LECTURE 3

Romain Veltz / Etienne Tanré

November 9th, 2023

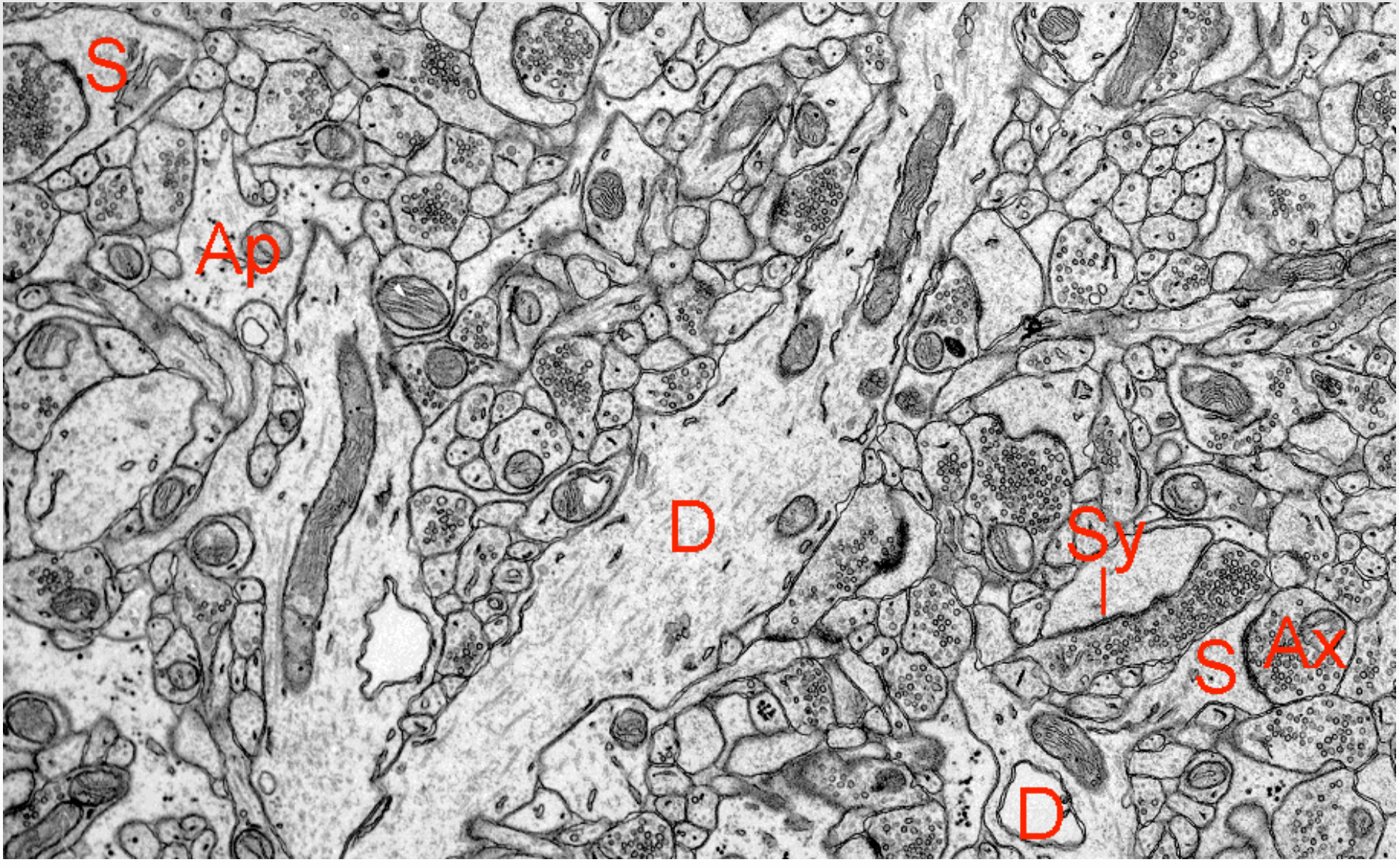
Outline

Synaptic transmission

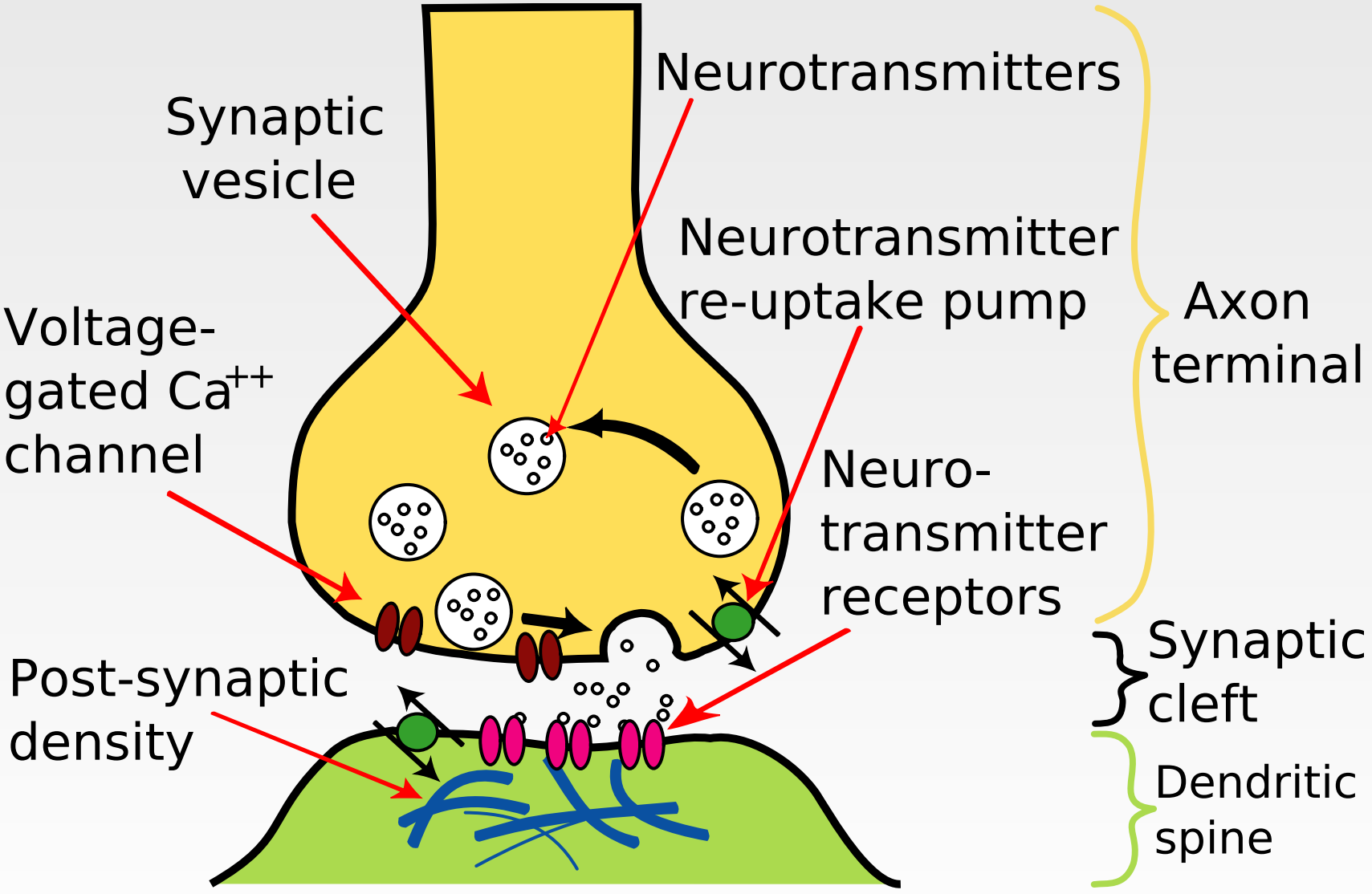
Anatomy of the synapse

Overview of neuropil structure

Recall...



Basics of (chemical) synaptic transmission



Different classes of receptors

Non-exhaustive list!

Dale's Law

Neurons have either excitatory or inhibitory action on all their post-synaptic targets.

- Highly stochastic transmission.

Some important receptors:

- **Glutamaergic receptors, (neurotransmitter: Glutamate, excitatory)**
  - AMPA receptor, channel for Na, K, Ca and $V_{rev} \approx 0mV$
  - NMDA receptor, channel for Na, K, Ca and $V_{rev} \approx 0mV$. It is voltage-dependent, channel blocked by Mg.
- **GABAergic receptor(s), (neurotransmitter: GABA, inhibitory)**
  - $GABA_A$ receptor, channel for Cl and $V_{rev} \approx -90mV$

- Ca currents constitute a small proportion 10%

2-states Markov model of synaptic conductance

Write $[T]$ the transmitter concentration, we seek for

$$I_{syn} = g_{syn}(t)\,(V_{post} - V_{rev})$$

where the conductance follows:

$$C \underset{\beta}{\overset{\alpha \cdot [T]}{\rightleftharpoons}} O, \quad g_{syn}(t) = \bar{g}_{syn} O(t)$$

- Square pulse shape for [T], amplitude T_{max}, fixed duration Δt.

