Page 1 : pics + review (2) 10-15

Outline (write this out)

1. Quantatative model of what happens when an actim potential invades pre-synaptic bouton

2. AMPA
   NMDA
   $GABA_A$
   GABAB

2 what determines synaptic strength?

3. how do weights change
   a) short term plasticim (STP, STD)
   b) long term plasticim (LTP, LTD, STDP)

~~////~~

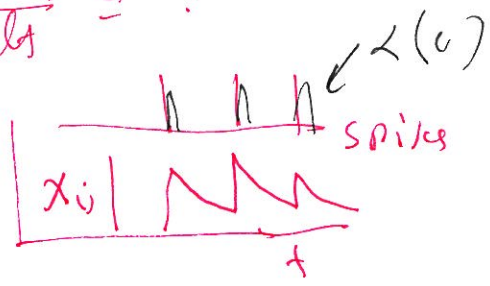
Start by writin dum eqns:

$$C_i \frac{dV_i}{dt} = -g_{L_i}(V-\mathcal{E}_L) - \bar{g}_{Na_i} m_i^3 h_i (V_i - \mathcal{E}_{Na}) - \dots$$

$$- \sum_j w_{ij} x_{ij} (V_i - \mathcal{E}_j)$$

$$\frac{dx_{ij}}{dt} = \alpha_{ij}(c)(1-x_{ij}) - \beta_{ij} x_{ij}$$

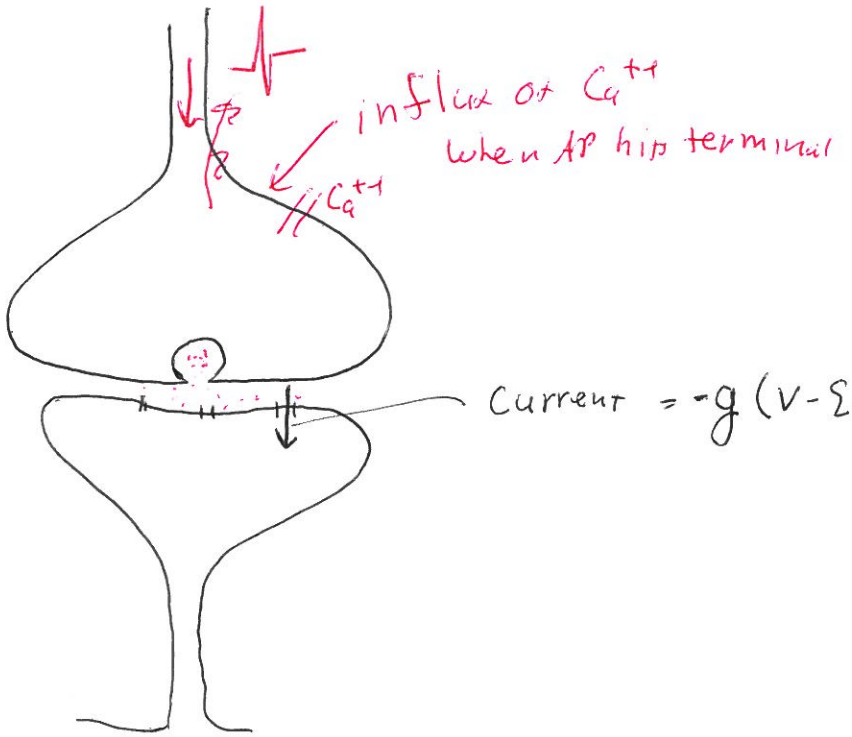
$$\frac{dw_{ij}}{dt} = ?$$



1. What determin time course of x_{ij}? mentim: failures, short + ~~long term~~ potentim

2. how does w_{ij} evolve (LTP, LTD, STDP)

(1) quantitative model of synapse



- g depends on concentration [and sometimes voltage]
- Σ_R depends on [presynaptic neuron type (E vs I); type of neurotransmitter released] ← approximately synonymous

Reversal potentials

Excitatory: AMPA, NMDA → glutamate receptors → channels are mix of Na^+, K^+, Ca^{++}

$\Sigma_R \approx 0$ mV

(NMDA named after antagonist)

