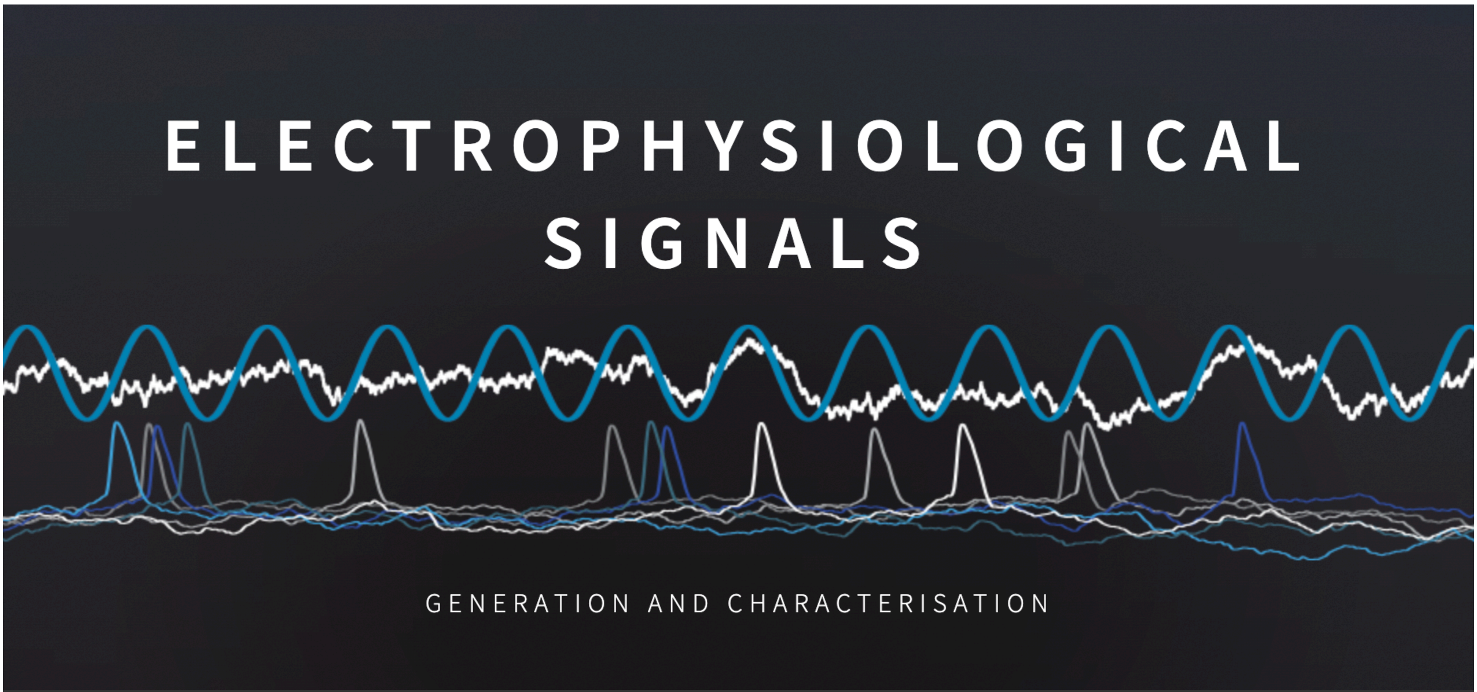
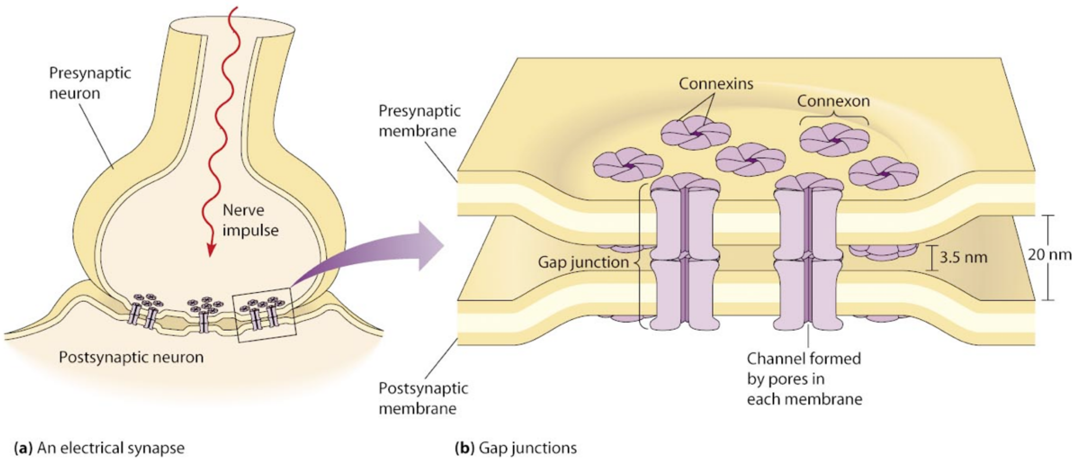


Michele GIUGLIANO

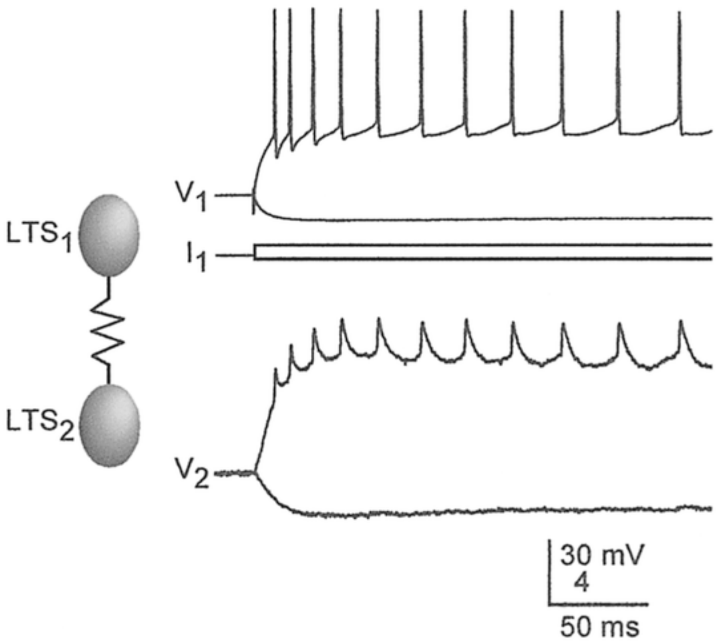
Synaptic transmission

- Electrical synaptic transmission
- Chemical Synaptic Transmission
- Nomenclature and classes of postsynaptic receptors
- *Excitatory* and *Inhibitory* synapses

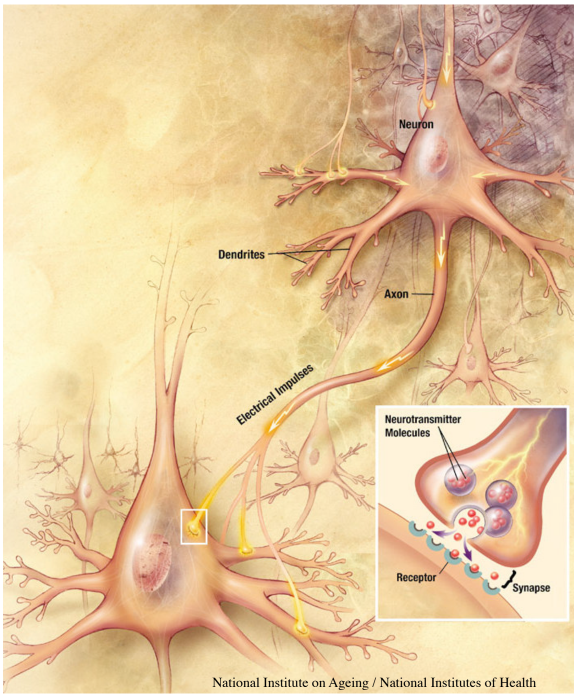
Electrical synaptic transmission
[bidirectional, slow, without "sign"]

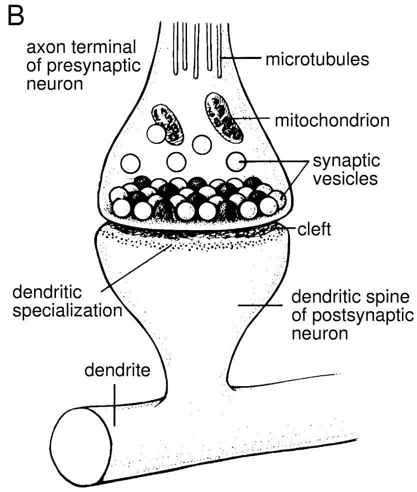


Electrical synaptic transmission
[bidirectional, slow, without "sign"]



Chemical synaptic transmission
[unidirectional, fast, with "sign"]