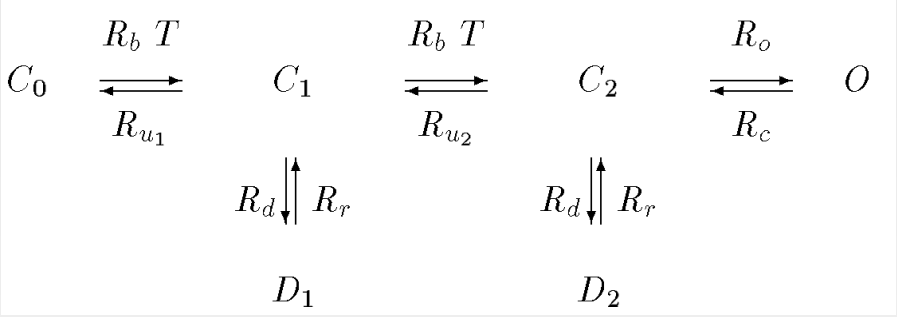
$$\begin{aligned} O(t) &= O_\infty + (O(0) - O_\infty)\, e^{-t/\tau_d}, \quad \tau_d = \frac{1}{\alpha \cdot T_{max} + \beta}, & [T] > 0 \\ &= O(\Delta t) e^{-t\beta}, & t > \Delta t \end{aligned}$$

- Difference of exponentials model

Link to pre-synaptic membrane [Destexhe-etal:94]

$$[T](V_{pre}) = \frac{T_{max}}{1 + e^{-(V_{pre} - V_T)/K_p}}$$

The AMPA receptor



1. Two glutamate molecules needed to open the channel (*cooperativity*).
2. Time course of current determined by Glu-unbinding time-constant
3. Fluctuating number (10-100) attached to the PSD
4. Desensitized states that saturate response $\rightarrow$ **depression**

However, it is often simply modeled with:

$$\begin{cases} I_{AMPA}(t) = g_0 e^{-t/\tau_{AMPA}} \left(\overbrace{E_{AMPA}}^{\approx 0mV} - V_{mem} \right) Heaviside(t), \\ \tau_{AMPA} \approx 1 - 5ms \end{cases}$$

The NMDA receptor 1/2

$$I_{syn} = \bar{g}_{NMDA} O(t) B(V) \cdot (E_{NMDA} - V)$$

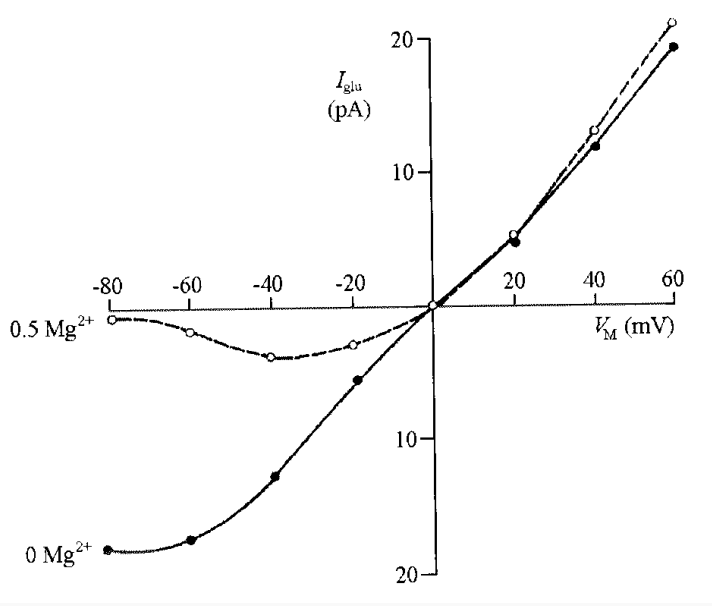
1. Longer time scales than for AMPA
2. $E_{NMDA} \approx 0$
3. Partially blocked by Mg, requires **depolarization** to open
4. **Coincidence** detector

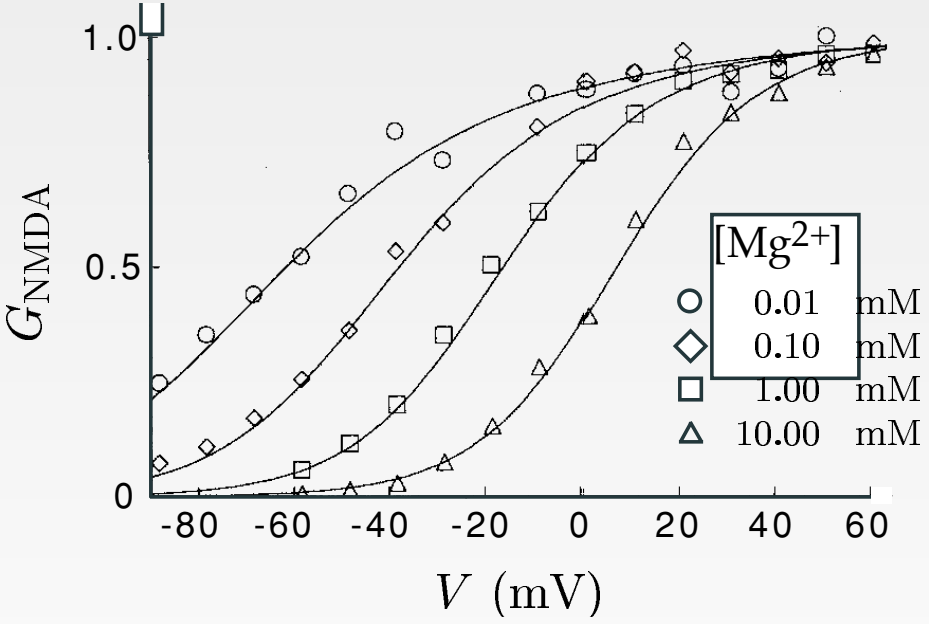
We have [Jahr-Stevens:90]:

$$\begin{cases} B(V) = \frac{1}{1+e^{-(V-V_T)/16.13}} \\ V_T = 16.13 \ln \frac{[Mg^{2+}]}{3.57} \end{cases}$$

The NMDA receptor 2/2

[Jahr-Stevens:90] Note the sigmoidal curve on the rhs.





The GABA receptors, Just for $GABA_A$... (there is a $GABA_B$)

1. Often found close to the cell body
2. Responsible for fast inhibition
3. Current mostly carried by Cl
4. $E_{GABA_A} \approx -80mV$

Current approximation like the AMPA one:

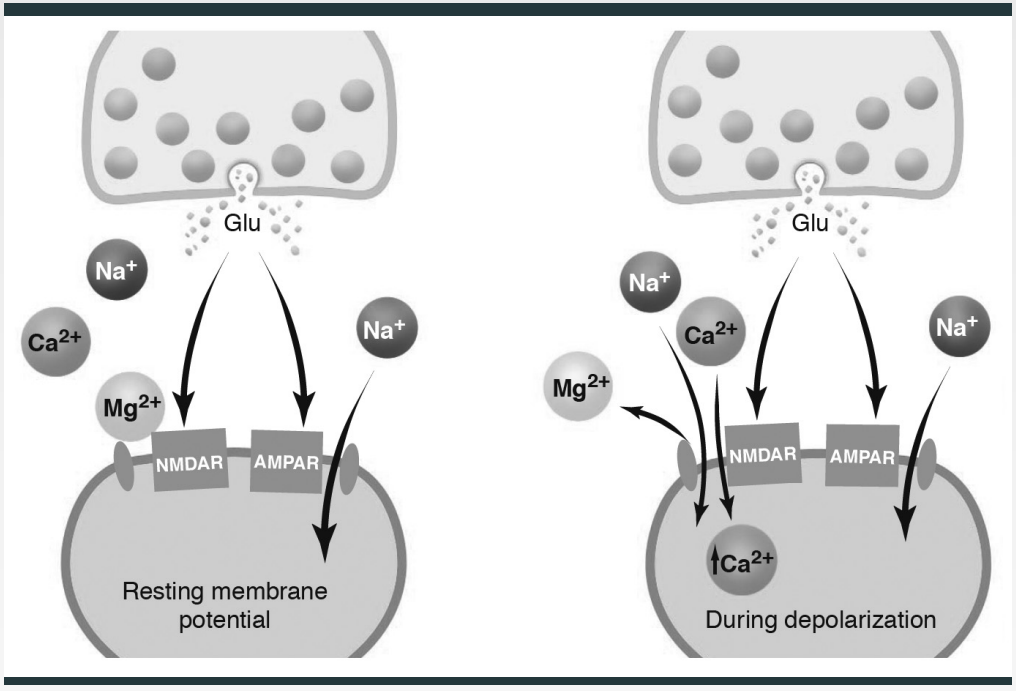
$$I_{GABA_A} = \bar{g}_{GABA_A} O(t) \left(E_{GABA_A} - V\right)$$

with

$$O(t) \sim e^{-t/\tau_r([GABA])} - e^{-t/\tau_d}$$

where $\alpha \approx 5mM^{-1}ms^{-1}$, $\beta \approx 0.18ms$

Synaptic transmission at Excitatory synapses



1. Binding of Glu opens AMPA leading to depolarization
2. Binding of Glu+sufficient depolarization opens NMDA leading to influx of Calcium

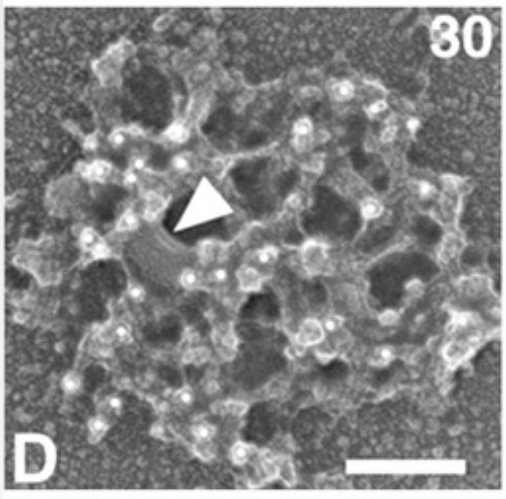
- Then what? What is Calcium for?

