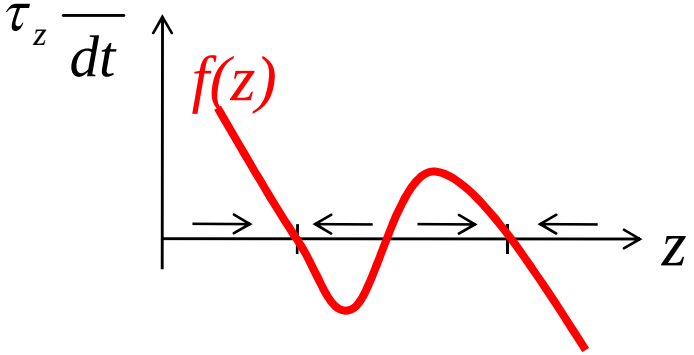


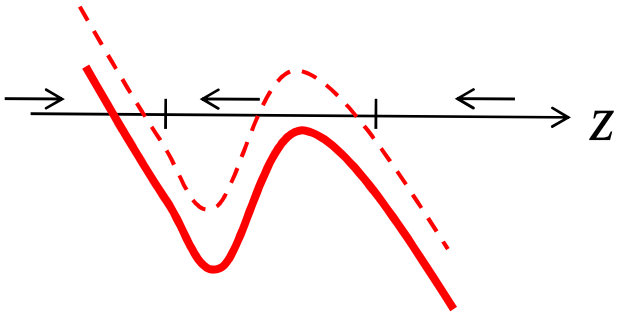
For a change we need:

- LTD tag (l=1)

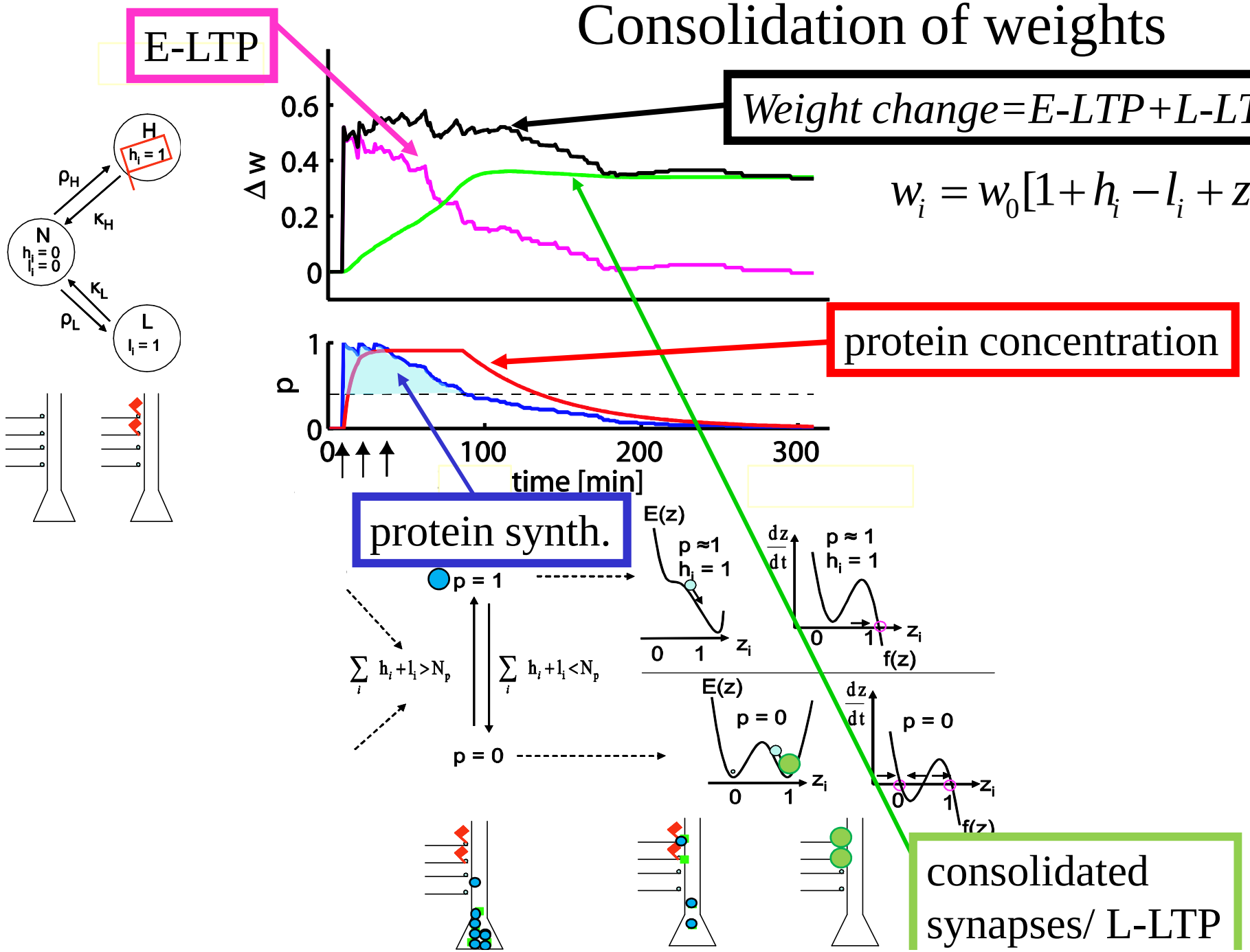
- protein (p>0.5)