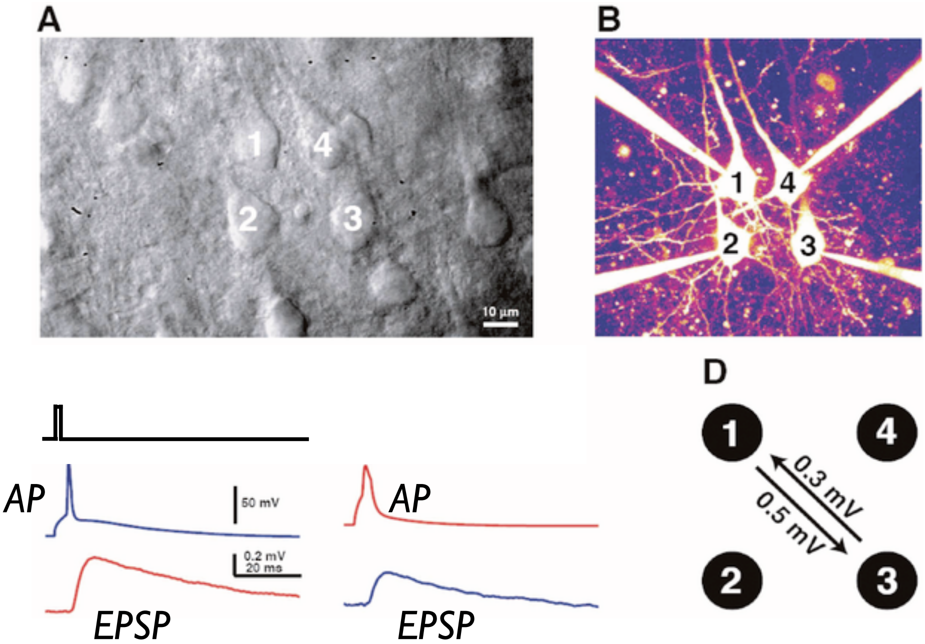




Simultaneous whole-cell patch-clamp recordings
from several neurons simultaneously

Song *et al.* [2005]

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



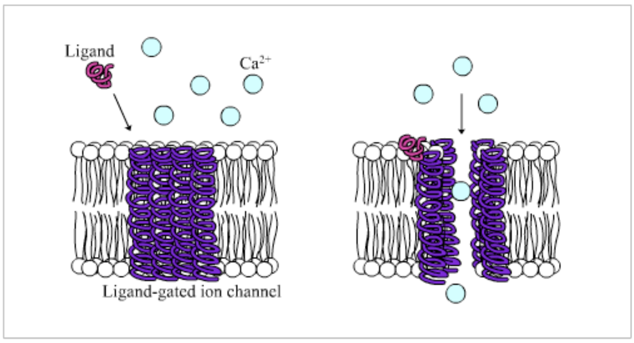
Song *et al.* [2005]

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

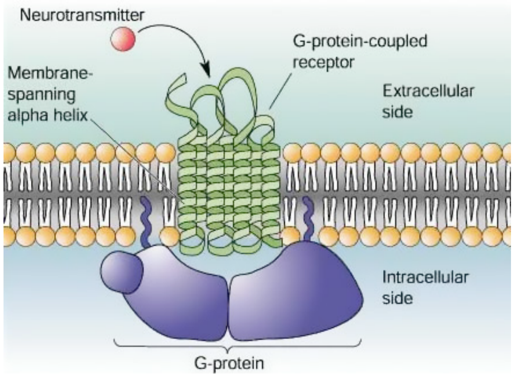
EPSCs - excitatory postsynaptic currents
EPSPs - excitatory postsynaptic potentials
[IPSCs - inhibitory postsynaptic currents]
[IPSPs - inhibitory postsynaptic potentials]

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+ and/or Ca++

Mediated by
"fast-activating" receptors

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

AMPAr
NMDAr
ACh r

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]

mGLUr

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

Inhibitory Synaptic transmission
mediated by receptors permeable to K+ or Cl-

Mediated by "fast-activating" receptors

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

GABA-A r
Gly r

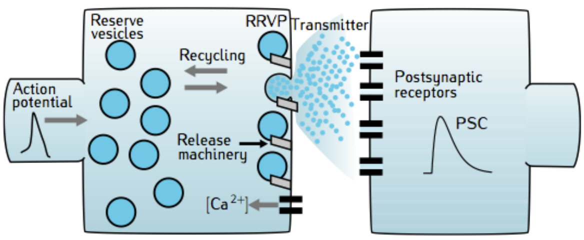
Mediated by "slow-activating" receptors

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

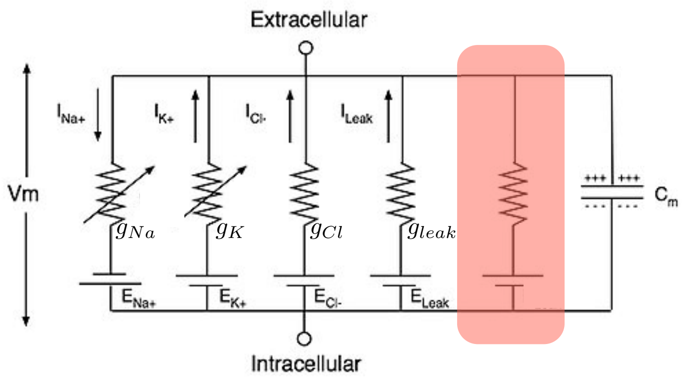
$$E_{syn} = \frac{R\ T}{z\ F} \log\left(\frac{C_{out}}{C_{in}}\right) < V_{rest}$$

Chemical synaptic transmission
[unidirectional, fast, with "sign"]

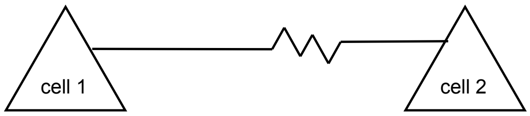


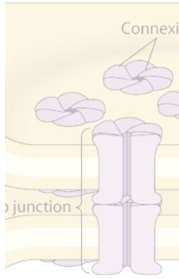
from Sterratt et al., 2011

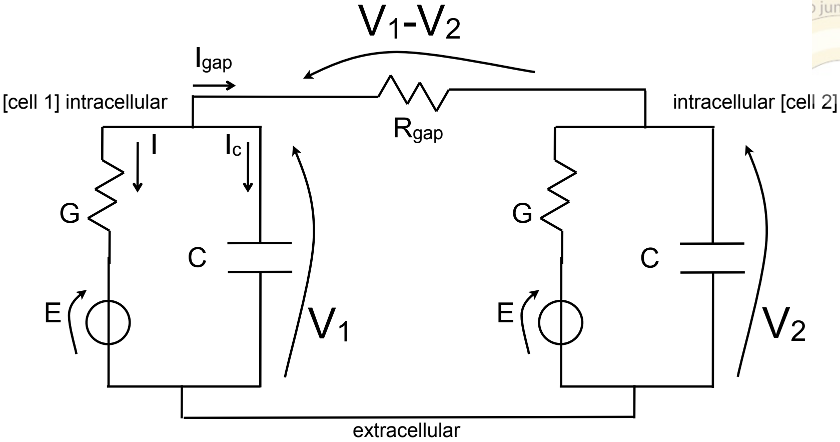
$$I_{syn} = g_{syn}(t)\ (E_{syn} - V_m)$$



Electrical synaptic transmission
[bidirectional, slow, without "sign"]