Inhibitory: $GABA_A$, $GABA_B$ → GABA receptors → Cl^- channels

$\Sigma_R \approx \begin{cases} -70 & GABA_A \\ -100 & GABA_B \end{cases}$

time course

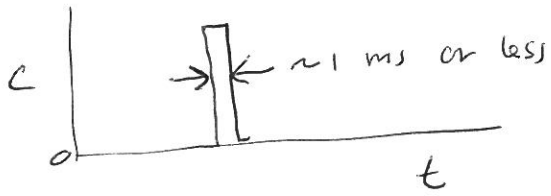
AMPA
$GABA_A$
$GABA_B$

$$I_E = -\bar{g}\, x\,(V - \Sigma_R)$$

$$\dot{x} = \alpha(c)(1-x) - \beta x$$

$\alpha(c)$: ~~dependence~~ neurotransmitter concentration

β: constant



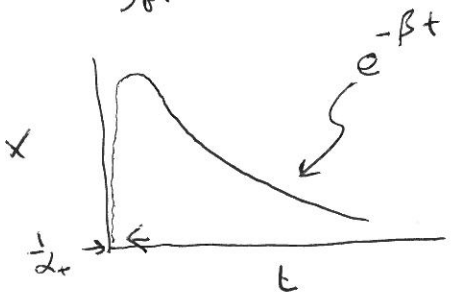
c ↑ $\quad \dot{x} \simeq \alpha_+(1-x) \Rightarrow x = 1 - e^{-\alpha_+ t}$

