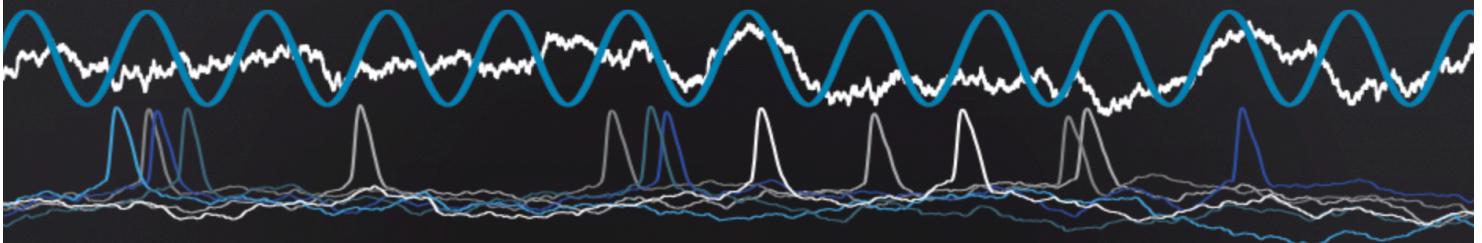
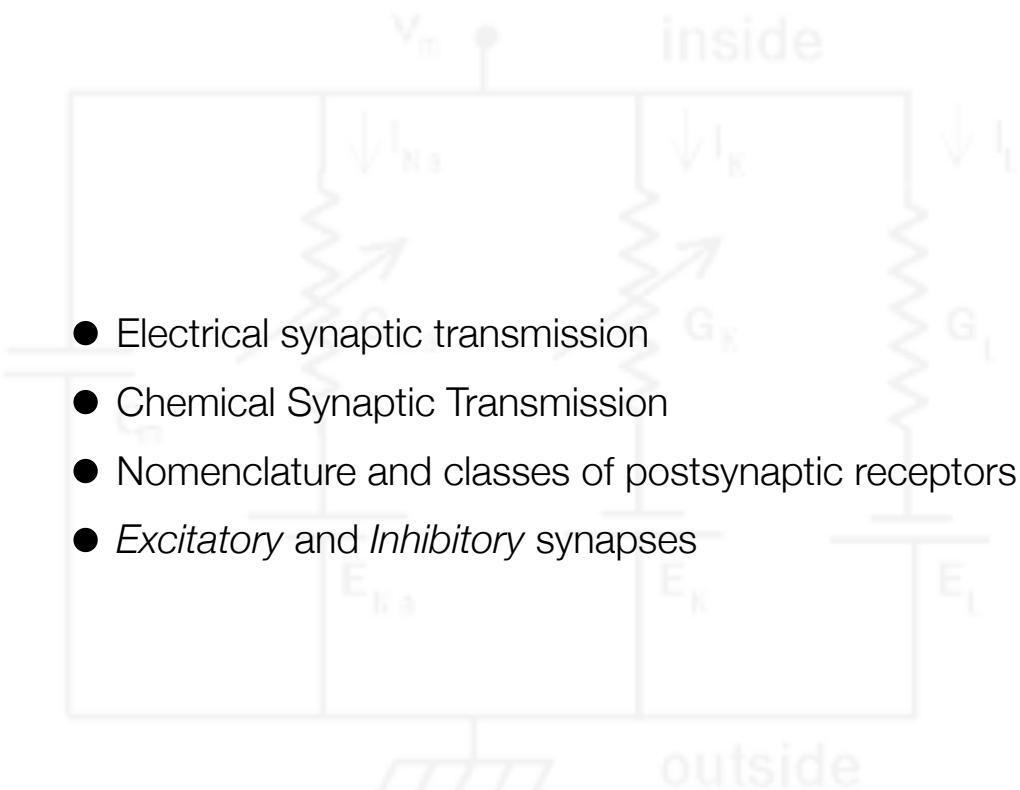


# ELECTROPHYSIOLOGICAL SIGNALS

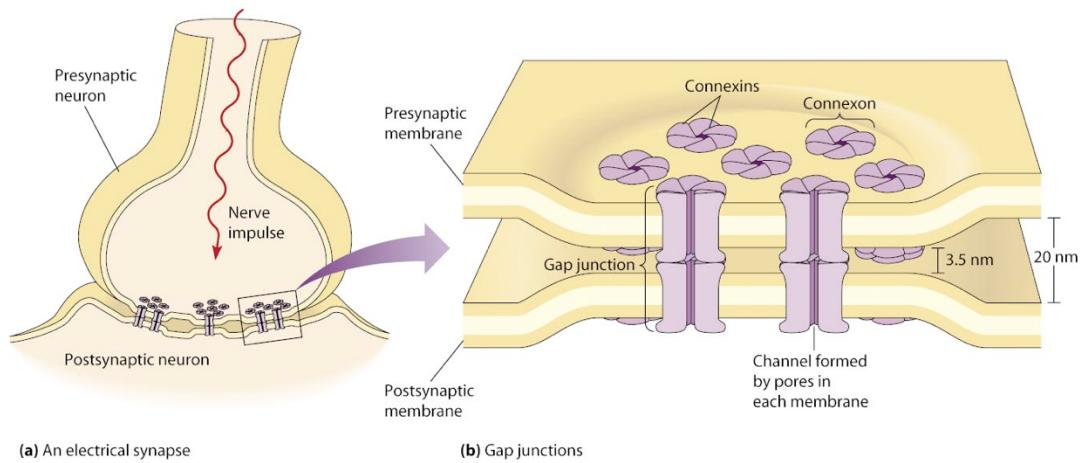


GENERATION AND CHARACTERISATION

Michele GIUGLIANO  
**Synaptic transmission**

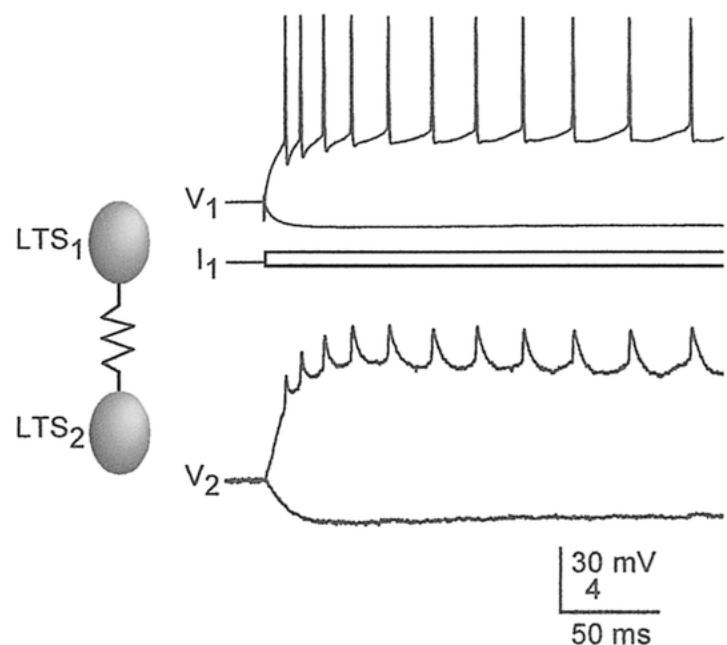


## Electrical synaptic transmission [bidirectional, slow, without “sign”]

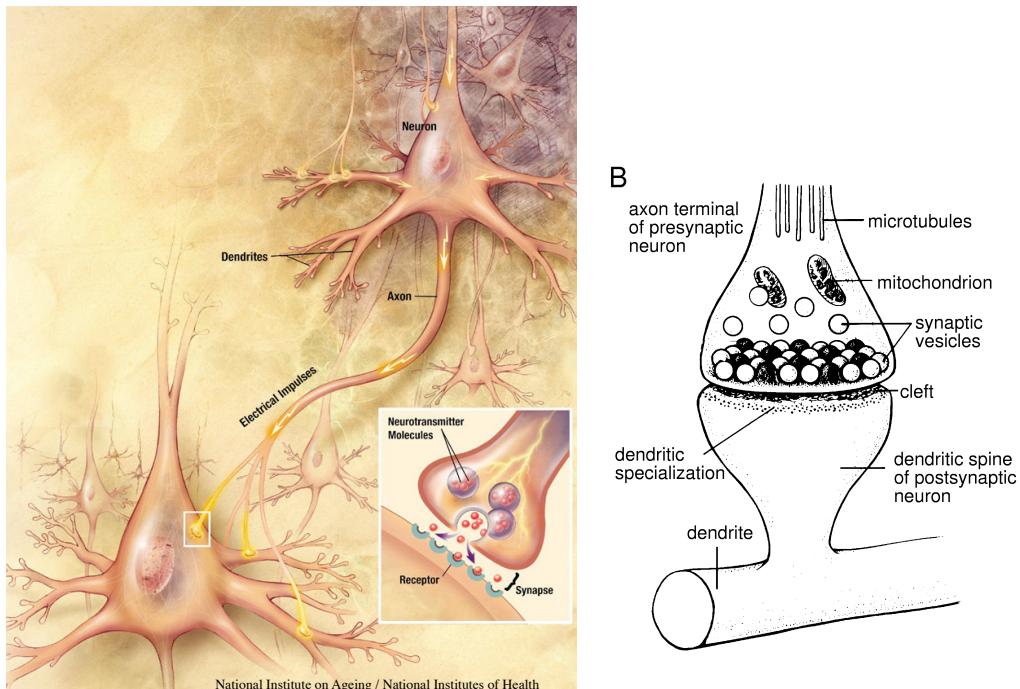


Copyright © 2009 Pearson Education, Inc.