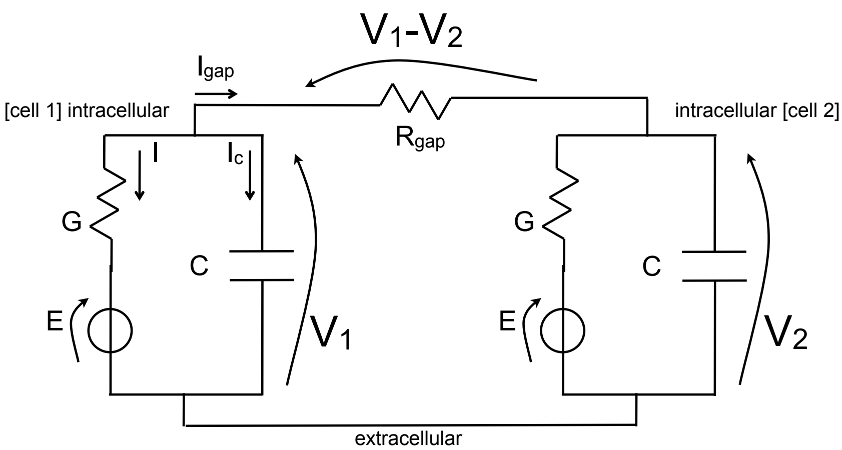




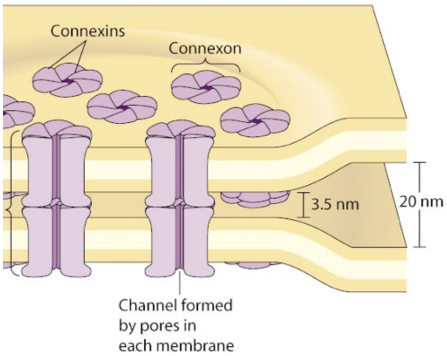


$$C\frac{dV_1}{dt} = G\ (E - V_1) - \boxed{\frac{(V_1 - V_2)}{R_{gap}}}$$

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



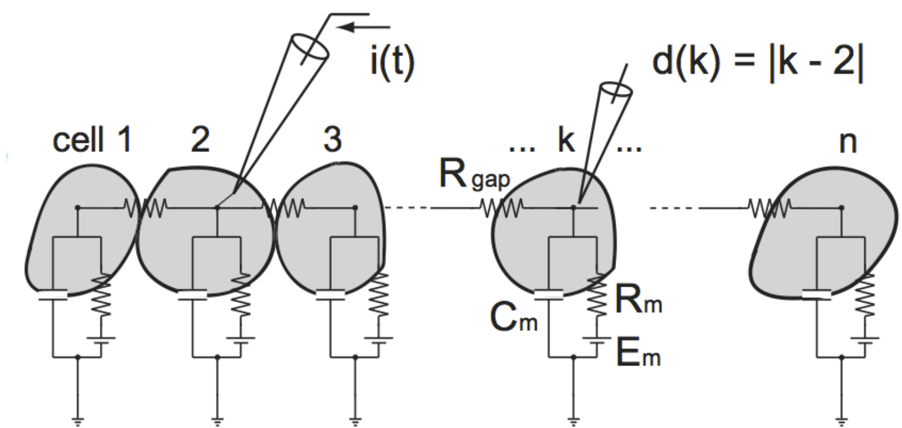
Electrical synaptic transmission
[bidirectional, slow, without "sign"]



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

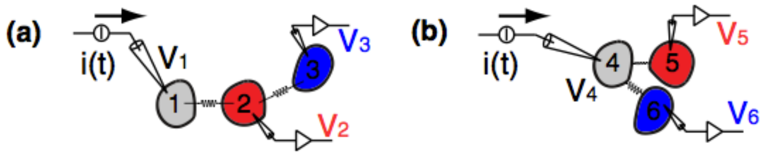
Electrical synaptic transmission
at the steady-state [i.e., DC regimes]

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



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

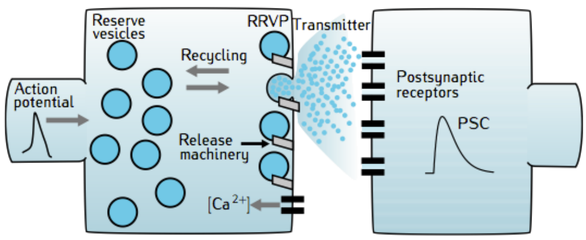
How to deduce experimentally the connectivity of electrically-coupled networks?



Cali' *et al.* [2007]

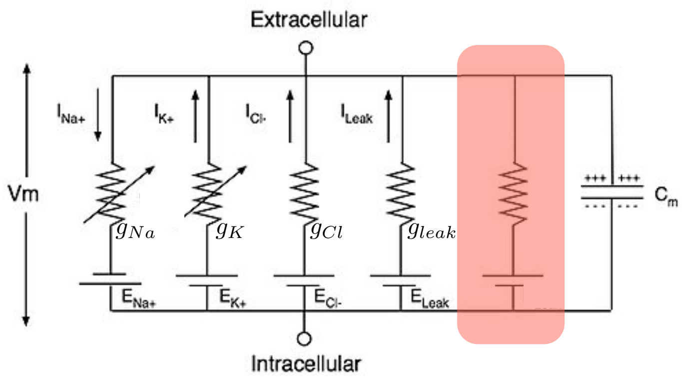
Chemical synaptic transmission

[unidirectional, fast, with "sign"]



from Sterratt et al., 2011

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



Chemical synaptic transmission

[unirectional, fast, with "sign"]
model of a ionotropic receptor

$$C \underset{\beta}{\overset{\alpha[T]}{\rightleftharpoons}} O \qquad\qquad g_{syn}(t) = \overline{g}_{syn} O(t)$$

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

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

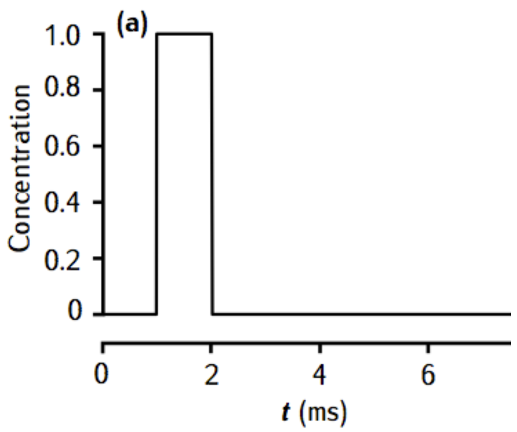
$$O(t) + C(t) = 1$$

Destexhe *et al.* [1994]

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

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

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

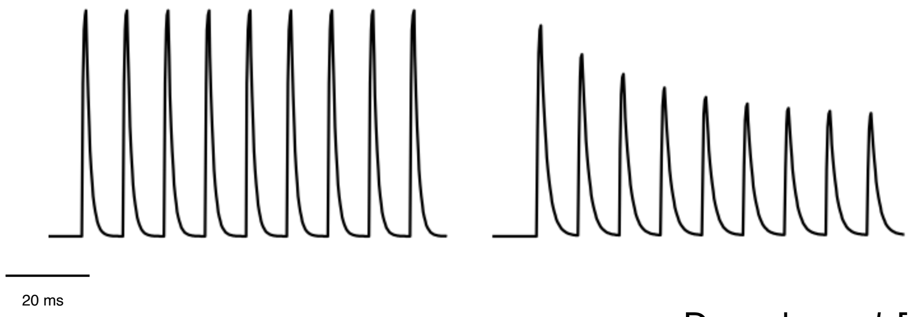


from Sterratt et al., 2011

$$C \underset{\beta}{\overset{\alpha[T]}{\rightleftharpoons}} O$$

$$\begin{array}{ccccccc} C_0 & \underset{R_{u1}}{\overset{R_b[T]}{\rightleftharpoons}} & C_1 & \underset{R_{u2}}{\overset{R_b[T]}{\rightleftharpoons}} & C_2 & \underset{R_c}{\overset{R_o}{\rightleftharpoons}} & O \\ & & & & R_d \upharpoonleft\downharpoonright R_r & & \\ & & & & D, & & \end{array}$$

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



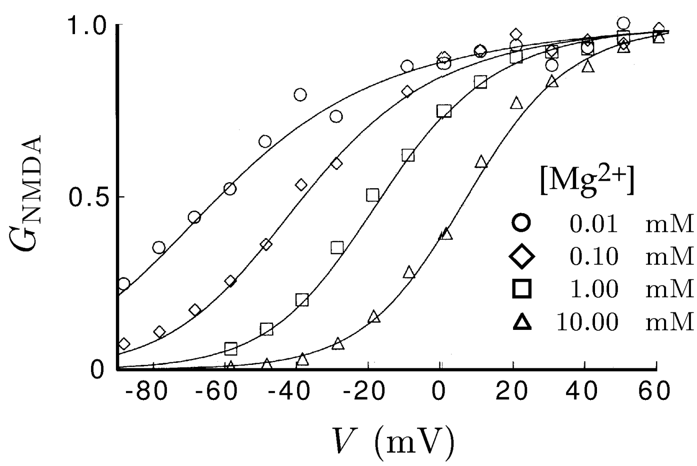
Destexhe *et al.* [1994]

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

$$
\begin{aligned}
&R_0 + T \rightleftharpoons R \rightleftharpoons D \\
&R + G_0 \rightleftharpoons RG \longrightarrow R + G \\
&G \longrightarrow G_0 \\
&C + nG \rightleftharpoons O,
\end{aligned}
$$

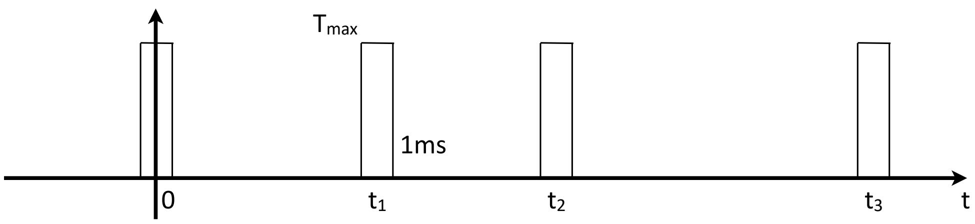
$$g_{syn}(t) = \overline{g}_{syn} O(t)$$

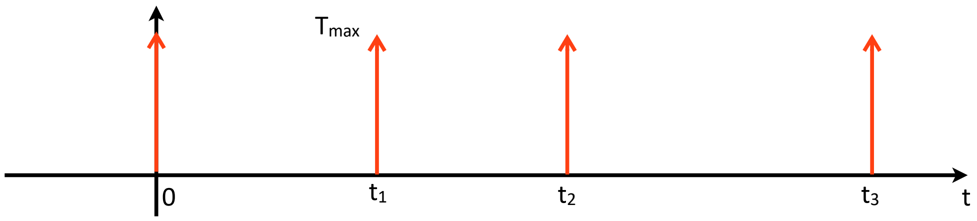
$$I_{syn} = \bar{g}_{syn}\ O(t)\ (E_{syn} - V_m)$$

Chemical synaptic transmission

<u>simplified</u> 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

$$C \underset{\beta}{\overset{\alpha[T]}{\rightleftharpoons}} O$$

[dynamical] steady-state??

