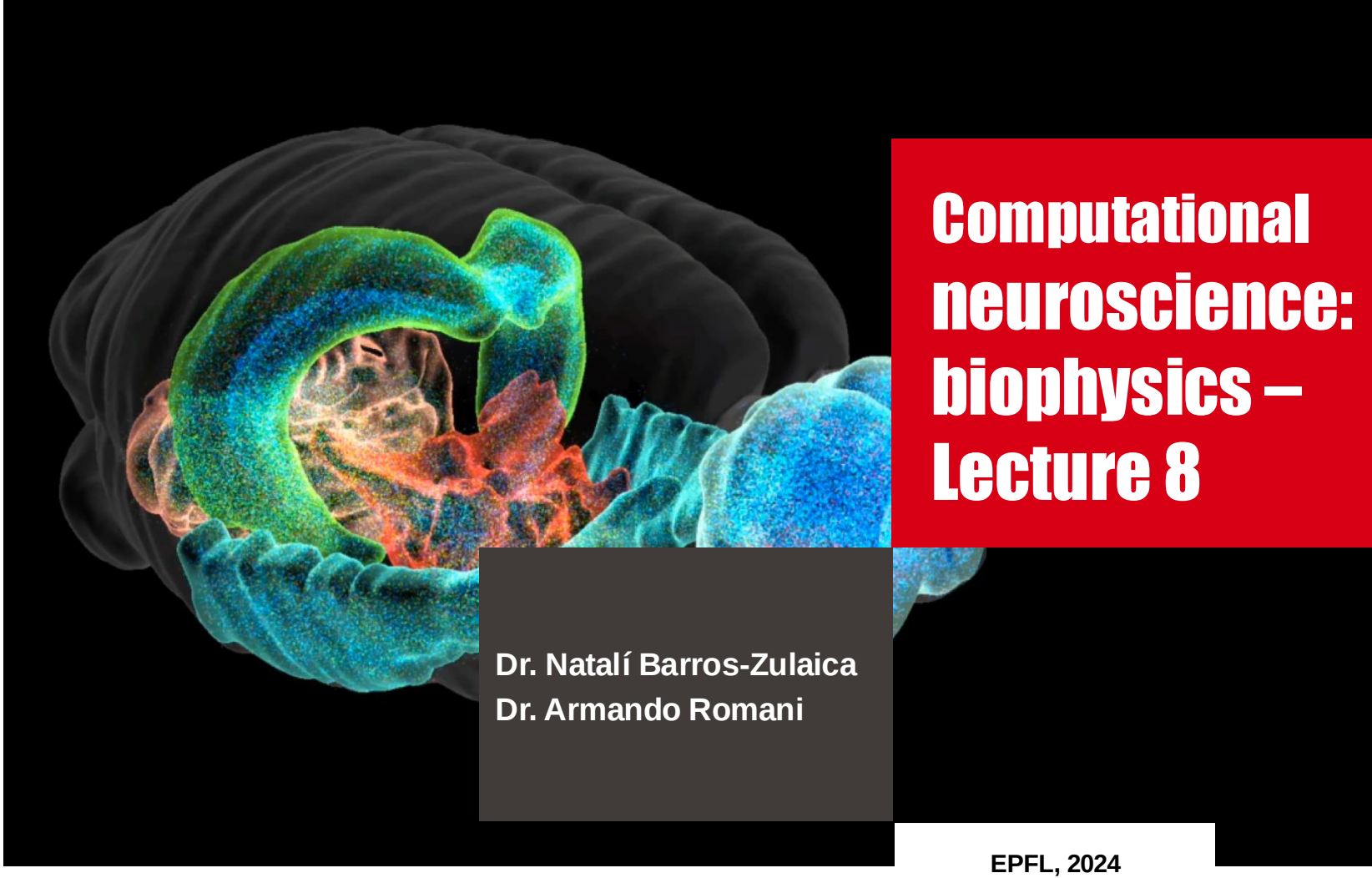


Computational neuroscience: biophysics – Lecture 8

Dr. Natalí Barros-Zulaica
Dr. Armando Romani

EPFL, 2024

Synapses

Lecture Overview

- Scope
- Approaches
- Applications

Lecture Overview

- **Scope**
- Approaches
- Applications

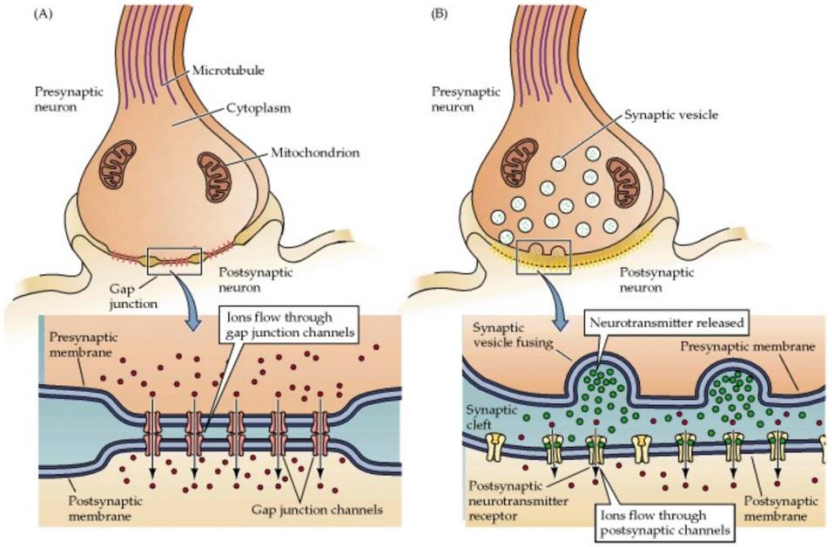
Synapse

- **Definition:** the point at which one neuron communicates with another (Charles Sherrington)
- Two types of synapses: electrical and chemical

Table 8–1 Distinguishing Properties of Electrical and Chemical Synapses

Type of synapse	Distance between pre- and postsynaptic cell membranes	Cytoplasmic continuity between pre- and postsynaptic cells	Ultrastructural components	Agent of transmission	Synaptic delay	Direction of transmission
Electrical	4 nm	Yes	Gap-junction channels	Ion current	Virtually absent	Usually bidirectional
Chemical	20–40 nm	No	Presynaptic vesicles and active zones; postsynaptic receptors	Chemical transmitter	Significant: at least 0.3 ms, usually 1–5 ms or longer	Unidirectional

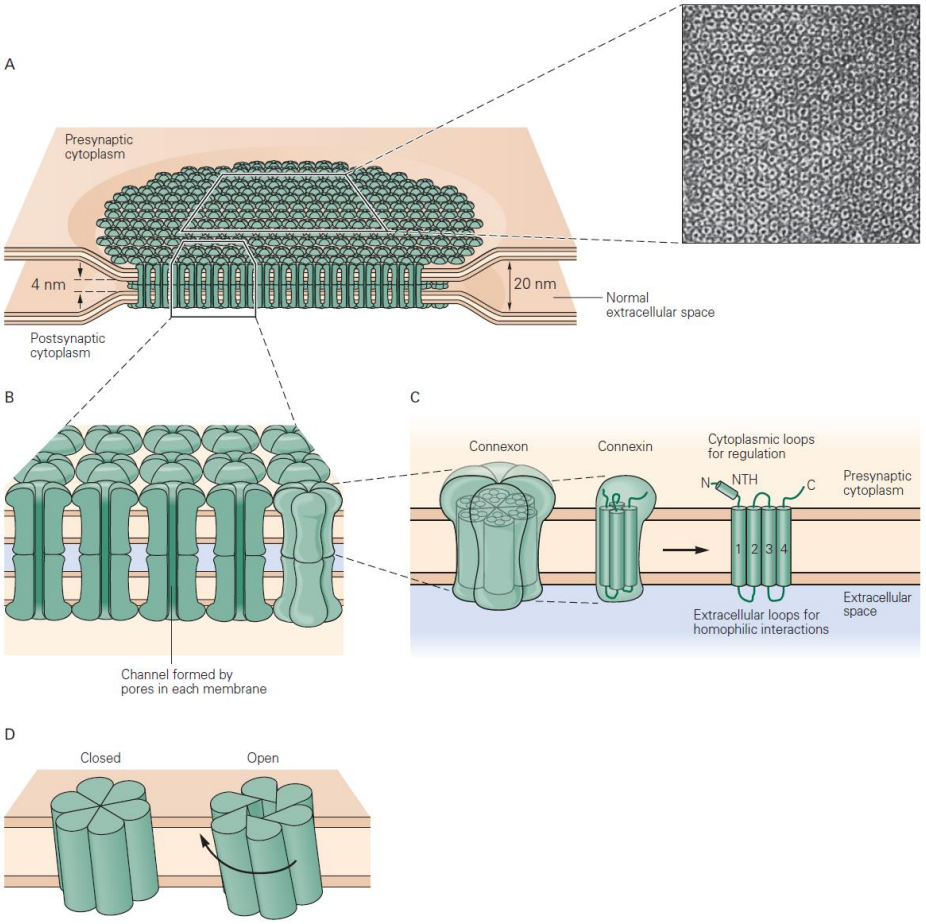
Principles of Neural Science, Kandel et al.



Neuroscience, Purves et al.

Electrical synapse

- Cytoplasmic continuity
- Through gap junction channels
- Faster
- Bidirectional
- ‘simpler’
- Fast motor responses or population activity synchronization



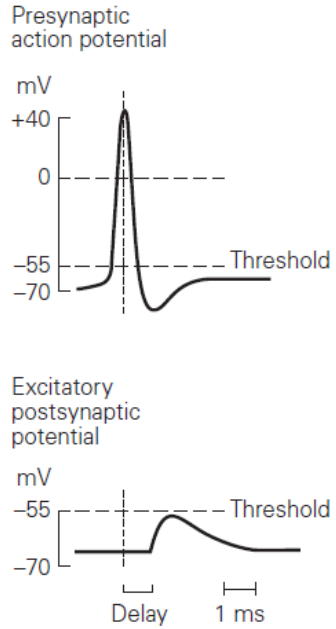
Kandel et al.

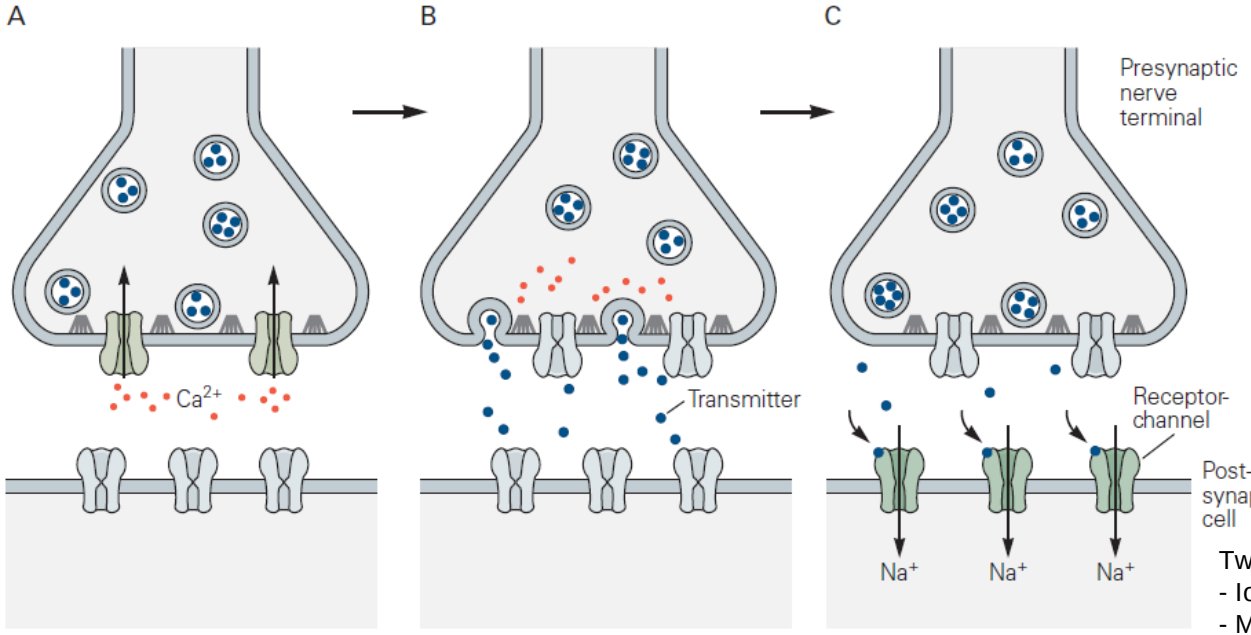
Chemical synapse

- No cytoplasmic continuity
- Through presynaptic vesicles, active zones and postsynaptic receptors

- Slower
- Unidirectional
- ‘more complex’

- They can produce changes in the postsynaptic cell



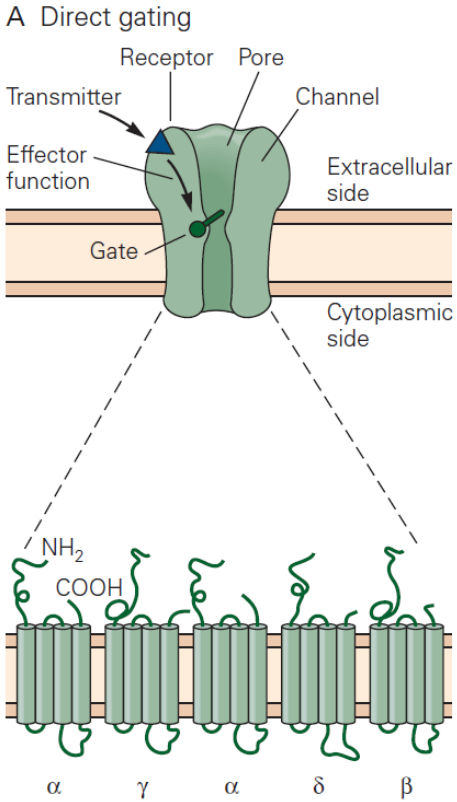


Two types of receptors:
- Ionotropic
- Metabotropic

Kandel et al.

Chemical synapse: ionotropic receptors

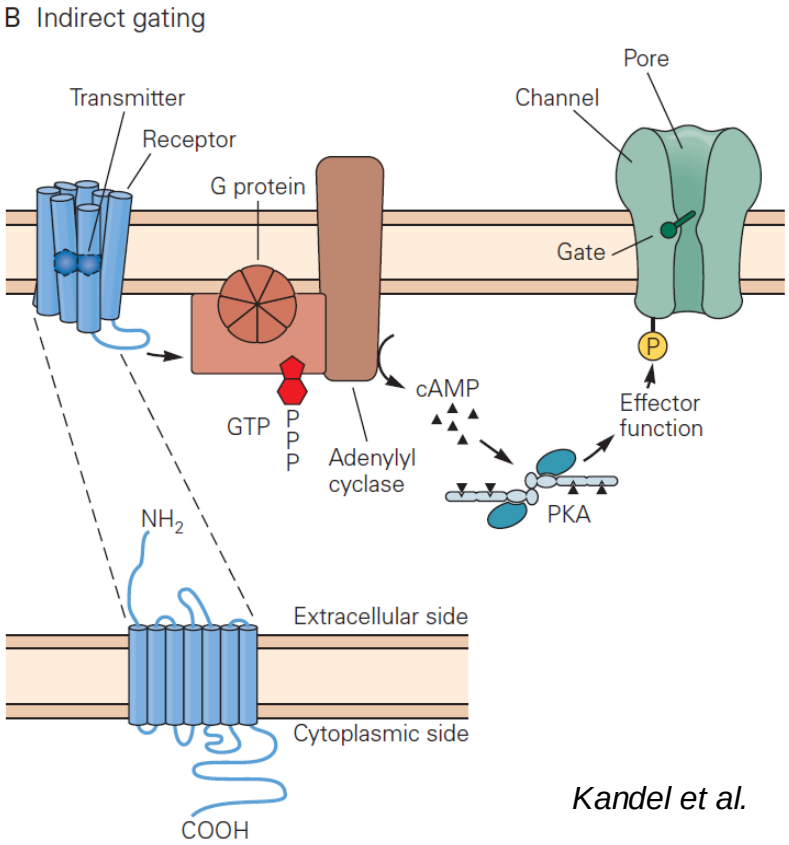
- Direct gating
- Fast synaptic actions (ms)
- Circuits that mediate rapid behaviors as stretch receptor reflex



Kandel et al.