$\dot{(1-x)} = -\alpha_+(1-x)$

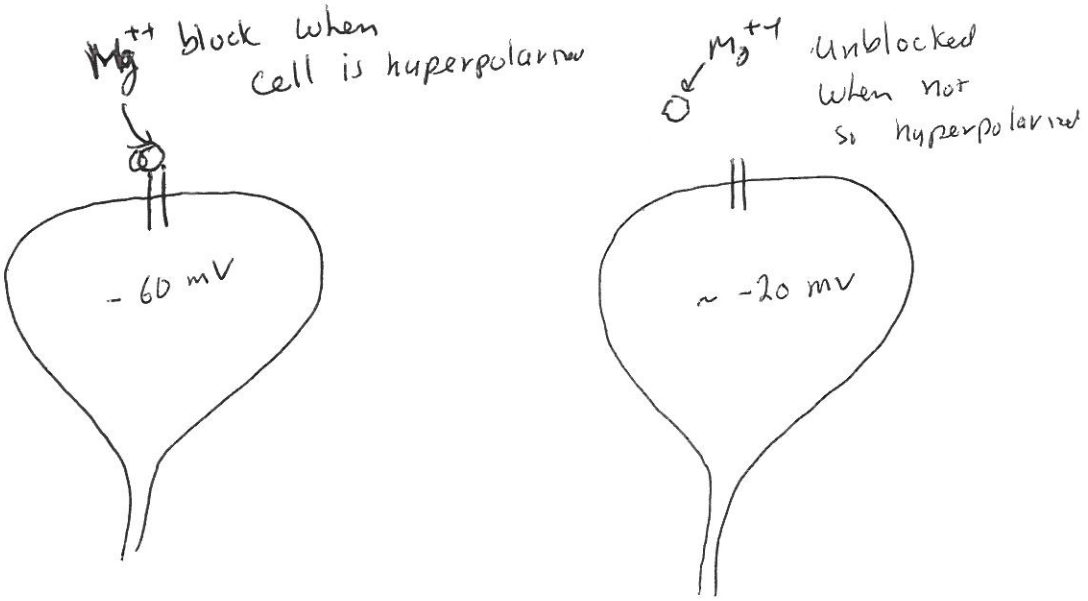
$(1-x) = [1-x(0)]\, e^{-\alpha_+ t}$

$x = 1 - [1-x(0)]\, e^{-\alpha_+ t}$

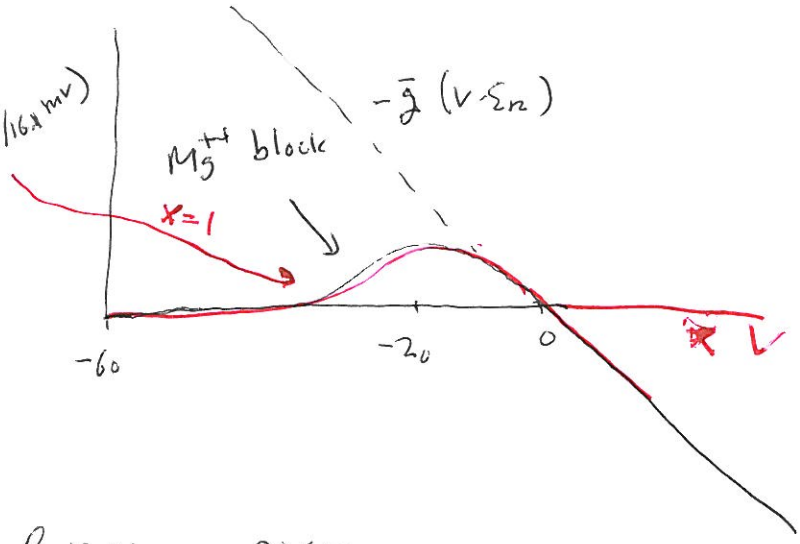
spike occurs



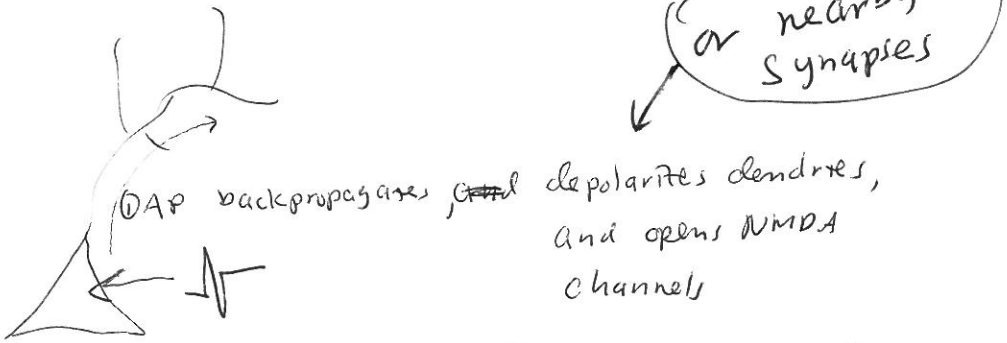
NMDA is different



$$I_E = -\bar{g} \times (V - \mathcal{E}_n)^0 \Big/ \left(1 + \frac{[Mg^{++}]}{3.57\ mM} \exp(-V/16.1\ mV)\right)$$



Coincidence detector. Picture

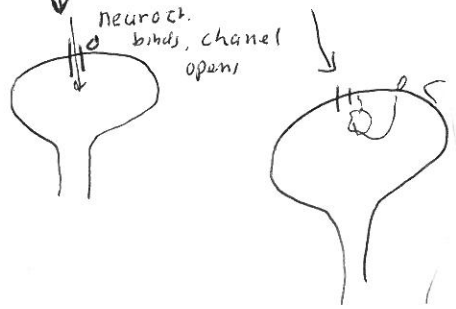


② if another spike arrives near that time, there is Ca^{++} influx through NMDA channels, and that leads to long term plasticity.

	τ_{rise} (ms)	τ_{decay} (ms)
AMPA	~0	~5
NMDA	1-5	~150-300
$GABA_A$	~0.3	~5
$GABA_B$	~10	~200

fast, slow → ionotropic

metabotropic



neurot. binds, Stuff happens inside cell, channel opens. usually slower.

full model (single compartment)

$$C\frac{dV_i}{dt} = -g_L(V_i - \mathcal{E}_L) - [\text{other, active currents}] \text{ ~~including~~}$$

$$-\sum_j \bar{g}_{ij} X_{ij} (V_i - \mathcal{E}_j)$$

~~synaptic~~ divided by Mg^{++} term for NMDA

$$\dot{X}_{ij} = \alpha_X (1 - X_{ij}) \sum_k \delta(t - t_j^k) - \beta_X X_{ij}$$

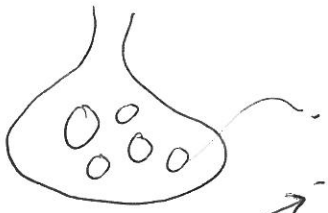
↳ instantaneous rise; could replace by square pulse

do a little math - pg. 11

- if we had a rule for how the $\bar{g}_{ij}$ evolves (LL / Learning), we would have a complete model of the brain (sort of)

(2) What determines synaptic strength?

- <u>quantal release</u> (key concept)



- n vesicles total
- each released independently w/ prob p
- amount released = q_0 (same for all

new concept:
probabilistic release.