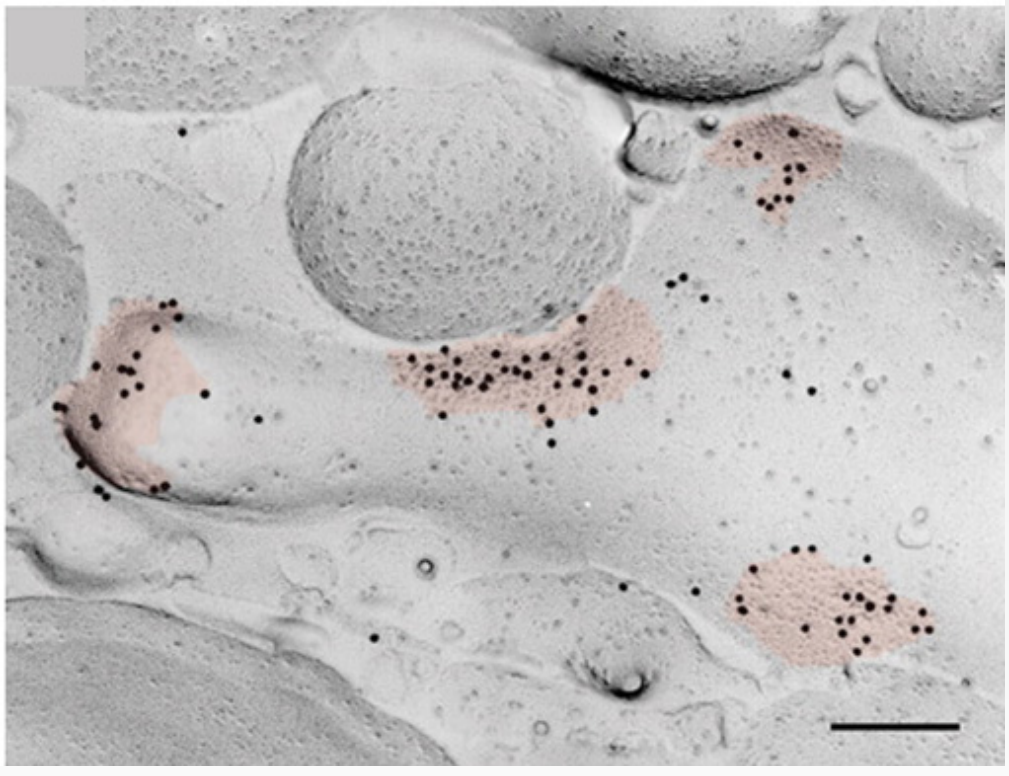
AMPA trafficking

Diffusion on the post-synaptic membrane Imaging of two single fluorescently tagged AMPA receptors (red), one immobile and co-localized with a synapse, the other freely moving in the extrasynaptic membrane. Green = presynaptic tag.

The post-synaptic density (PSD)

Locus of stable receptor + anchor molecules,
[petersen-etal:03,Masugi-Tokita-etal:2007]





Scale bar 100nm

Synaptic weight dynamics: plasticity

Outline

Synaptic Plasticity

Long Term Plasticity was found in 1973 by Bliss-etal.

Definition

The **synaptic weight** is the amplitude of the post-synaptic membrane potential.

It can be affected by changes in the

1. release probability of neurotransmitter ($\rightsquigarrow$ STP)
2. number of release sites
3. maximal conductance of AMPA receptor ($\rightsquigarrow$ LTP)
4. AMPA number ($\rightsquigarrow$ LTP)
5. etc

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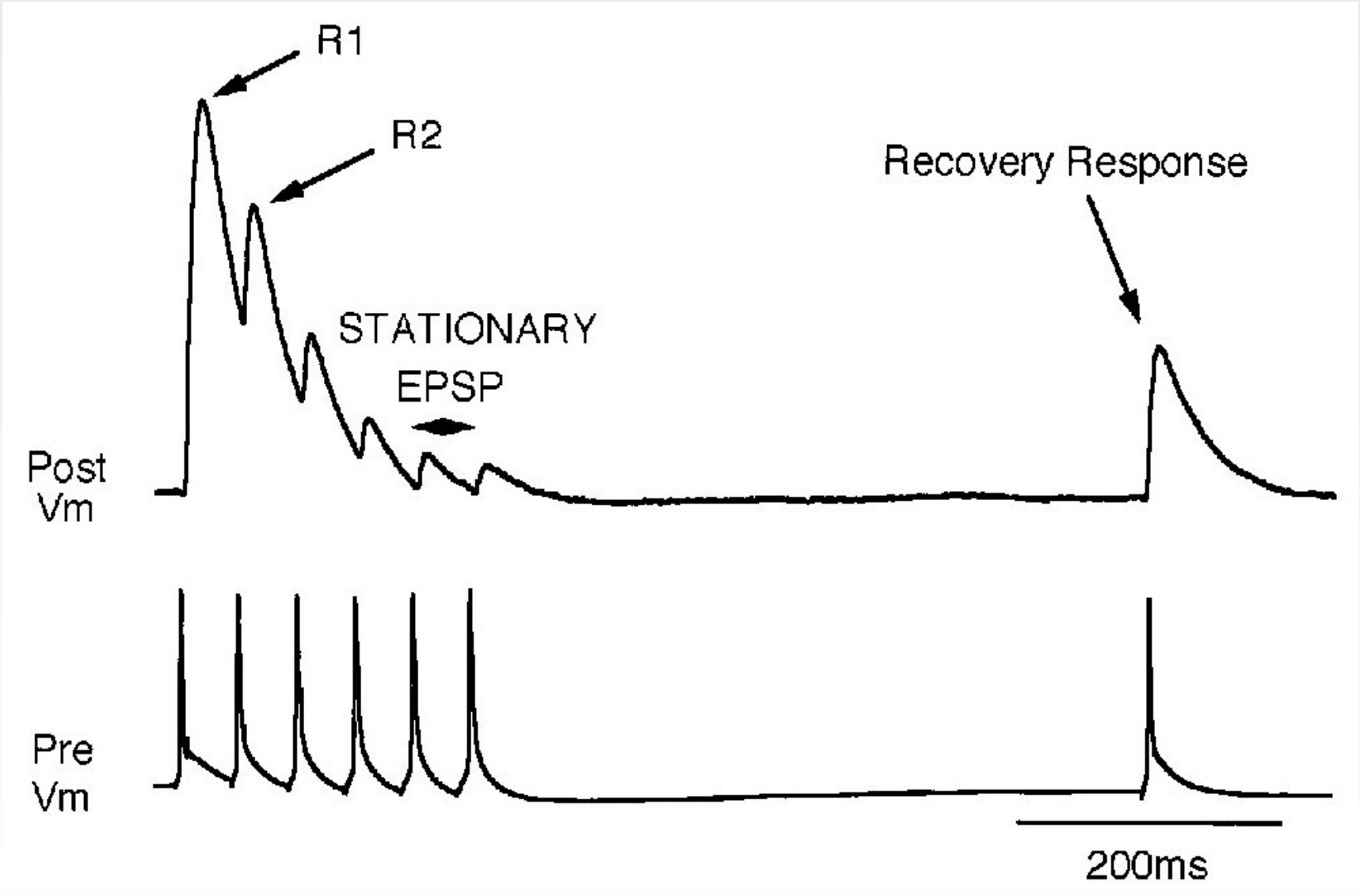
5. etc

The synapse response displays:

1. **facilitation:** progressive increase in the weight (last few sec.)
2. **potentiation:** as facilitation, slower to develop but outlasts the stimulus
3. **depression:** opposite of potentiation

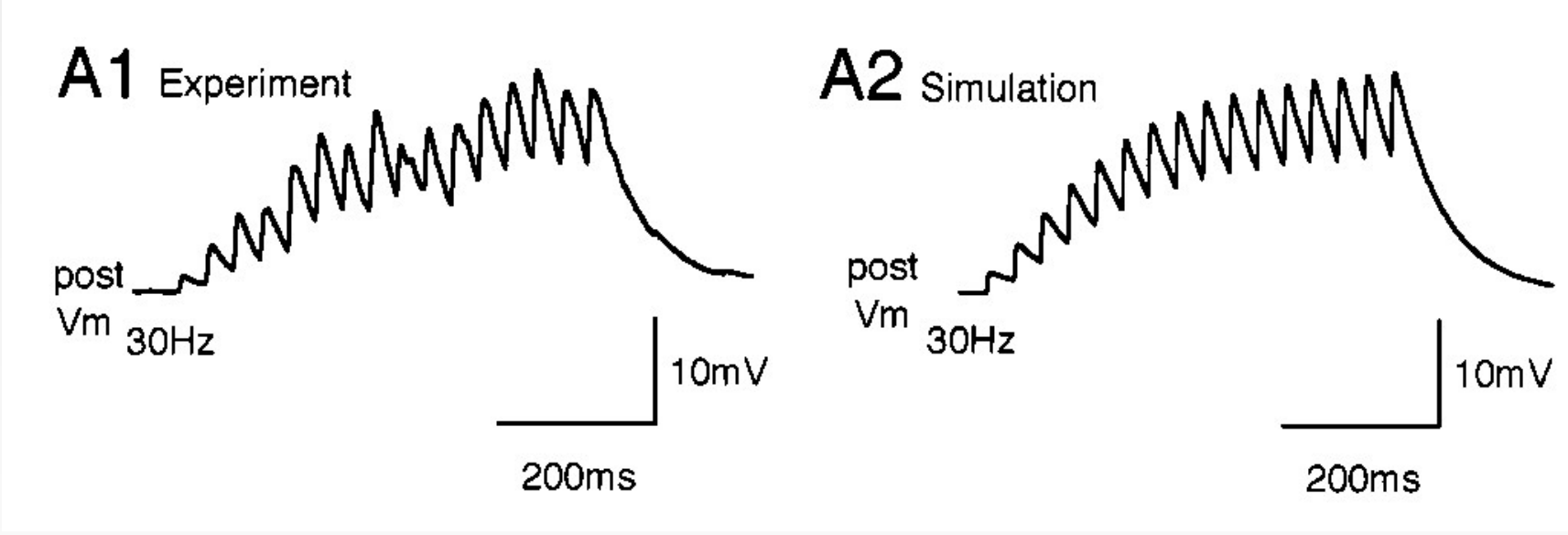
Short-term depression (lasts few sec.)