Chemical synapse: metabotropic receptors

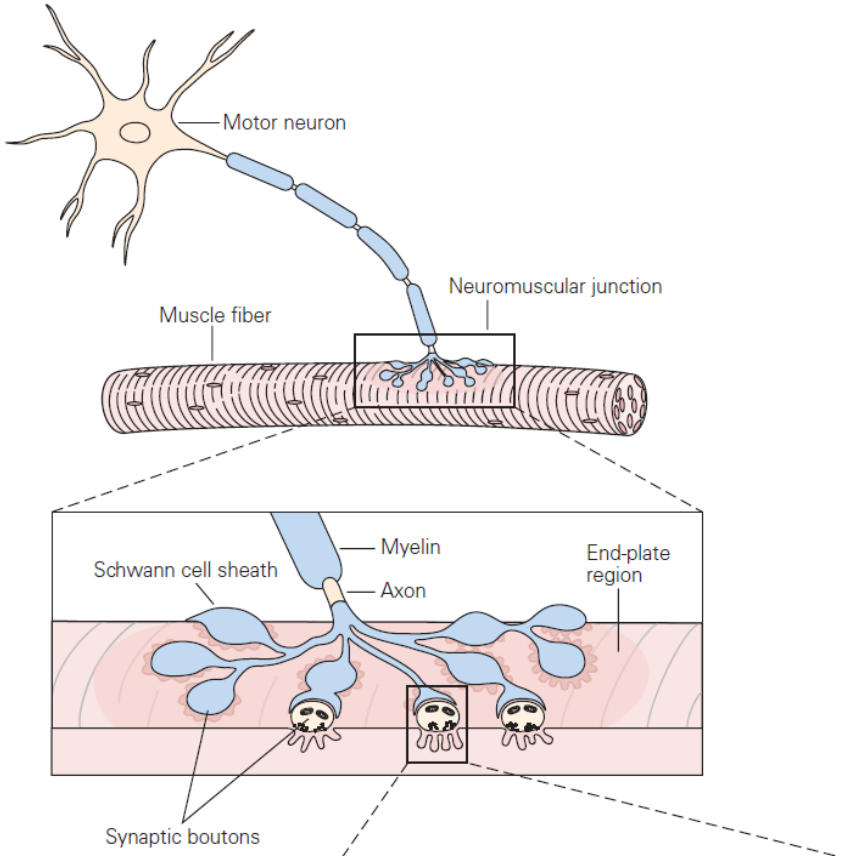
- Indirect gating
- Slow synaptic actions (sec to min)
- Channel activation through intracellular cascade
- Can modulate the strength of the synapse
- In circuits related to learning



Kandel et al.

Example: the neuromuscular junction

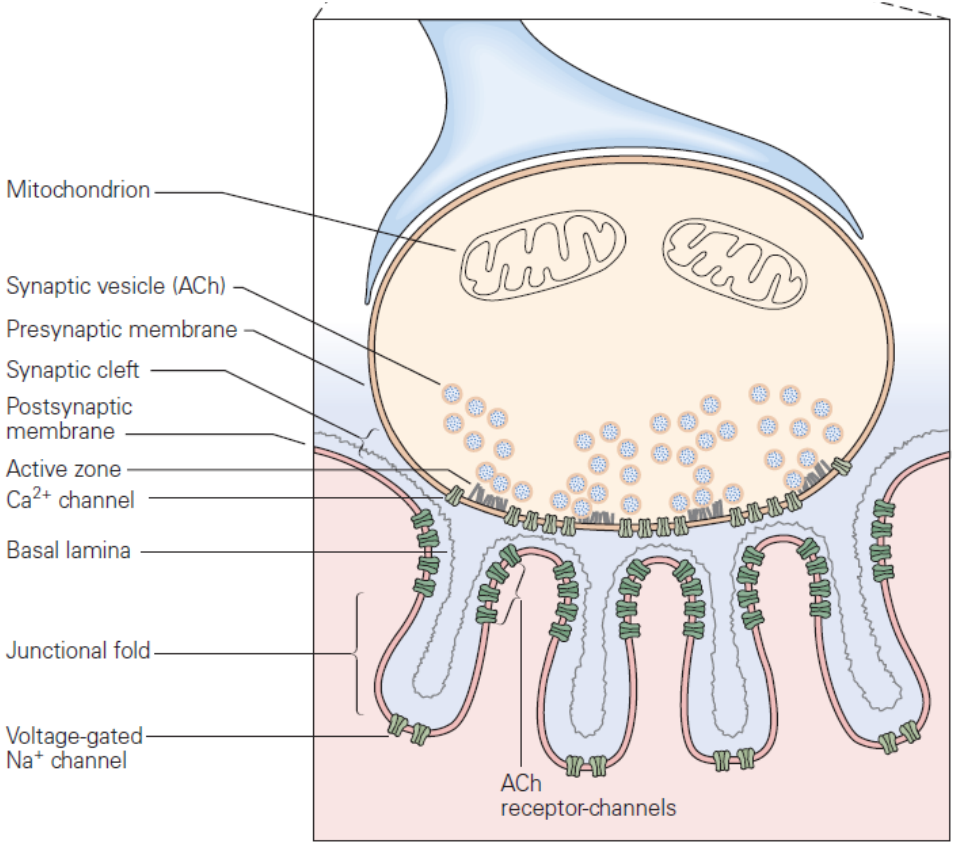
- José del Castillo and Bernard Katz studied the neuromuscular junction
- Their results can be generalized to the other synapses in the CNS
- Each motor neuron makes several contacts (boutons) on the muscle



Kandel et al.

Neuromuscular junction: one bouton

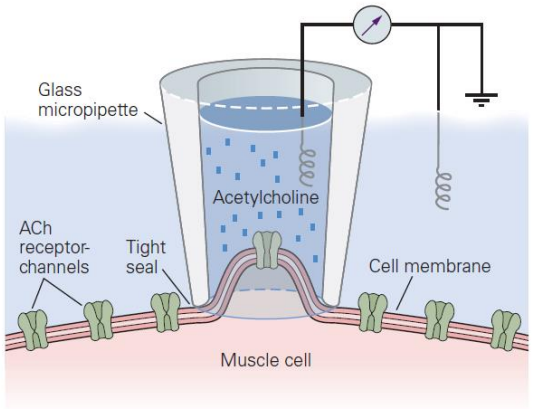
- Each bouton forms a synapse
- Both pre- and post-synaptic membranes are specialized structures
- Vesicles are released at the level of active zones

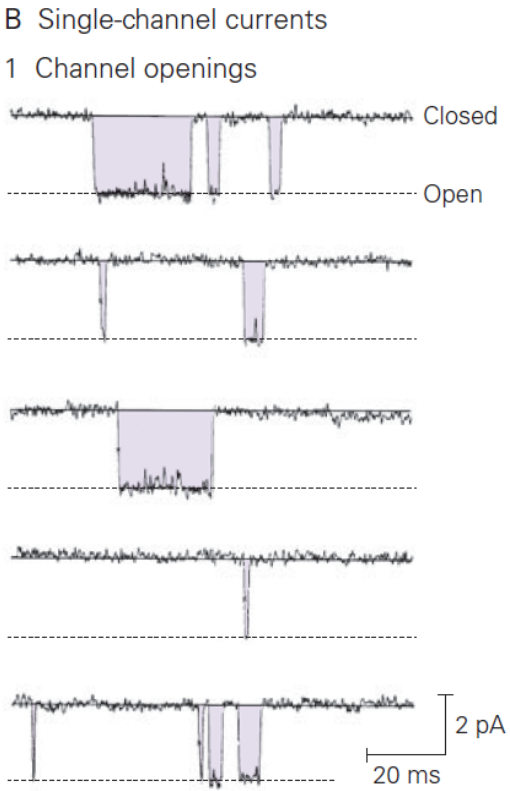


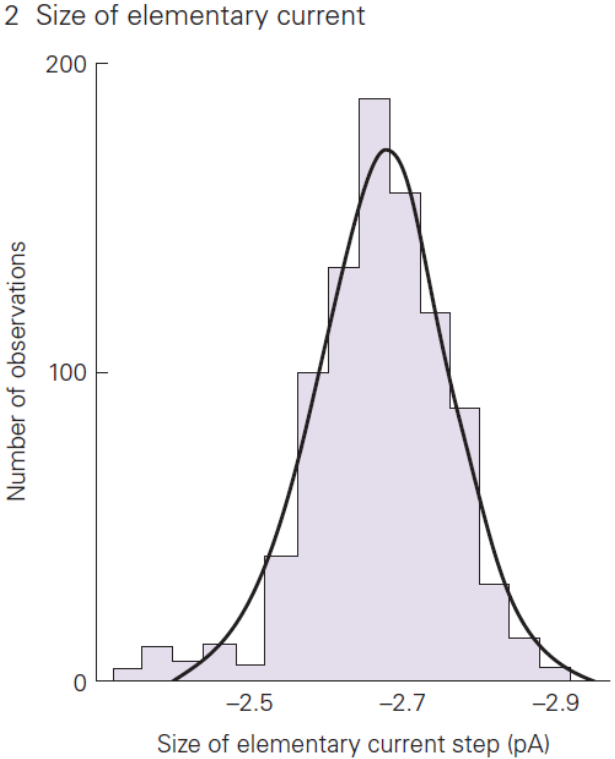
Kandel et al.

Neuromuscular junction: receptors

nicotinic acetylcholine receptors (nAChRs) are stochastic



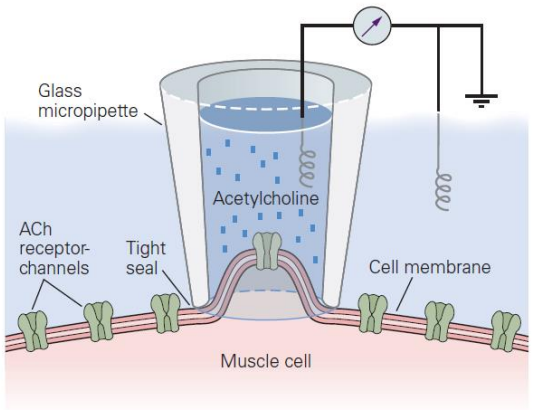


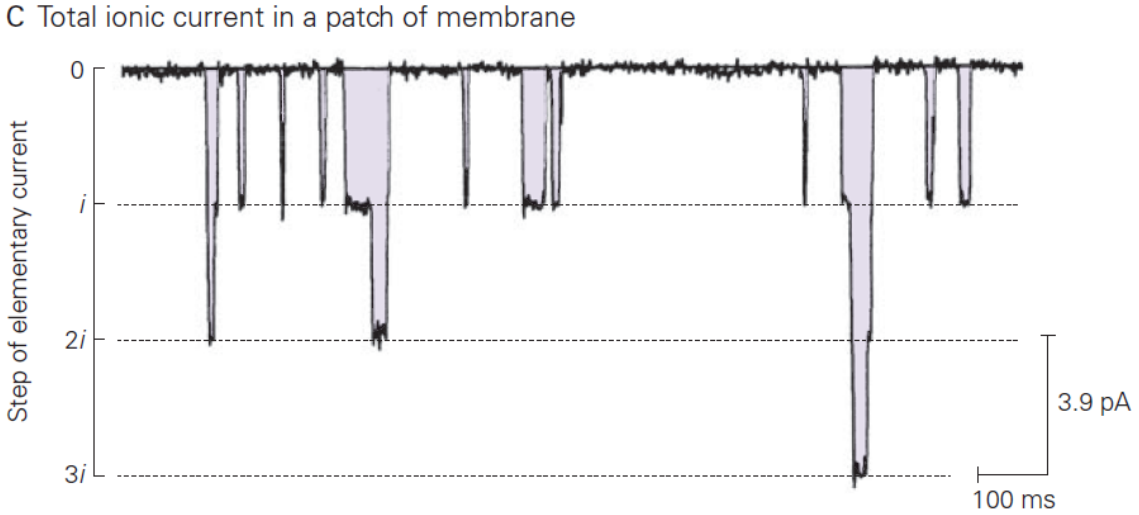


Kandel et al.

Neuromuscular junction: receptors

nicotinic acetylcholine receptors (nAChRs) are stochastic

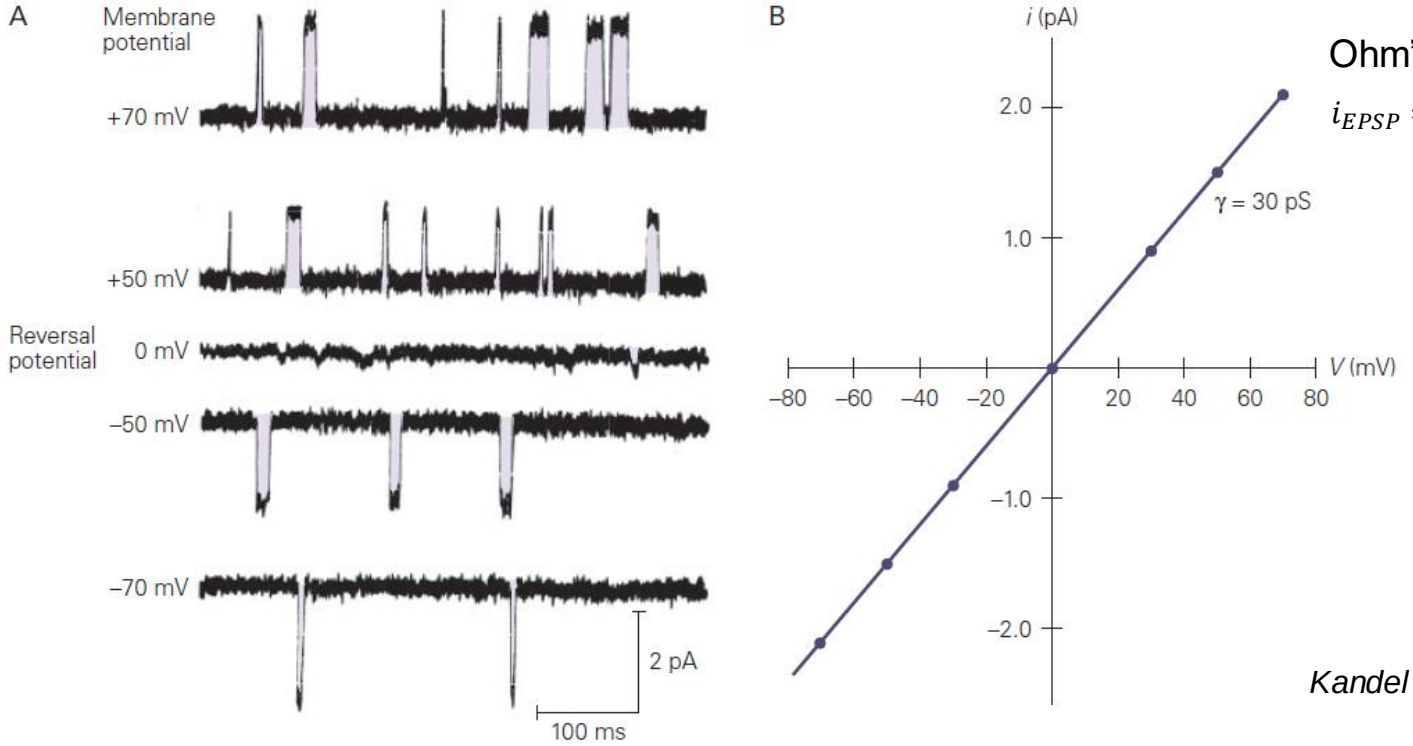




Kandel et al.