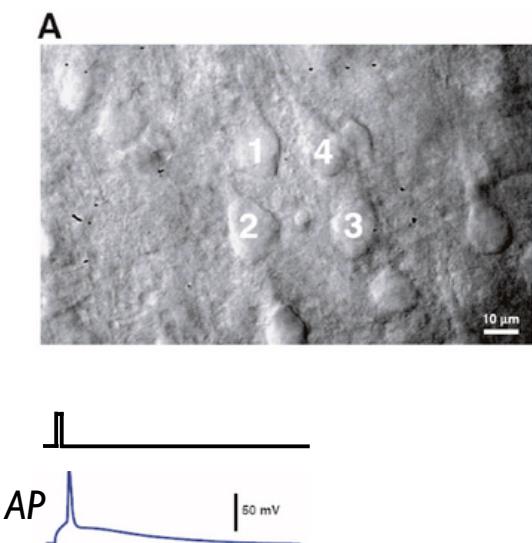
## Electrical synaptic transmission [bidirectional, slow, without “sign”]



## Chemical synaptic transmission [unidirectional, fast, with “sign”]

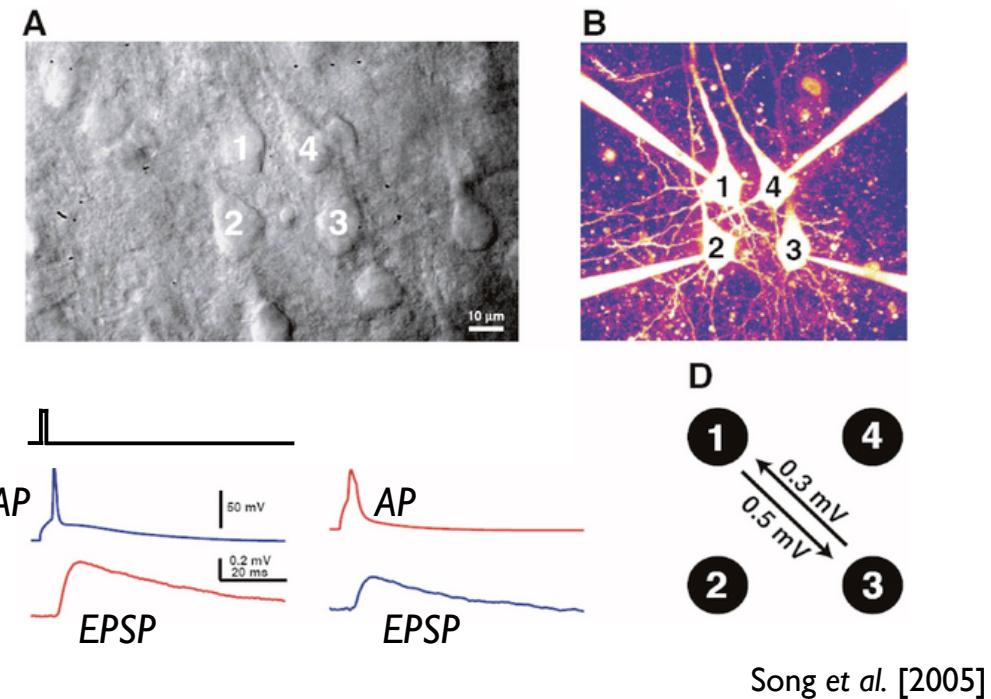


Simultaneous whole-cell patch-clamp recordings  
from several neurons simultaneously



Song et al. [2005]

## Simultaneous whole-cell patch-clamp recordings from several neurons simultaneously



Song et al. [2005]

Chemical synaptic transmission:  
release of neurotransmitter upon arrival of an AP

EPSCs - excitatory postsynaptic currents

EPSPs - excitatory postsynaptic potentials

[IPSCs - inhibitory postsynaptic currents]

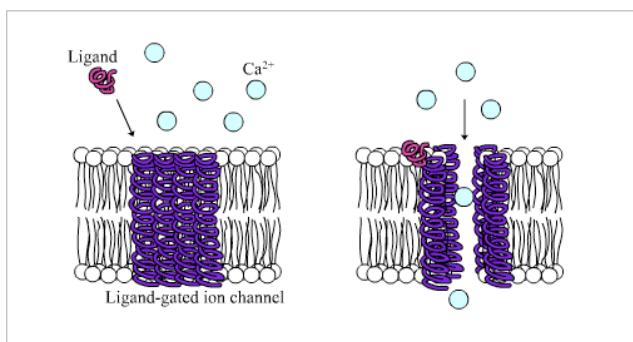
[IPSPs - inhibitory postsynaptic potentials]



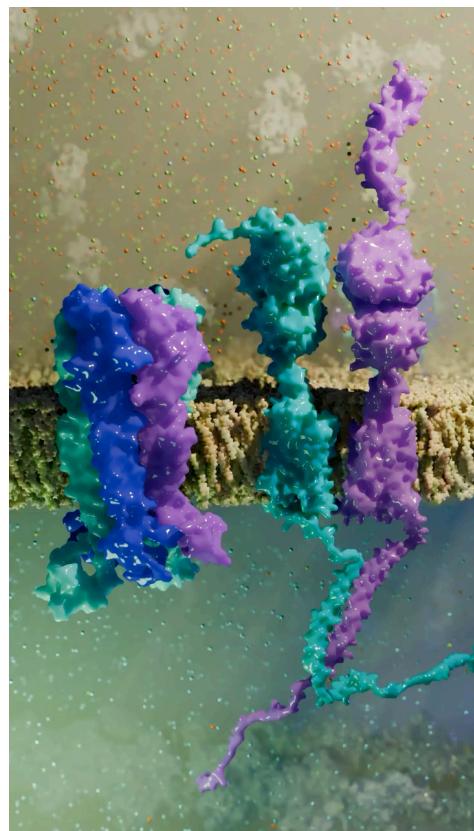
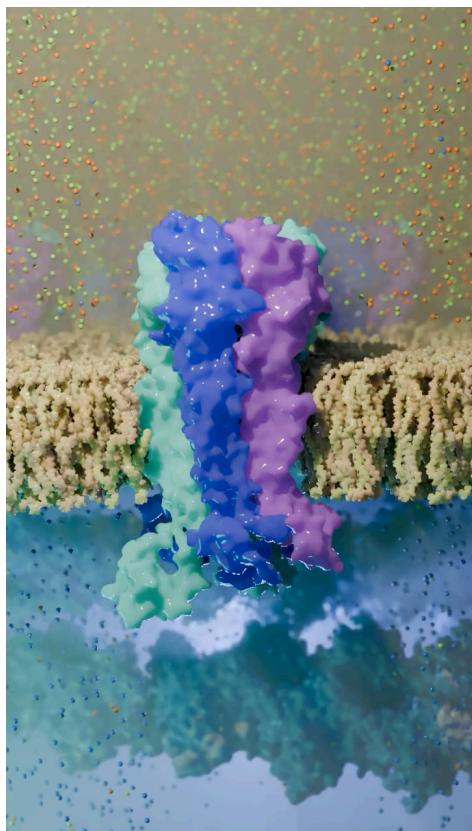
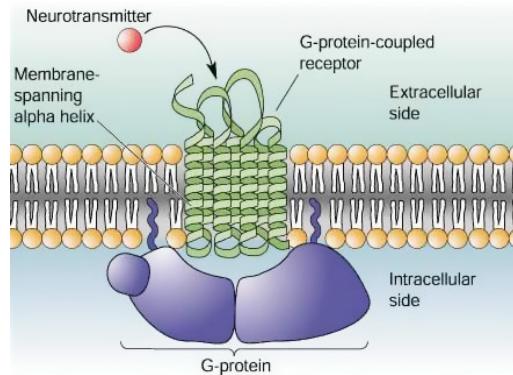
# Synaptic receptors

[located on the membrane of the postsynaptic - i.e. target - neuron]

## *Ionotropic receptors* [i.e. pore]



## *Metabotropic receptors* [i.e. no pore exists!]



## Excitatory Synaptic transmission mediated by receptors permeable to Na<sup>+</sup> and/or Ca<sup>++</sup>

**Mediated by  
“fast-activating” receptors**

receptors are ligand-gated  
ion channels  
[i.e. ionotropic receptors]

AMPAr

NMDAr

ACh r

$$E_{syn} = \frac{R T}{z F} \log \left( \frac{C_{out}}{C_{in}} \right) > V_{rest}$$

**Mediated by  
“slow-activating” receptors**

receptors are ligand-activated  
protein that trigger an intracellular  
cascade of reactions leading to  
[intracellular-side] gating of channels  
[i.e. metabotropic receptors]

## Inhibitory Synaptic transmission mediated by receptors permeable to K<sup>+</sup> or Cl<sup>-</sup>

**Mediated by  
“fast-activating” receptors**

receptors are ligand-gated  
ion channels  
[i.e. ionotropic receptors]

GABA-A r

Gly r

$$E_{syn} = \frac{R T}{z F} \log \left( \frac{C_{out}}{C_{in}} \right) < V_{rest}$$

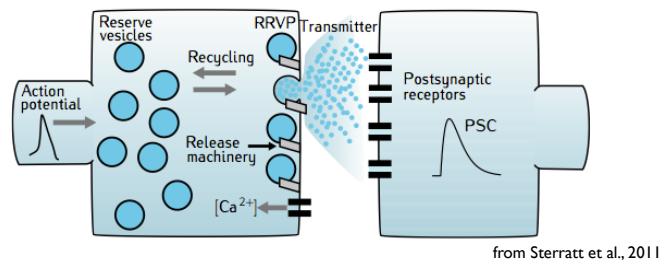
**Mediated by  
“slow-activating” receptors**

receptors are ligand-activated  
protein that trigger an intracellular  
cascade of reactions leading to  
[intracellular-side] gating of channels  
[i.e. metabotropic receptors]

GABA-B r

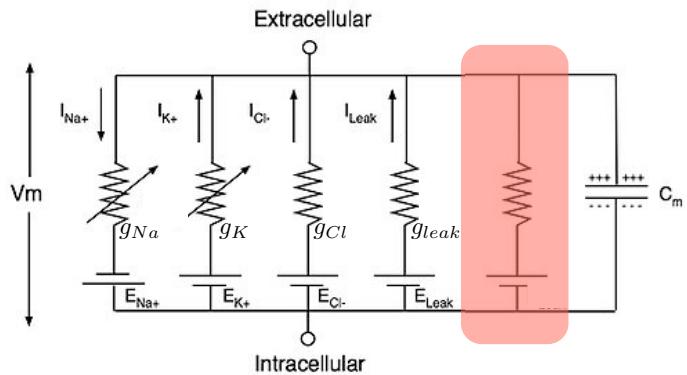
## Chemical synaptic transmission

[unidirectional, fast, with “sign”]