Experimental results [Tsodyks-Markram:97]



Short-term facilitation

[Markram-Tsodyks:98]



Frequency dependence

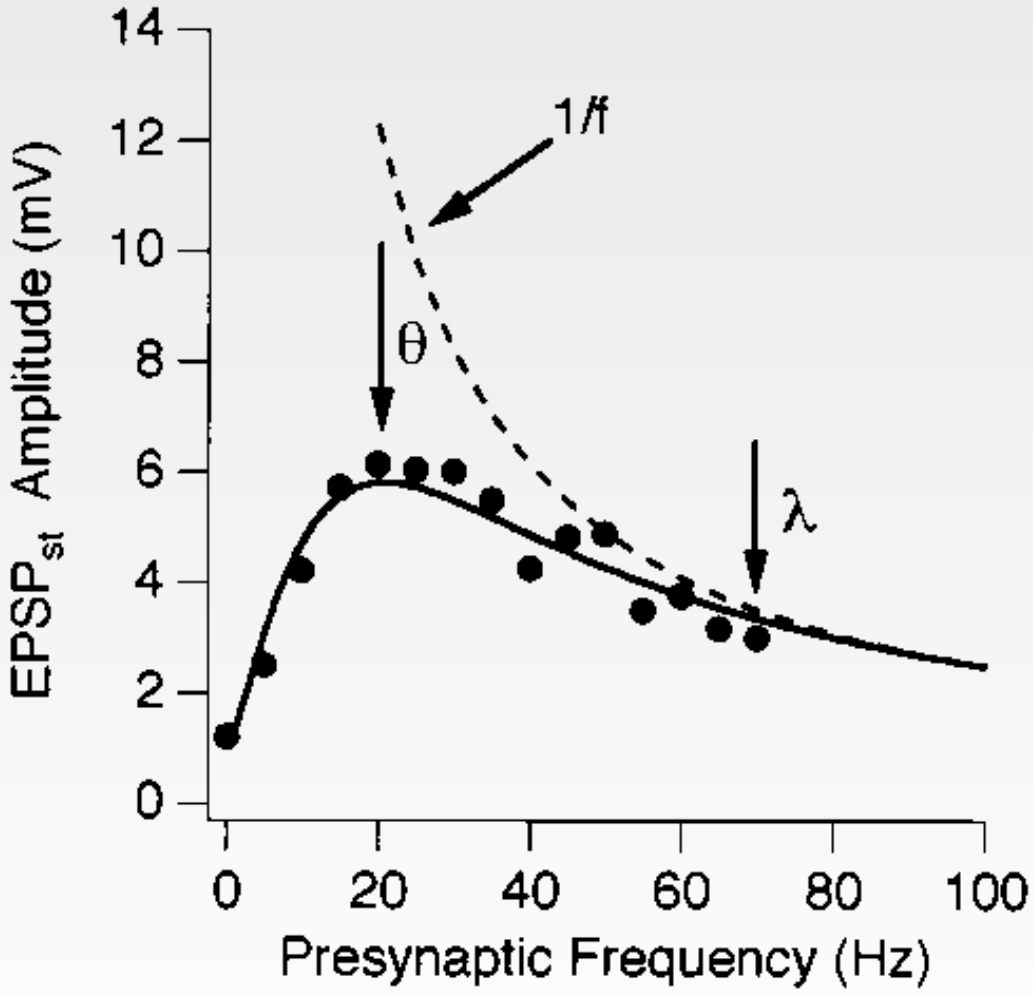


Figure 1: Markram-Tsodyks:98

Hebbian Learning

The basic mechanism for activity-dependent synaptic plasticity was first formally postulated

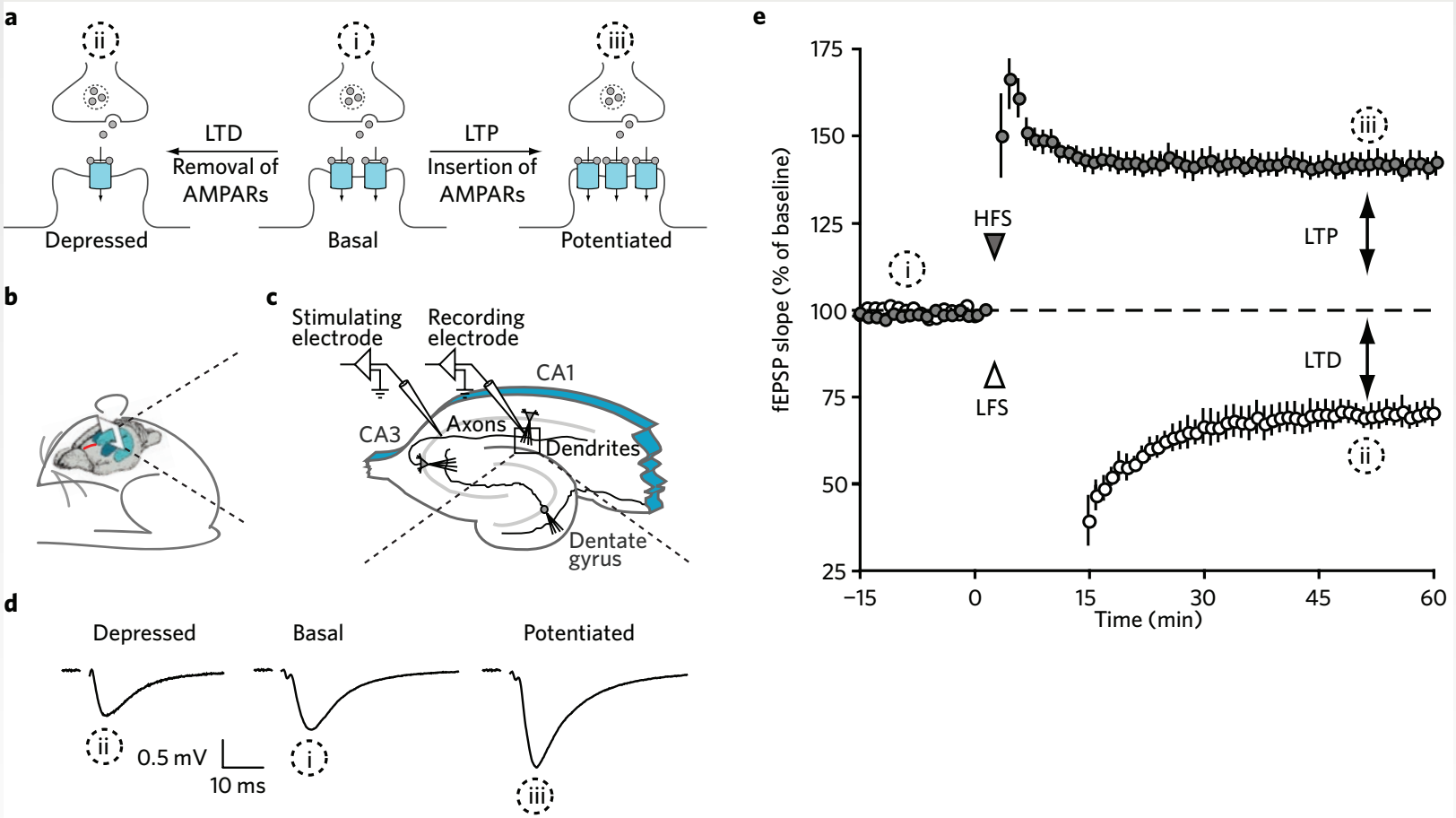
Hebb's rule (1949)

When an axon of cell A is near enough to excite cell B or 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."

Simply restated, when a presynaptic cell and its postsynaptic cell are repetitively active together, the efficacy of the synaptic transmission between them improves.

LTP and LTD

Experimental support for Hebb's rule [Fleming-etal:10]

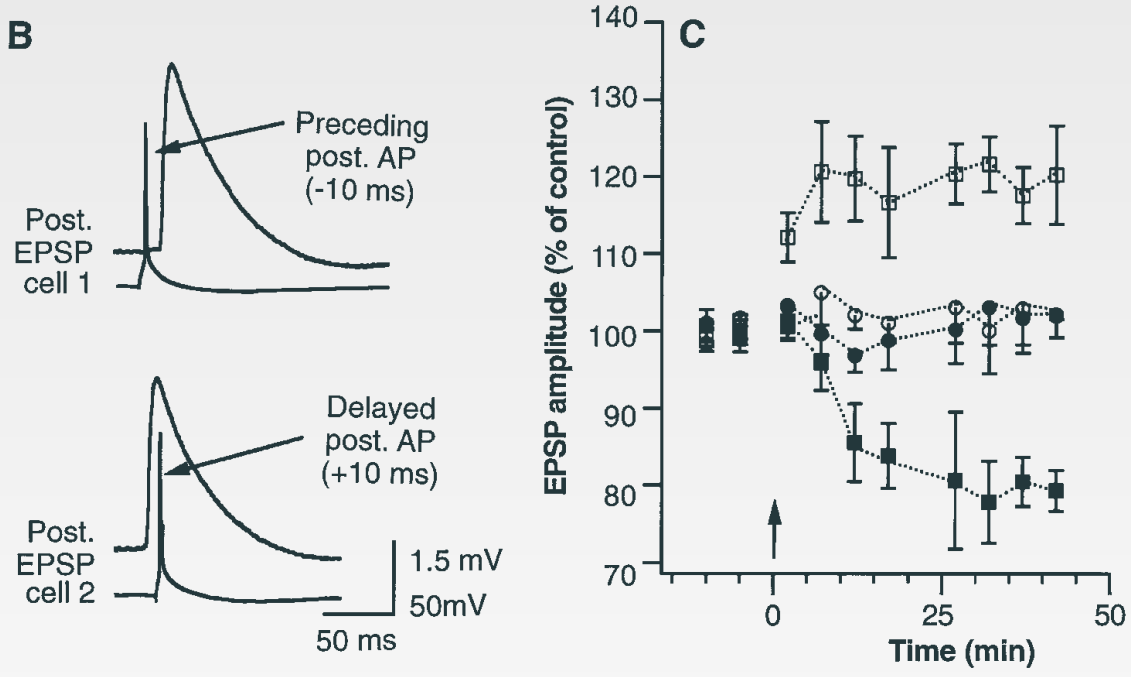


- Synaptic weight $w_{ij} \propto \#AMPA$
- Synaptic weight $w_{ij} \propto \bar{g}_{AMPA}$

How are these changes induced?