Neuromuscular junction: I-V curve

The current has a linear relationship with voltage



The channel behaves as a simple resistor

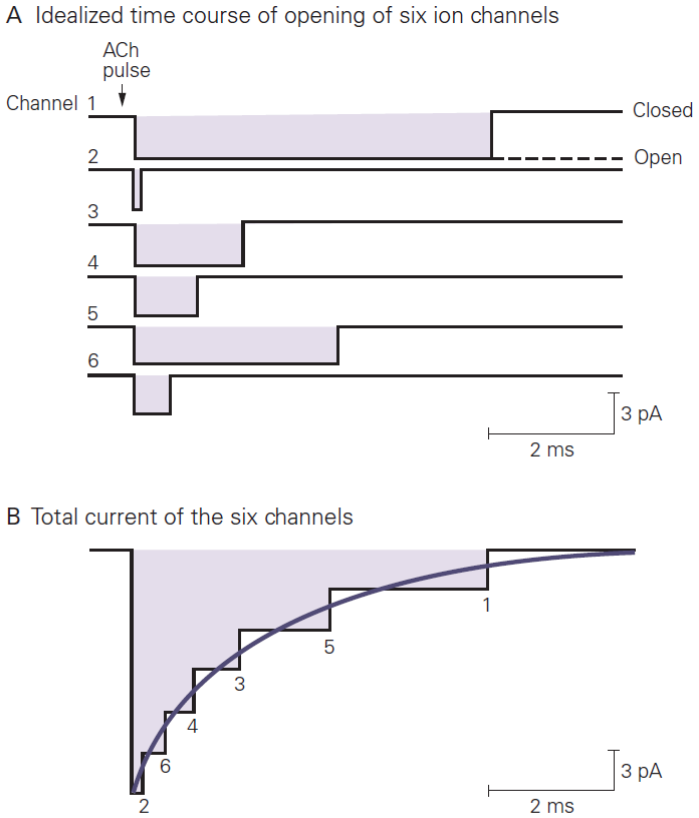
Ohm's law

$$i_{EPSP} = \gamma_{EPSP} x (V_m - E_{EPSP})$$

Kandel et al.

Neuromuscular junction: many channels

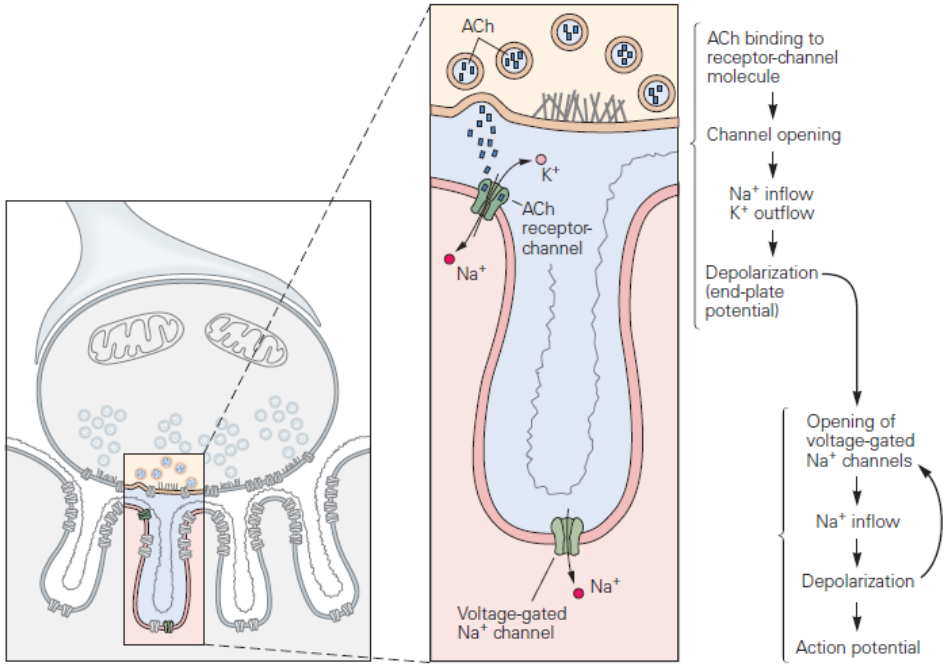
While each receptor is stochastic, the average current through many channels in response to a pulse of acetylcholine has a consistent shape



Kandel et al.

Neuromuscular junction: one active zone

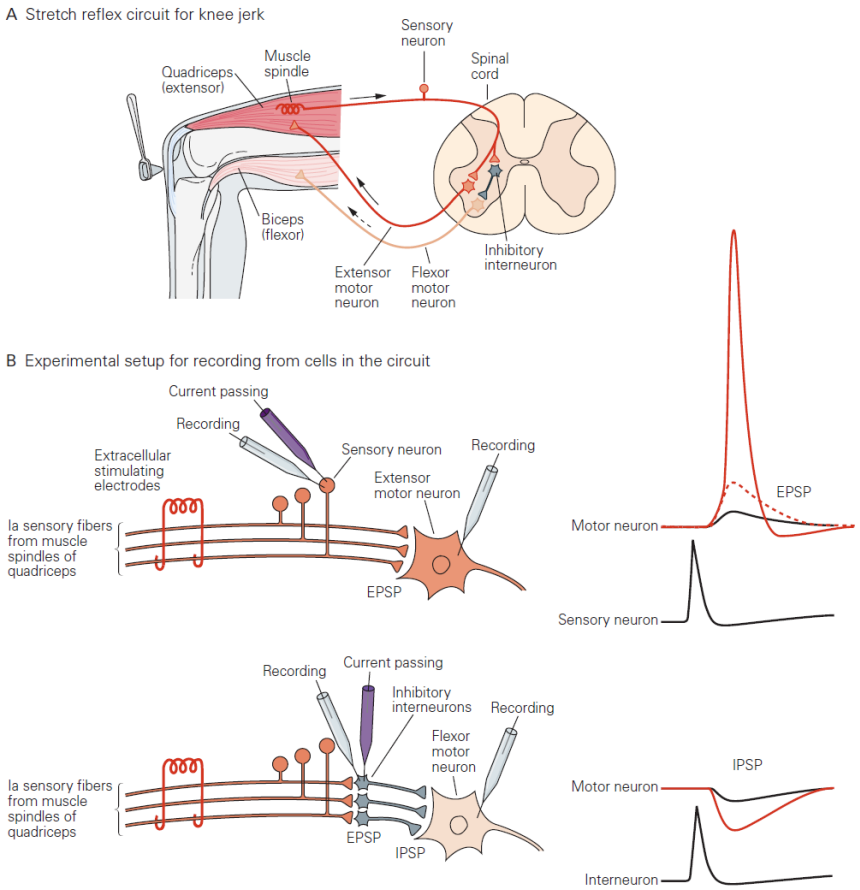
- nAChRs allow the entrance of Na+ and the exit of K+
- At the resting membrane potential, the net current tends to depolarize the membrane
- If the depolarization is sufficient, it can trigger an action potential via voltage-gated sodium channels



Kandel et al.

Chemical synapses in CNS

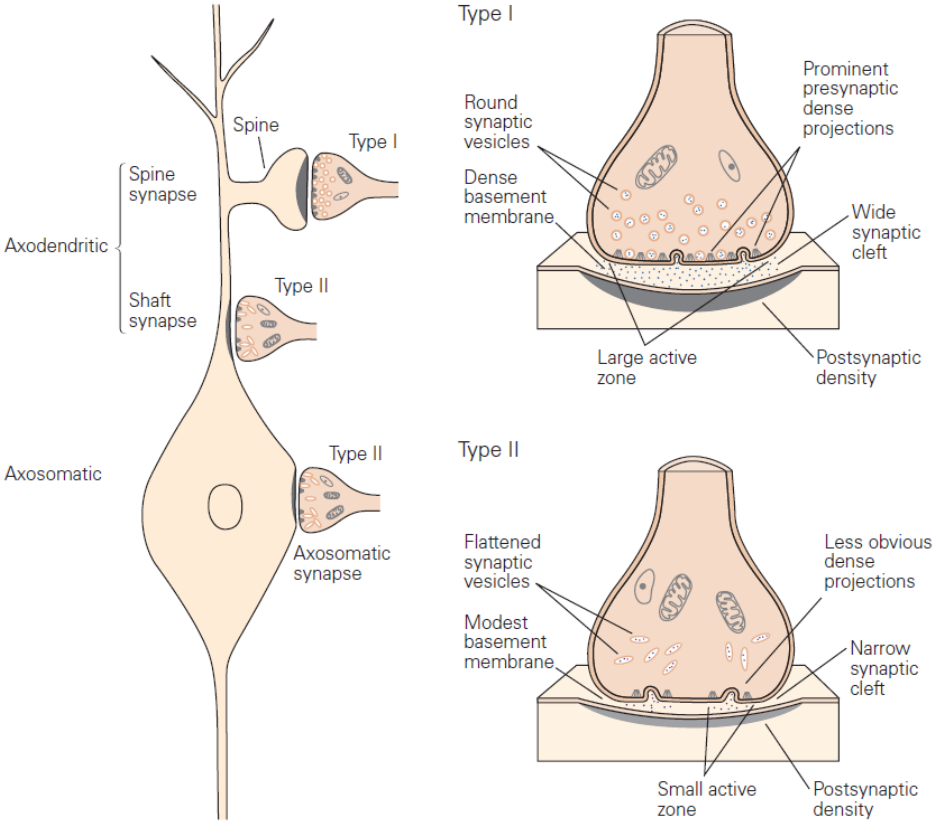
- In the CNS, we have two major types of chemical synapses: excitatory and inhibitory
- Excitatory synapses generate excitatory post-synaptic potentials (EPSPs or EPSCs)
- Inhibitory synapses generate inhibitory post-synaptic potentials (IPSPs or IPSCs)



Kandel et al.

Chemical synapses in CNS

- Excitatory synapses are also called Gray type I and use glutamate as neurotransmitter
- Inhibitory synapses are also called Gray type II and use GABA as neurotransmitter



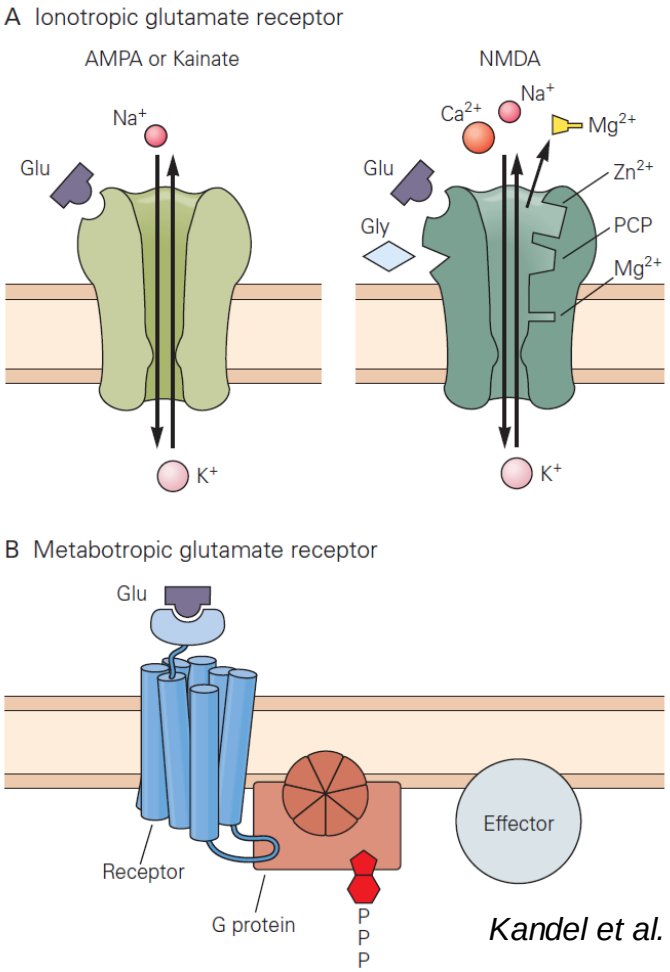
Kandel et al.

Synaptic behaviour characterization

Neurotransmitter	Receptor	Type	Comments
Glutamate (excitatory)	AMPA	Ionotropic	Very fast
	NMDA	Ionotropic	Voltage-dependent
	mGlu	Metabotropic	IP_3 coupled
GABA (inhibitory)	$GABA_A$	Ionotropic	Fast inhibition
	$GABA_B$	Metabotropic	Slow inhibition
Acetylcholine	Nicotinic	Ionotropic	Neuromuscular junction
	m1 - m5	Metabotropic	Many effects coupled to second messengers
Noradrenaline	α_1 , α_2		
	β_1 , β_2		
Serotonin	$5HT_1$ *et al.*		
Dopamine	D1 - D5		
Histamine	H1 , H2		

Glutamatergic synapses

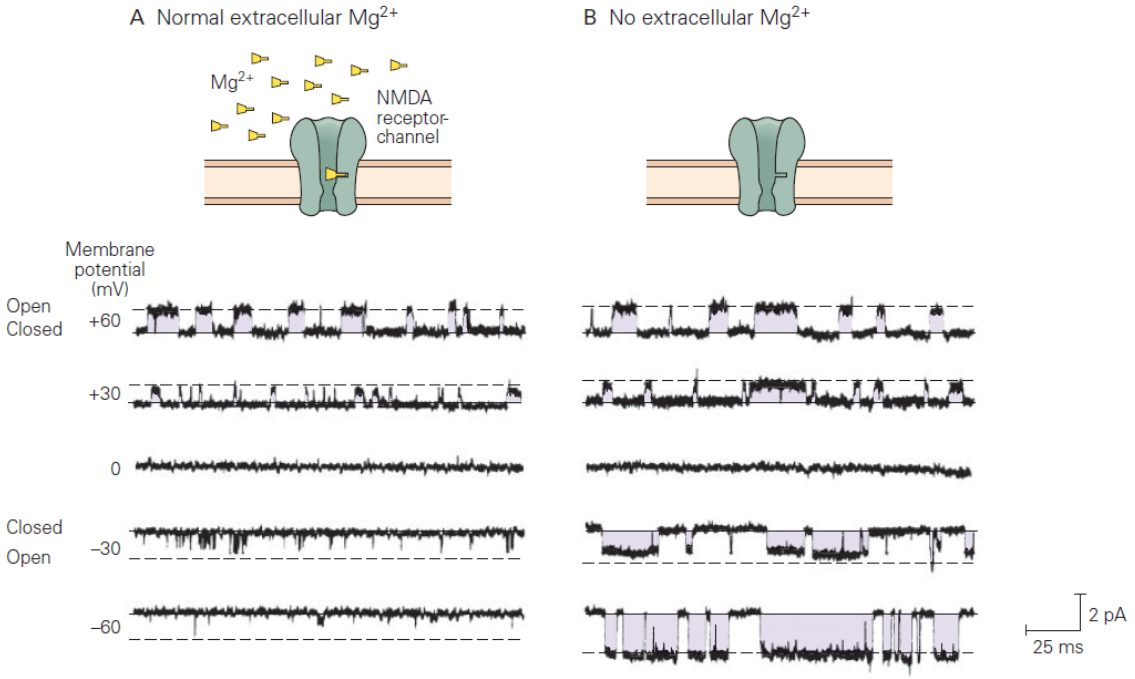
- Glutamatergic receptors can be ionotropic or metabotropic
- Ionotropic receptors are AMPAR and NMDAR



Kandel et al.