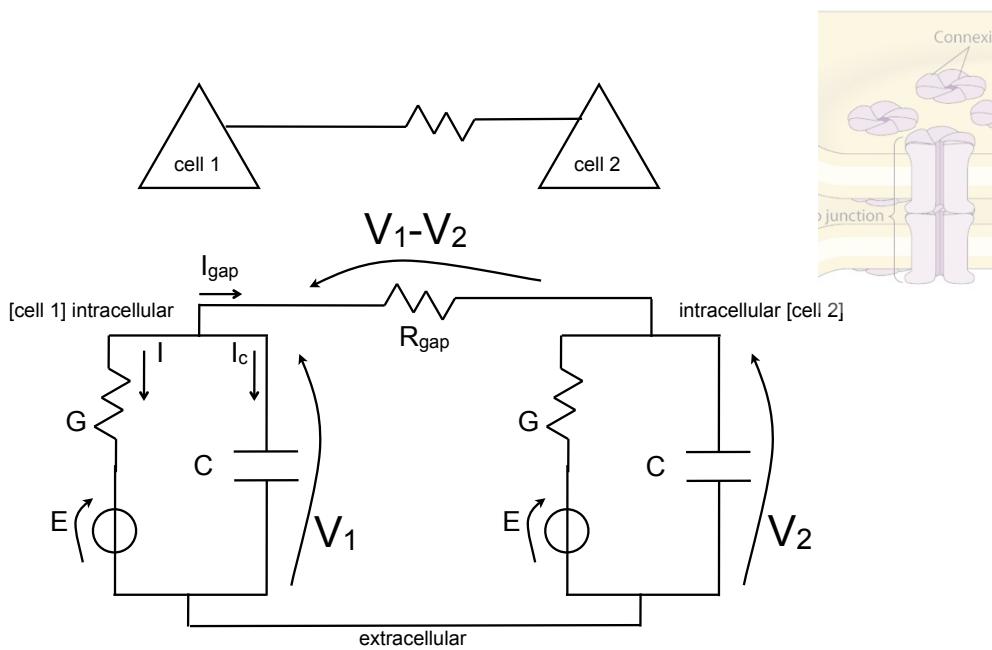
from Sterratt et al., 2011

$$I_{syn} = g_{syn}(t) (E_{syn} - V_m)$$



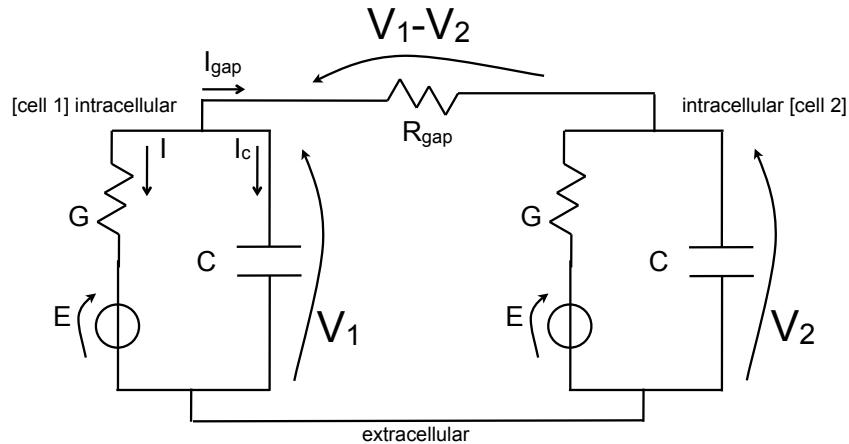
## Electrical synaptic transmission

[bidirectional, slow, without “sign”]

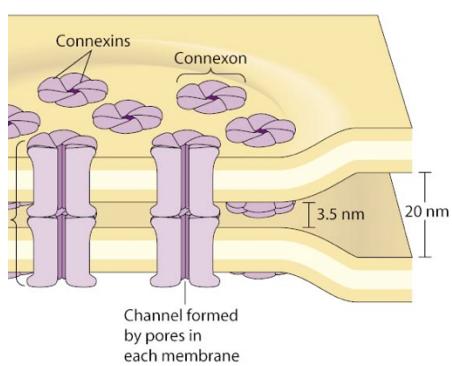


$$C \frac{dV_1}{dt} = G (E - V_1) - \frac{(V_1 - V_2)}{R_{gap}}$$

$$C \frac{dV_2}{dt} = G (E - V_2) + \frac{(V_1 - V_2)}{R_{gap}}$$



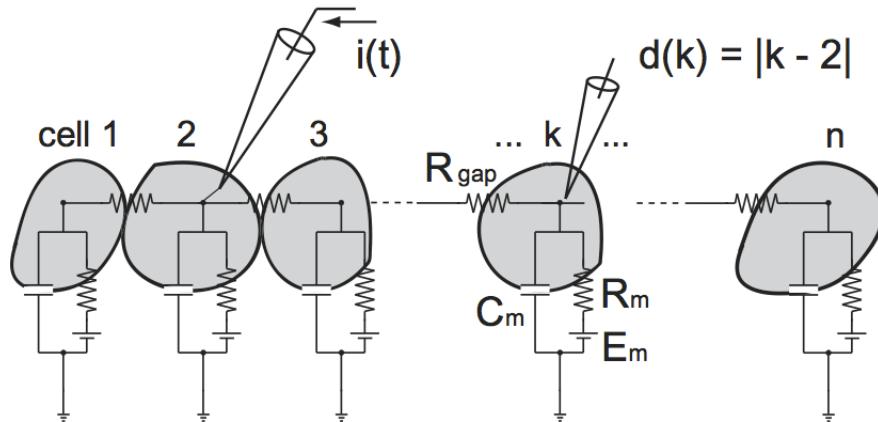
**Electrical synaptic transmission**  
[bidirectional, slow, without “sign”]



$$I_{syn} = g_{gap} (V_{pre} - V_{post})$$

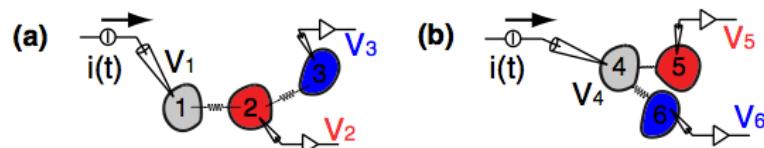
## Electrical synaptic transmission at the steady-state [i.e., DC regimes]

$$\frac{dV_1}{dt} = \frac{dV_2}{dt} = 0$$



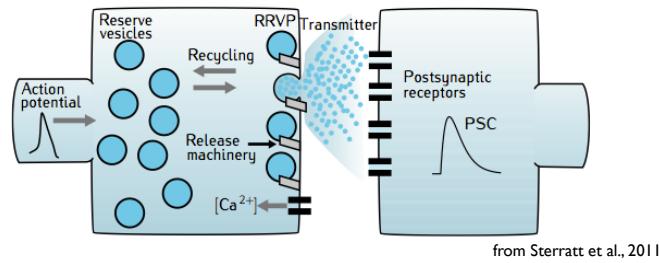
A cascade of gap-junction coupled neurons is like a **series** of resistors....

How to deduce experimentally  
the connectivity of electrically-coupled networks?



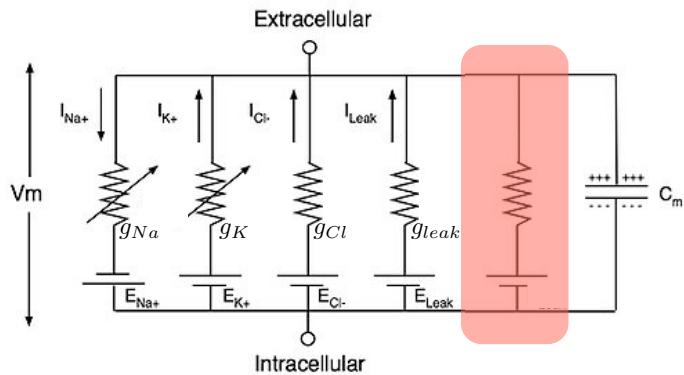
## Chemical synaptic transmission

[unidirectional, fast, with “sign”]



from Sterratt et al., 2011

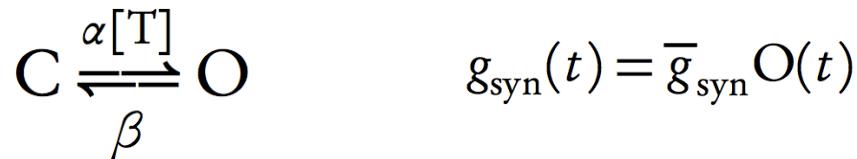
$$I_{syn} = g_{syn}(t) (E_{syn} - V_m)$$



## Chemical synaptic transmission

[unidirectional, fast, with “sign”]

model of a ionotropic receptor



$$\frac{dO(t)}{dt} = -\beta O + \alpha [T] C$$

$$\frac{dC(t)}{dt} = +\beta O - \alpha [T] C$$

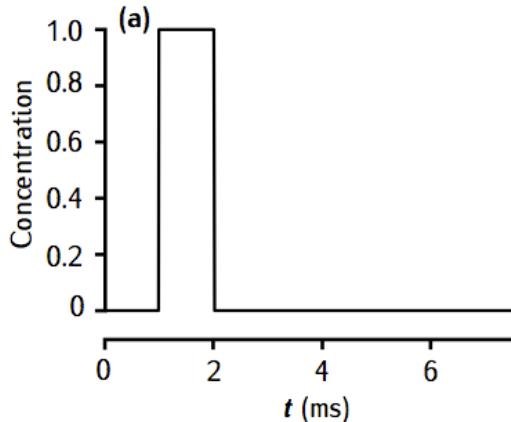
$$O(t) + C(t) = 1$$

Destexhe et al. [1994]

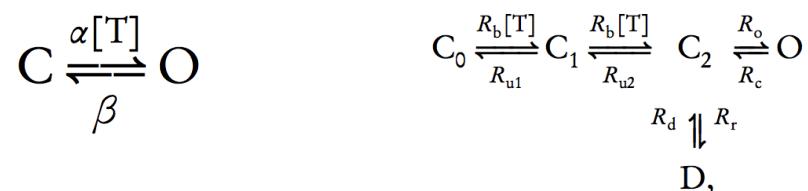
$$\frac{dO}{dt} = \frac{O_\infty - O}{\tau_O}$$

$$O_\infty = \frac{\alpha T(t)}{\alpha T(t) + \beta}$$

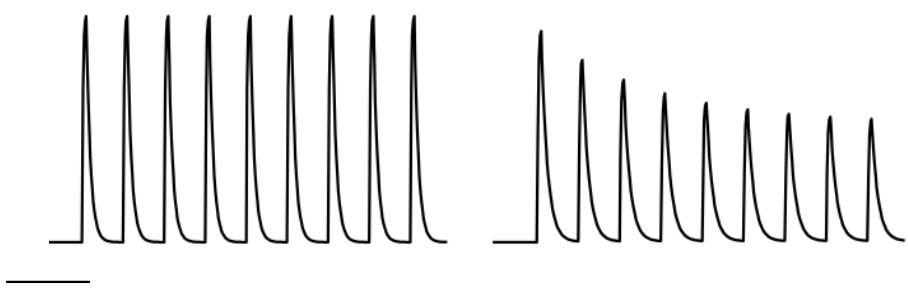
$$\tau_O = \frac{1}{\alpha T(t) + \beta}$$



from Sterratt et al., 2011



$$I_{syn} = \bar{g}_{syn} O(t) (E_{syn} - V_m)$$



Destexhe et al. [1994]