<u>binomial</u>

$$p(k) = p^k (1-p)^{n-k} \frac{n!}{k!(n-k)!}$$ [motivate this]

Average release: $q_0 \langle k \rangle$

~~Standard dev~~ variance: $q_0^2 [\langle k^2 \rangle - \langle k \rangle^2]$

$$\langle k^\ell \rangle = \sum_{k=0}^{np} k^\ell \, p^k (1-p)^{n-k} \frac{n!}{k!(n-k)!}$$

$$= \sum_k k^\ell \, p^k q^{n-k} \Big|_{q=1-p} \binom{n}{k}$$

$$= \left(p \frac{d}{dp}\right)^\ell \sum_k p^k q^{n-k} \Big|_{q=1-p} \binom{n}{k}$$

[take deriv first!]

$$= \left(p \frac{d}{dp}\right)^\ell (p+q)^n \Big|_{\text{treat as } p+q=1}$$

$$\langle k \rangle = p \frac{d}{dp} (p+q)^n \Big|_{p+q=1} = np$$

$$\langle k^2 \rangle = \left(p \frac{d}{dp}\right)\left(p \frac{d}{dp}\right)(p+q)^n$$

$$= p\left[\frac{dp}{dp}\frac{d}{dp} + p\frac{d^2}{dp^2}\right](p+q)^n$$

$$= \left(p \frac{d}{dp} + p^2 \frac{d^2}{dp^2}\right)(p+q)^n$$

$$= np + p^2 n(n-1)$$

$$\langle k^2 \rangle - \langle k \rangle^2 = np + p^2 n^2 - p^2 n - p^2 n$$

$$= np(1-p)$$

$$\langle q \rangle = q_0 np$$

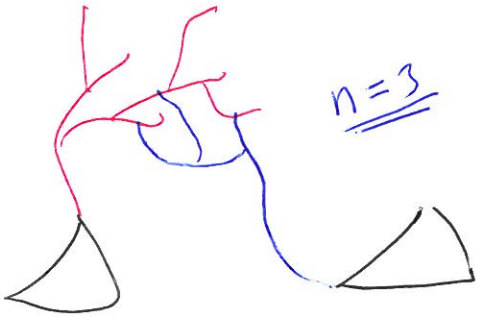
$$\langle dq^2 \rangle = q_0^2 np(1-p)$$

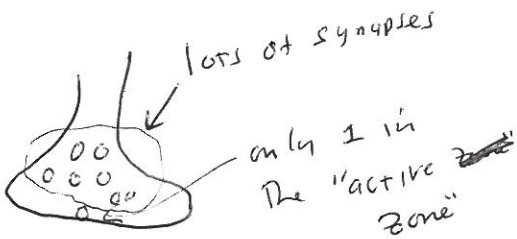
$q_0, n + p$ determine strength

NMJ (neuromuscular junction), Katz

$n = 100 - 1000$

Central synapses: $n = 1$ per synapse, but





$p = 0.1 - 0.9$ — **Why is a total mystery**

at central synapses, brain can adjust:

- n (add or subtract synapses) ← -but typically n = 1
- p (probability of release)
- ~~q~~ [q_0 is typically fixed)

it can also adjust $\bar{g}$, typically by "inserting" channel)

AMPA channel added due to plasticity. "silent synapse" hypothesis

(3) How do weights change.

a) Short term

- affect only probability of release. two kinds:

1. Facilitation (AKA augmentation or potentiation) probably results from buildup of Ca^{++} (remember, Ca^{++} triggers release) — slower phase

2. Depression probably results from a depletion of vesicles in the active zone.

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eqns for P_{rel}

$$\tau_F \frac{dP_{rel}}{dt} = P_0 - P_{rel} + \left[\sum_i \delta(t-t_i)\right] \begin{cases} -\tau(1-f_D)P_{rel} & \text{depression} \\ +\tau f_F(1-P_{rel}) & \text{facilitation} \end{cases}$$

↑ spikes

between spikes: $P_{rel}(t) = P_0 + [P_{rel}(0) - P_0]e^{-t/\tau}$

depression ind. of ν!