$$\tau_z \frac{dz}{dt} = f(z) +$$





Consolidation of weights

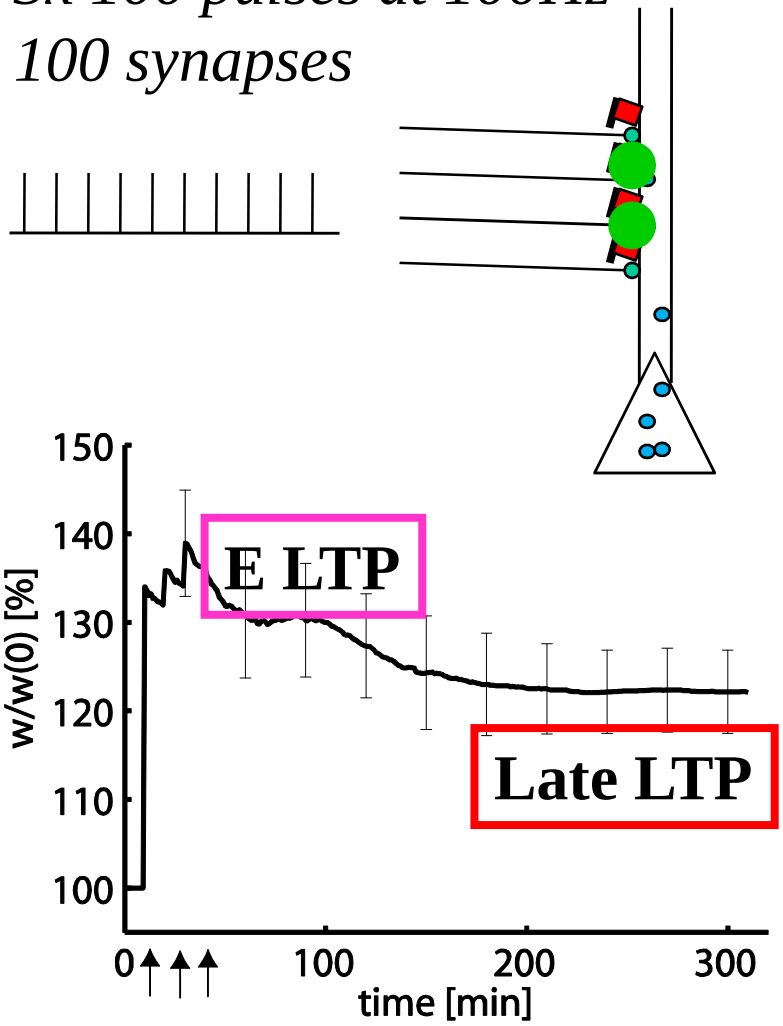


TagTriC Model - Results

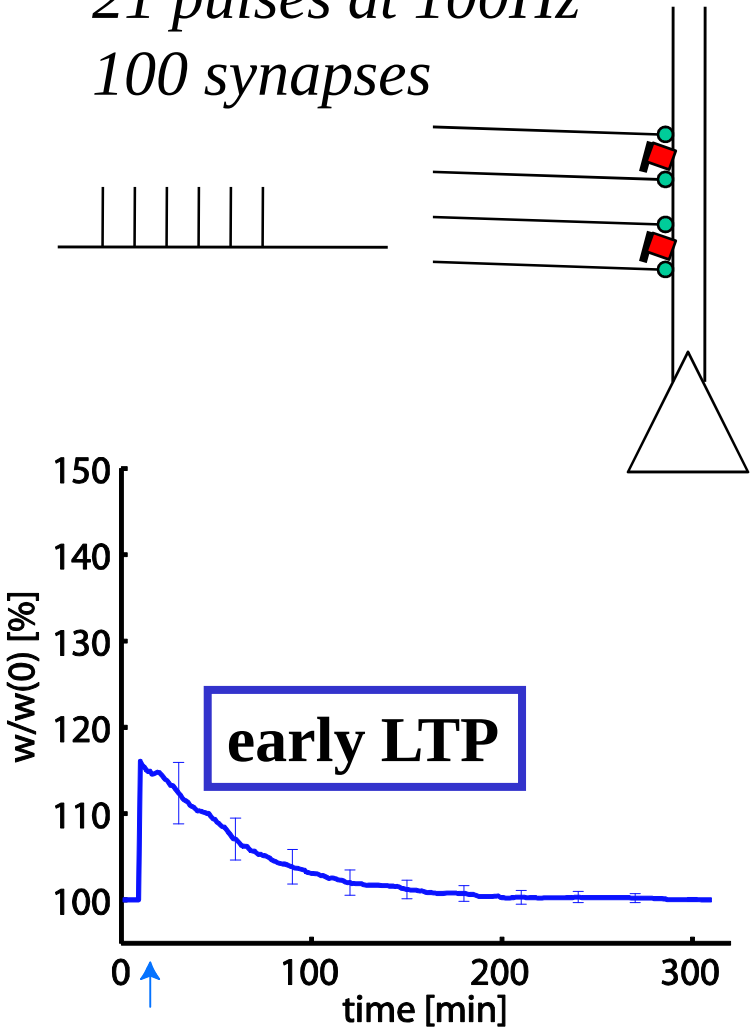
- Standard tagging paradigm *(Frey and Morris 1997)*
- Cross-tagging *(Sajikumar et al. 2005)*
- Protein synthesis blocker *(Frey and Morris 1997)*