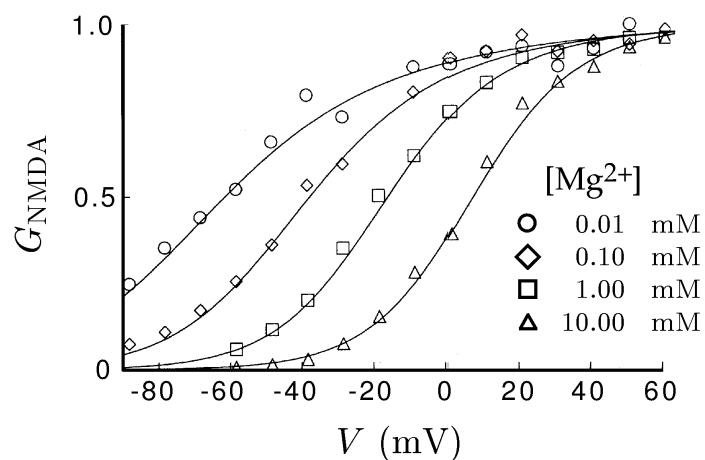
# NMDAr and hyperactivity: why?



NMDAr: Ligand- and voltage-dependent synaptic currents  
 [this has the potential for pre/post coincidence-detection]

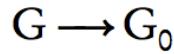
$$I_{NMDA_R} = G_{NMDA_R} r(t) (E_{NMDA_r} - V_m)$$

$$G_{NMDA_R} = G_{NMDA_R}(V, [Mg^{2+}])$$



## Chemical synaptic transmission

model of a metabotropic receptor



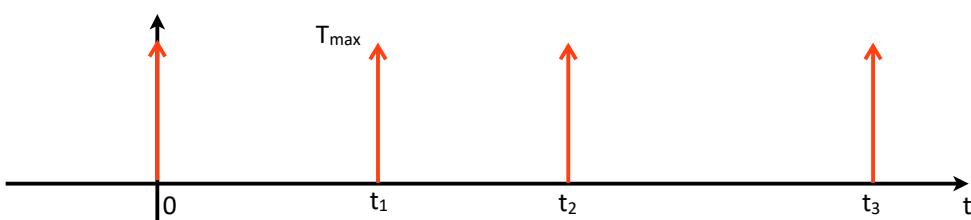
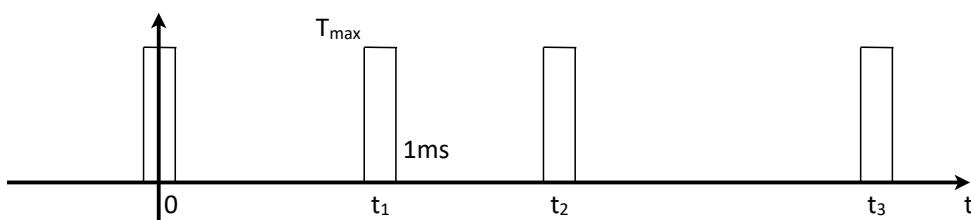
$$g_{syn}(t) = \bar{g}_{syn} O(t)$$

$$I_{syn} = \bar{g}_{syn} O(t) (E_{syn} - V_m)$$

## Chemical synaptic transmission

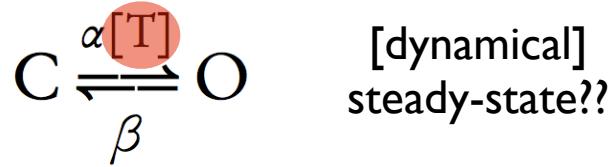
simplified description of [a population of] ionotropic receptors

- A **train** of presynaptic action potentials leads to a “train” of pulses  $[T](t)$ :



## Chemical synaptic transmission

simplified description of [a population of] ionotropic receptors



$$\frac{dO(t)}{dt} = -\beta O + \alpha [T] C$$

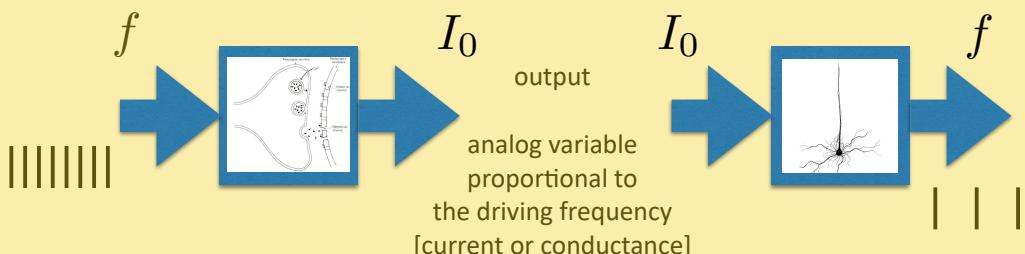
$$\frac{dO}{dt} = -\beta O + \alpha T_{max}(1 - O) \sum_k \delta(t - t_k)$$

$$\frac{dO}{dt} \approx -\beta O + \alpha T_{max} \sum_k \delta(t - t_k)$$

$$O(t_{k+1}^+) \approx O(t_k^+) e^{-\beta (t_{k+1} - t_k)} + \alpha T_{max}$$

$$O_{SS} \approx \alpha T_{max} \beta^{-1} f$$

Very rough (functional) approximation



$$O_{SS} \approx \alpha T_{max} \beta^{-1} f$$

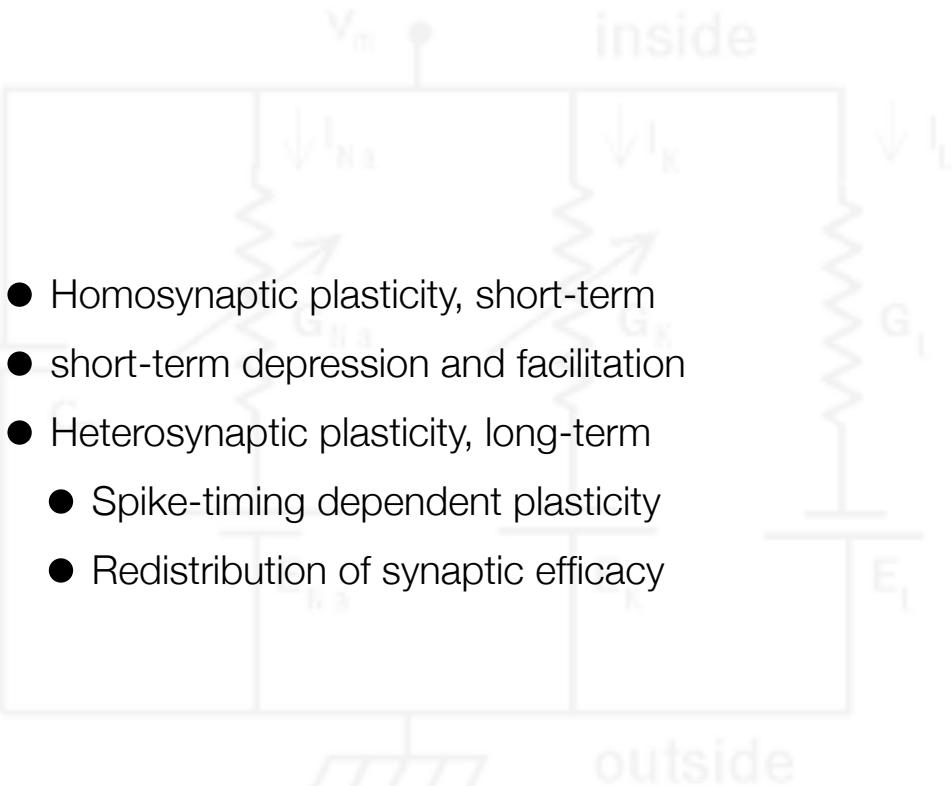
$$f(I) \approx \frac{I_0}{C(V_{th} - E)}$$

A synapse is a device that converts input spike trains with a certain **frequency**, into an average current (**amplitude**).

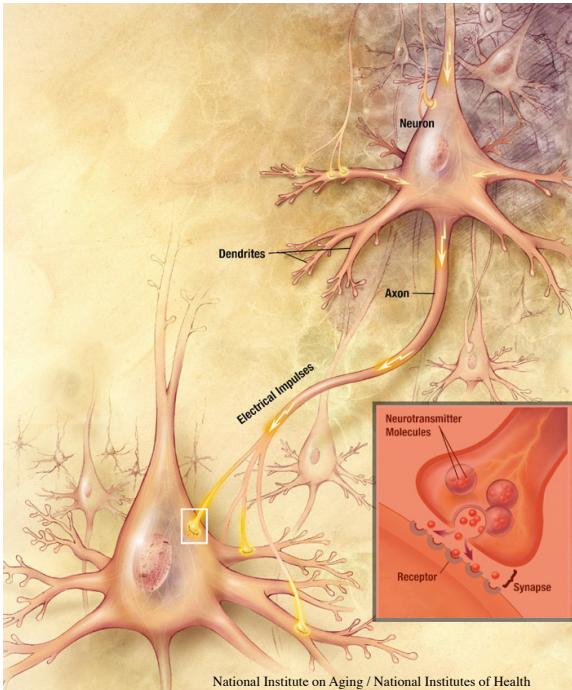
# ATTENDANCE TRACKING - **code ???**

(for statistical purposes only)