Spike Time Dependant Plasticity

Also called STDP, [Markram-etal:97]

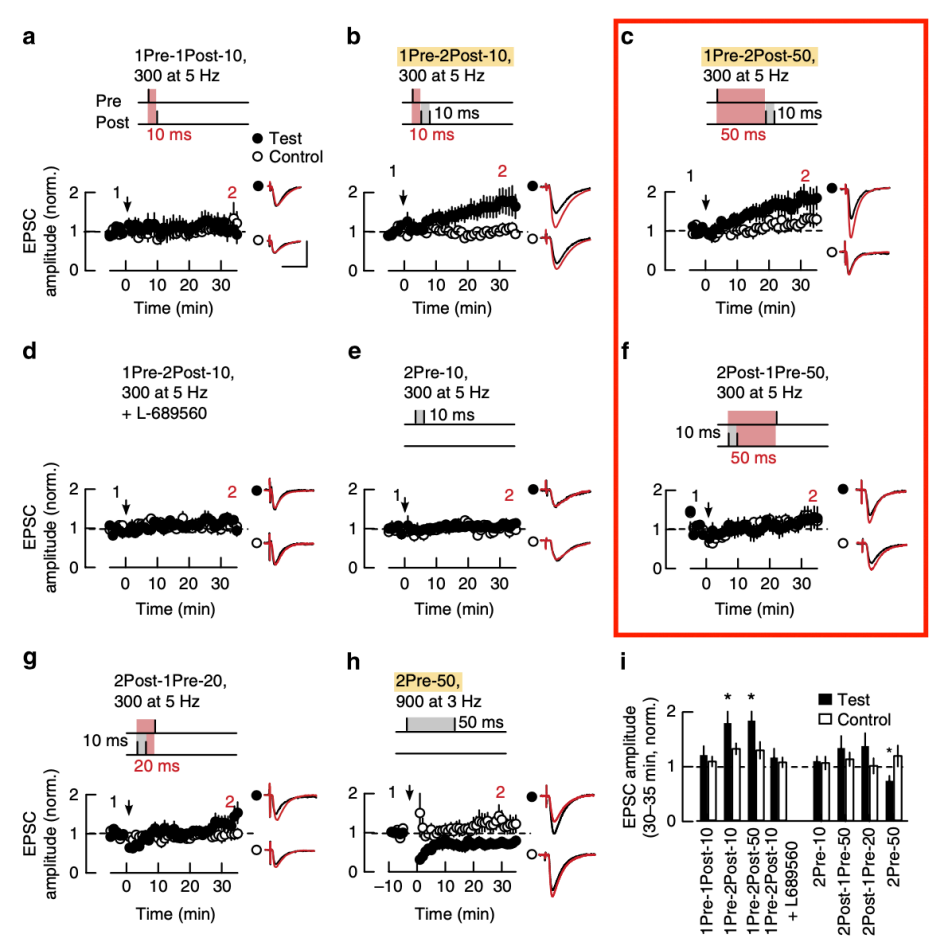


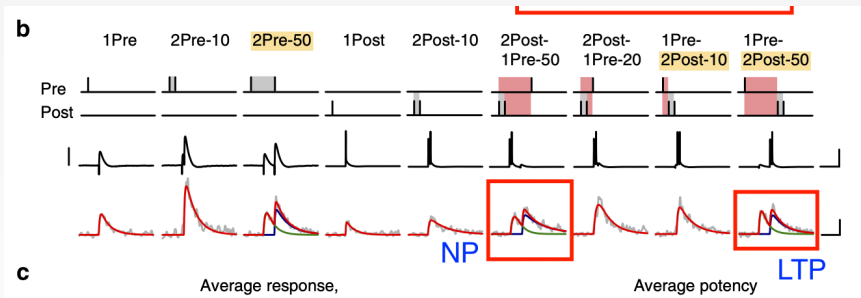
Often **wrongly** stated as:

$$\Delta w_{ij} = \begin{cases} A_+ e^{-dt/\tau_+}, & dt > 0 \\ -A_+ e^{dt/\tau_-}, & dt < 0 \end{cases}, \quad dt = t_{pre} - t_{post}$$

- Quid frequency, in-vivo results, bAP is not critical...?
- It is static description, what about DS? → Open question...

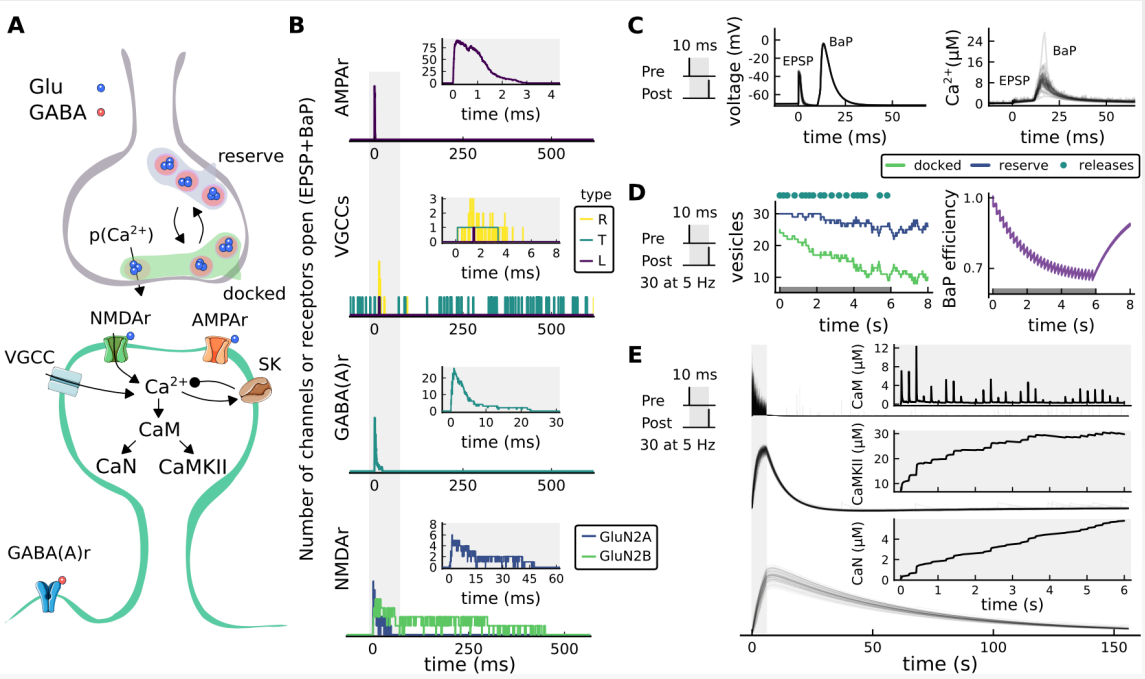
Is it this simple? [Tigaret-etal:14]

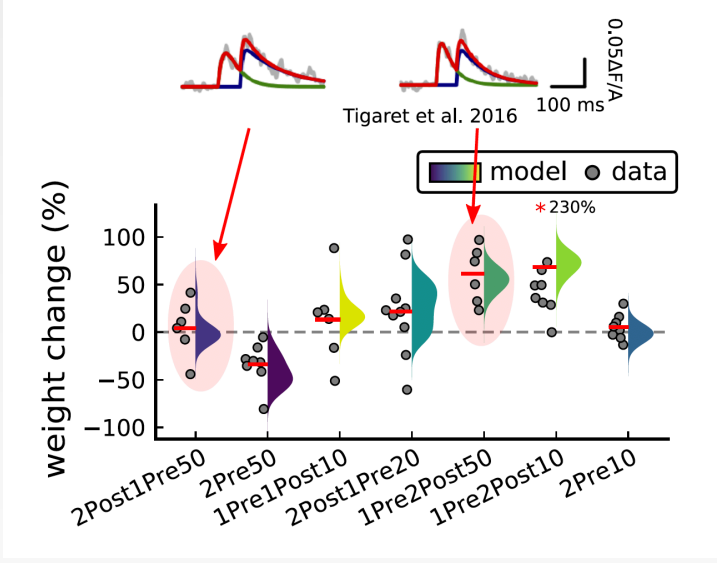




⇒ Former PhD Student Y. Rodrigues tackles this with a PDMP.

Model of [Rodrigues-etal:23]





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Summary of important plasticity results

Shouval-etal:10

High-frequency stimulation (LTP)

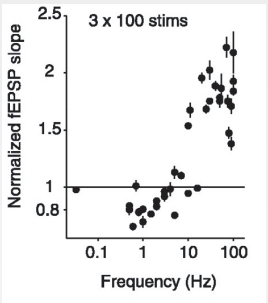
Presynaptic stimulation: 100 Hz, 1 s

Postsynaptic activity: not controlled, not measured

Low-frequency stimulation (LTD)

Presynaptic stimulation: 1 Hz, 900 s

Postsynaptic activity: not controlled, not measured



Strong depolarization (LTP)

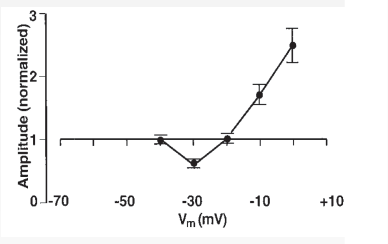
Presynaptic stimulation: 1 Hz, 100 s

Postsynaptic activity: 0 mV / -70 mV

Weak depolarization (LTD)

Presynaptic stimulation: 1 Hz, 100 s

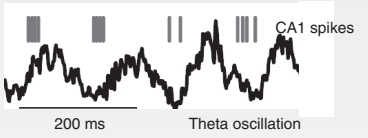
Postsynaptic activity: -30 mV / -70 mV



Theta-burst stimulation (LTP)

Presynaptic stimulation: 100 Hz bursts at 5 Hz

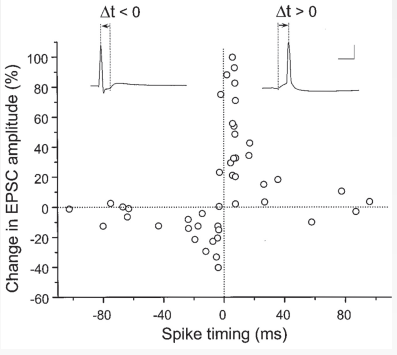
Postsynaptic activity: not controlled, not measured