NMDA receptors

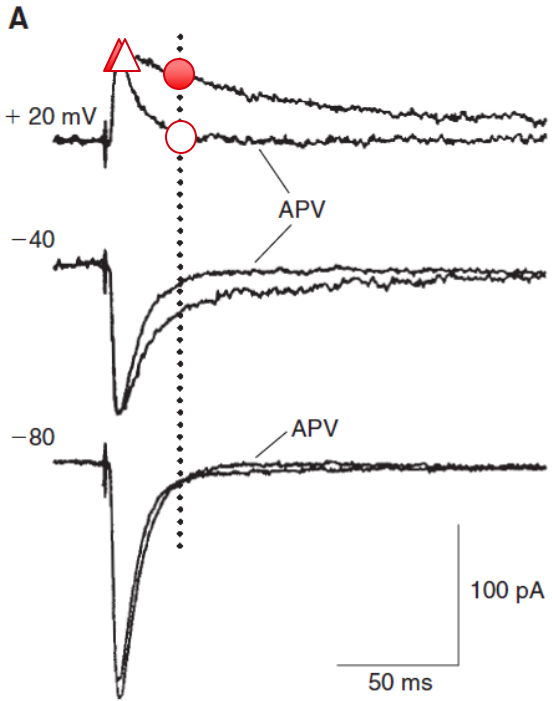
- At resting membrane potential Mg2+ blocks the NMDARs
- Depolarization releases the Mg block
- Note the reversal potential at 0 mV

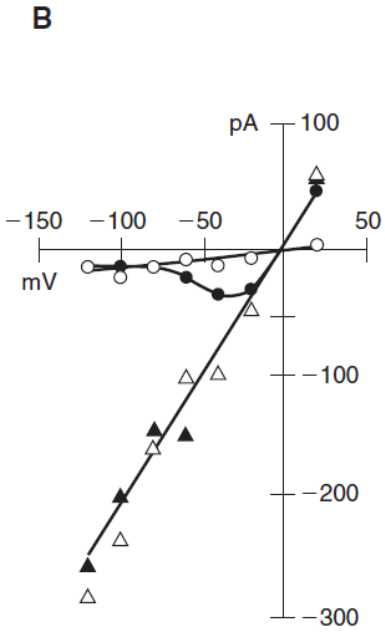


Kandel et al.

AMPA and NMDA receptors

- AMPAR and NMDAR currents made evident using the NMDAR blocker APV
- Triangle: V at the peak, circle: V at dot line in A, filled: control, open: APV

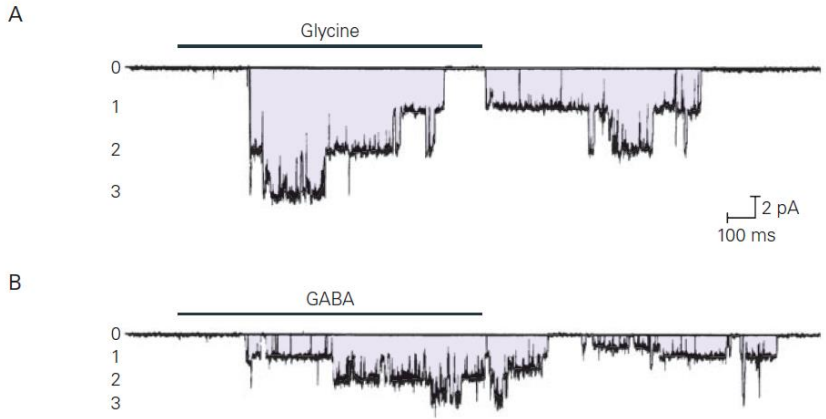


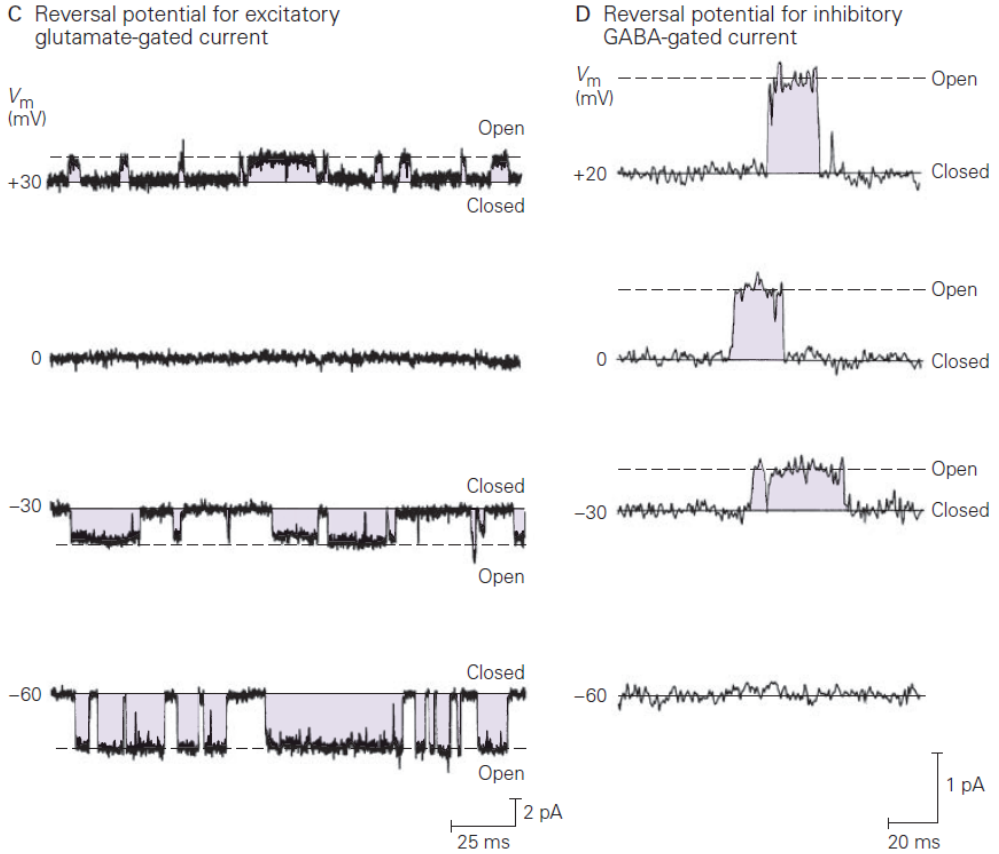


Hippocampus book

$GABA_A$ receptors

$GABA_A$ receptor is an ionotropic receptor that directly opens a Cl^- channel





Kandel et al.

Synaptic plasticity

"When an axon of cell *A* is near enough to excite a 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"

Donald Hebb 1949

TABLE 13.1
Different Forms of Synaptic Plasticity

Phenomenon	Duration	Locus of induction
Short-term enhancement		
Paired-pulse facilitation (PPF)	100 msec	Pre
Augmentation	10 sec	Pre
Posttetanic potentiation (PTP)	1 min	Pre
Long-term enhancement		
Short-term potentiation (STP)	15 min	Post
Long-term potentiation (LTP)	>30 min	Pre and post
Depression		
Paired-pulse depression (PPD)	100 msec	Pre
Depletion	10 sec	Pre
Long-term depression (LTD)	>30 min	Pre and post

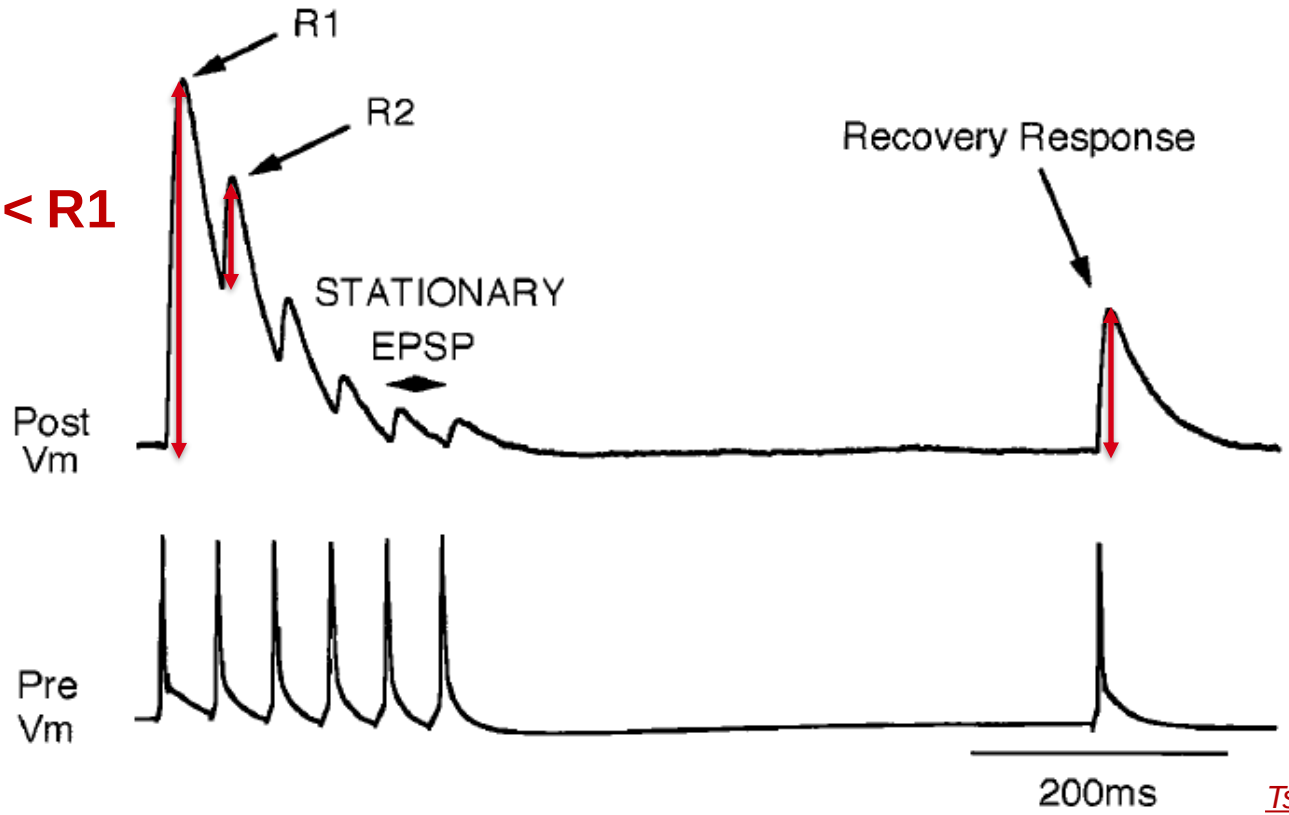
Synaptic plasticity occurs across many time scales. This table lists some of the better studied forms of plasticity together with a very approximate estimate of their associated decay constants, and whether the conditions required for induction depend on pre- or postsynaptic activity, or both. This distinction is crucial from a computational point of view, since Hebbian learning rules require a postsynaptic locus for the induction of plasticity. Note that for LTP and LTD, we are referring specifically to the form found at the Schaffer collateral input to neurons in the CA1 region of the rodent hippocampus; other forms have different requirements.

Koch, 2004

Definition: change in synaptic strength over time

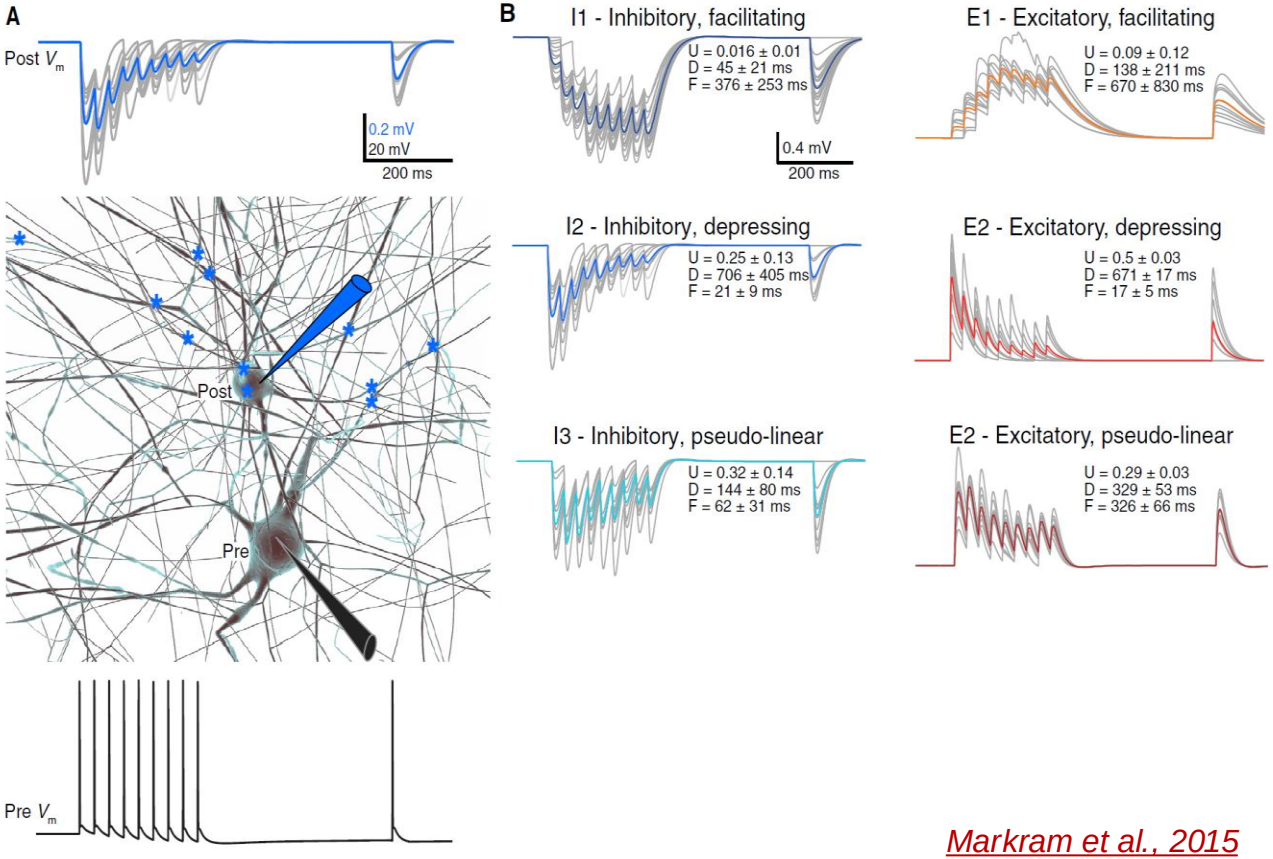
Short-term plasticity (STP)

R2 < R1



Tsodyks and Markram, 1997

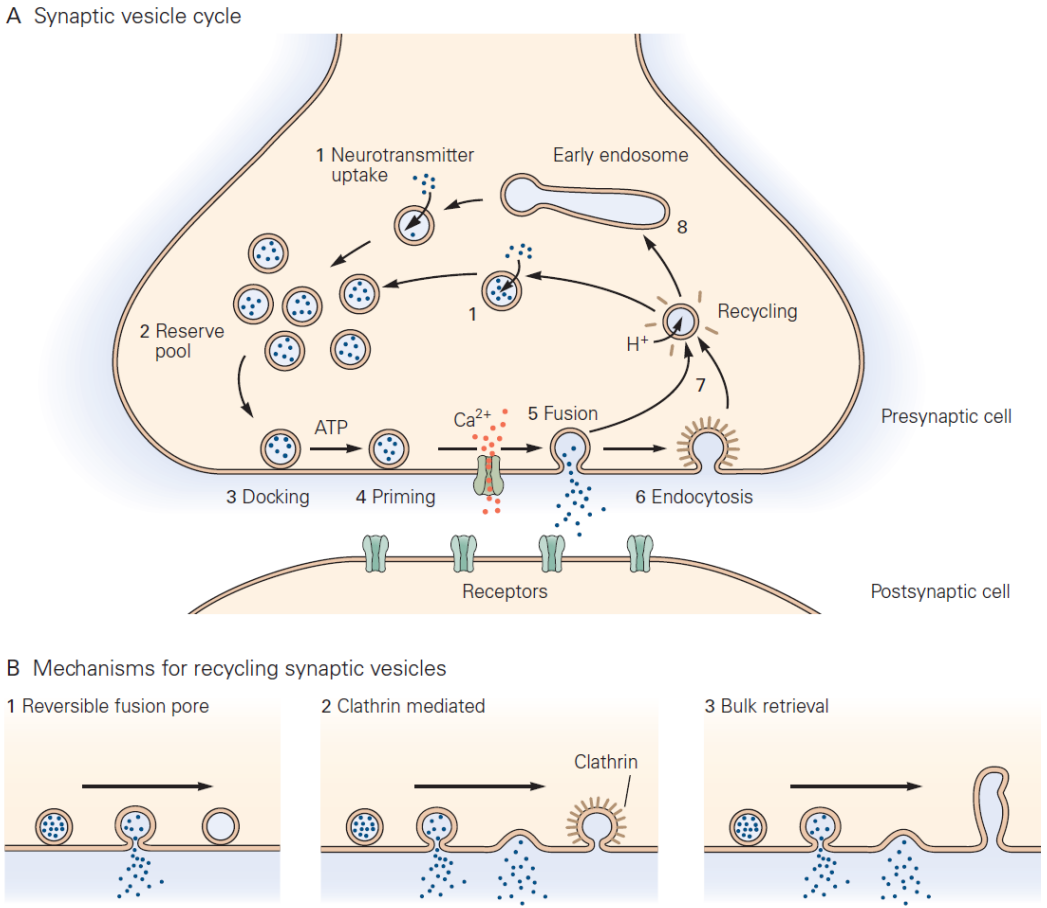
Short-term plasticity: synaptic dynamics



Markram et al., 2015

Short-term plasticity

- Short-term plasticity can be explained by two competing factors: vesicle depletion and accumulation of Ca^{2+}
- If one of the two factors prevails, we have facilitation or depression



Kandel et al.