<https://www.unimore.it/it/servizi/unimore-app>



## Synaptic connections are more than connecting plugs



National Institute on Aging / National Institutes of Health

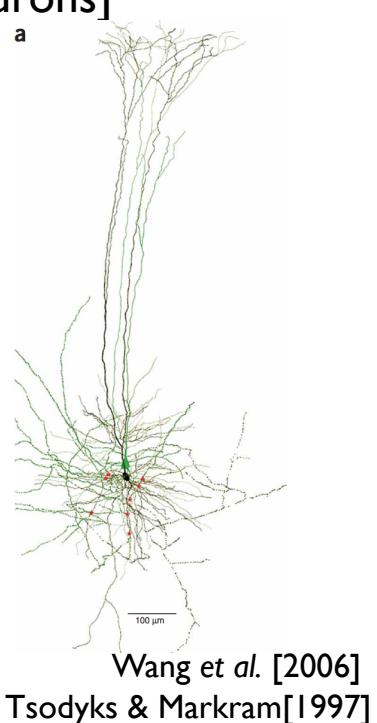
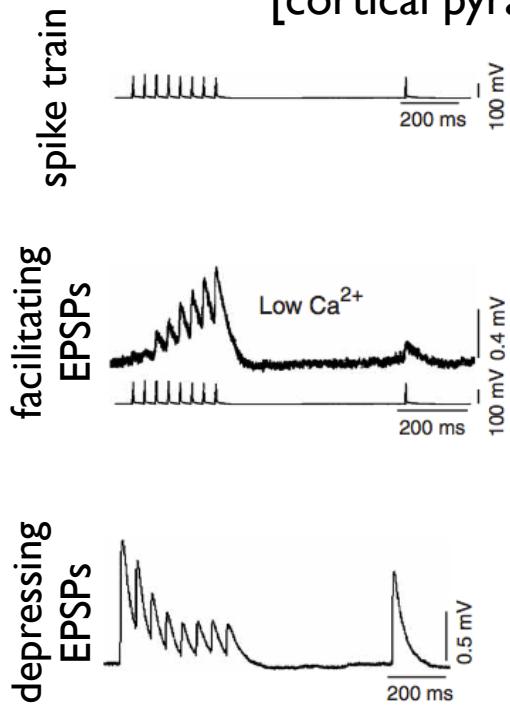
They are physical systems  
implementing a **dynamical**  
communication channel...

Like all physical system they may show  
[**transient**] inertia, fatigue, or  
depression during repeated activation.

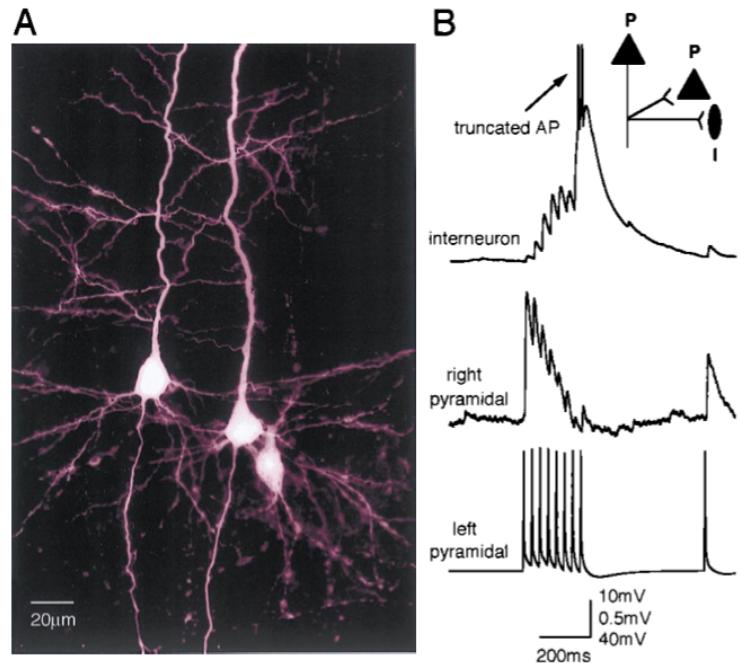
They may also, on the contrary,  
[**transiently**] warm up upon use and  
facilitate further communications.

**Short-term** [homosynaptic] plasticity.  
[neuromuscular junction, central syn.]

### Short-term plasticity: facilitation and depression [cortical pyramidal neurons]

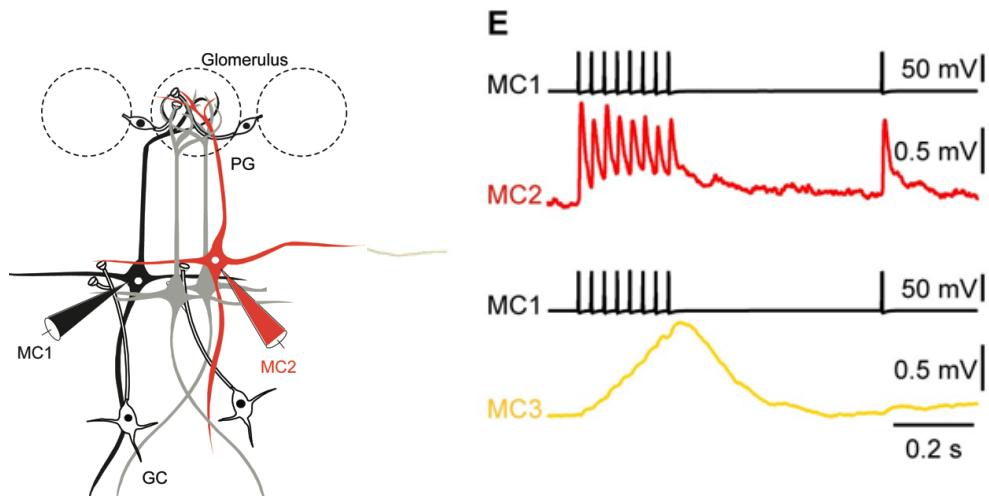


## Short-term plasticity: facilitation and depression



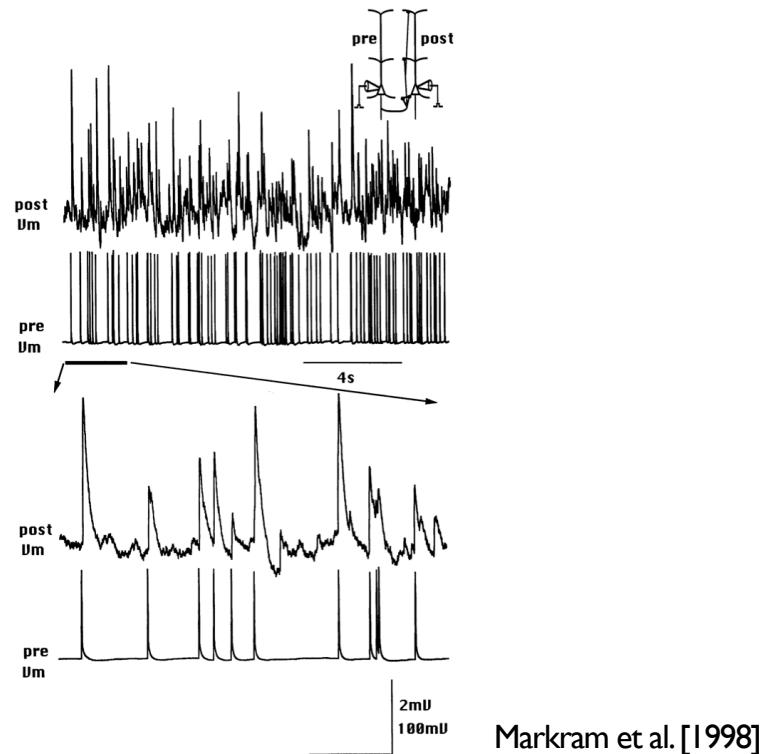
Markram et al. [1998]

## Short-term plasticity: facilitation and depression [olfactory bulb, mitral cells, same glomerulus]

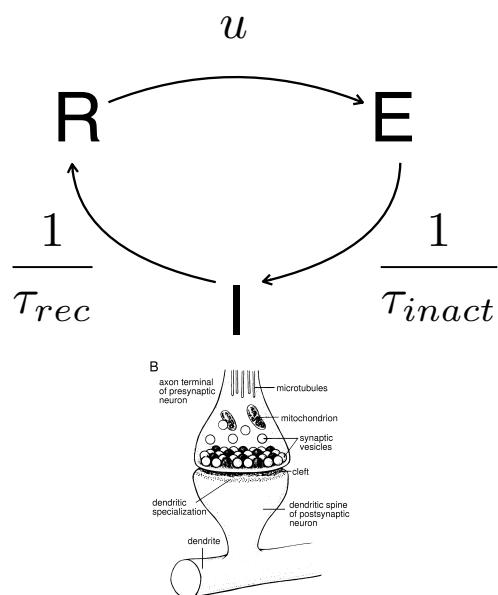


Pignatelli et al.

## Impact of short-term synaptic plasticity



## Short-term synaptic depression



$$\frac{dR}{dt} = -uR + \frac{1}{\tau_{rec}}I$$

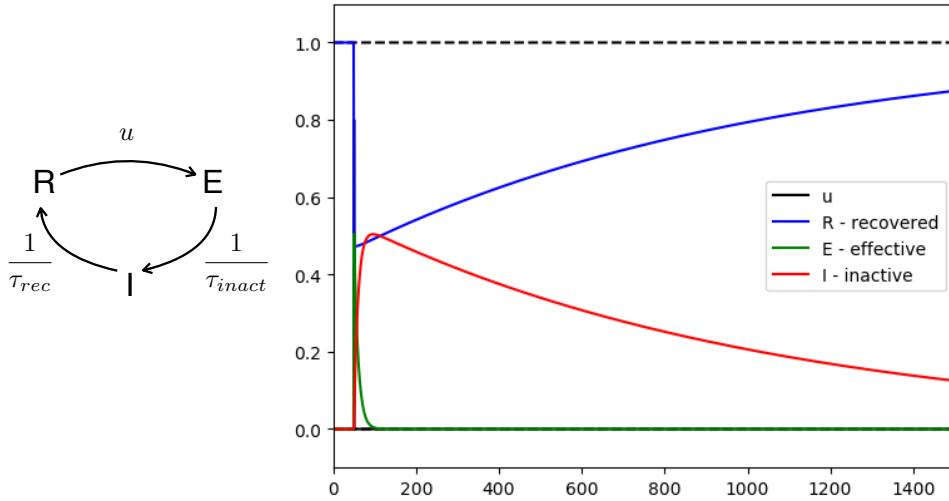
$$\frac{dE}{dt} = +uR - \frac{1}{\tau_{inact}}E$$

$$\frac{dI}{dt} = +\frac{1}{\tau_{inact}}E - \frac{1}{\tau_{rec}}I$$

$$\tau_{rec} \gg \tau_{inact}$$

[Pre]synaptic resources [e.g., vesicles]

## Short-term synaptic depression



- (i) Activation of vesicles (exocytosis), upon a presynaptic AP, is extremely fast.
- (ii) The inactivation processes are fast and (iii) vesicles replenishing is much slower.