Timed-spike stimulation

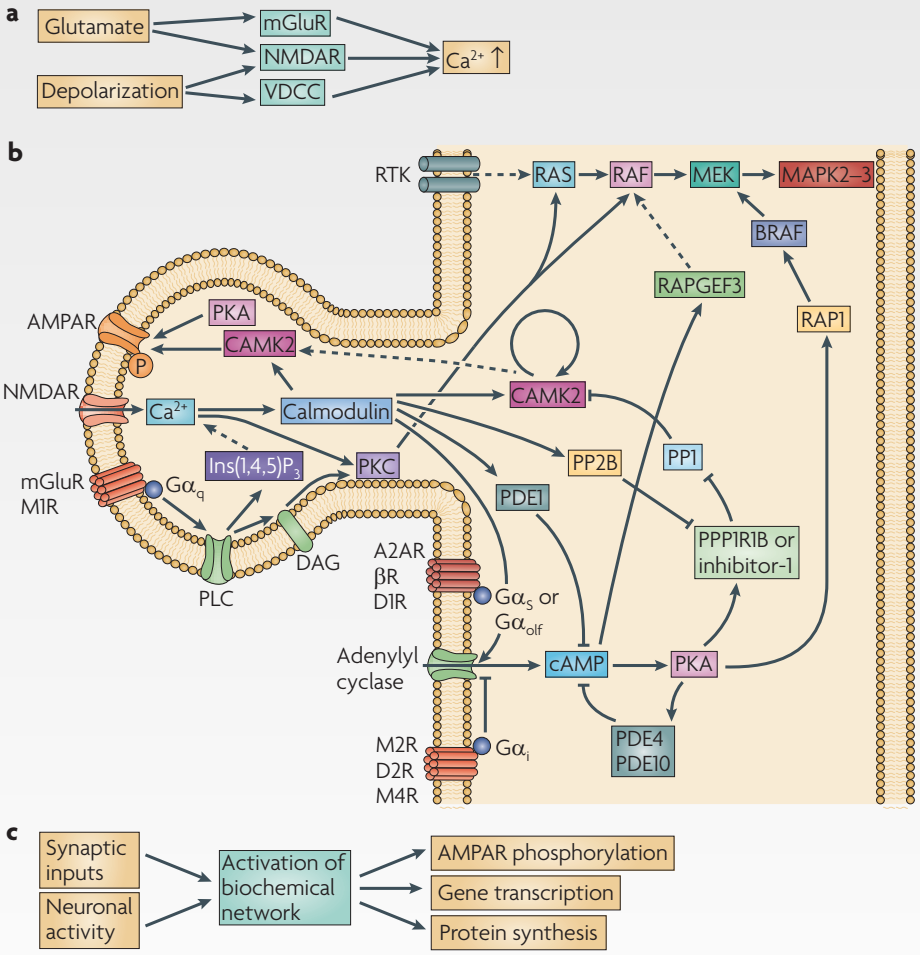
Presynaptic stimulation: $1/f$, Δt

Postsynaptic activity:



Mechanisms of Long-Term plasticity

METTRE TIGARRET ET RESULTATS DE YURI [Kotaleski-etal:10]



- Induced by Calcium entry (NMDA/VDCC)
- Cascade of reactions that affect PSD
- Change $\bar{g}_{AMPA}$ (Phosphorylation)
- Add/Remove AMPA receptors on the PSD
- Structural change of spine size (few sec.)

Proteins involved: $Ca \rightarrow CaM \rightarrow \cdots$

- Kinases (CaMKII,PKA,...)
- Phosphatases (calcineurin, PP1,...)

Mean field model from a network of coupled HH neurons

Motivation, network architecture from Brunel-etal:05, 1/2

The neurons are described by a Hodgkin-Huxley type

$$C\frac{dV}{dt} = -I_L - I_{Na} - I_K - I_{rec} + I_{ext}$$

spread on a 1d chain (variable θ) with periodic boundary conditions

1. N excitatory neurons
2. N inhibitory neurons

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3. $J_{\alpha\beta}(\theta - \theta')/N$: probability of a connection from a neuron at θ' in population β to a neuron at θ in population α

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4. $\alpha, \beta = E, I$

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spread on a 1d chain (variable θ) with periodic boundary conditions

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4. $\alpha, \beta = E, I$
5. $J_{\alpha\beta}(\theta - \theta')$ is 2π-periodic.

Assume

$$J_\alpha(r) = J_{\alpha,0} + J_{\alpha,1}\cos(r)$$

Motivation, network architecture from Brunel-etal:05, 2/2

The recurrent connections between neurons are AMPA/GABA ($\alpha \to \beta$):

$$I_{rec,i} \quad = \quad -g_{\alpha\beta} s_{\alpha,i}(t) \left(V_i - E_{syn,\alpha}\right)$$

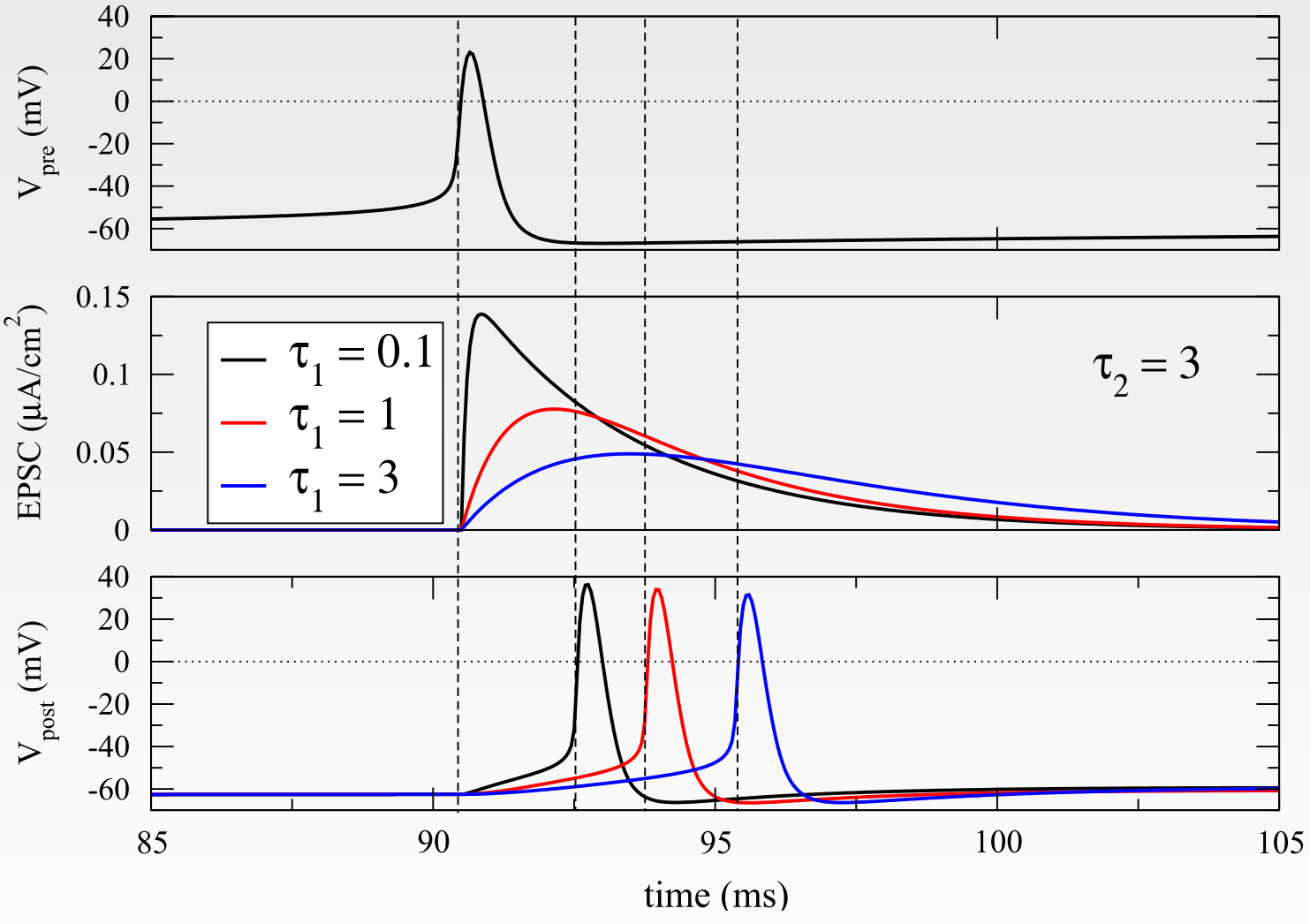
If there is a connection between i and j, we use AMPA current:

$$s_{\alpha,i} = \frac{1}{\tau_2 - \tau_1} \left(e^{-(t-t_j)/\tau_2} - e^{-(t-t_j)/\tau_1} \right)$$