Strong and weak Tetanus

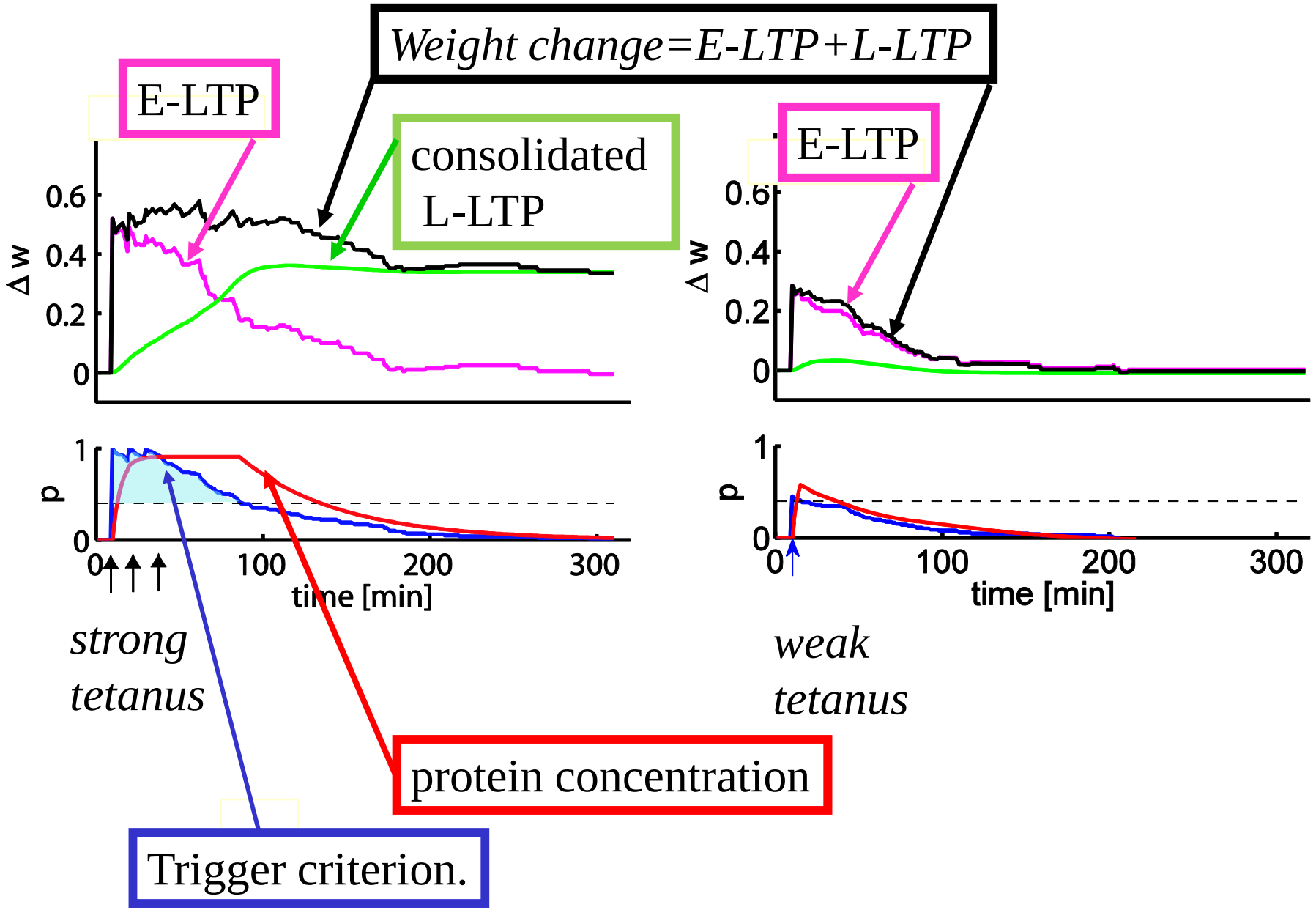
3x 100 pulses at 100Hz
100 synapses



21 pulses at 100Hz
100 synapses



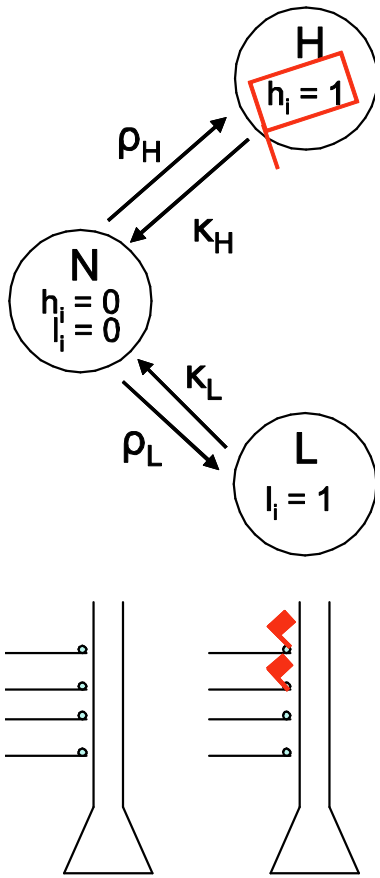
TagTriC model dynamics



TagTriC Model