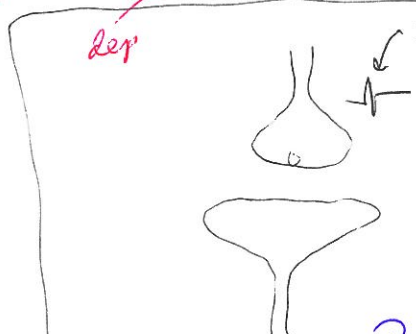
do both average: -change detected! (a la Larry Abbott)

at spikes:

$\bar{P} = \frac{P_0 + \nu\tau f_F}{1+\nu\tau f_F}$, $\frac{P_{\bar{0}}}{1+\nu T(1-f_D)}$

fac. dep.

$\langle P_{rel} \rangle \to f_F(1-\langle P_{rel}\rangle)$ τ



prob. release is a function of history of presynaptic spikes

second spike

$P_0 + (\langle P_{rel}\rangle + f_F(1-\langle P_{rel}\rangle) - P_0)e^{-\tau/\tau_p}$

Average over $\int d\tau\, r e^{-r\tau}$

$\langle P_{rel}\rangle = P_0 + (\langle P_{rel}\rangle + f_p(1-\langle P_{rel}\rangle) - P_0)\frac{r\tau_p}{1+r\tau_p} \to P_{rel} = \frac{P_0 + f_p r\tau_p}{1+r f_p \tau_p}$

Math

$$\frac{dx}{dt} = f(x) + g(x)\,\delta(t - t_0)$$

$$x(t+dt) = x(t) + f(x)\,dt + \int_t^{t+dt} g(x)\,\delta(t-t_0)\,dt$$

$t < t_0 < t+dt \Rightarrow$ jump

$$x(t+dt) \to x(t) + g(x) \underbrace{\int \delta(t-t_0)\,dt}_{1}$$

↑ ambiguous whether to use $g(x)$ before or after jump. for spikes, __before__ jump.

---

at spike

Facilitation: evaluated right before spike

$$P_{rel} \to P_{rel} + f_F(1 - P_{rel})$$

Depression:

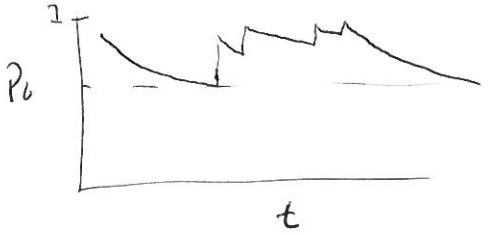
$$P_{rel} \to P_{rel} - (1 - f_D)P_{rel} = f_D P_{rel}$$

[in principle there should be ~~release~~ depression only if ~~spike~~ transmitter is released, but we'll ignore this]

↑ not [illegible]

Depression

Facilitation



Fitting parameters

$$\tau \frac{dP_{rel}}{dt} = P_0 - P_{rel} + \tau f_F (1 - P_{rel}) \sum_i \delta(t - T_i)$$

you ~~observe~~ know P_0 + τ

you observe $\{t_i\}$, $\{$~~Z_0~~$\}$

$\{t_i\}$ ↖ spike times

~~Z_0~~ ↖ whether or not there was a release.

what is ~~P_0~~ f_F ?

$$P(f_F \mid \{t_i, z_i\}) \propto P(\{t_i, z_i\} \mid f_F)\, P(f_F)$$

↑ ignore

$$P(\{t_i, z_i\} \mid f_F) = \prod_i P_{free}(t_i)^{z_i}$$

$$\prod_i P_{free}(t_i; f_F)^{z_i} \left(1 - P_{free}(t_i; f_F)\right)^{1-z_i}$$

~~prob.~~ ↑ prob. of release ↑ prob. of no release

$P_{free}(t_i; f_F)$ can be found by solving ODE.

typically, maximize $\mathcal{L} = \log P(\{t_i, z_i\} \mid f_F)$

$$= \sum_i z_i \log P_{free}(t_i; f_F) + (1 - z_i) \log\left(1 - P_{free}(t_i; f_F)\right)$$

↑ compute numerically

36 Long term plasticity

LTP Potentiation
LTD Depression

Long Term

- p can change
- n can change (new/eliminated synapses remember, 1 release/synapse)
- g can change