where t_j is the spike from neuron j

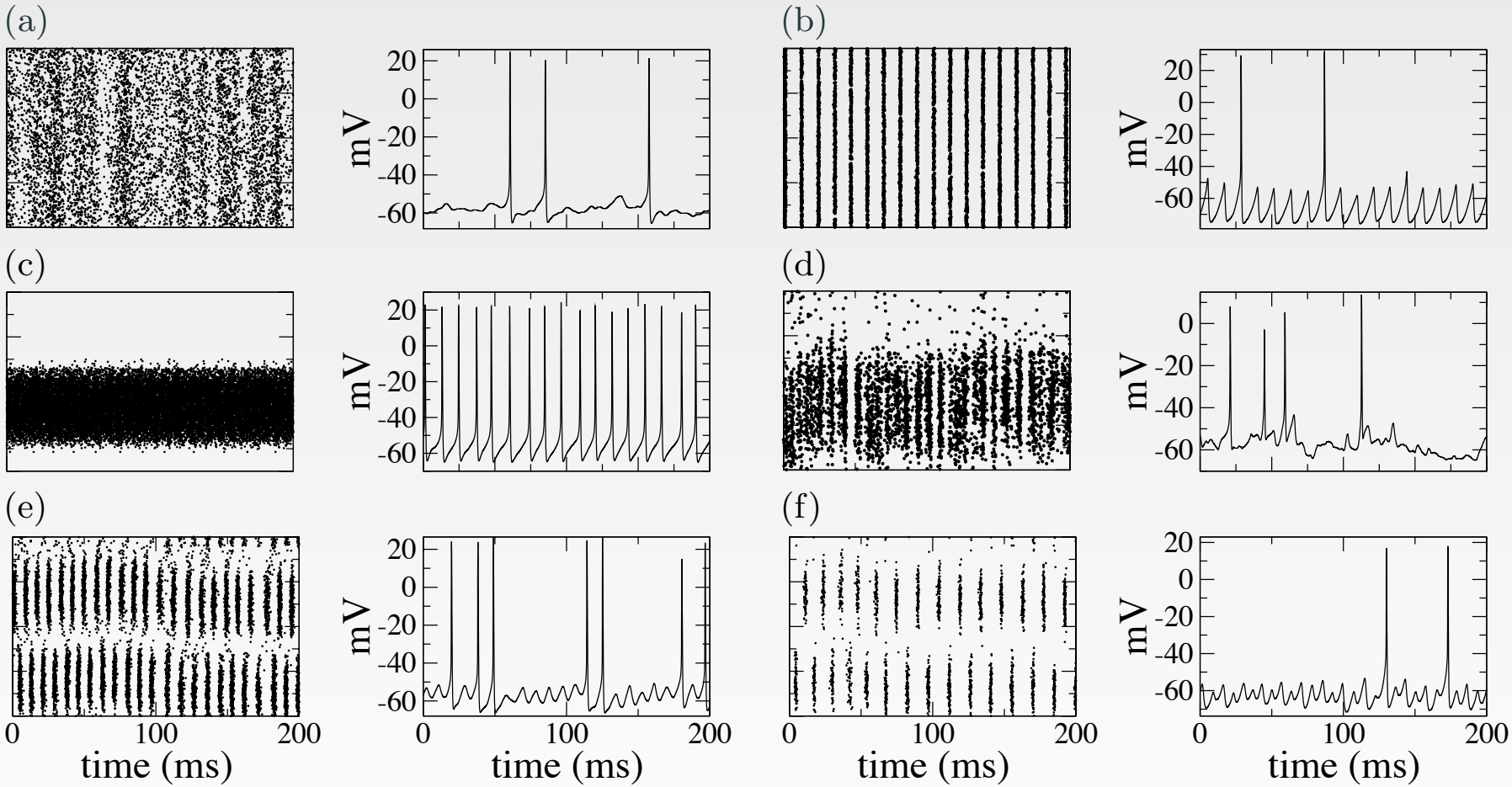
Spike initiation time

Link between two neurons.



Effective delays $D \approx 5ms$ for the time it takes to go trough a synapse.

Example of network dynamics



We look at an **empirical** approximation of the network by **firing rate** equations:

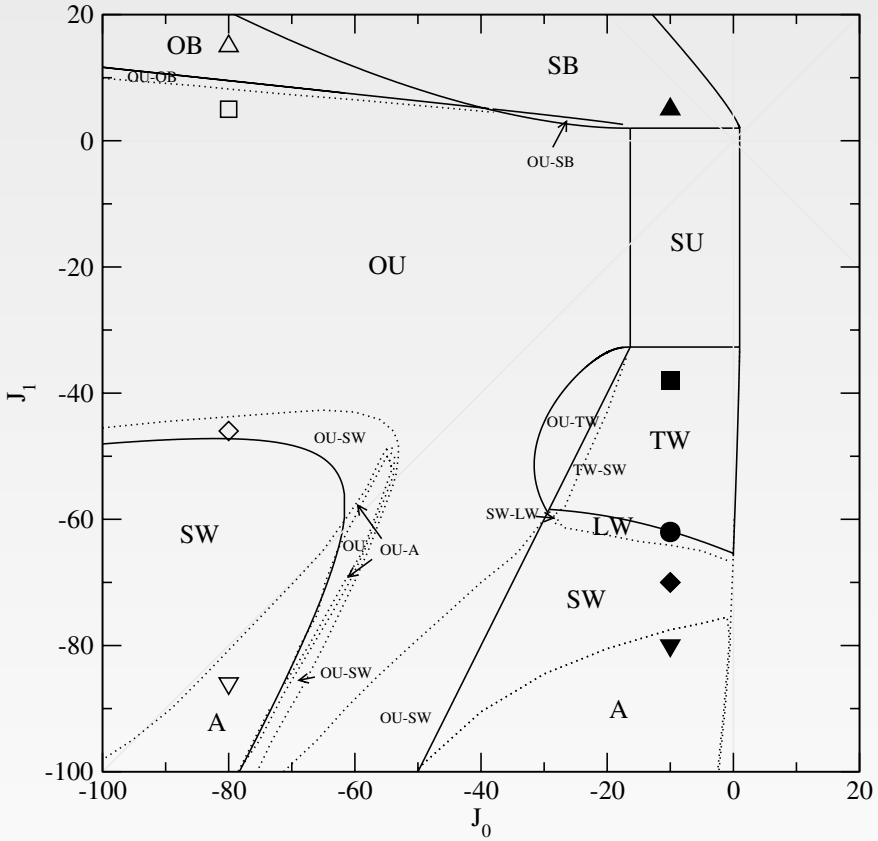
$$\tau \frac{dm_k(\theta,t)}{dt} = -m_k(\theta,t) + S\Big(I_{ext}(\theta,t) + \sum_{l=E,I} \int_{-\pi}^{\pi} J_{kl}(\theta-\theta') m_l(\theta', t-D_l) d\theta'\Big)$$

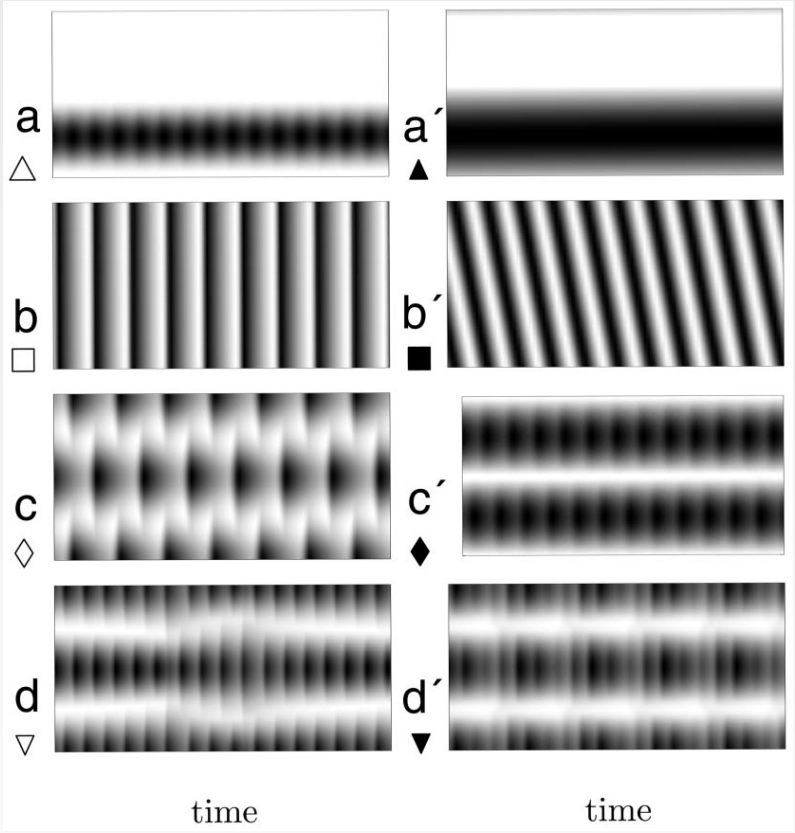
where

1. $m_k(\theta,t)$ is the **firing rate** of population k at position θ
2. S is the $f-I$ **curve** of the network model (positive, increasing)
3. D_l is the synaptic delay introduced earlier

- Delay differential equations (DDE)

Bifurcation diagram of the Brunel model





Normal form theory

Normal form theory 1/2

The idea is to find a polynomial CHV which *improves* locally a nonlinear system, in order to analyze its dynamics more easily.

$$\dot{x} = \mathsf{L}x + \mathsf{R}(x;\alpha),\ \mathsf{L} \in \mathcal{L}(\mathbb{R}^n),\ \mathsf{R} \in C^k(\mathcal{V}_x \times \mathcal{V}_\alpha, \mathbb{R}^n) \quad (1)$$

$$\mathsf{R}(0;0) = 0,\ d\mathsf{R}(0;0) = 0$$

Theorem 1/2

$\forall p \in [2,k]$, there are neighborhoods $\mathcal{V}_1$ and $\mathcal{V}_2$ of 0 in $\mathbb{R}^n$ and $\mathbb{R}^m$, respectively, such that for any $\alpha \in \mathcal{V}_2$, there is a polynomial $\Phi_\alpha : \mathbb{R}^n \to \mathbb{R}^n$ of degree p with the following properties:

- The coefficients of the monomials of degree q in Φ_α are functions of α of class C^{k-q}, and

$$\Phi_0(0) = 0,\ d\Phi_0(0) = 0$$

Theorem 2/2

- For any $x \in \mathcal{V}_1$, the polynomial CHV $x = y + \Phi_\alpha(y)$ transforms (1) into the normal form

$$\dot{y} = \mathsf{L}y + \mathbf{N}_\alpha(y) + \rho(y, \alpha)$$

  where $\mathbf{N}_\alpha : \mathbb{R}^n \to \mathbb{R}^n$ is a polynomials of degree p
- The coefficients of the monomials of degree q in $\mathbf{N}_\alpha$ are functions of α of class C^{k-q}, and

$$\mathbf{N}_0(0) = 0,\ d_x\mathbf{N}_0(0) = 0$$

- the equality $\boxed{\mathbf{N}_\alpha(e^{t\mathsf{L}^*}y) = e^{t\mathsf{L}^*}\mathbf{N}_\alpha(y)}$ holds for all $(t, y) \in \mathbb{R} \times \mathbb{R}^n$ and $\alpha \in \mathcal{V}_2$
- the maps ρ belongs to $C^k(\mathcal{V}_1 \times \mathcal{V}_2, \mathbb{R}^n)$ and

$$\forall \alpha \in \mathcal{V}_2,\ \rho(y; \alpha) = o(y^p)$$

An example

Consider the case $\mathbf{L} = \begin{bmatrix} 0 & -\omega \\ \omega & 0 \end{bmatrix}$, $\omega > 0$.