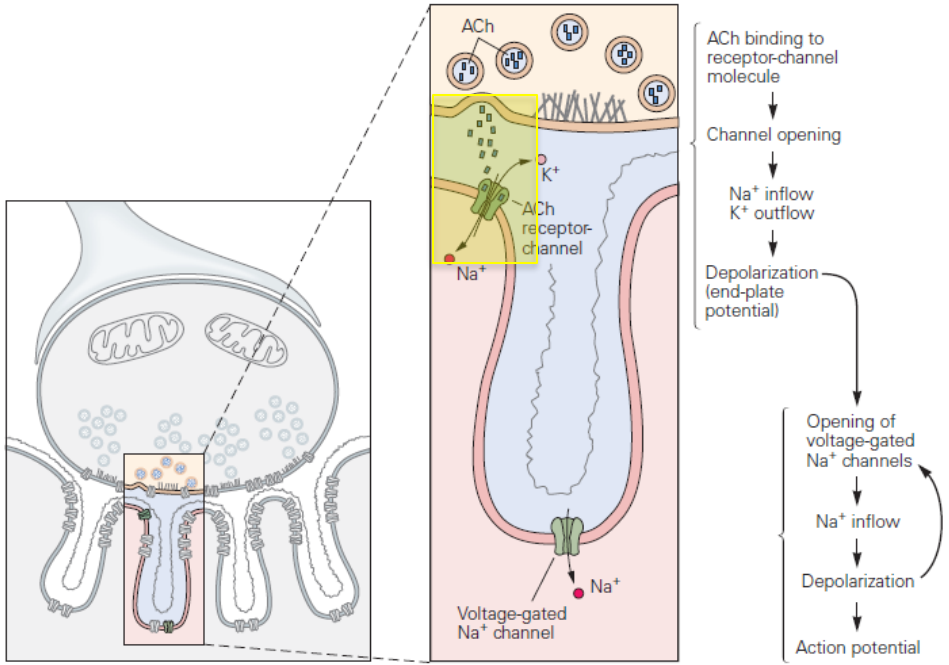
Summary 1

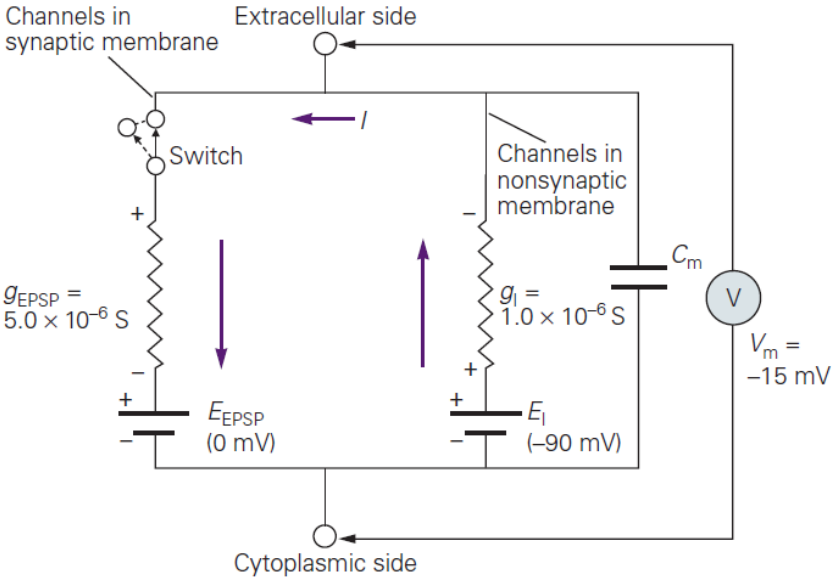
- There is a multitude of synapses in the brain, each characterized by specific neurotransmitters, receptors, pre- and post-synaptic mechanisms, types of plasticity
- We will focus on glutamatergic and GABAergic ionotropic receptors, and short-term plasticity
- The complex synaptic mechanisms and their stochastic nature require extensive resources if we want to simulate them in large networks
- We will take a phenomenological approach to model the synapses

Lecture Overview

- Scope
- **Approaches**
- Applications

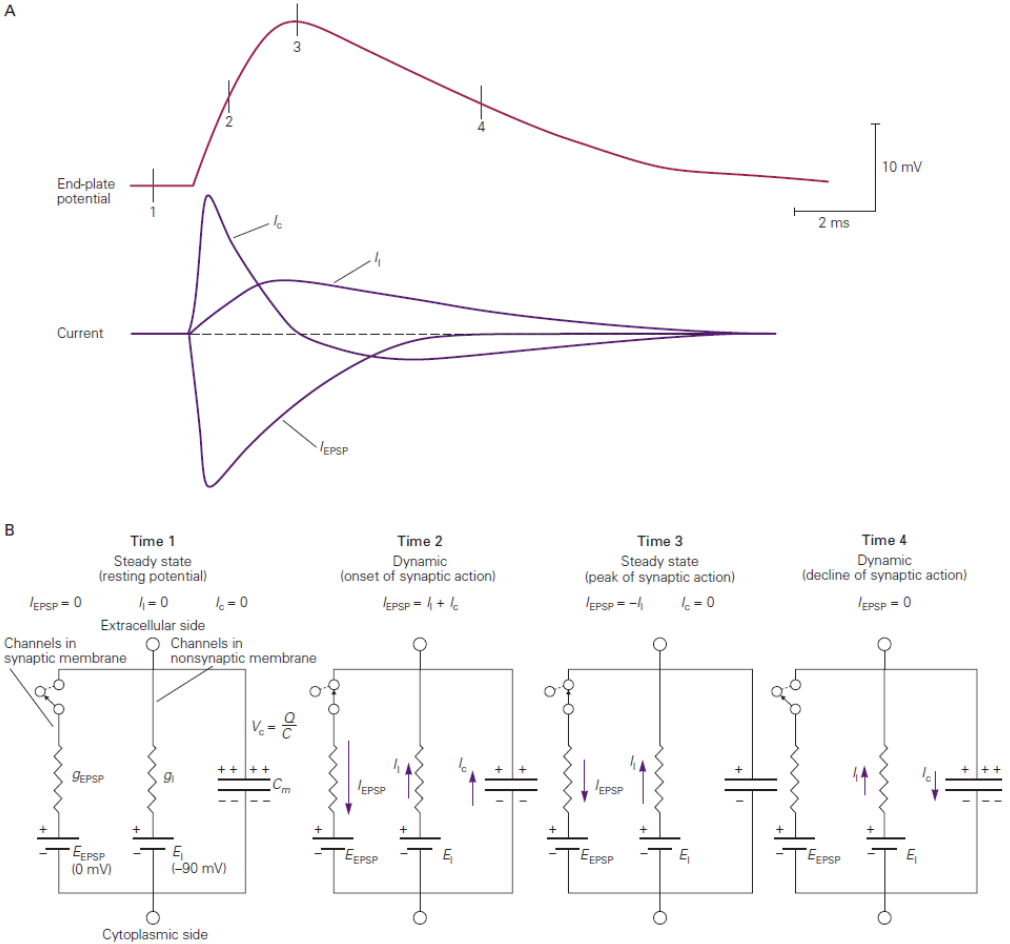
Synapse as an equivalent circuit





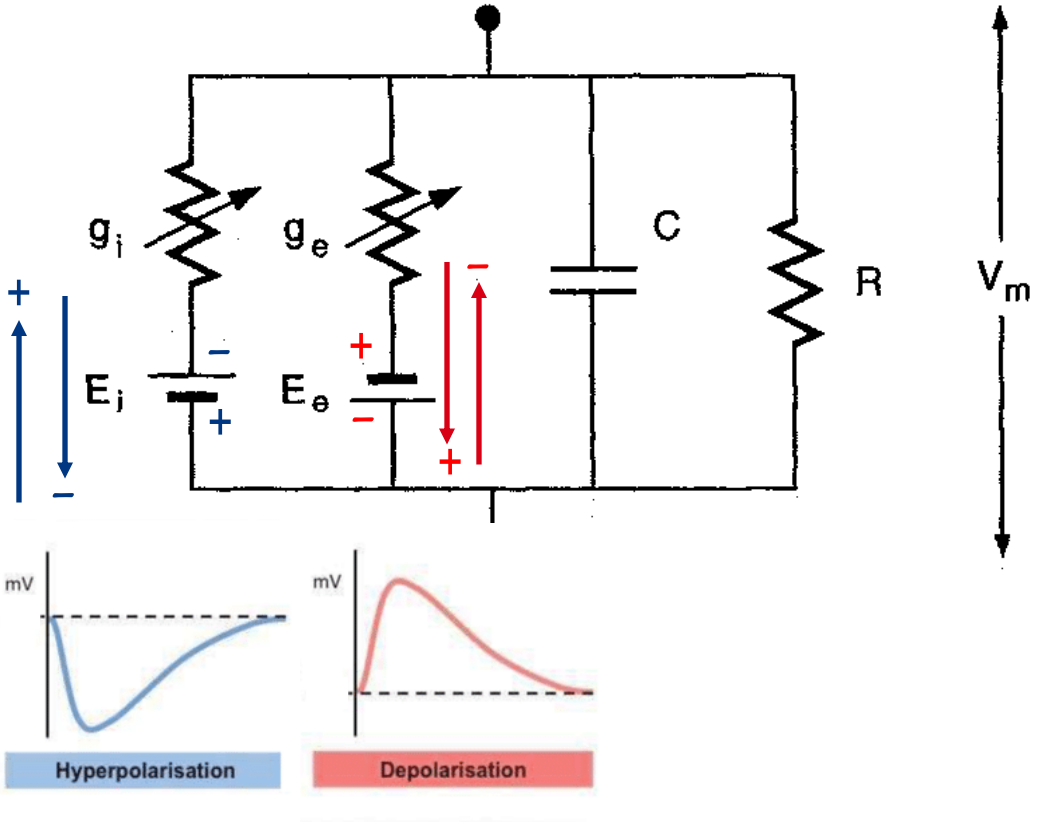
Kandel et al.

Synapse as an equivalent circuit



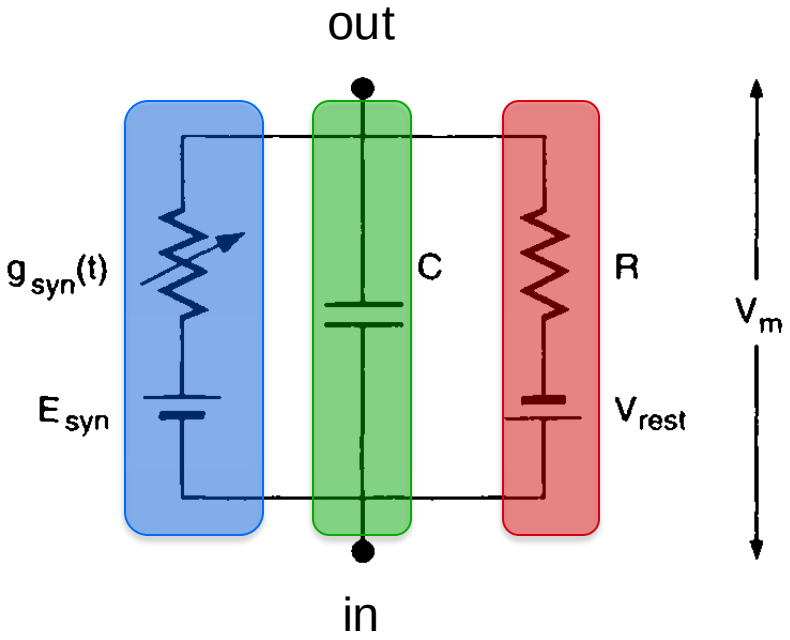
Kandel et al.