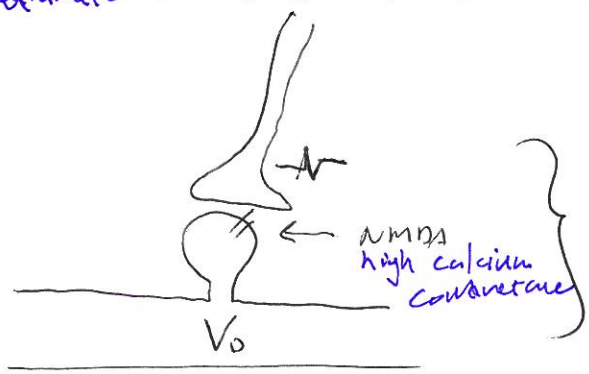
pre post } long argument over which it was

answer: both

typically
Change caused by Ca^{++} influx through NMDA channel

why → 1) increase in $[Ca^{++}]$ intracellular during stimulation injecting Ca buffer prevents
2) increasing $[Ca^{++}]$ by other means

(Most glutamate-sensitive cells express both NMDA & non-NMDA.



if spike arrives when $V_0 > \sim -20$ mV, (so that Mg^{++} block is gone),

Synaptic strength changes (either p or g)

Current picture

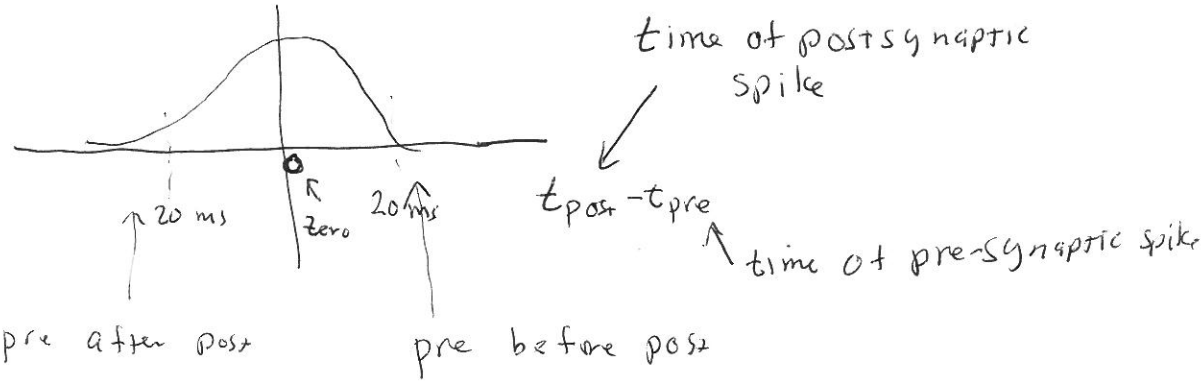
NMDA → Ca^{++} influx → CaMKII → AMPA inserted !!!

Up-Regulation of AMPA
GluR1 tagged with GFP
Before & stimulation
half spines

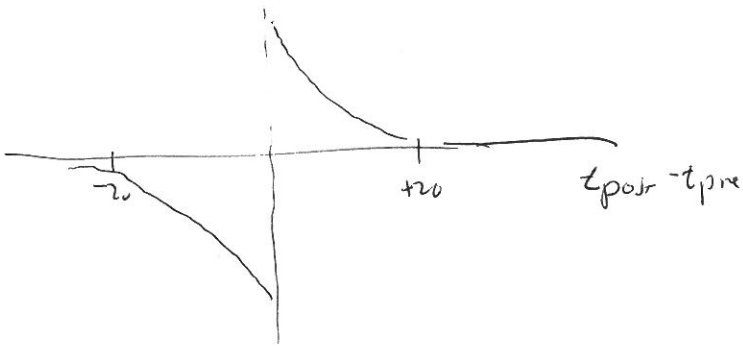
Mossy fibers of Dentate → CA3
Presynaptic LTP

Weight change, Δw, depends on timing of pre and post-synaptic spike,

Hebb

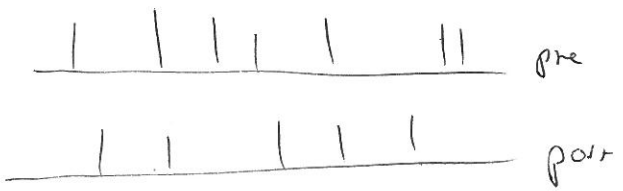


STDP



- both are unstable unless a normalization rule is applied.