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

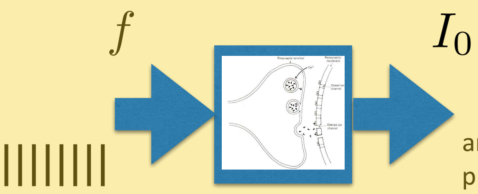
$$\frac{dO}{dt} = -\beta\, O + \alpha\, T_{max}(1-O) \sum_k \delta(t-t_k)$$

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

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

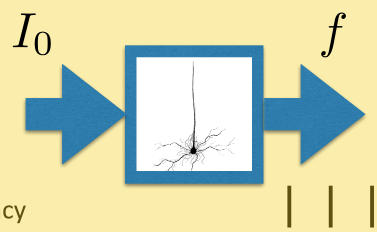
$$\boxed{O_{SS} \approx \alpha\, T_{max}\, \beta^{-1}\, f}$$

Very rough (functional) approximation



output

analog variable
proportional to
the driving frequency
[current or conductance]

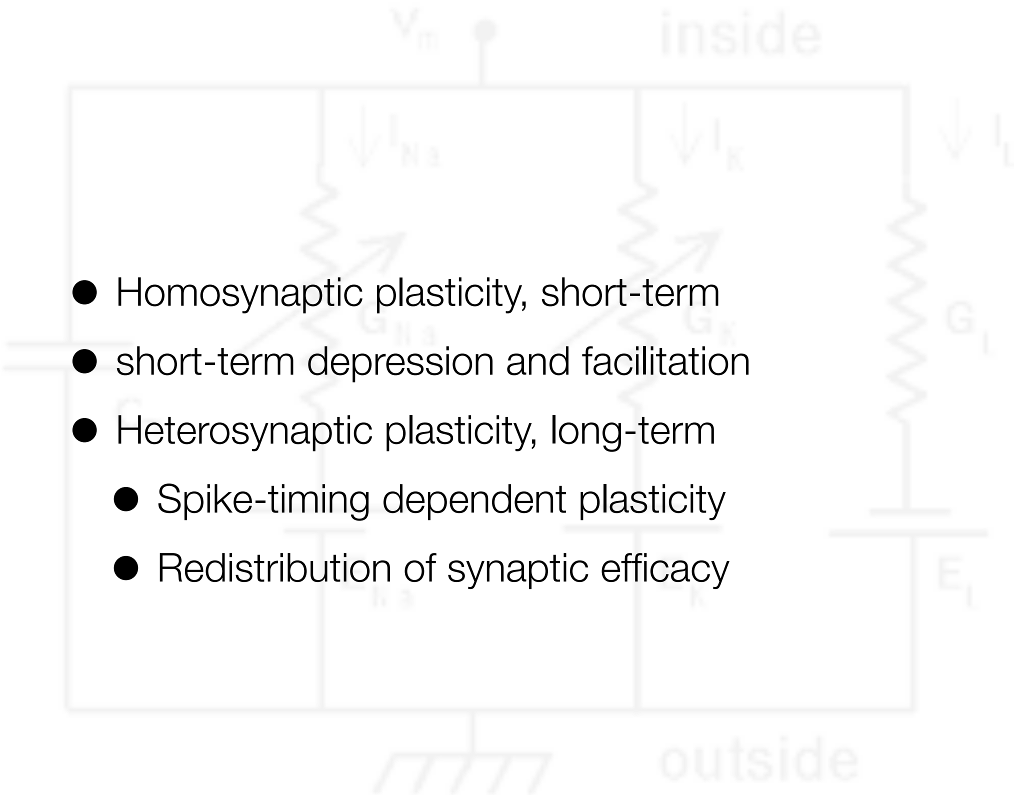


$$O_{SS} \approx \alpha\, T_{max}\, \beta^{-1}\, f \qquad f(I) \approx \frac{I_0}{C(V_{th}-E)}$$

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

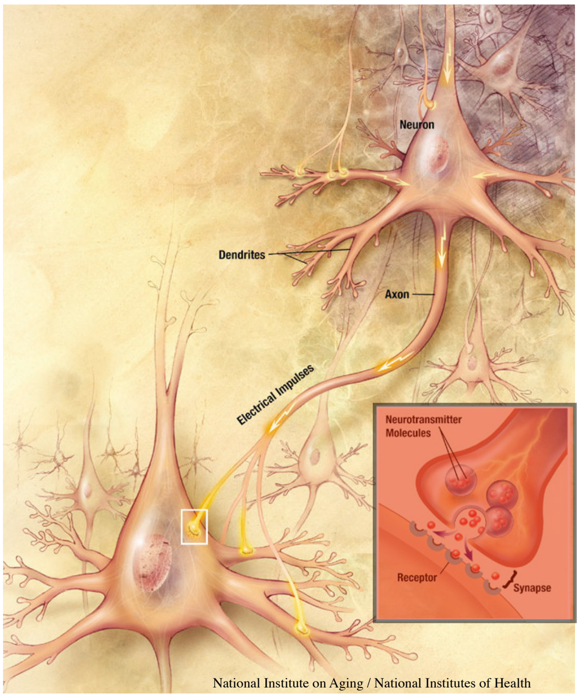
ATTENDANCE TRACKING - **code ???**
(for statistical purposes only)

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



- Homosynaptic plasticity, short-term
- short-term depression and facilitation
- Heterosynaptic plasticity, long-term
  - Spike-timing dependent plasticity
  - Redistribution of synaptic efficacy

Synaptic connections are more than *connecting plugs*



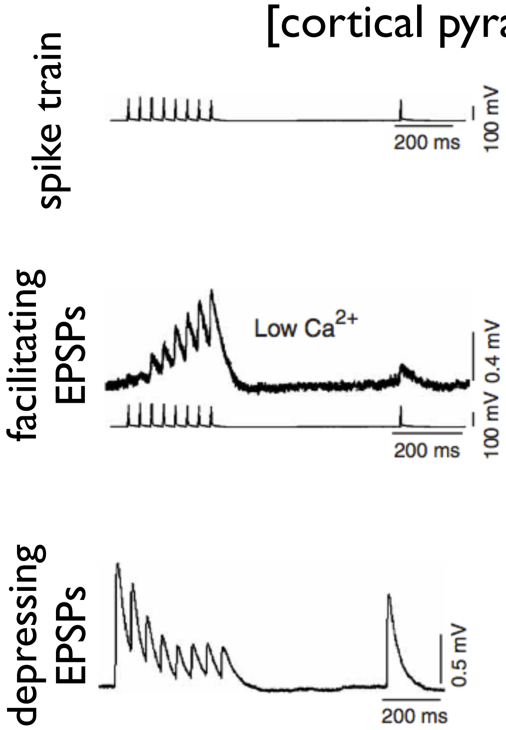
They are physical systems implementing a ***dynamical*** communication channel...

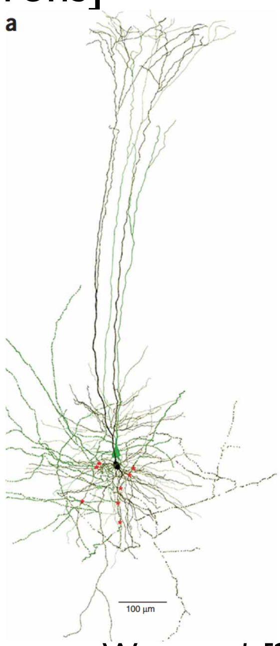
Like all physical system they may show [**transient**] inertia, fatigue, or *depression* during repeated activation.