Synapse as an equivalent circuit: excitatory and inhibitory synapse



EPFL

Synapse as an equivalent circuit: equations



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

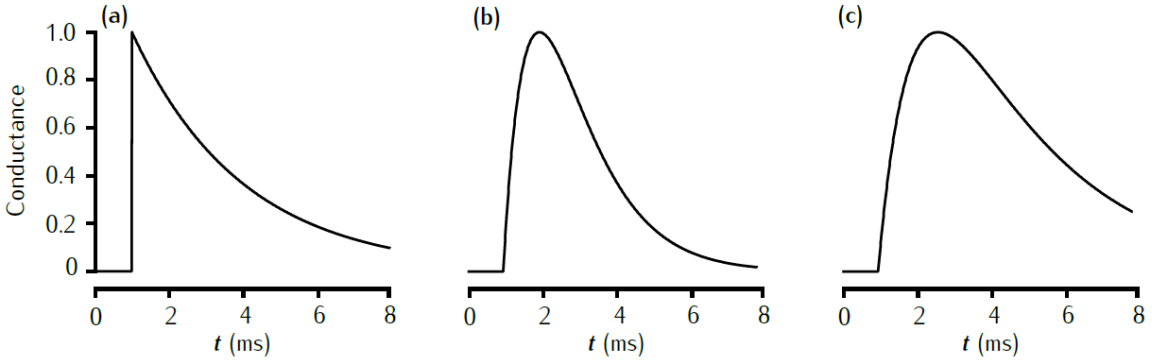
$$C\frac{dV_m}{dt} + g_{syn}(t)(V_m - E_{syn}) + \frac{V_m - V_{rest}}{R} = 0$$

$$\tau\frac{dV_m}{dt} = -(1 + Rg_{syn}(t))V_m + Rg_{syn}(t)E_{syn} + V_{rest}$$

$$\tau = RC$$

Synapse as an equivalent circuit: g_syn

(a) single exponential decay (b) alpha function (Rall, 1967) (c) dual exponential function



(a) $$g_{syn}(t) = \overline{g}_{syn} \exp\left(-\frac{t - t_s}{\tau}\right)$$

(b) $$g_{syn}(t) = \overline{g}_{syn} \frac{t - t_s}{\tau} \exp\left(-\frac{t - t_s}{\tau}\right)$$

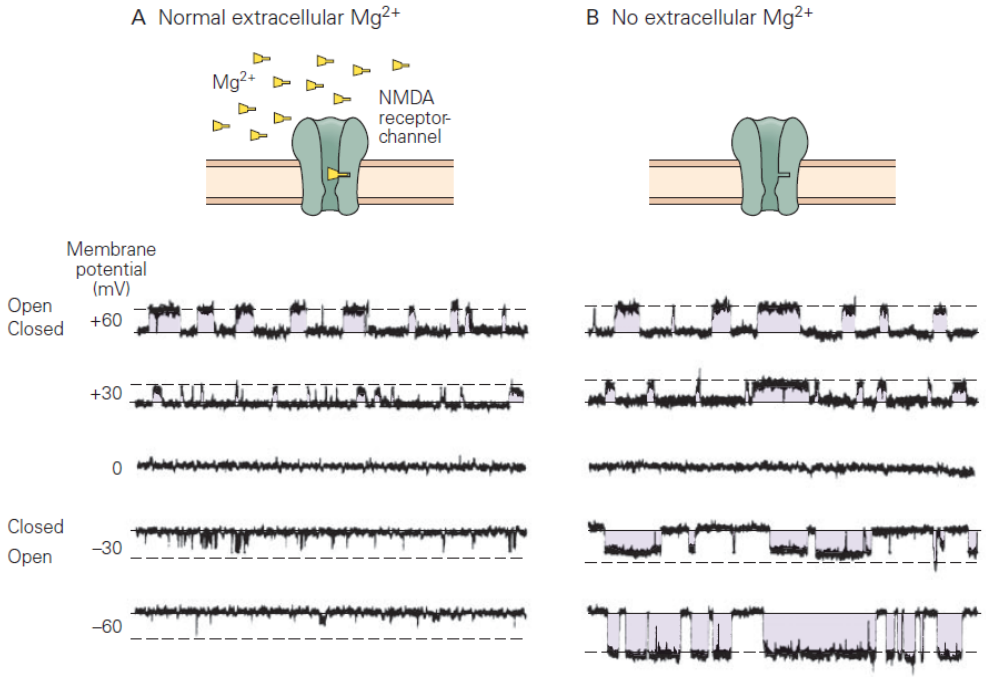
(c) $$g_{syn}(t) = \overline{g}_{syn} \frac{\tau_1 \tau_2}{\tau_1 - \tau_2} \left(\exp\left(-\frac{t - t_s}{\tau_1}\right) - \exp\left(-\frac{t - t_s}{\tau_2}\right)\right)$$

$\overline{g}_{syn}$= conductance at the peak
t_s = time of release of neurotransmitter

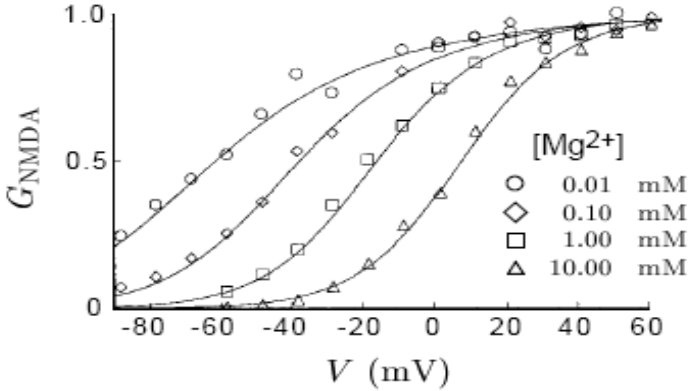
Sufficient to describe AMPAR and $GABA_AR$

Synapse as an equivalent circuit : NMDAR

$$I_{Syn} = G_{NMDA}([Mg^{2+}], V)\, g(t)\, (V - E_{rev})$$

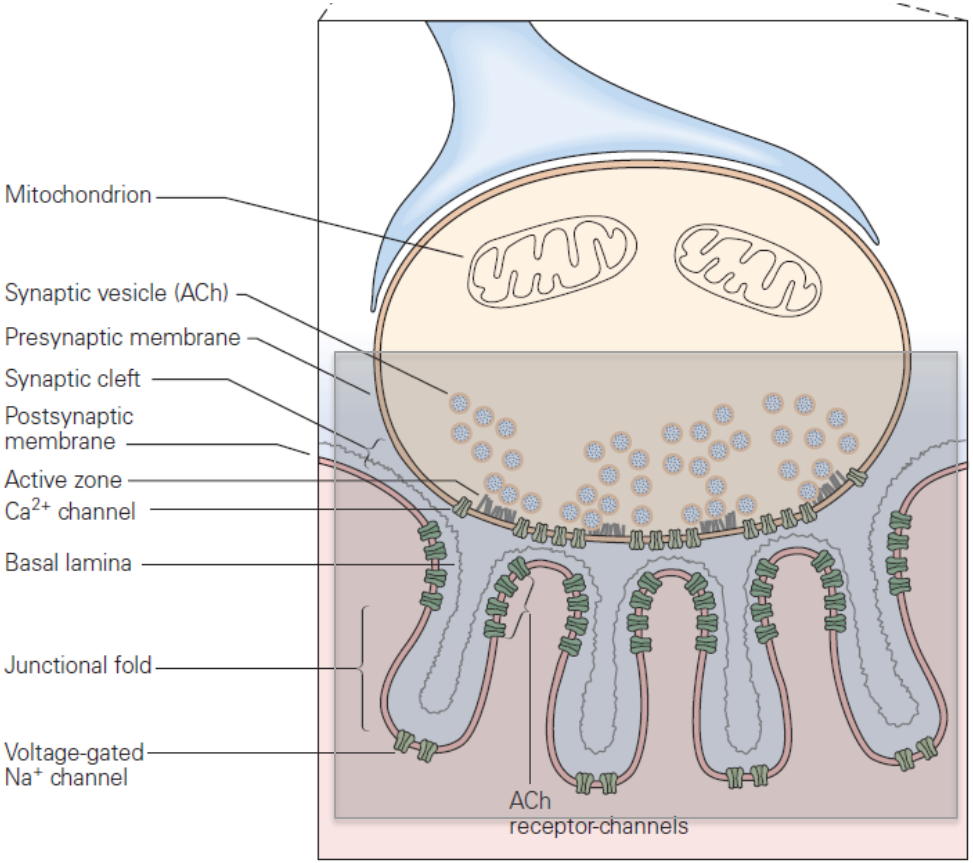


$$G_{\mathrm{NMDA}} = \left(1 + \frac{[\mathrm{Mg}^{2+}]}{3.57\ \mathrm{mM}} \exp(V/16.13\ \mathrm{mV})\right)^{-1}$$



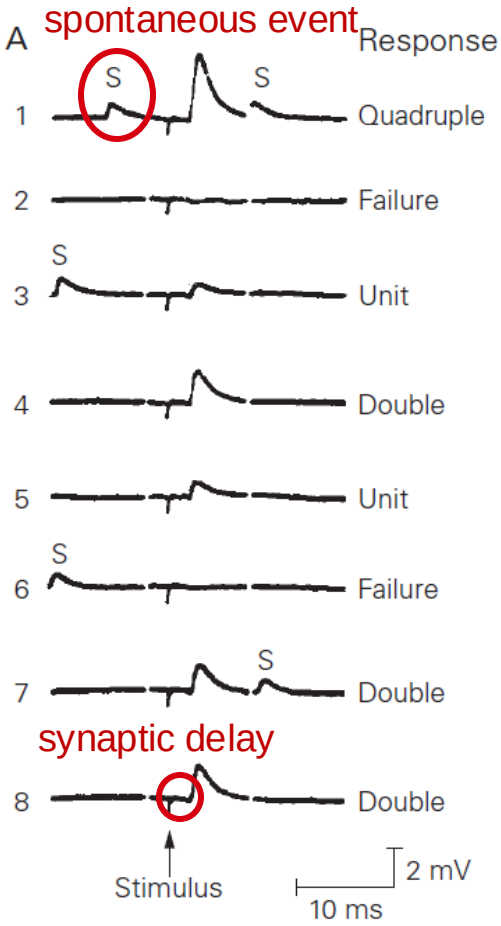
Jahr and Stevens, 1990

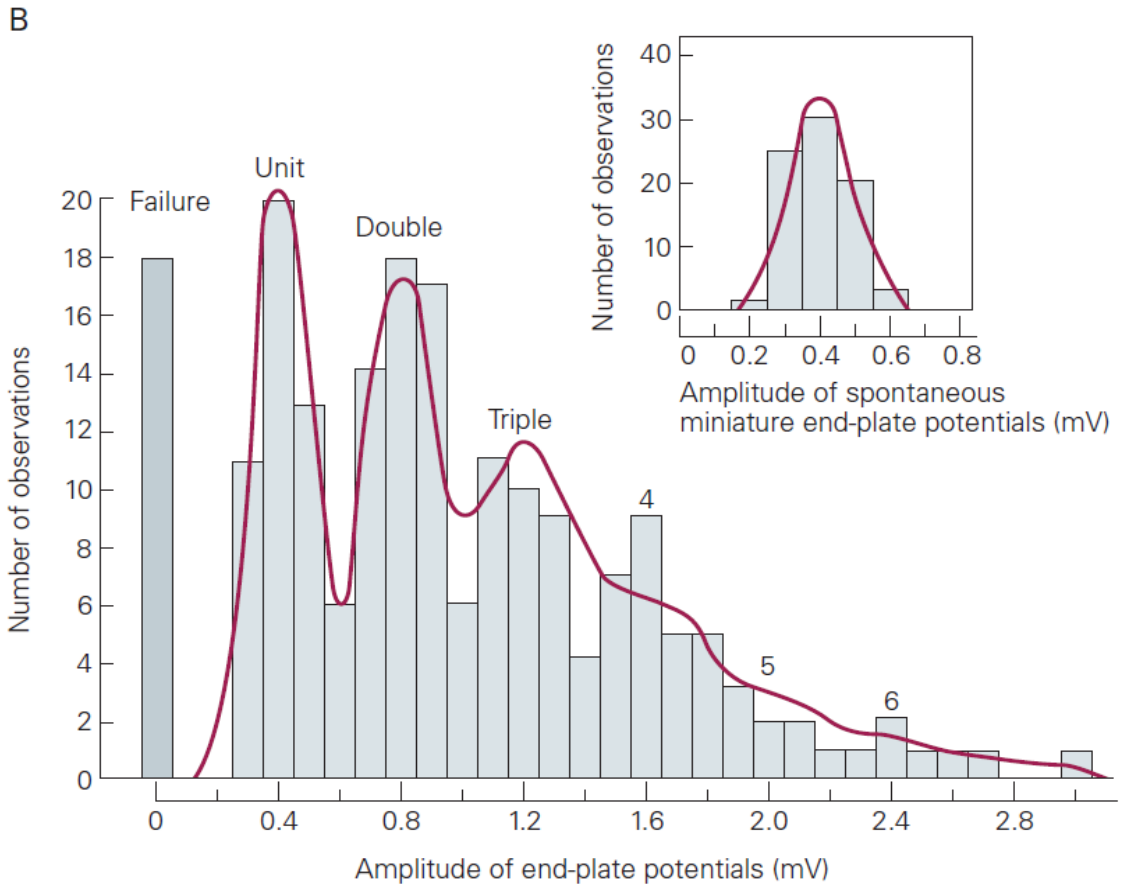
How can we model several active zones?



Kandel et al.

Experimental behaviour of several active zones





Modelling several active zones: Quantal release model

- Neurotransmitters are released into a synapse in packaged vesicles called **quanta**
- One quantum generates what is known as a miniature end plate potential (MEPP), which is the smallest amount of stimulation that one neuron can send to another neuron
- Each synapse has a number of independent release sites (*n*)
- Each site releases a single quantum (vesicle) with probability of release *p*
- The number of released vesicles obeys a binomial distribution

$$p(n,k) = \frac{n!}{(n-k)!k!} p^k (1-p)^{n-k}$$

Probability of releasing *k* quanta

Modelling several active zones: Quantal release model

Probability of releasing *k* quanta ⟶ $p(n,k) = \frac{n!}{(n-k)!k!} p^k (1-p)^{n-k}$

Mean released quanta ⟶ $\langle k \rangle = np$

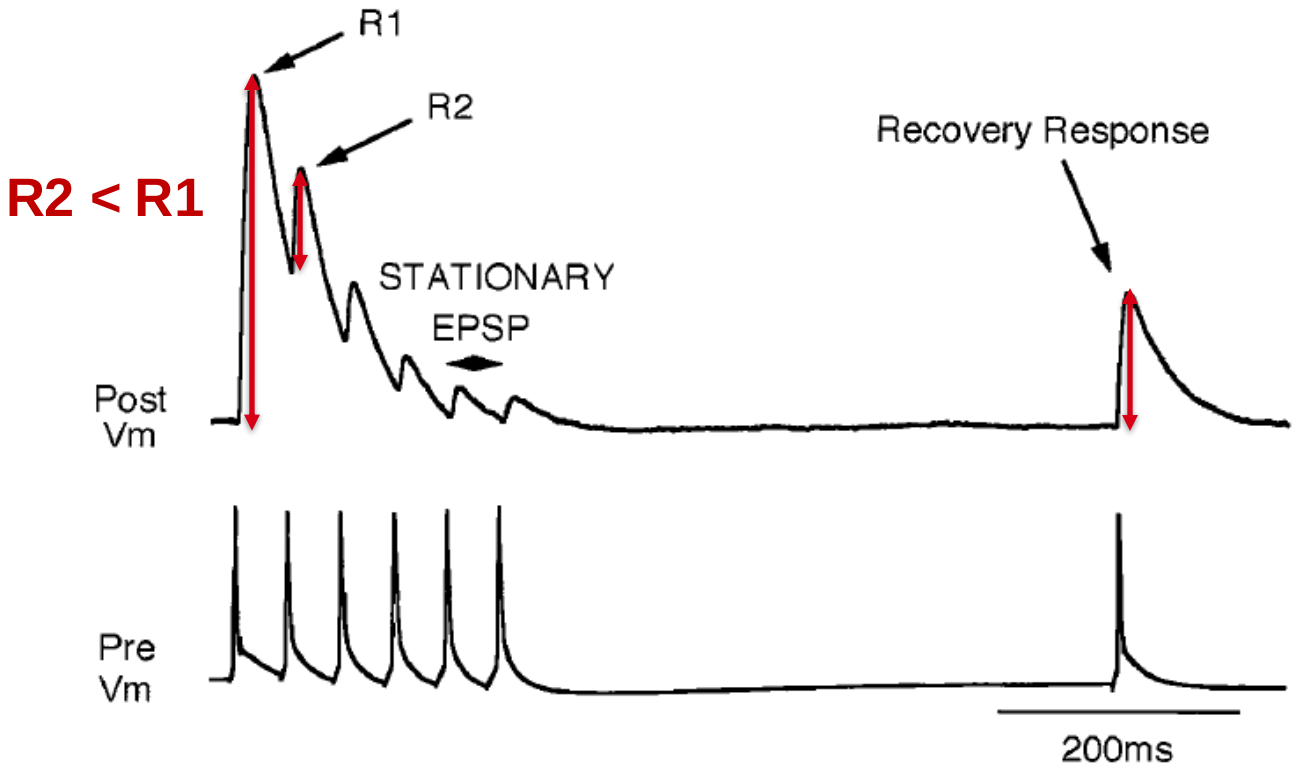
R = mean synaptic response ⟶ $R = npq$ (q = unitary postsynaptic effect of the synapse)

q can be the peak conductance, the maximal synaptic current at some potential, or the peak EPSP. R varies accordingly