Early LTP *Protein synthesis* *Late LTP*

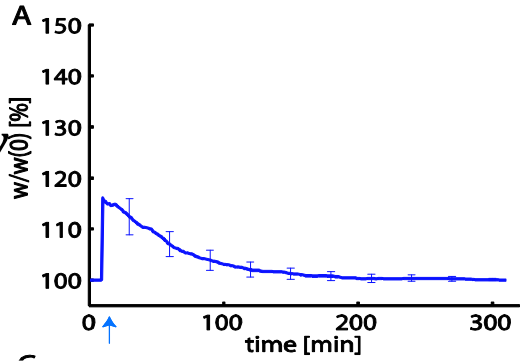
Tag

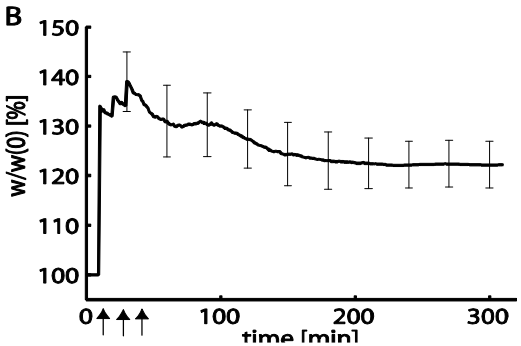


Protein shared by all synapses

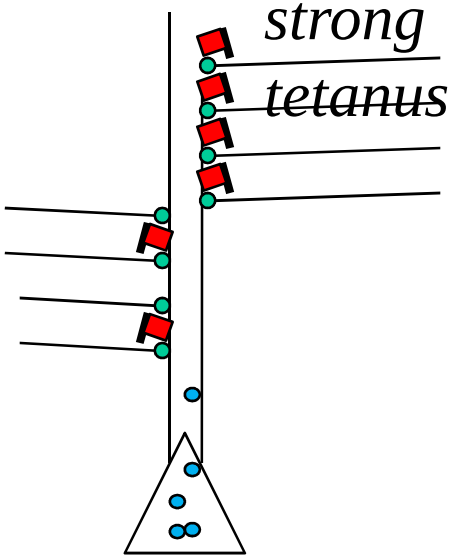
Weakly tetanized synapses stabilized by other input