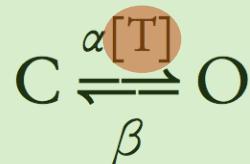
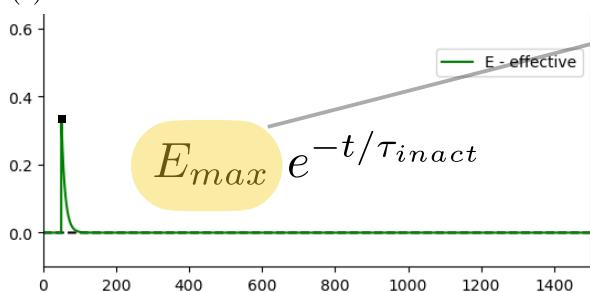
$$u = U\delta(t - t_{AP}) \quad \tau_{rec} \gg \tau_{inact}$$

$$\frac{dE}{dt} = +uR - \frac{1}{\tau_{inact}}E \quad u = U\delta(t - t_{AP})$$

$$\tau_{inact} \frac{dE}{dt} = uR\tau_{inact} - E$$

(ii) The inactivation processes are fast  
therefore  $E$  is approximately at its steady-state...

$$E \approx uR\tau_{inact}$$



$$\frac{dO}{dt} \approx -\beta O + \alpha T_{max} \sum_k \delta(t - t_k)$$

$$E_{max} = \frac{1}{\tau_{inact}} \int_{-\infty}^{+\infty} E(t) dt$$

$$E_{max} \approx UR(t_{AP})$$

## Short-term synaptic depression

$$E \approx uR\tau_{inact} \quad E_{max} \approx UR(t_{AP})$$

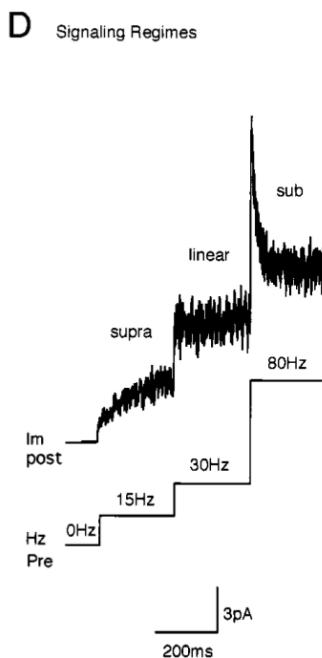
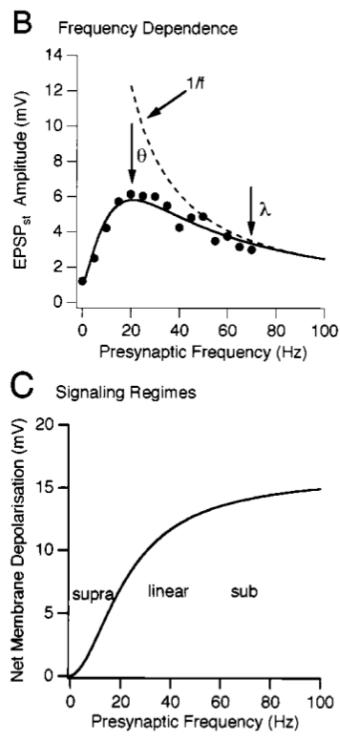
$$I = 1 - R - E \approx 1 - (1 + U\delta(t - t_{AP}))R$$

$$\frac{dR}{dt} = -uR + \frac{1}{\tau_{rec}}I$$

$$\frac{dR}{dt} \approx \frac{1 - R}{\tau_{rec}} - U\delta(t - t_{AP})R(1 + \frac{\tau_{inact}}{\tau_{rec}})$$

$$\frac{dR}{dt} \approx \frac{1 - R}{\tau_{rec}} - U\delta(t - t_{AP})R$$

## Impact of short-term synaptic plasticity



$$R_\infty = \frac{1 - e^{-T/\tau_{rec}}}{1 - (1 - U)e^{-T/\tau_{rec}}}$$

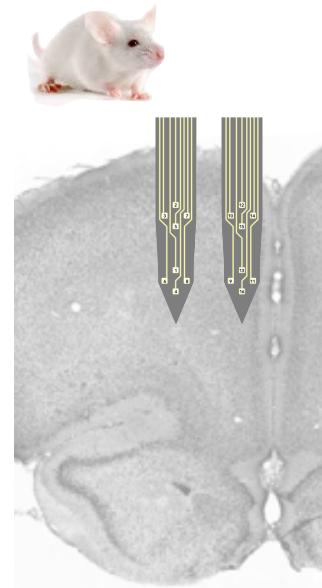
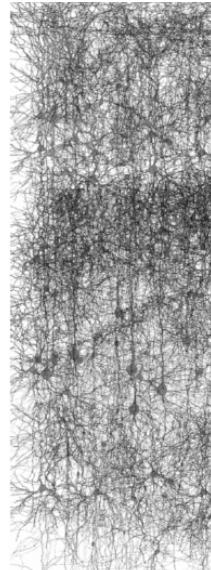
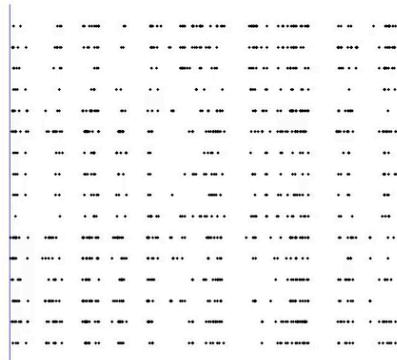
$$\approx \frac{A}{f \cdot \tau_{rec}}$$

Markram et al. [1998]

# *In vivo* cortical networks [transient] synchronisation

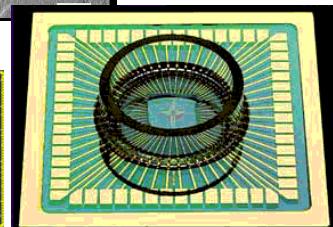
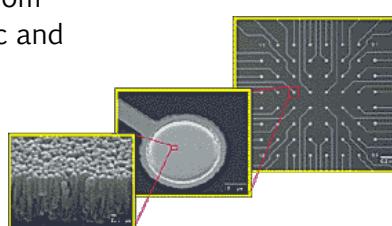
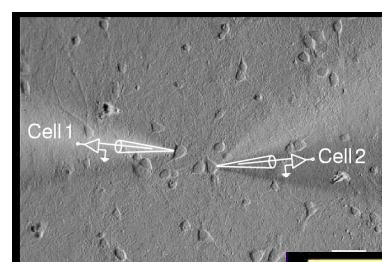


J. Couto

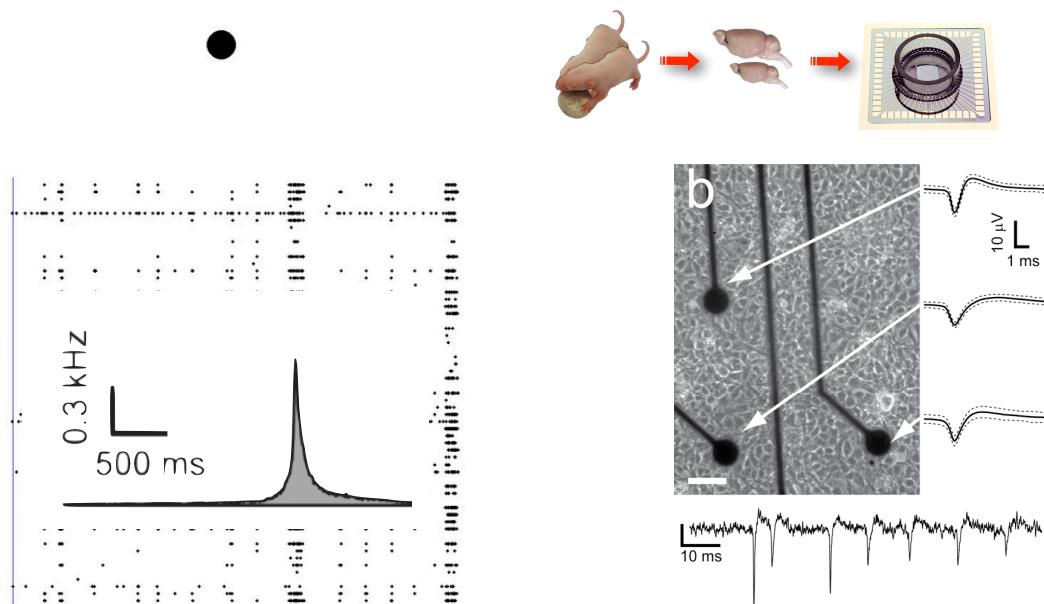


in vitro: spontaneous activity  
cultured dissociated neurons

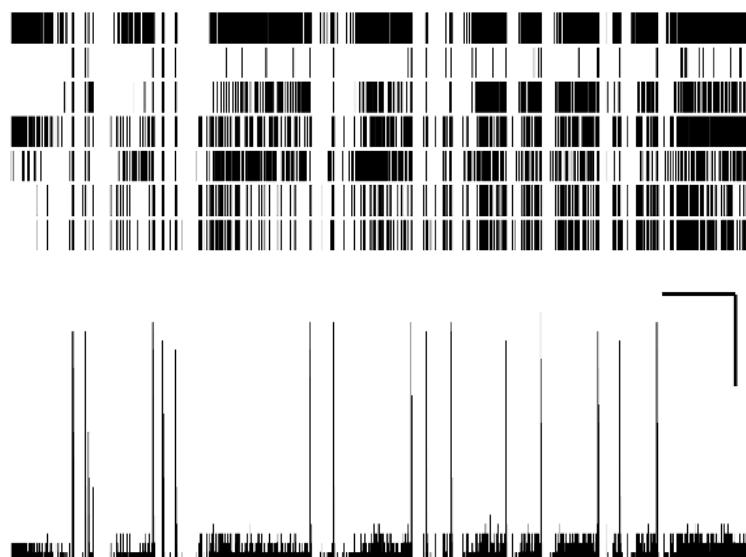
- dissociated from the cortical tissue,
- neurons develop ex vivo, reorganising into 2D random networks of glutamatergic and gabaergic cells