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

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

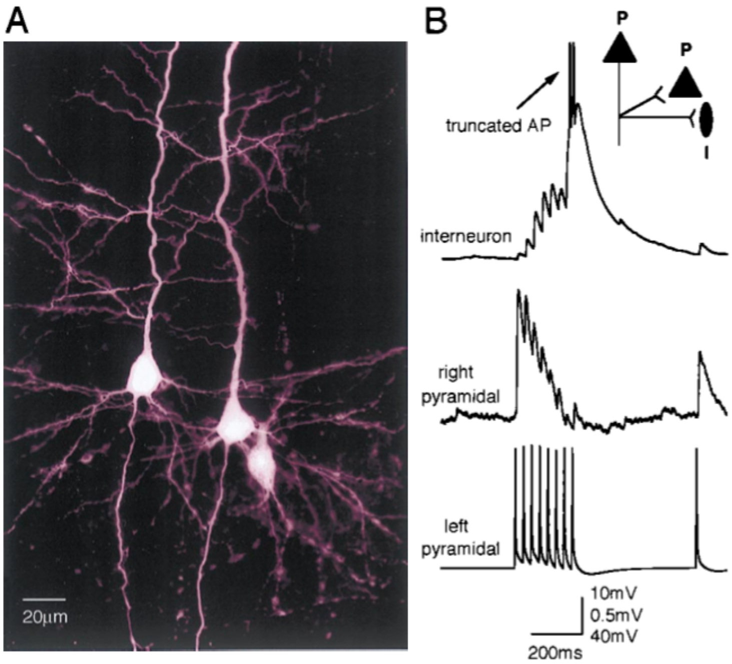
Short-term plasticity: facilitation and depression [cortical pyramidal neurons]





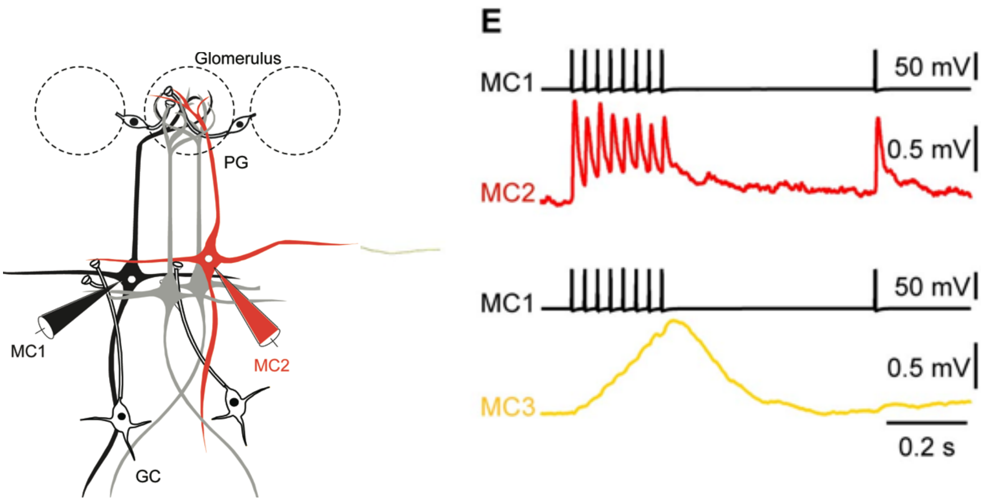
Wang *et al.* [2006]
Tsodyks & Markram[1997]

Short-term plasticity: facilitation and depression



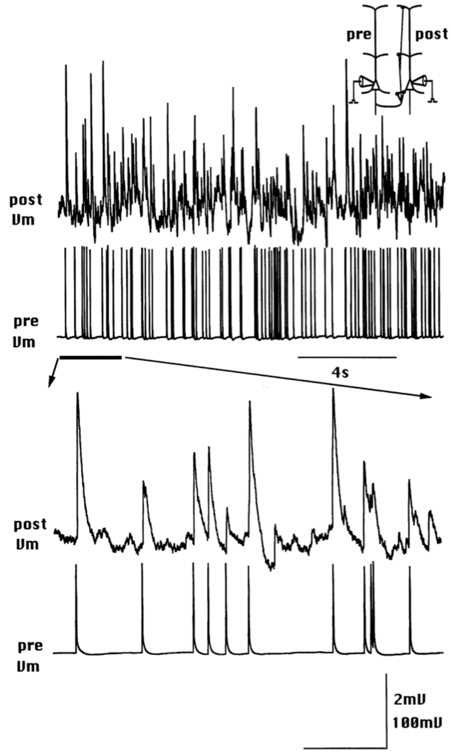
Markram et al. [1998]

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



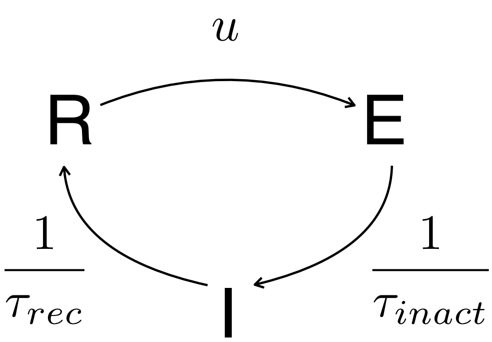
Pignatelli et al.

Impact of short-term synaptic plasticity



Markram et al. [1998]

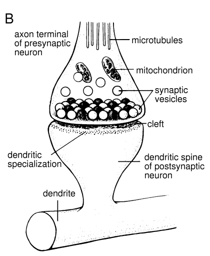
Short-term synaptic depression



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

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

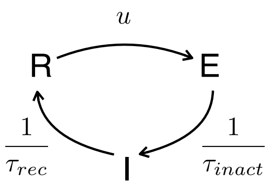
$$\frac{dI}{dt} = +\frac{1}{\tau_{inact}} E - \frac{1}{\tau_{rec}} I$$

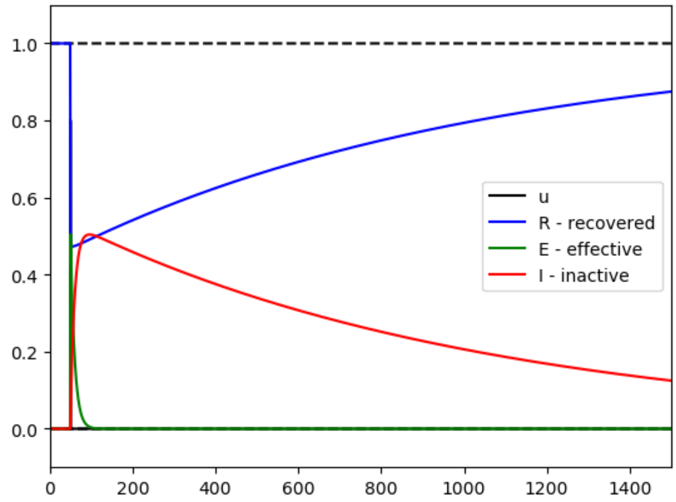


$$\tau_{rec} >> \tau_{inact}$$

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

Short-term synaptic depression





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

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

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

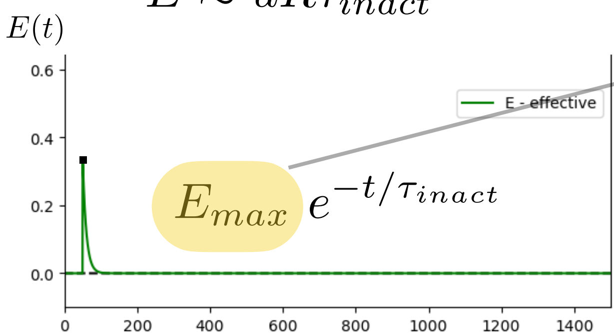
$$\tau_{inact}\frac{dE}{dt} = uR\tau_{inact} - E$$

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

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

$$\mathrm{C} \underset{\beta}{\overset{\alpha[\mathrm{T}]}{\rightleftharpoons}} \mathrm{O}$$

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



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

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

Short-term synaptic depression

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

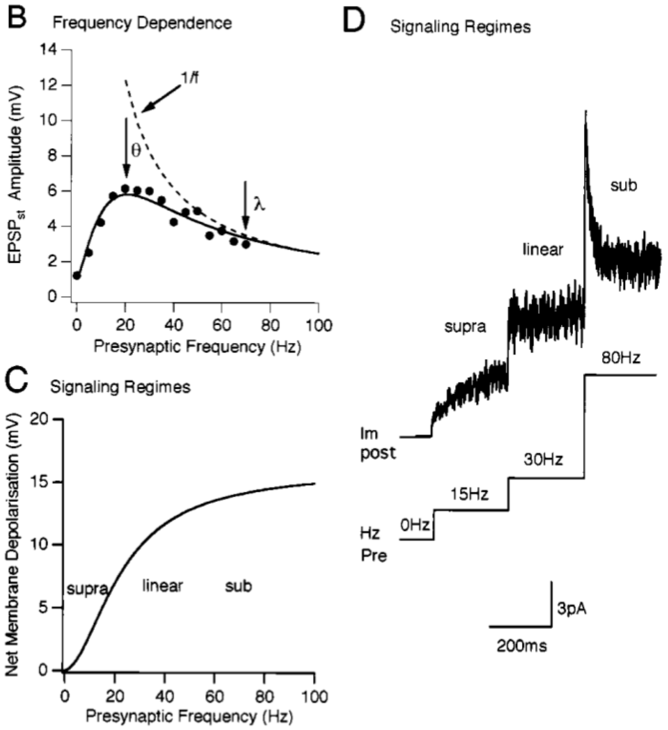
$$I = 1 - R - E \approx 1 - (1 + U\delta(t - t_{AP}))R$$