- In the basis $(\zeta, \bar{\zeta}), \zeta = (1, -i)$: $\mathbf{L} = \begin{bmatrix} i\omega & 0 \\ 0 & -i\omega \end{bmatrix}$
- Write $x = y + \Phi_\alpha(y)$, the change of variable with $y = A\zeta + \overline{A\zeta}$

Lemma

$$\mathbf{N}_\alpha(A\zeta + \overline{A\zeta}) = AQ_\alpha(|A|^2)\zeta + \overline{AQ_\alpha}(|A|^2)\bar{\zeta}.$$

How do we show this? ($N_\alpha(A\zeta + \overline{A\zeta}) = AQ_\alpha(|A|^2)\zeta + \overline{AQ_\alpha}(|A|^2)\bar{\zeta}$)

- In the basis $(\zeta, \bar{\zeta}), \zeta = (1, -i)$: $\mathbf{L} = \begin{bmatrix} i\omega & 0 \\ 0 & -i\omega \end{bmatrix}$
- Write $x = y + \Phi_\alpha(y)$, the change of variable with $y = A\zeta + \overline{A\zeta}$
- Use
$$\mathbf{N}_\alpha(e^{t\mathbf{L}^*} y) = e^{t\mathbf{L}^*} \mathbf{N}_\alpha(y)$$
- Write $\mathbf{N}_\alpha(A\zeta + \overline{A\zeta}) = P_\alpha(A, \bar{A})\zeta + \overline{P_\alpha}(A, \bar{A}))\bar{\zeta}$ and note that $e^{t\mathbf{L}^*} = diag\left(e^{-i\omega t}, e^{i\omega t}\right)$ which gives
$$P_\alpha\left(e^{-i\omega t}A, e^{i\omega t}\bar{A}\right) = e^{-i\omega t}P_\alpha(A, \bar{A}).$$
- Looking for monomials $P(A, B) = A^p B^q$ gives the condition $\forall t,\ e^{i\omega t(q-p)} = e^{-i\omega t}$ *i.e.* $p = q + 1$ and $P(A, \bar{A}) = A|A|^{2q}$.

The machinary

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So to compute the normal form N, we have to compute Ψ, Φ? No we can combine the two computations in a single step. (See book **[Haragus-etal:2011]**)

Hopf bifurcation, the come back

We consider $\dot{u} = \mathbf{F}(u, \mu) \in \mathbb{R}^2 \quad (E)$.

Theorem (Hopf bifurcation)

Assume that $\mathbf{F} \in C^k(\mathbb{R}^2, \mathbb{R}^2), k \geq 5$ with $\mathbf{F}(0,0) = 0$ and $\mathbf{L} := d_u\mathbf{F}(0,0)$. Assume further that

- the two eigenvalues of $\mathbf{L}$ are $\pm i\omega$ for some $\omega > 0$
- the normal form at 3rd order reads $\dot{A} = A(a\mu + i\omega + b|A|^2) + \rho(A, \bar{A}, \mu)$. Assume that $a_r := \Re(a) \neq 0, b_r := \Re(b) \neq 0$ (see previous slides)

b is called the **Lyapunov** coefficient.

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Then, (1) has a **supercritical** (resp., **subcritical**) Hopf bifurcation occurs at $\mu = 0$ when $b_r < 0$ (resp., $b_r > 0$). And, in a neighborhood of 0 in $\mathbb{R}^2$ for sufficiently small μ:

1. If $a_r b_r < 0$ (resp., $a_r b_r > 0$), (1) has precisely one equilibrium $u(\mu)$ for $\mu < 0$ (resp., for $\mu > 0$) with $u(0) = 0$. $u(\mu)$ is stable when $b_r < 0$ and unstable when $b_r > 0$.
2. If $a_r b_r < 0$ (resp., $a_r b_r > 0$), (1) possesses for $\mu > 0$ (resp., for $\mu < 0$) an equilibrium $u(\mu)$ and a unique periodic orbit $u(\mu) = O(\sqrt{|\mu|})$, which surrounds this equilibrium. The periodic orbit is stable (resp. unstable) when $b_r < 0$ (resp. $b_r > 0$), whereas the equilibrium has opposite stability.

b is called the **Lyapunov** coefficient.

Hopf bifurcation, the come back

We consider $\dot{u} = \mathbf{F}(u, \mu) = \mathbf{L}u + \mathbf{R}(u, \mu) \in \mathbb{R}^n$.

Theorem (Hopf bifurcation)

Assume that $\mathbf{F} \in C^k(\mathbb{R}^n \times \mathbb{R}^p, \mathbb{R}^n), k \geq 5$ with $\mathbf{F}(0,0) = 0$ and $\mathbf{L} := d_u\mathbf{F}(0,0)$ and

- two eigenvalues of $\mathbf{L}$ are $\pm i\omega$ for some $\omega > 0$, eigenvectors $\zeta, \bar{\zeta}$
- no other eigenvalue has zero real part
- the normal form at 3rd order reads $\dot{A} = A(a\mu + i\omega + b|A|^2) + \rho(A, \bar{A}, \mu)$. Assume that $a_r := \Re(a) \neq 0, b_r := \Re(b) \neq 0$ (see previous slides)

$$a = \langle \mathbf{R}_{11}(\zeta) + 2\mathbf{R}_{20}\left(\zeta, \Psi_{001}\right), \zeta^* \rangle$$

b is called the **Lyapunov** coefficient.

$$b = \left\langle 2\mathbf{R}_{20}\left(\zeta, \Psi_{110}\right) + 2\mathbf{R}_{20}\left(\bar{\zeta}, \Psi_{200}\right) + 3\mathbf{R}_{30}(\zeta, \zeta, \bar{\zeta}), \zeta^* \right\rangle$$

with $\mathbf{L}^*\zeta^* = -i\omega\zeta^*$ and

$$\begin{aligned} -\mathbf{L}\Psi_{001} &= \mathbf{R}_{01} \\ (2i\omega - \mathbf{L})\Psi_{200} &= \mathbf{R}_{20}(\zeta, \zeta) \\ -\mathbf{L}\Psi_{110} &= 2\mathbf{R}_{20}(\zeta, \bar{\zeta}) \end{aligned}$$

Introduction to delay differential equations

Let us consider an equation for the membrane voltage potential

$$\dot{V}(t) = \mathbf{F}(V(t); \mu) \tag{1}$$

Information needed to compute the right hand-side at t_0:

- a scalar, *e.g.* $V(t_0)$.

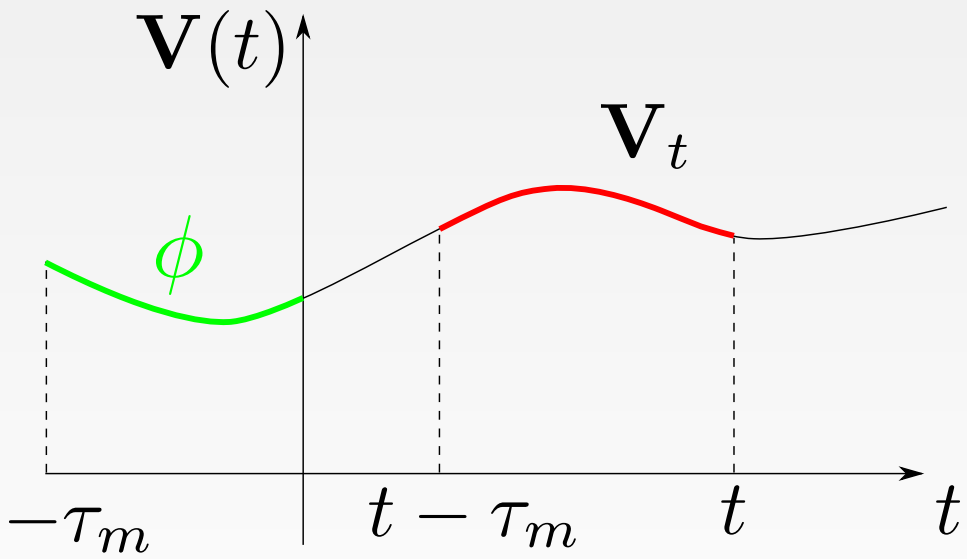
Delayed systems [Hale-Lunel:93]

Let us consider an equation for the membrane voltage potential with a feedback ($\tau_m > 0$)

$$\dot{V}(t) = \mathsf{F}(V(t), V(t-\tau_m); \mu) \tag{2}$$

Information needed to compute the right hand side at t_0:

- a history segment, *e.g.* $V(t), t \in [t_0 - \tau_m, t_0]$.



$\Rightarrow$ It is an infinite dimensional problem even if V is a scalar.

Delay differential equation DDE

This suggests to look at (delay $D > 0$)

$$\begin{cases} \dot{V}(t) &= \mathbf{F}(V(t), V(t-D), \mu) \\ V(t) &= \phi(t),\ t \in [-D, 0] \end{cases} \quad \text{(DDE)}$$

$\Rightarrow$ Nonlinear stability / Center manifold is difficult to investigate. It is possible but quite technical, you can have a look at my paper

Veltz, R., and O. Faugeras. *A Center Manifold Result for Delayed Neural Fields Equations.* 2013.