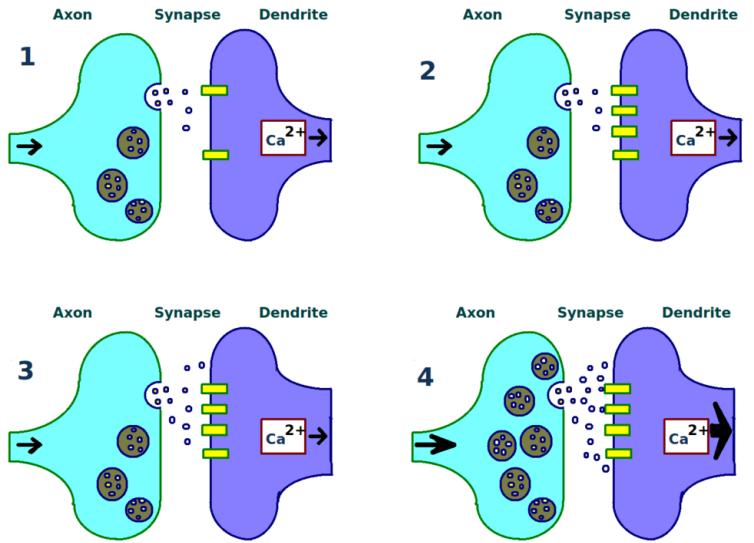
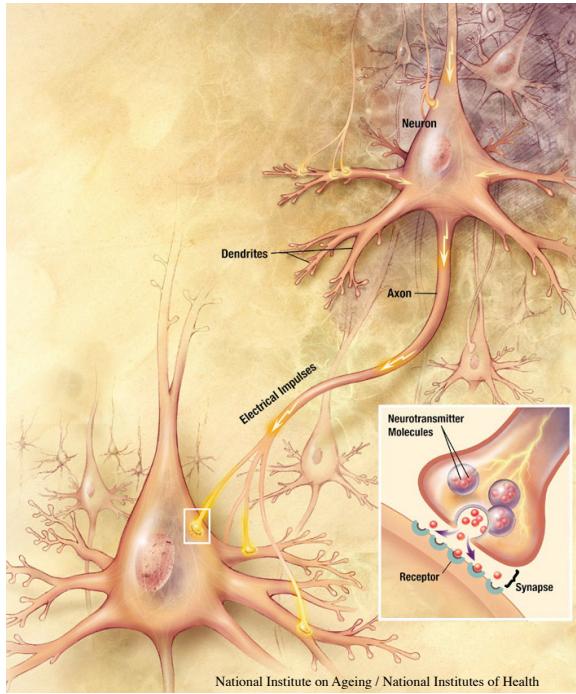
# *Ex vivo* cortical networks spontaneous [transient] synchronisation



# *Ex vivo* cortical networks spontaneous [transient] synchronisation



## Long-term synaptic plasticity



Levy & Stewart (1988)  
Gerstner et al. (1996)  
Markram et al. (1997)  
Bi & Poo (1998)  
Sjöström et al. (2001)

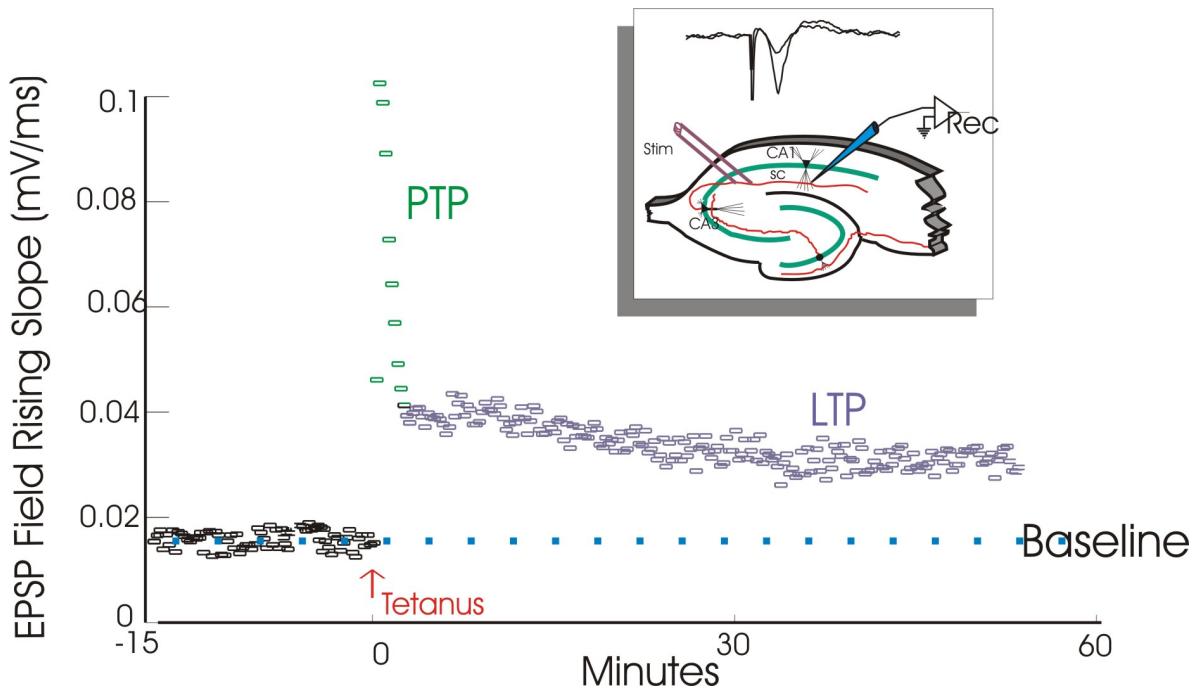


Donald Hebb, 1949

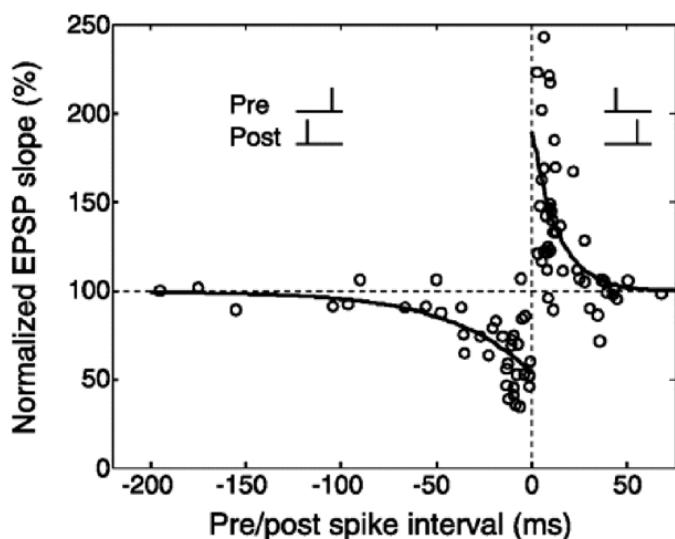
*“When an axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased.”*

*Cells that “fire” together, “wire” together.*

## e.g. Classic (hippocampal) LTP



## Long-term (hetero)synaptic plasticity (STDP)

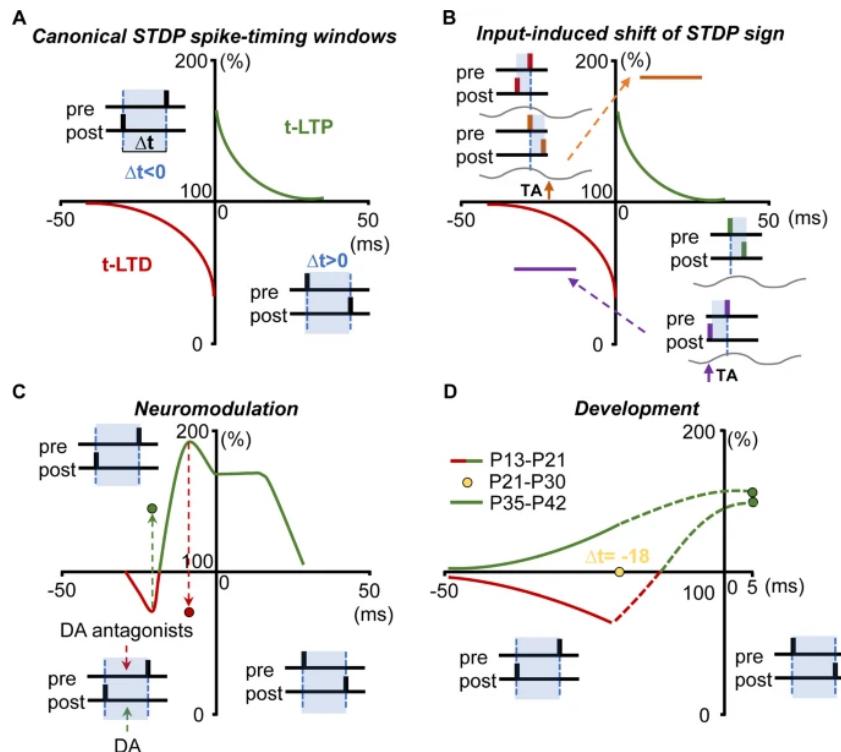


It has been found in neocortical, hippocampal, olfactory systems.

It depends on the causal relationship between pre- and post-synaptic timing.