weak tet. only

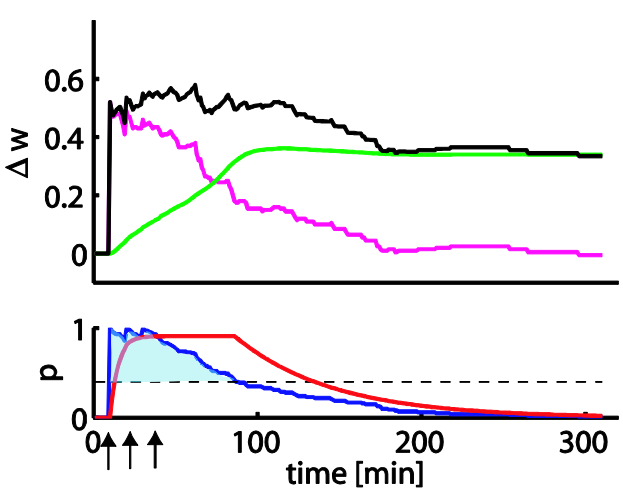


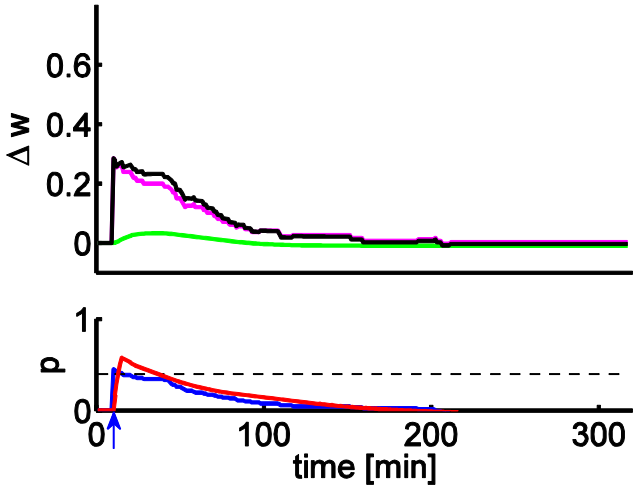


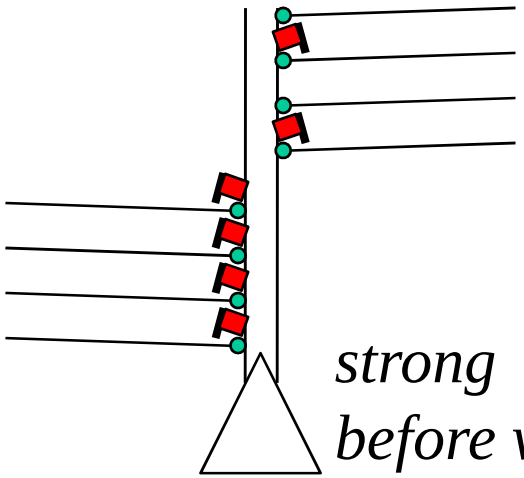
Strong tet. only



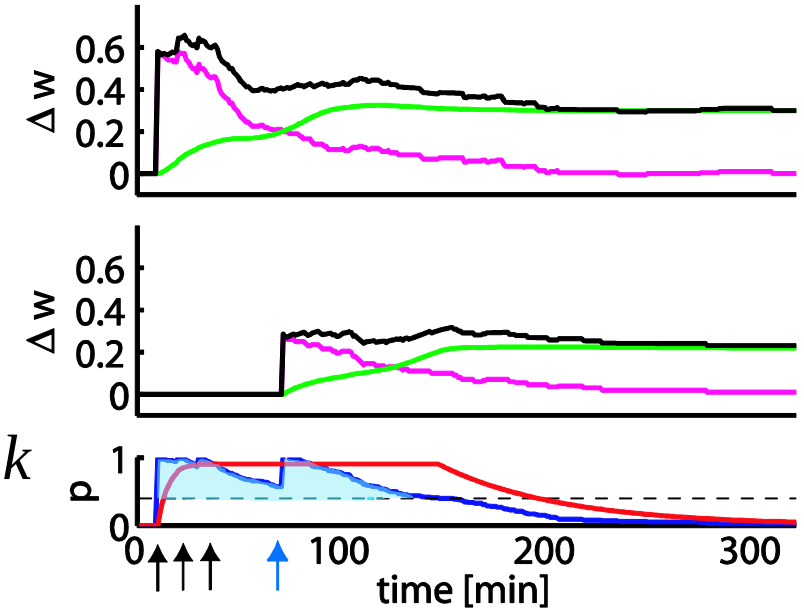
TagTriC model dynamics



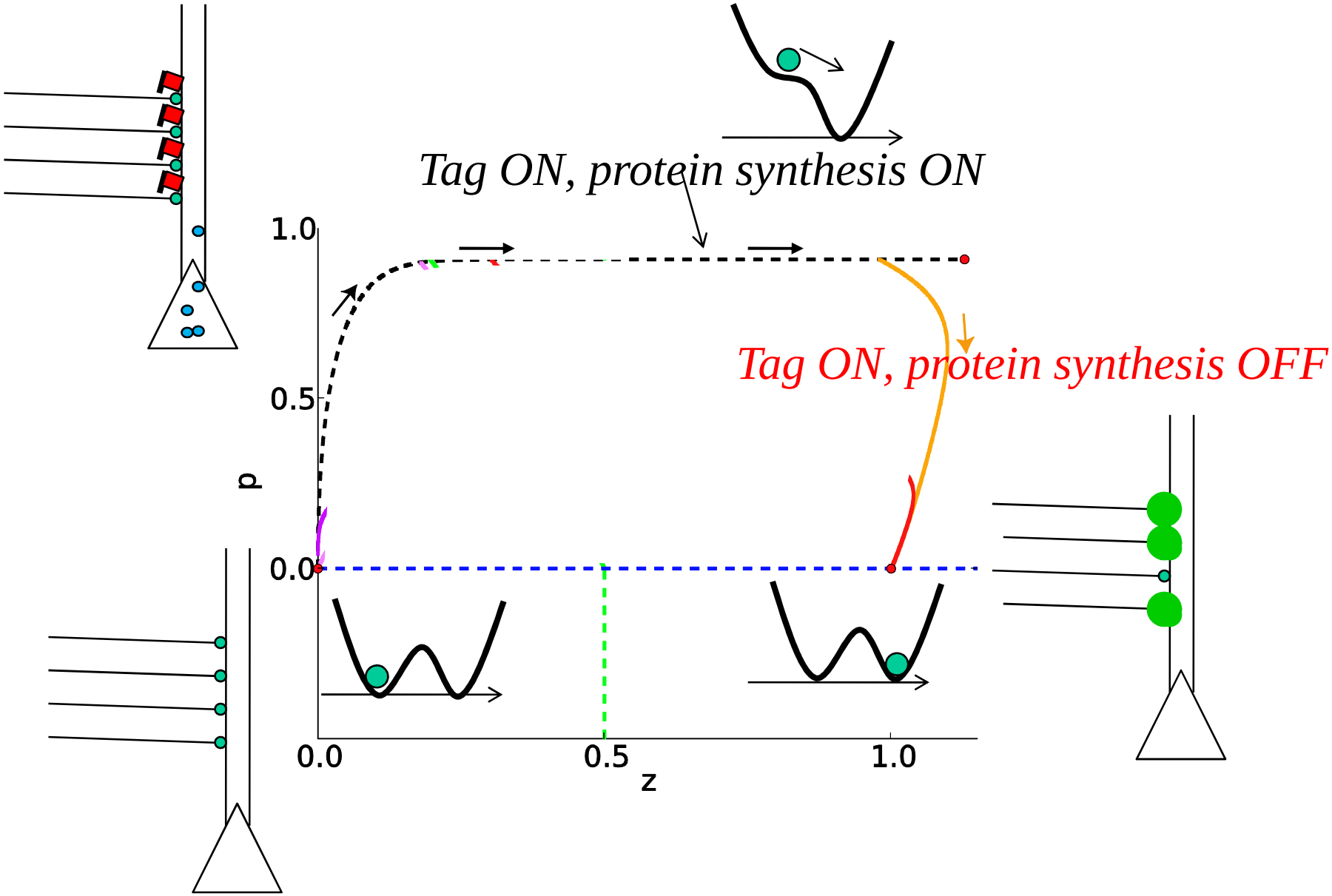




strong before weak tetanus

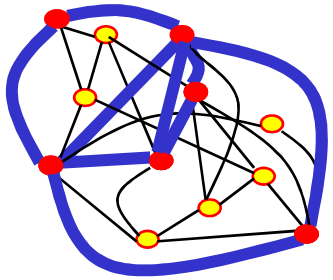


both protein synthesis and tags must be active



Hebbian Learning: Functional Postulates

1) Useful for memory



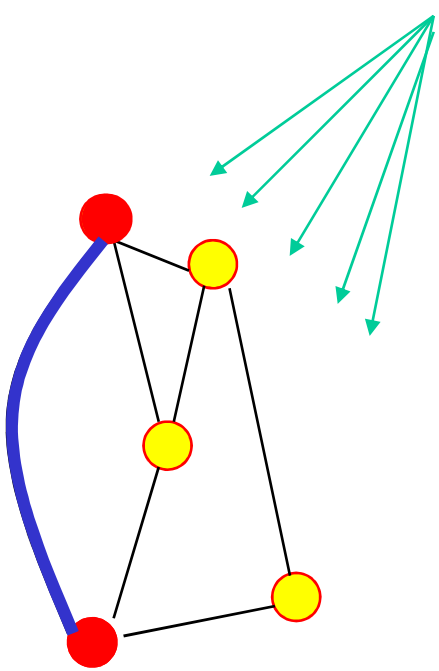
My problem (1):

Our model combines Hebbian learning (induction) of synaptic changes with consolidation/maintenance

My problem (3):

Our model describes different induction protocols and experiments across different time scales

Reinforcement Learning
= reward + Hebb



$$\Delta w_{ij} \propto F(pre, post, SUCCESS)$$

local global

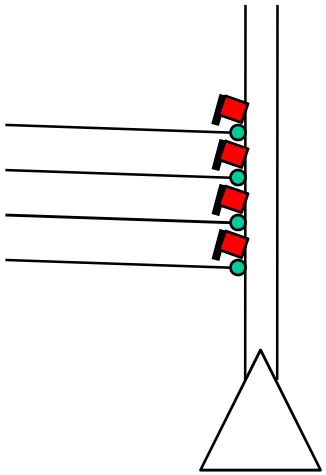
My problem (2):
Protein synthesis depends on neuromodulators, in particular dopamine → success signal