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

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

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

Impact of short-term synaptic plasticity



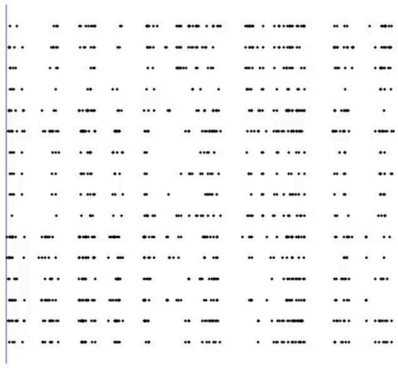
$$R_\infty = \frac{1 - e^{-T/\tau_{rec}}}{1 - (1 - U)e^{-T/\tau_{rec}}}$$

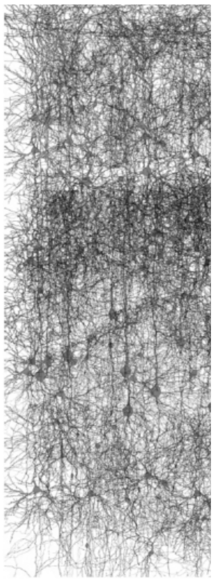
$$\cong \frac{A}{f \cdot \tau_{rec}}$$

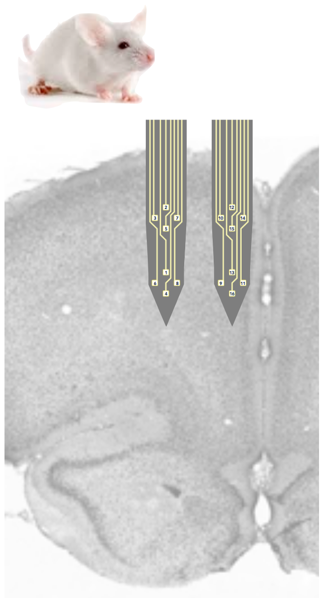
Markram et al. [1998]

In vivo cortical networks [transient] synchronisation

J. Couto

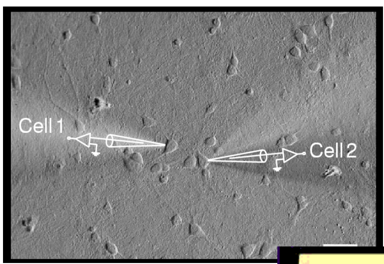


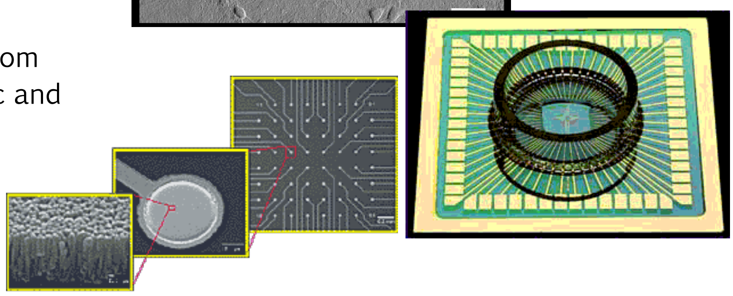




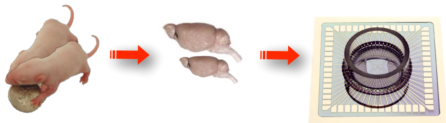
in vitro: spontaneous activity cultured dissociated neurons

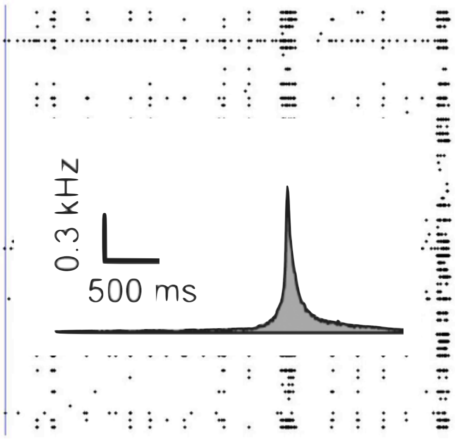
- dissociated from the cortical tissue,
- neurons develop ex vivo, reorganising into 2D random networks of glutamatergic and gabaergic cells

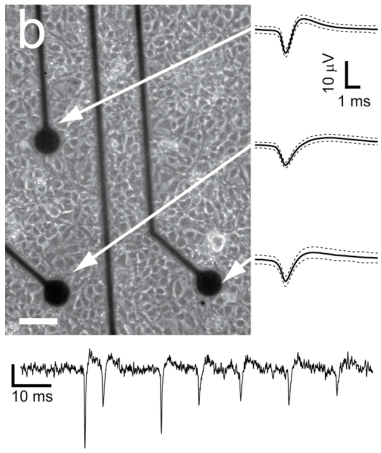




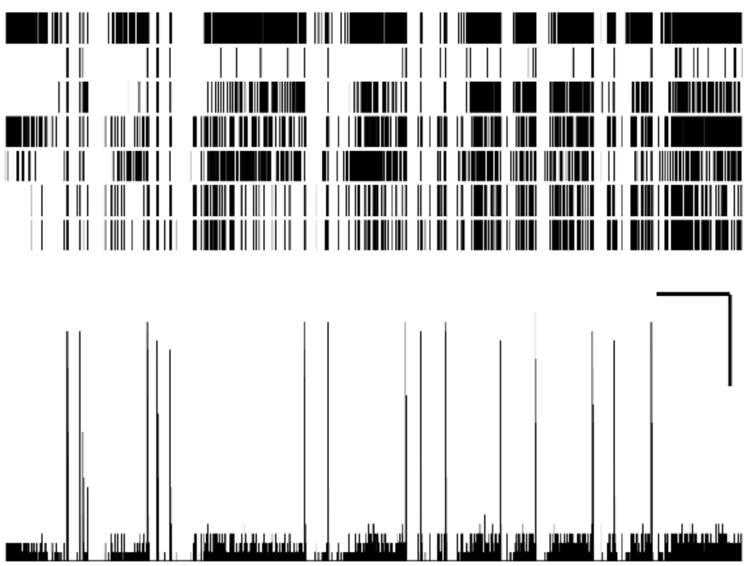
Ex vivo cortical networks spontaneous [transient] synchronisation