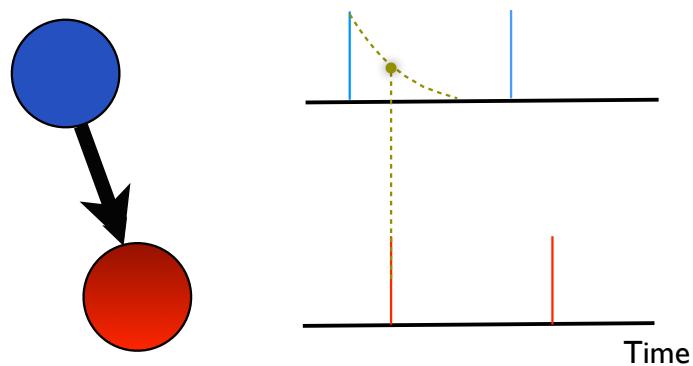
LTD                    LTP

Levy & Stewart (1988)  
Gerstner et al. (1996)  
Markram et al. (1997)  
Bi & Poo (1998)  
Sjöström et al. (2001)



Andrade-Talavera et al., 2023

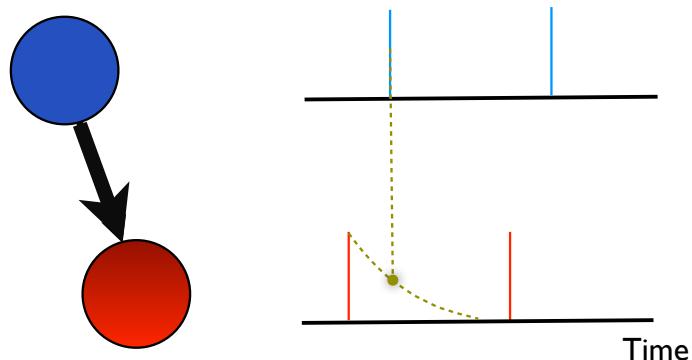
## Spike Timing Dependent Plasticity



### Long-Term Potentiation

Markram et al. (1997)  
Sjöström et al. (2001)  
**Pfister & Gerstner (2006)**  
Clopath et al. (2010)

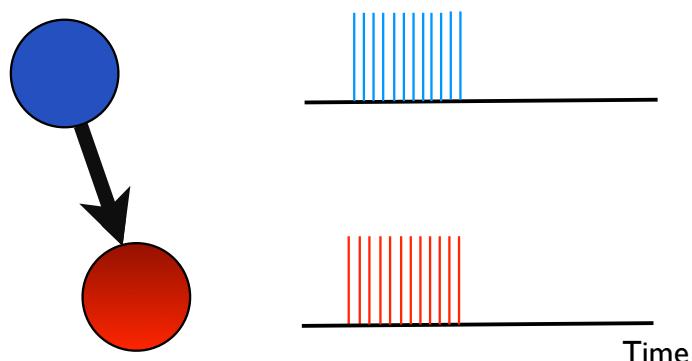
## Spike Timing Dependent Plasticity



Pair interactions Term and Diprass STDP

Markram et al. (1997)  
Sjöström et al. (2001)  
**Pfister & Gerstner (2006)**  
Clopath et al. (2010)

## Spike Timing Dependent Plasticity



Long-Term Potentiation

Markram et al. (1997)  
Sjöström et al. (2001)  
**Pfister & Gerstner (2006)**  
Clopath et al. (2010)

## Interpretation of (seemingly) contradicting results

Layer 5 pyramidal neurons in the rat visual cortex

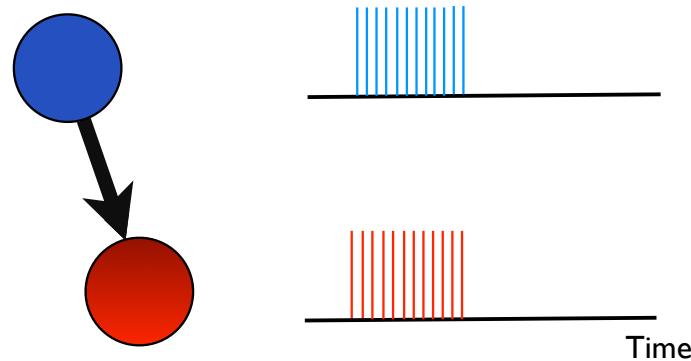


C2 barrel column of mouse primary somatosensory cortex



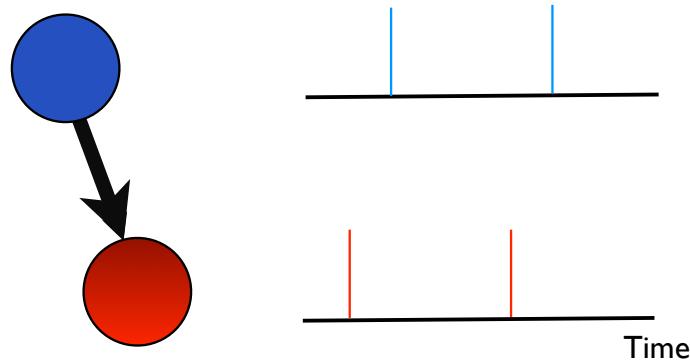
Connectivity is shaped by the neuronal code

Rate code



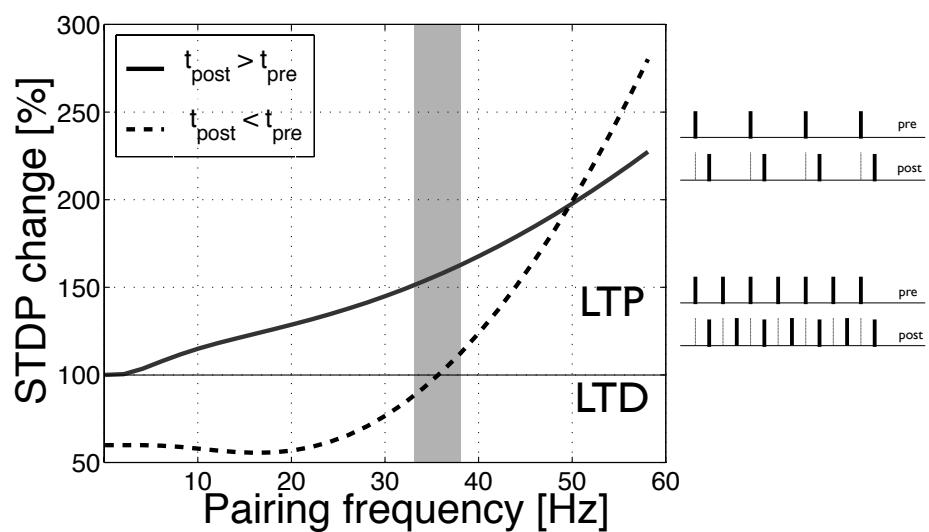
Spikes per time unit

## Temporal code



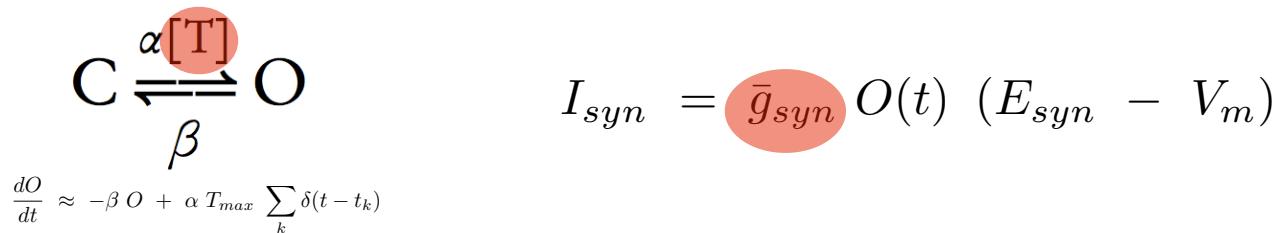
## Timing of the Spike

Frequency-dep. of STDP, described by  
*The triplet rule*



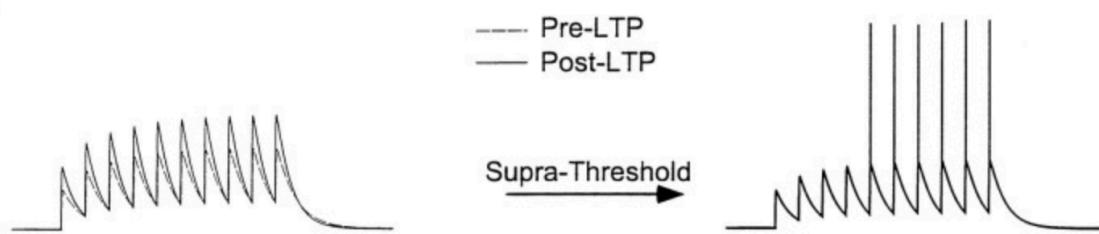
Markram et al. (1997)  
Sjöström et al. (2001)  
**Pfister & Gerstner (2006)**  
Clopath et al. (2010)

## Interactions between long-term and short-term synaptic plasticities

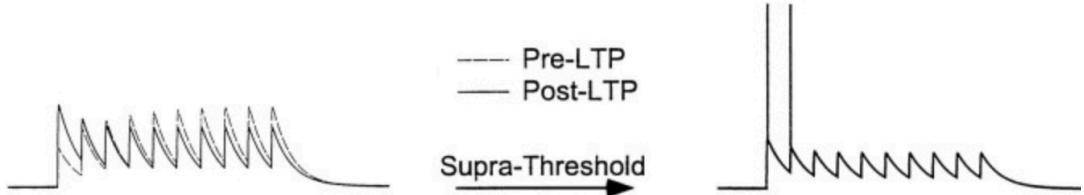


Distinct functional types of associative long-term potentiation in neocortical and hippocampal pyramidal neurons

A.



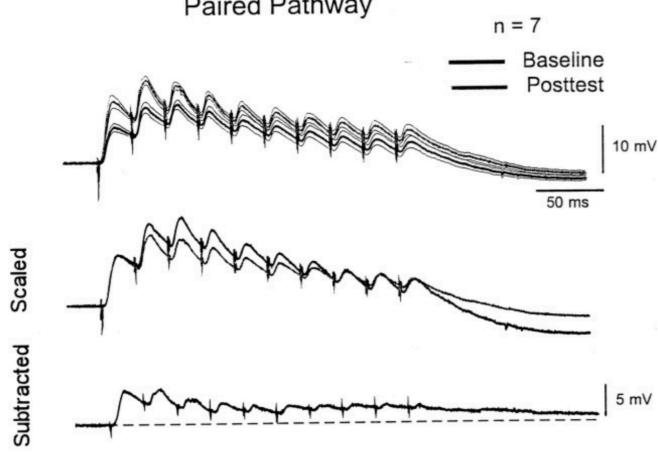
B.



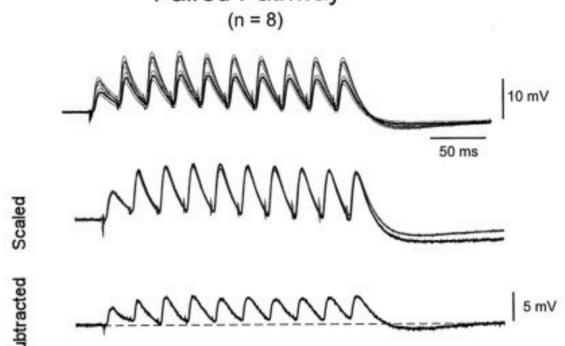
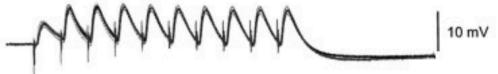
Buonomano (1999)

**Cortex**

A.

**Paired Pathway**

B.

**Unpaired Pathway****Hippocampus****Paired Pathway****Unpaired Pathway**

Buonomano (1999)