Total conductance —R as g(t)⟶ g(t)= $np\gamma(t)$ (γ = single channel conductance)

$$I_S = np\gamma(t)(V - E_S)$$

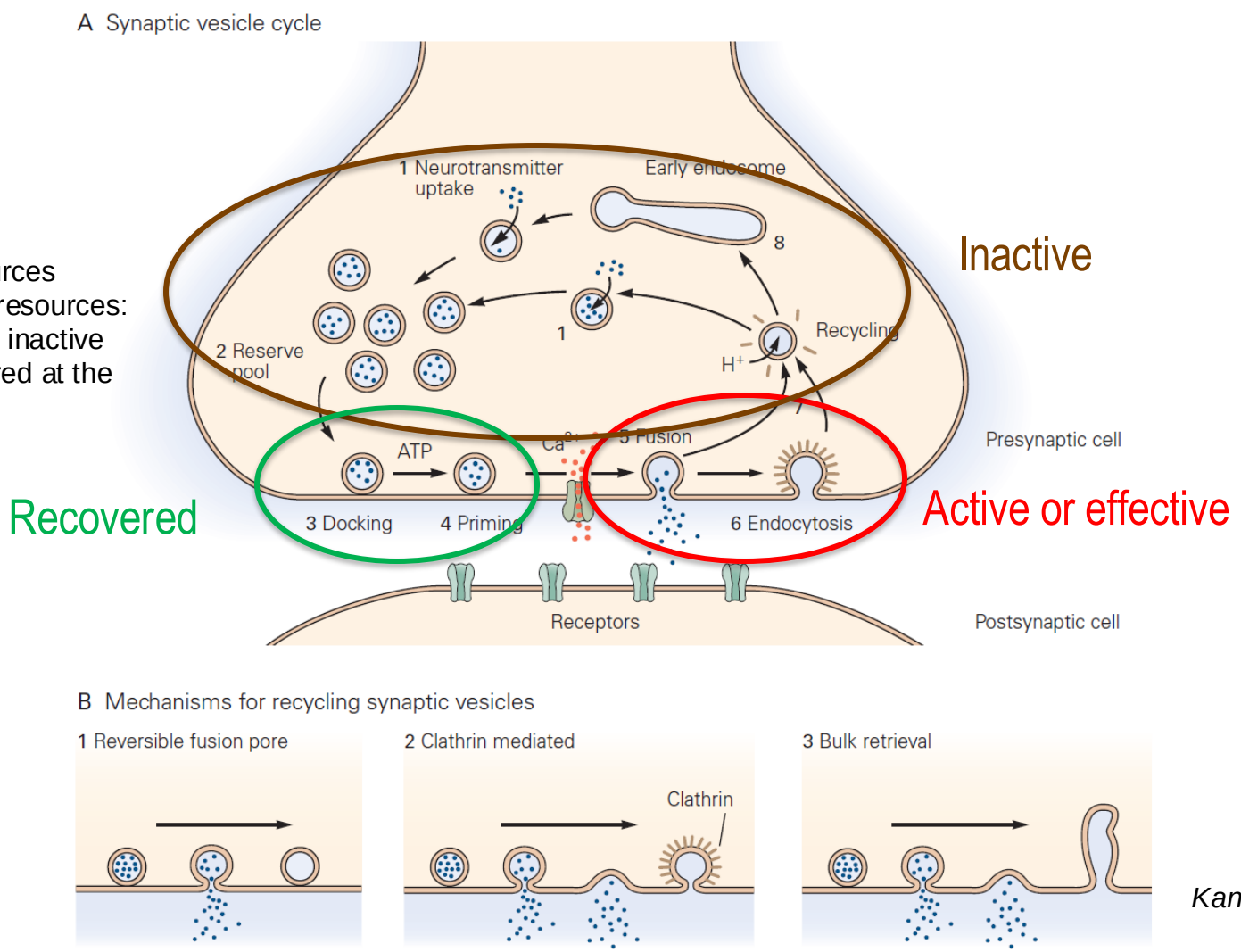
Short-term depression: Tsodyks and Markram's model



Tsodyks and Markram, 1997

Model assumptions:

- finite amount of resources
- three major states of resources: recovered, active and inactive
- All vesicles in recovered at the resting state



Kandel et al.

Short-term depression: Tsodyks and Markram's model

The model assumes that there is a limited amount of resources

Resources in state:

RECOVERED $$\frac{dx}{dt} = \frac{z}{\tau_{rec}} - U_{SE}x(t_{sp})\partial(t - t_{sp})$$

ACTIVE (effective) $$\frac{dy}{dt} = -\frac{y}{\tau_{in}} + U_{SE}x(t_{sp})\partial(t - t_{sp})$$

INACTIVE $$\frac{dz}{dt} = \frac{y}{\tau_{in}} - \frac{z}{\tau_{rec}}$$

Tsodyks and Markram, 1997

- x = reserve pool of resources (vesicles)
- z = pool of inactive resources from which you can recover resources
- y = pool of active resources
- τ_{in} = how long it takes to inactivate the used resources (~ 1 ms)
- τ_{rec} = how long it takes until the synapse is as strong as before the first AP arrived (~ 100 ms)
- U_{SE} = which percentage of resources are released when an AP occurs (fixed).
- $U_{SE}x(t_{sp})$ = some % of the available resources used at the spike time.
- $\partial(t - t_{sp})$ = delta function, cero all the time but 1 when a spike occurs.

Resources in state:

RECOVERED

$$\frac{dx}{dt} = \frac{z}{\tau_{rec}} - U_{SE}x(t_{sp})\partial(t - t_{sp})$$

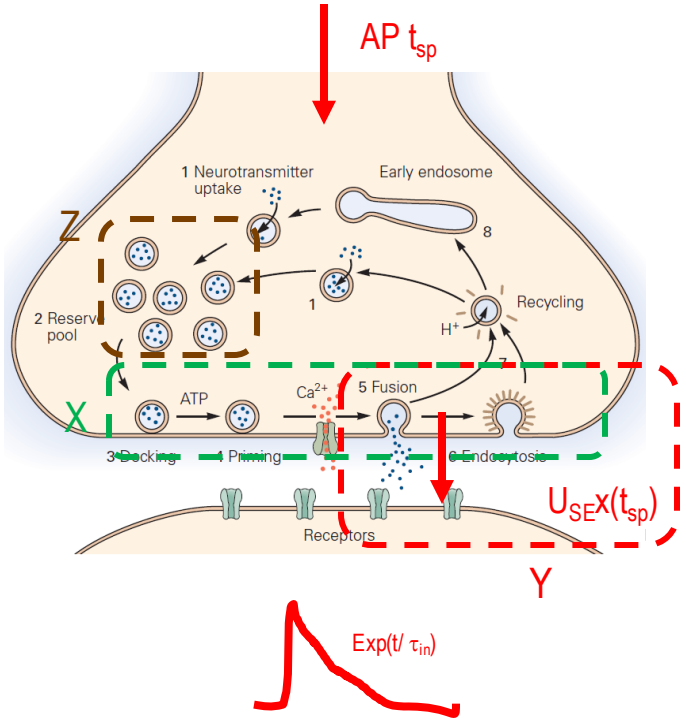
ACTIVE

$$\frac{dy}{dt} = -\frac{y}{\tau_{in}} + U_{SE}x(t_{sp})\partial(t - t_{sp})$$

INACTIVE

$$\frac{dz}{dt} = \frac{y}{\tau_{in}} - \frac{z}{\tau_{rec}}$$

New z

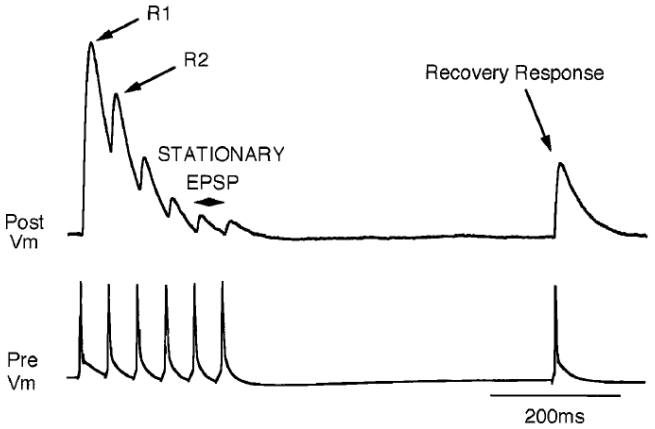


Short-term depression: Tsodyks and Markram's model

Solution to reconstruct the excitatory postsynaptic current

$$EPSC_{n+1} = EPSC_n(1 - U_{SE})e^{-\Delta t/\tau_{rec}} + A_{SE} \cdot U_{SE}(1 - e^{-\Delta t/\tau_{rec}}),$$

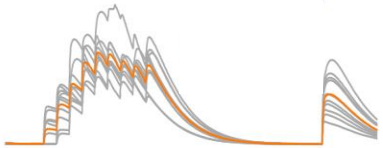
A_{SE} = absolute synaptic efficacy (all resourses in effective state)
Δt = time interval between nth and (n + 1)th AP



Tsodyks and Markram, 1997

Δt was assumed to be much larger than the inactivation time constant, hence the dependence on t_{inact} dropped out of this equation

TM-model: synaptic depression + facilitation



Intracellular flow of Ca^{2+} (facilitation)

Extracellular flow of Ca^{2+} AP

% of resources used, no longer constant

$$U_{SE}^1 = U_{SE}^1(t)(1 - U_{SE}) + U_{SE}$$

Resources in state:

RECOVERED $$\frac{dx}{dt} = \frac{z}{\tau_{rec}} - U_{SE}^1 x(t_{sp})\partial(t - t_{sp})$$

ACTIVE $$\frac{dy}{dt} = -\frac{y}{\tau_{in}} - U_{SE}^1 x(t_{sp})\partial(t - t_{sp})$$

INACTIVE $$\frac{dz}{dt} = \frac{y}{\tau_{in}} - \frac{z}{\tau_{rec}}$$

Facilitation factor

FACILITATION $$\frac{dU_{SE}^1}{dt} = -\frac{dU_{SE}^1}{\tau_{fac}} + U_{SE}(1 - U_{SE}^1)\partial(t - t_{sp})$$

The use of transmitter goes up or down every time there is a spike

Output, post-synaptic current:

$$I_s(t) = A_{SE}y(t)$$

A_{SE} = absolute synaptic efficacy (all vesicles released)

Tsodyks et al., 1998

Introduce short-term facilitation

Increase in U_{SE} could reflect, for example, the accumulation of calcium ions caused by spikes arriving in the presynaptic terminal, which is responsible for the release of neurotransmitter (Bertram, Sherman,&Stanely, 1996).
For a simple kinetic scheme, assume that an AP causes a fraction of U_{SE} calcium channels to open, which subsequently close with a time constant of τ_{facil}.
The fraction of opened calcium channels determines the current value of U^1_{SE}.

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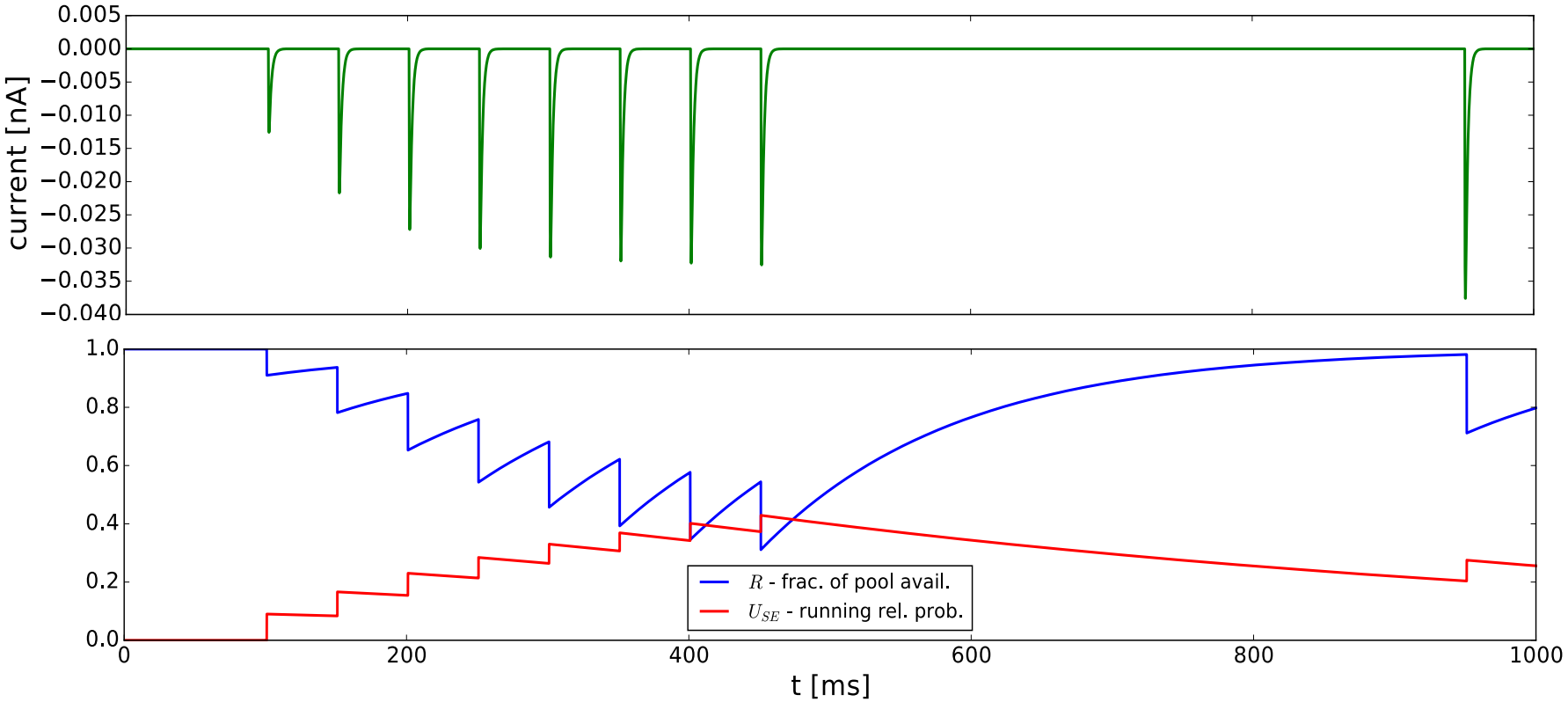
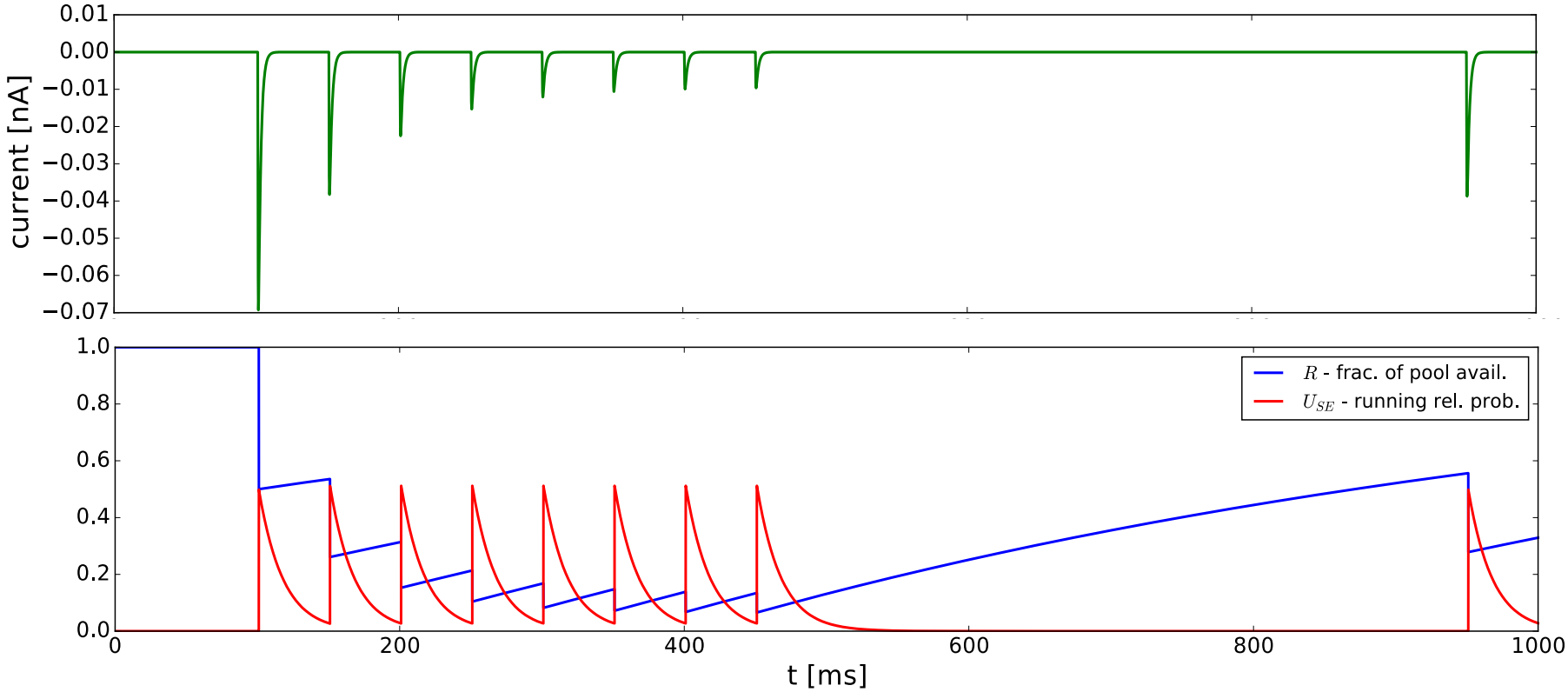
Tsodyks et al., 1998