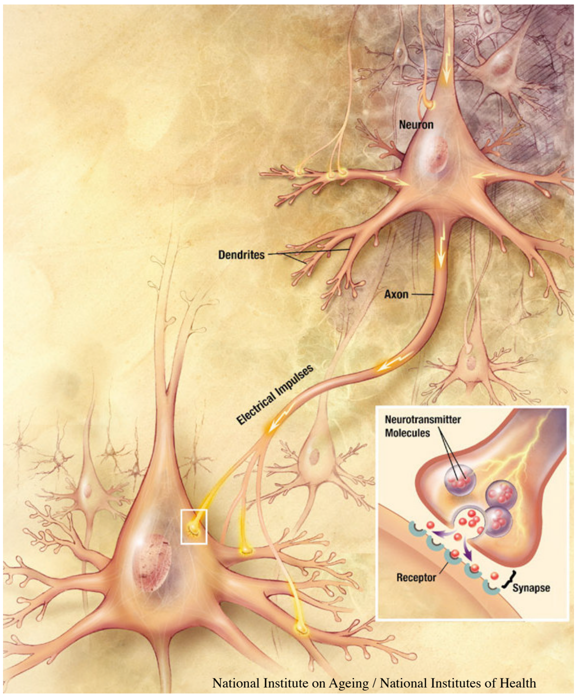


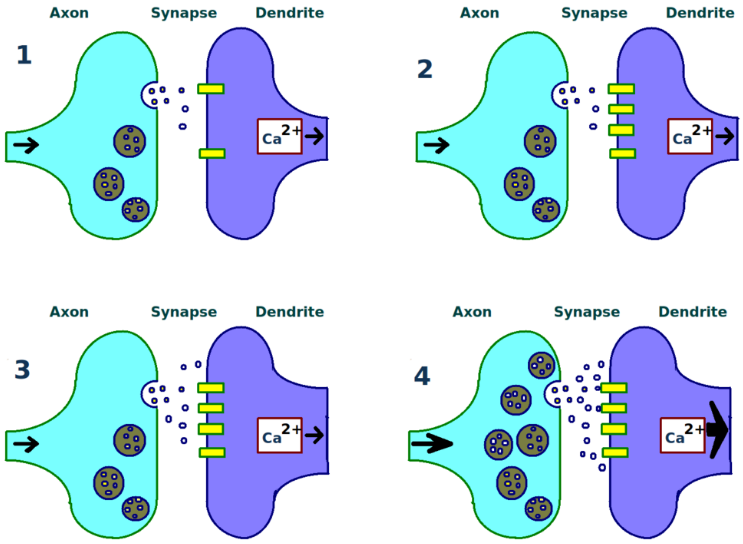


Ex vivo cortical networks spontaneous [transient] synchronisation



Long-term synaptic plasticity





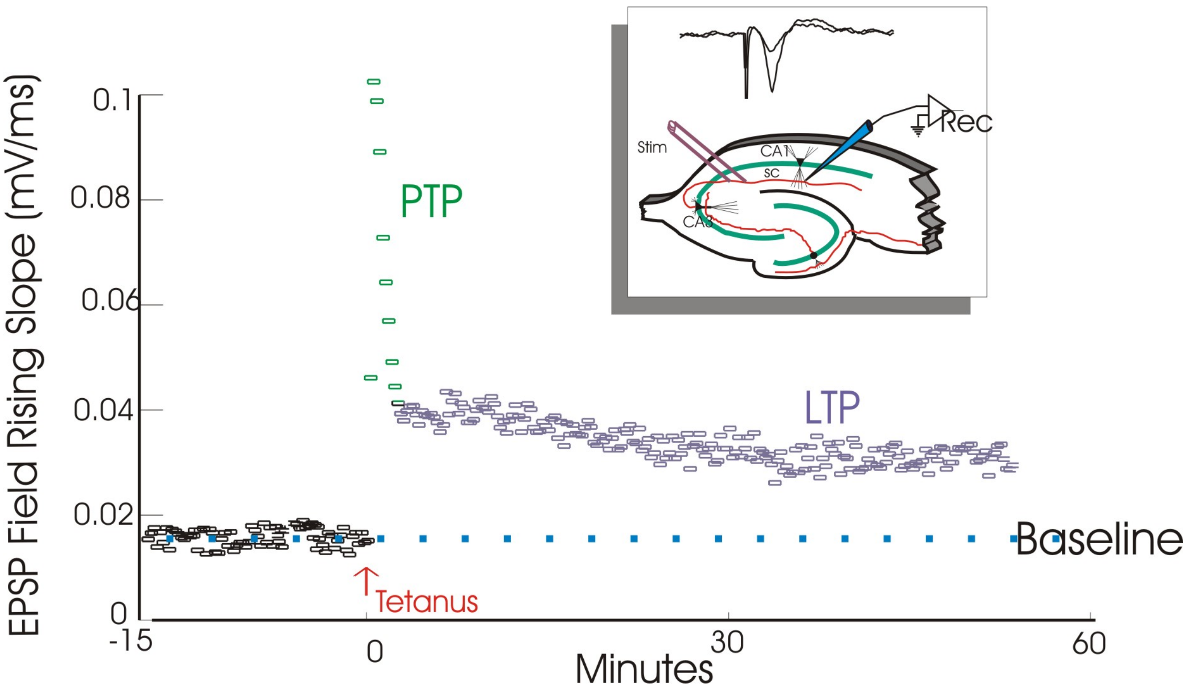
Levy & Stewart (1988)
Gerstner et al. (1996)
Markram et al. (1997)
Bi & Poo (1998)
Sjöström et al. (2001)

Donald Hebb, 1949

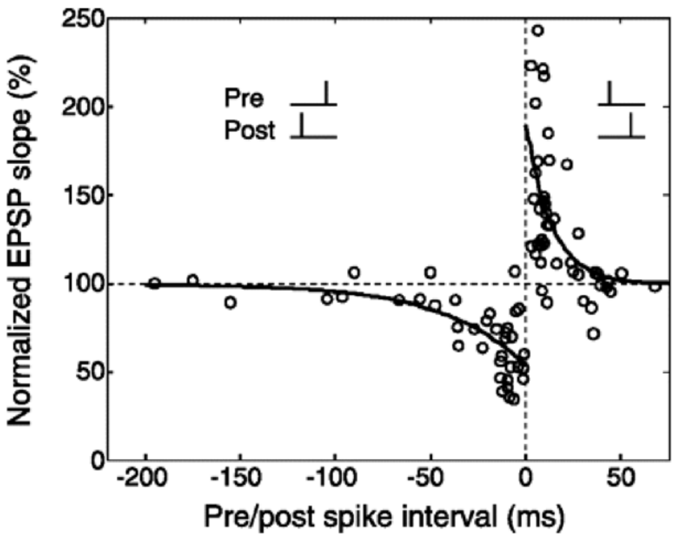
"When an axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased."

Cells that "fire" together, "wire" together.

e.g. Classic (hippocampal) LTP



Long-term (hetero)synaptic plasticity (STDP)

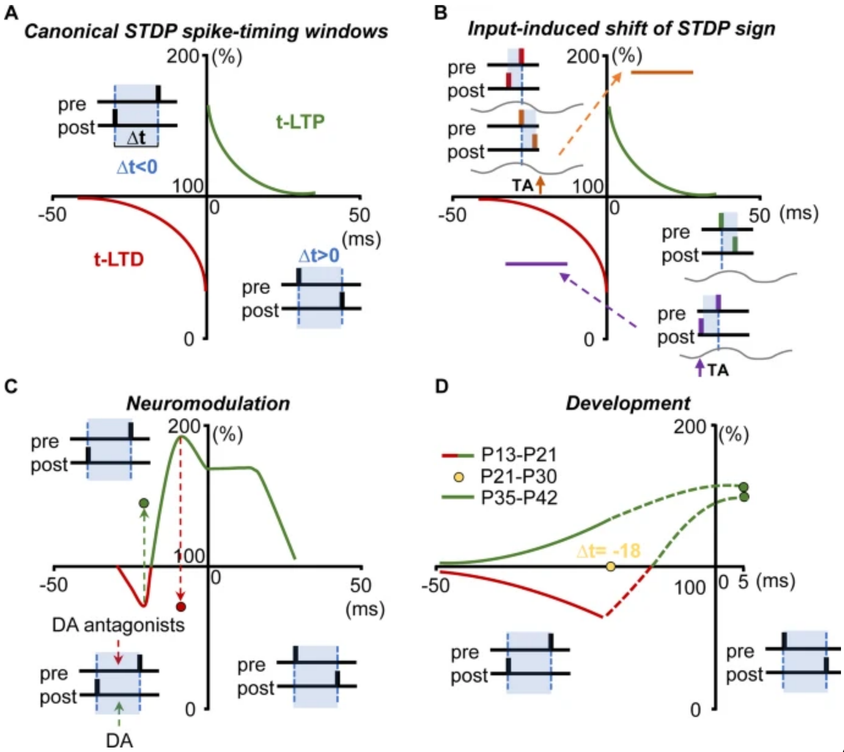


It has been found in neocortical, hippocampal, olfactory systems.

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

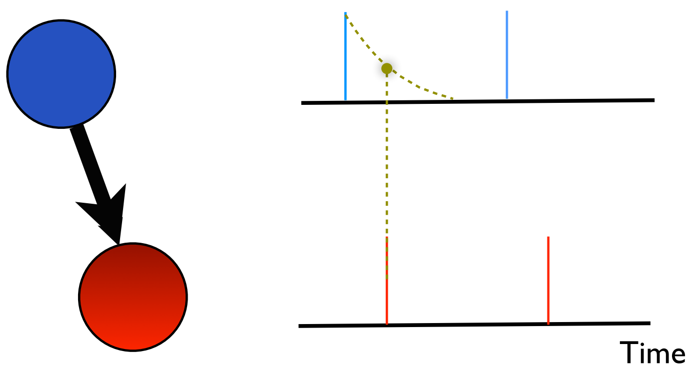
LTD LTP

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



Andrade-Talavera *et al.,* 2023

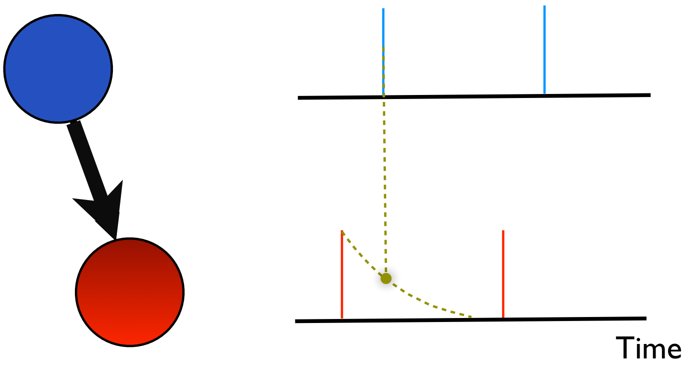
Spike Timing Dependent Plasticity



Long-Term Potentiation

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

Spike Timing Dependent Plasticity

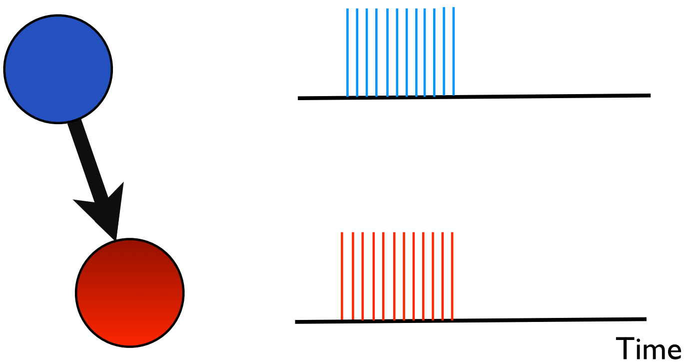


Pair interactions (traditional STDP)