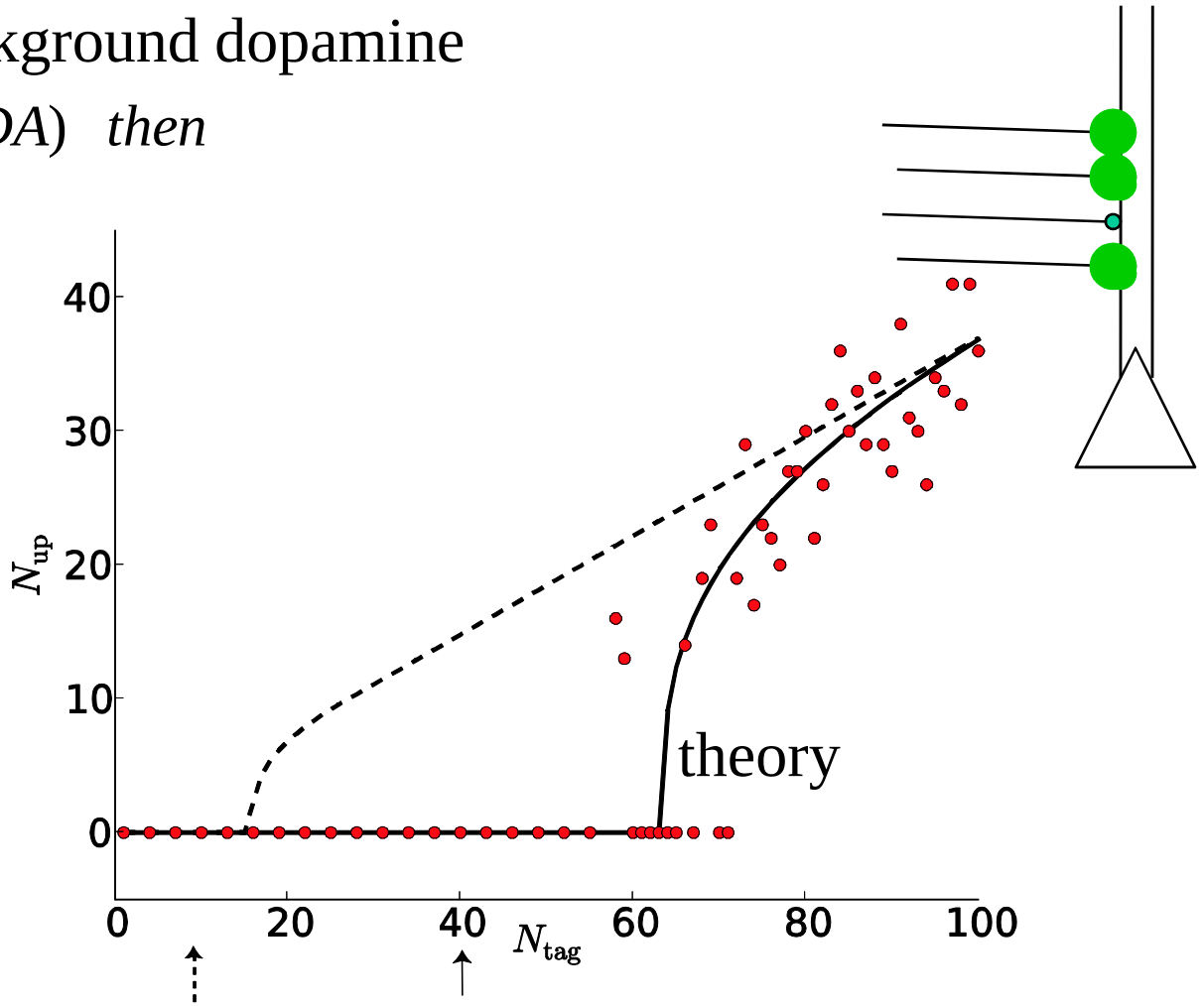
Number of consolidated synapses as a function of tagged synapses

phasic dopamine Background dopamine

$$if \quad \sum_i h_i + l_i > N_p(DA) \quad then$$

$$\frac{dp}{dt} = k_p(1-p) - \frac{p}{\tau}$$





Discussion and conclusions

- Other induction protocols should give consolidation, e.g., STDP
- LTD tags could occur even with LTP protocols
- Consolidation is non-Hebbian (non-local)
- Trigger threshold depends on neuromodulators
- 2-stable states only: Consolidation of LTP is only possible if synapses start in down state
- Resetting of tags: E-LTP not equal LTP-tag (additional hidden states)

See paper of Billings et al. 2009

The End

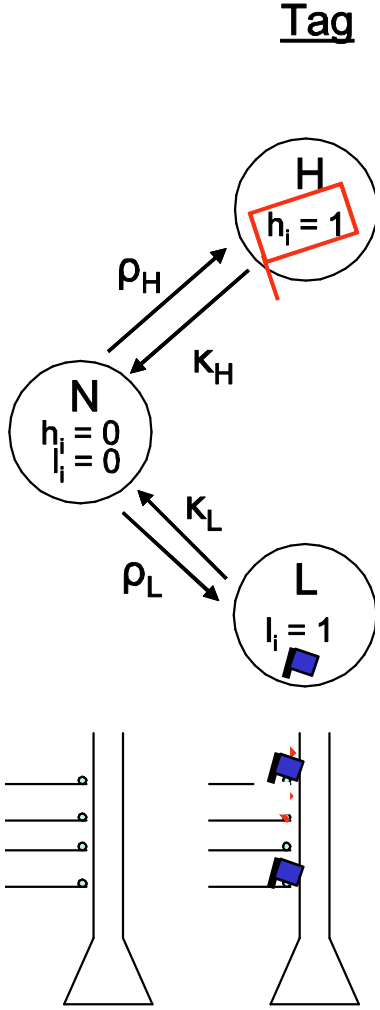
- a phenomenological model of early and late LTP/LTD
-clarifies existing ideas on tagging and capture
-does not depend on specific molecules