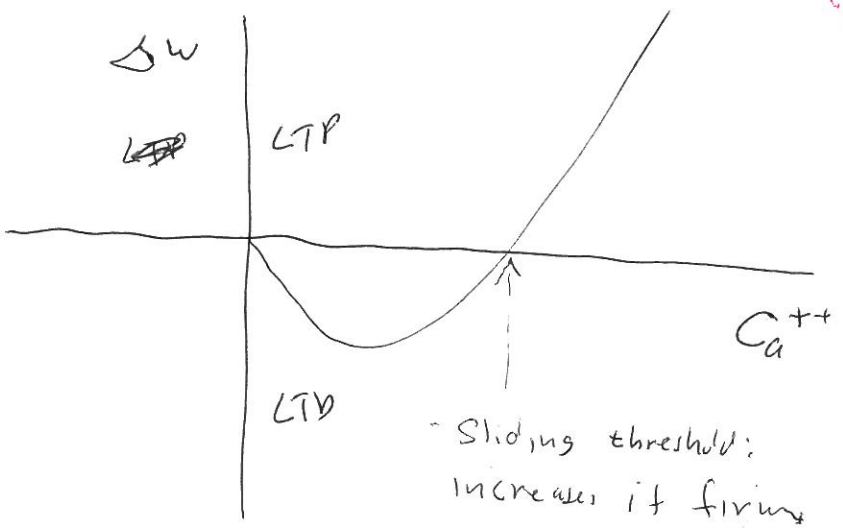
Situation is more complicated



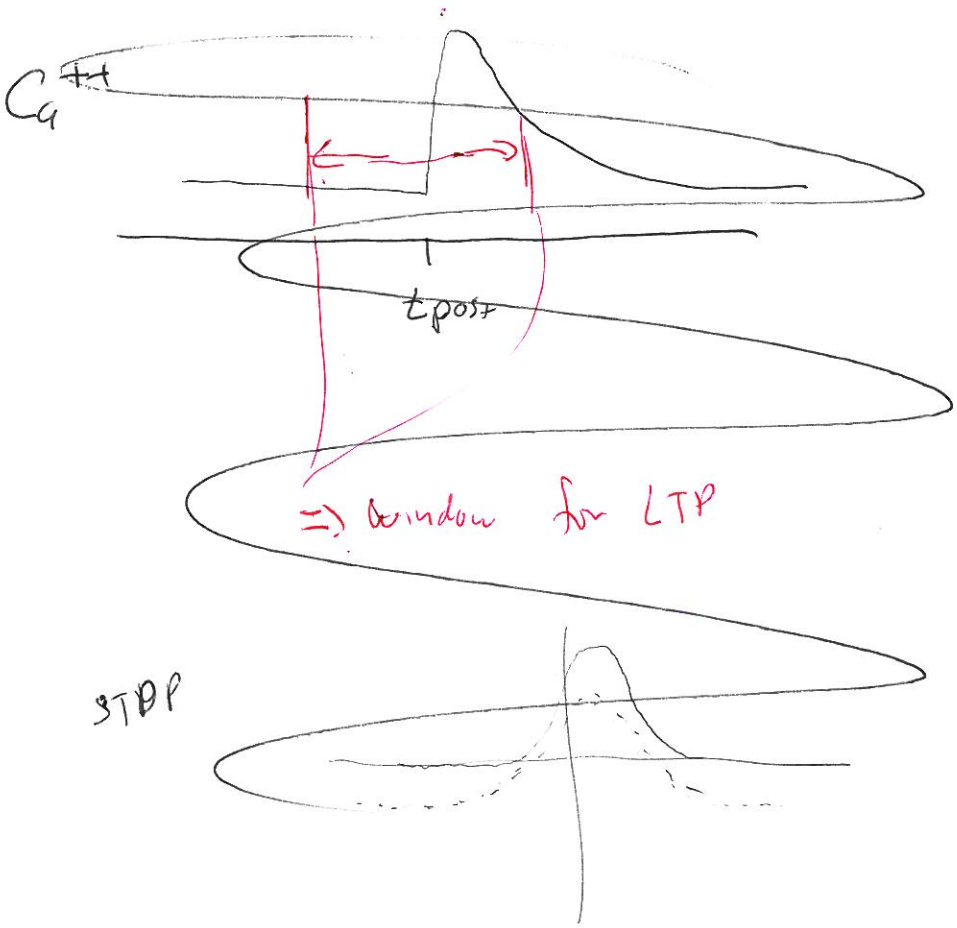
} Which is pre + which is post?
no complete model yet!