Long-Term Depression

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

Spike Timing Dependent Plasticity



Long-Term Potentiation

Triplet interactions

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

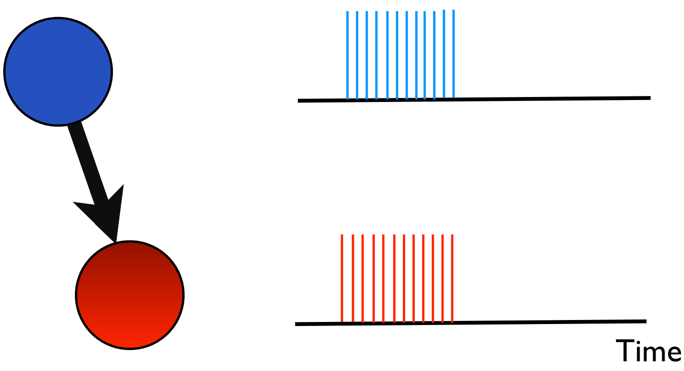
Interpretation of (seemingly) contradicting results

Layer 5 pyramidal neurons in the rat visual cortex

C2 barrel column of mouse primary somatosensory cortex

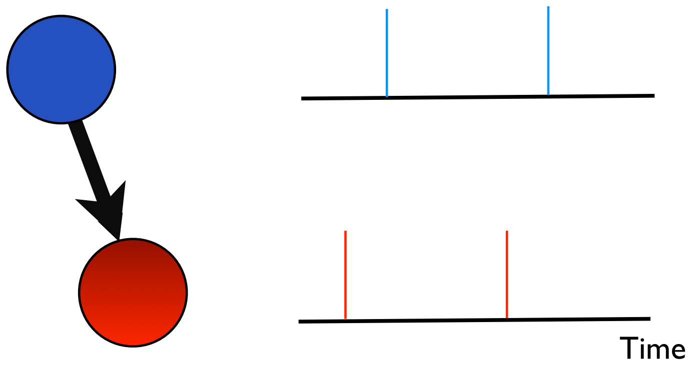
Connectivity is shaped by the neuronal code

Rate code



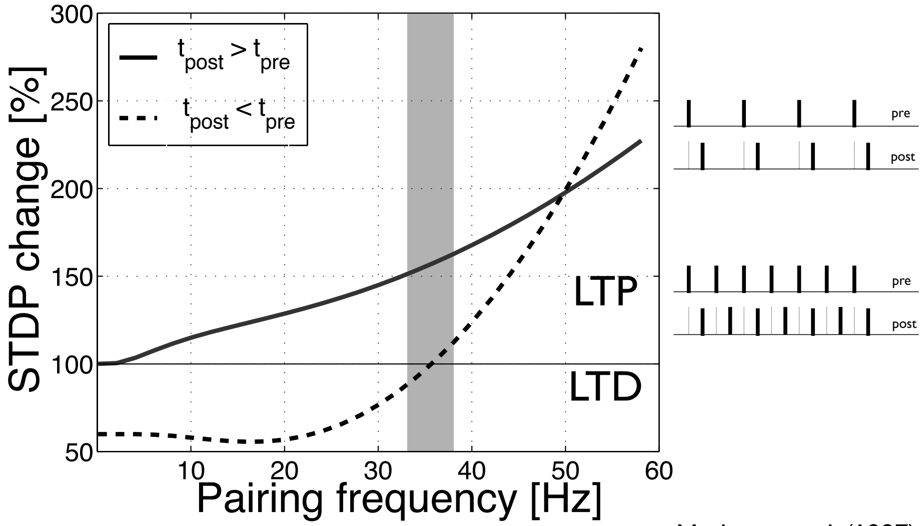
Spikes per time unit

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)

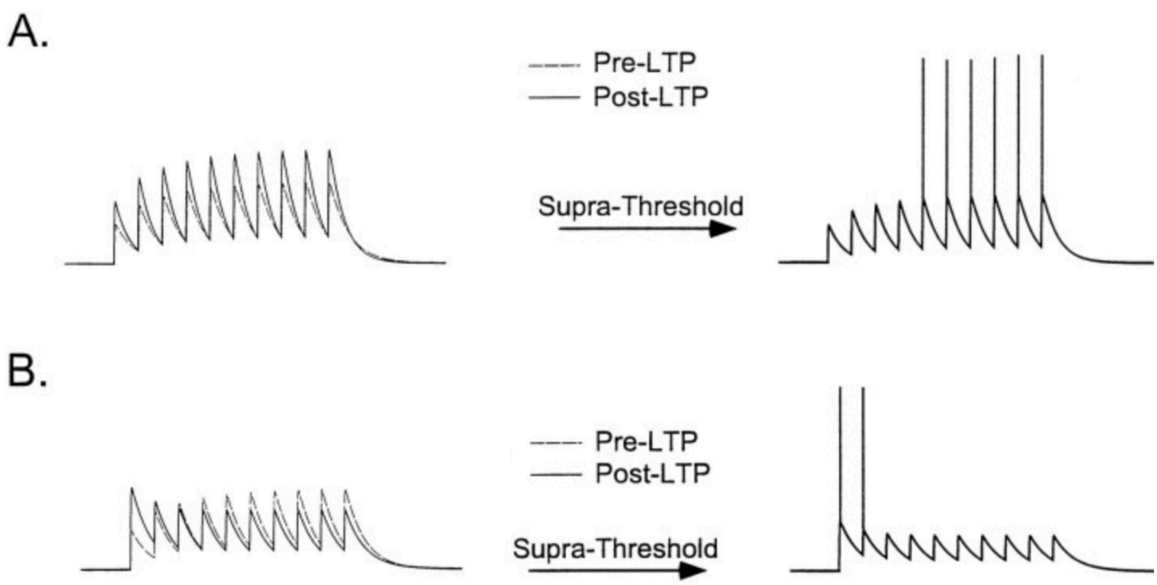
Interactions between long-term and short-term synaptic plasticities

$$C \underset{\beta}{\overset{\alpha[T]}{\rightleftharpoons}} O$$

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

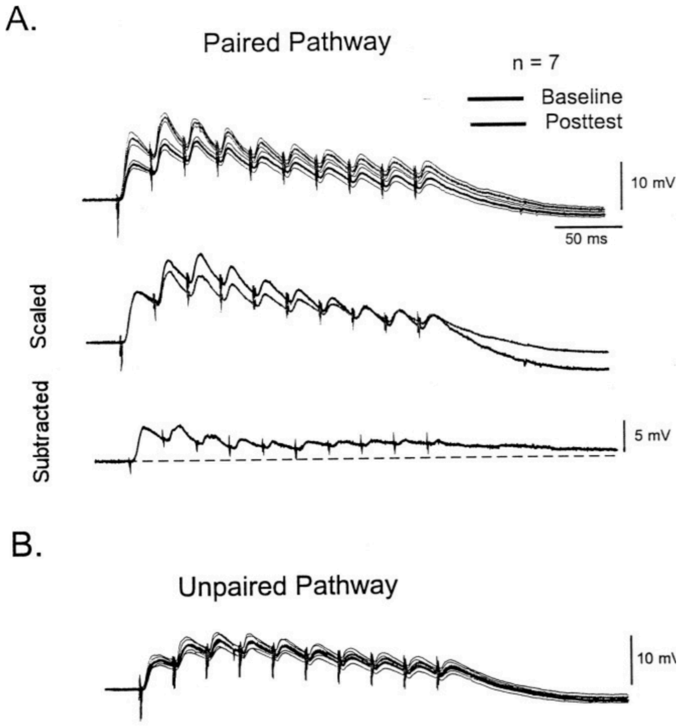
$$I_{syn} \;=\; \bar{g}_{syn}\, O(t)\; (E_{syn} \;-\; V_m)$$

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

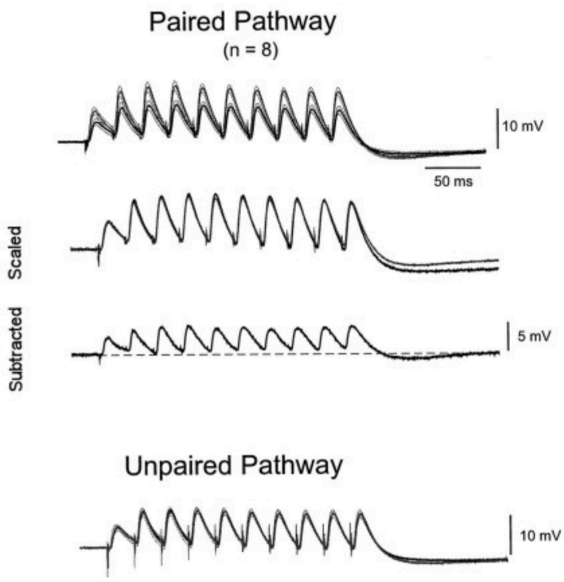


Buonomano (1999)

Cortex



Hippocampus



Buonomano (1999)