Thanks to:
Jean-Pascal Pfister (STDP model of E-LTP/LTD)
Claudia Clopath, Lars Busing, Eleni Vasilaki (voltage model of E-LTP)
Lorric Ziegler (consolidation model of L-LTP/LTD)

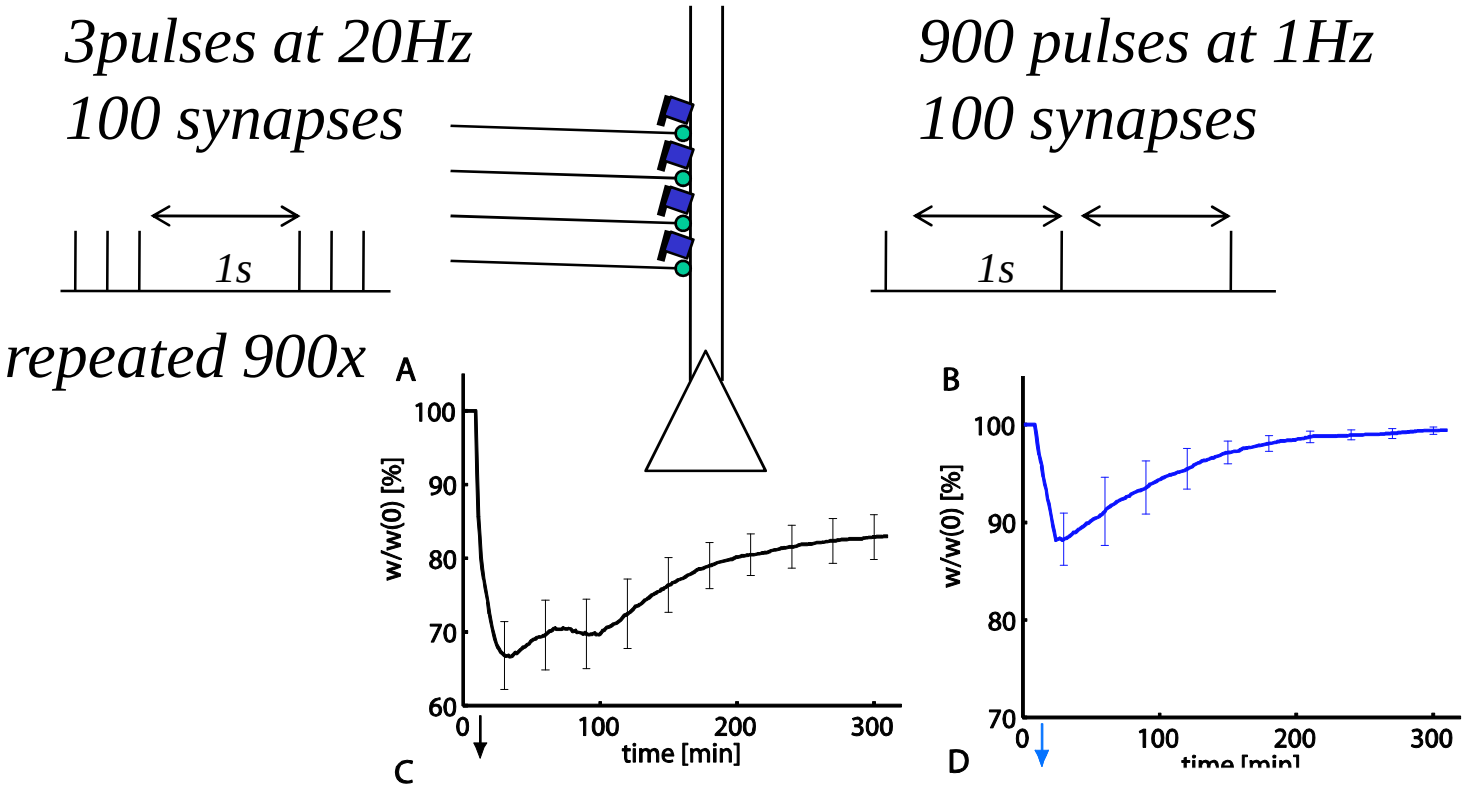
See: Clopath et al., *PLOS Comput. Biol. 2009 (to appear)*
See also: Billings, Adams, Morris, van Rossum *(to appear)*

TagTriC Model

Early LTP *Protein synthesis* *Late LTP*



Crosstagging/cross-capture



Protein synthesis blocker