Normalization: BCM

BCS: Bardeen Cooper ~~Schrieffer~~ Schrieffer - nobel prize for superconductivity
look up!



- Sliding threshold: increases if firing rate of cell is too high
- some experimental evidence
- doesn't account for STDP



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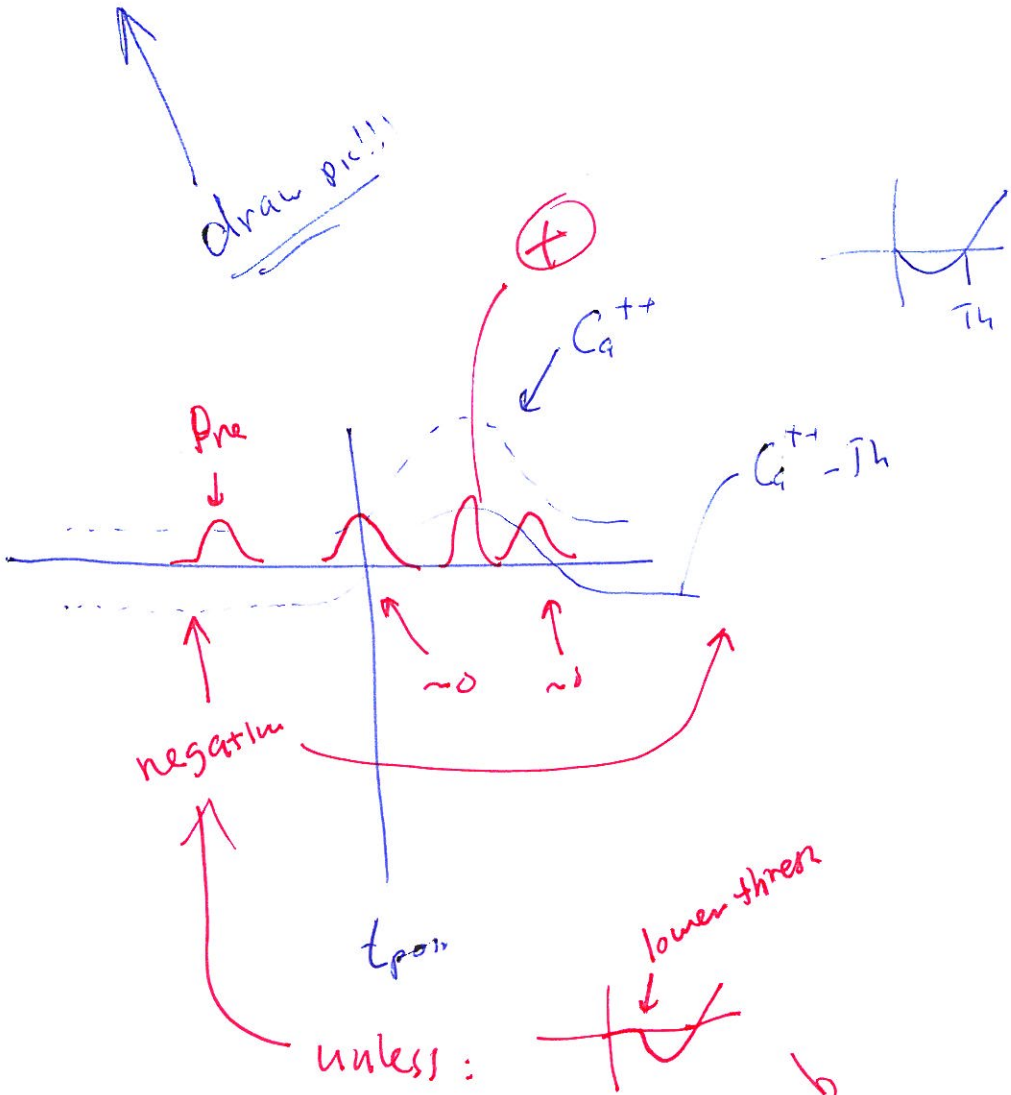
Ca++
LTP
LTD
LTD
tpost - tpre


draw pic!!!
+
Ca++
Th
Pre
Ca++ - Th
~0
~0
negativ
tpost
unless:
lower threshold
hard to see real effect!