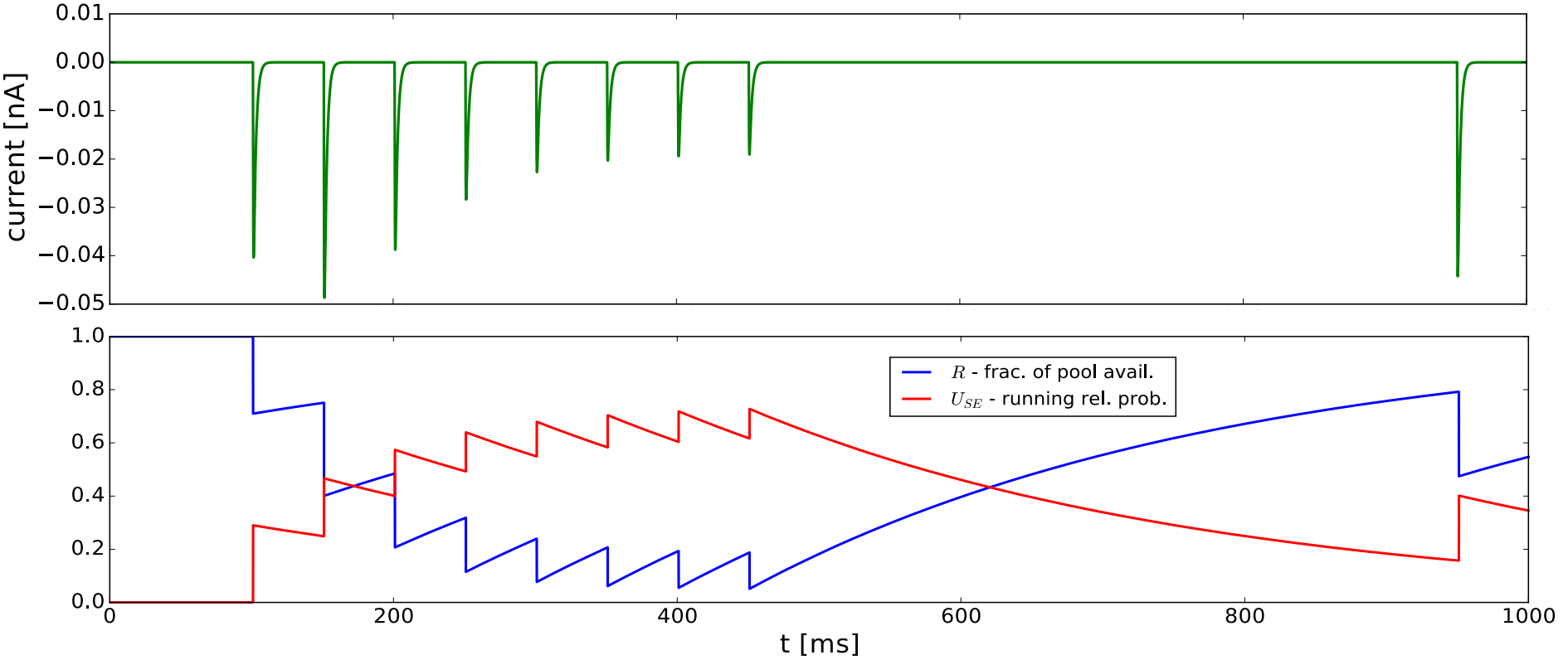
Excitatory, facilitating (E1)



Excitatory, depressing (E2)



Excitatory, pseudo linear (E3)



Summary 2

- Phenomenological models of synapses and short-term plasticity
- Even if the model should be considered phenomenological, they mimic biophysical mechanisms: accumulation of calcium and vesicle depletion in the presynaptic terminal, and neurotransmitter receptors in postsynaptic terminal
- Those can be combined with multi-compartimental models of single neurons to create networks

Lecture Overview

- Scope
- Approaches
- **Applications**

Synaptic Data Source: example 1

File Edit View History Bookmarks Tools Help

Hippocampome

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Search

Hippocampome.org

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WELCOME TO THE HIPPOCAMPOME PORTAL

v1.7 - Released: 10/08/2019
23,238 Pieces of Knowledge (PoK) and 30,035 Pieces of Evidence (PoE)

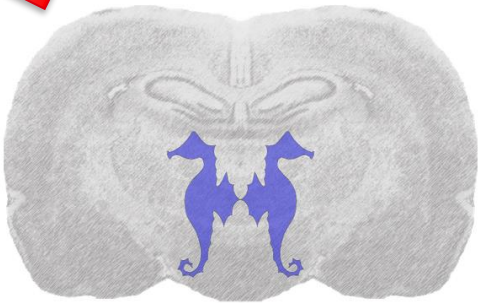
The Hippocampome is a curated knowledge base of the circuitry of the hippocampus of normal adult, or adolescent, rodents at the mesoscopic level of neuronal types. Knowledge concerning dentate gyrus, CA3, CA2, CA1, subiculum, and entorhinal cortex is distilled from published evidence and is continuously updated as new information becomes available. Each reported neuronal property is documented with a pointer to, and excerpt from, relevant published evidence, such as citation quotes or illustrations.

The goal of the Hippocampome is dense coverage of available data characterizing neuronal types. The Hippocampome is a public and free resource for the neuroscience community, and the knowledge is presented for user-friendly browsing and searching and for machine-readable downloading.

If you have feedback on either functionality or content, or if you would like to be informed when the first official version is released, please fill out the feedback form or email us at Hippocampome.org@gmail.com.

The release of v1.0 on 09/23/2015 includes 3,697 PoK and 13,888 PoE. Reference: **Wheeler et al., 2015**. *Hippocampome.org: A knowledge base of neuron types in the rodent hippocampus*. eLife 2015;4:e09960.

The release of v1.1 on 10/17/2016 includes 3,697 PoK, 13,888 PoE, and the Neuron Term Portal, which allows one to view definitions for terms and phrases used on this website. Reference: **Hamilton et al., 2016** *Name-calling in the hippocampus (and beyond): coming to terms with neuron types and properties*. Brain Informatics (2016); doi:10.1007/s40708-016-0053-3.



The release of v1.4 on 08/15/2019 includes an additional 7,946 PoK, 8,486 PoE, and the ability to access the Synapse Knowledge Base. Reference: **Moradi and Ascoli, 2019** *A comprehensive knowledge base of synaptic electrophysiology in the rodent hippocampal formation.* Hippocampus 2019 Aug 31; doi: https://doi.org/10.1002/hipo.23148.

The release of v1.5 on 09/06/2019 includes an additional 830 PoK, 77 PoE, and relational expression inferences in the knowledge base. Reference: **White, et al., 2019** *Molecular Expression Profiles of Morphologically Defined Hippocampal Neuron Types: Empirical Evidence and Relational Inferences.* Hippocampus 2019 Oct 9; doi: 10.1002/hipo.23165.

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- Morphology
- Molecular markers
- Membrane biophysics
- Connectivity
- Synaptic physiology
- Firing patterns
- Izhikevich models

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pointer to, and excerpt from, relevant published evide
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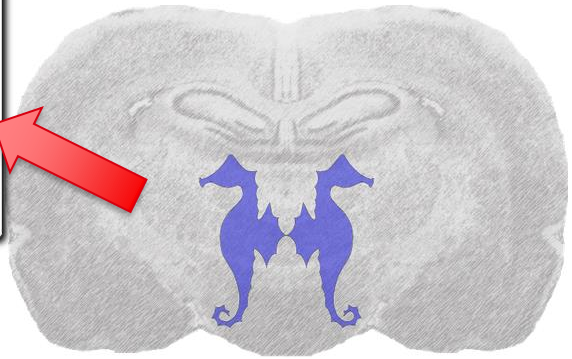

The release of v1.4 on 08/15/2019 includes an additional 7,946 PoK, 8,486 PoE, and the ability to access the Synapse Knowledge Base. Reference: **Moradi and Ascoli, 2019** *A comprehensive knowledge base of synaptic electrophysiology in the rodent hippocampal formation.* Hippocampus 2019 Aug 31; doi: https://doi.org/10.1002/hipo.23148.

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hippocampome.org/php/synaptome.php

Type here to search

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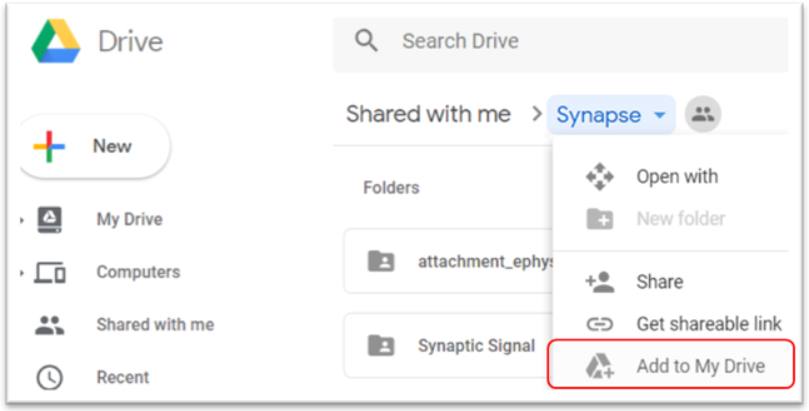
Hippocampome.org Synapse Knowledge Base

Requirements:

- Our data mining tool relies on web technologies currently available in Chromium-based browsers, including Google Chrome, Opera and Chromium itself. These technologies will soon be available in Mozilla Firefox and Microsoft Edge as well.
- You also need a Google (i.e. Gmail) account that is already signed-in.

Easy access:

(1) To access data, please open the following link and add the "synapse" folder to your own Google Drive. You need to do this only once.



(2) Go to the "synapse" folder and make a copy of the "Hippocampome.org/Synapse" and "FormTemplateReview" files. You need to do this step only once as well. The copied files will appear in the root of your drive, so you need to go back to "My Drive" to access these copies.

Received: 17 May 2019 | Revised: 16 July 2019 | Accepted: 6 August 2019

DOI: 10.1002/hipo.23148

WILEY

RESEARCH ARTICLE

A comprehensive knowledge base of synaptic electrophysiology in the rodent hippocampal formation

Keivan Moradi[1] | Giorgio A. Ascoli[1,2]

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Hippocampome.org

- +1,200 published journal articles
- 8 different signal modalities
- 90 different methods to measure synaptic amplitude, kinetics, and plasticity in hippocampal neurons
- data structure that both reflects the differences and maintains the existing relations among experimental modalities
- 40,000 synaptic data entities
- covering 88% of the 3,120 potential connections

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Summary

In transverse hippocampal slices, paired recording is done from non-Fast-Spiking neurons (max frequency = 25±4 Hz (n=14)) within DG:SG and DG:H border so-called non-FS IN to DG Granule cells in voltage-clamp mode. Non-FS INs had CB1R+ INs (***Axons***:DG:*?1?0* & DSI+), HICAP (***Axons***:DG:*?1?0* & DSI-), HIPP (***Axons***:DG:*1?00* **AND** ***Dendrites***:DG:*0002*) and HIPP-like (***Axons***:DG:*1?00* **AND** ***Dendrites***:DG:*2222*) subtypes. One presynaptic instance had DG HIPP-CAP (-)1102 morphology. Authors have grouped all the presynaptic non-FS IN neuron types when analyzing the synaptic electrophysiology data.

Ratios and Notes

Connectivity: 151:391 pairs were connected.
Types: 6:39 neurons in DG:SG and DG:H border were so-called FS IN (DG Basket PV+), 6:39 CB1+ IN (probably DG Basket CCK+), 14:39 DG HICAP, and 9:39 DG HIPP (probably DG HIPP or DG HIPP-CAP) or 4:39 HIPP-like (DG MOLAX).

Solutions

Bath: 125 NaCl, 25 $NaHCO_3$, 1.25 NaH_2PO_4, 2.5 KCl, 2 $CaCl_2$, 1 $MgCl_2$.
Whole-cell pipette: 15 K-gluconate, 140 KCl, 0.1 EGTA, 2 $MgCl_2$, 4 Na_2ATP, 10 HEPES

Synaptic Signal

Recorded Modality: uPSC
V_m = -80 {without V_j correction};
-84.91 {with V_j correction}@3300073 {V_h}
Calculated E_{rev}:
-0.09 {$GABA_A$}; 0.21 {$GABA_A$-gluconate Permeable}; -85.92 {$GABA_B$}

Assumptions

Any non-Fast-Spiking neuron (max_fr:<50) with soma in DG:SG and DG:H border and most of their axons in DG:SM is a potential presynaptic cell type. DG HICAP is the main presynaptic population based on cell type ratios reported in this paper.

Machine-readable Search Query

```
Connection:(
 Presynaptic:(
  (Neurotransmitter:Inhibitory AND
   Morphology:(
     Dendrites:DG:???2          AND
     Axons:DG:???0              AND
    (Soma:DG:??1?               OR
     Soma:DG:???1))
  )                             NOT
   Electrophysiology:max_fr:>50,
   Include:(1046)
 ),
 Postsynaptic:(
  Morphology:(
     Axons:DG:0001              AND
     Dendrites:DG:2200)
  )
)
```

Search Engine Results

Presynaptic	Postsynaptic
DG Basket CCK+	DG Granule
DG HICAP	DG Granule
DG HIPP-CAP	DG Granule
DG MOLAX	DG Granule
DG Outer Molecular Layer	DG Granule
DG HIPP	DG Granule

PMID: 24453325 **eID:** 67 **dID:** 73; 74

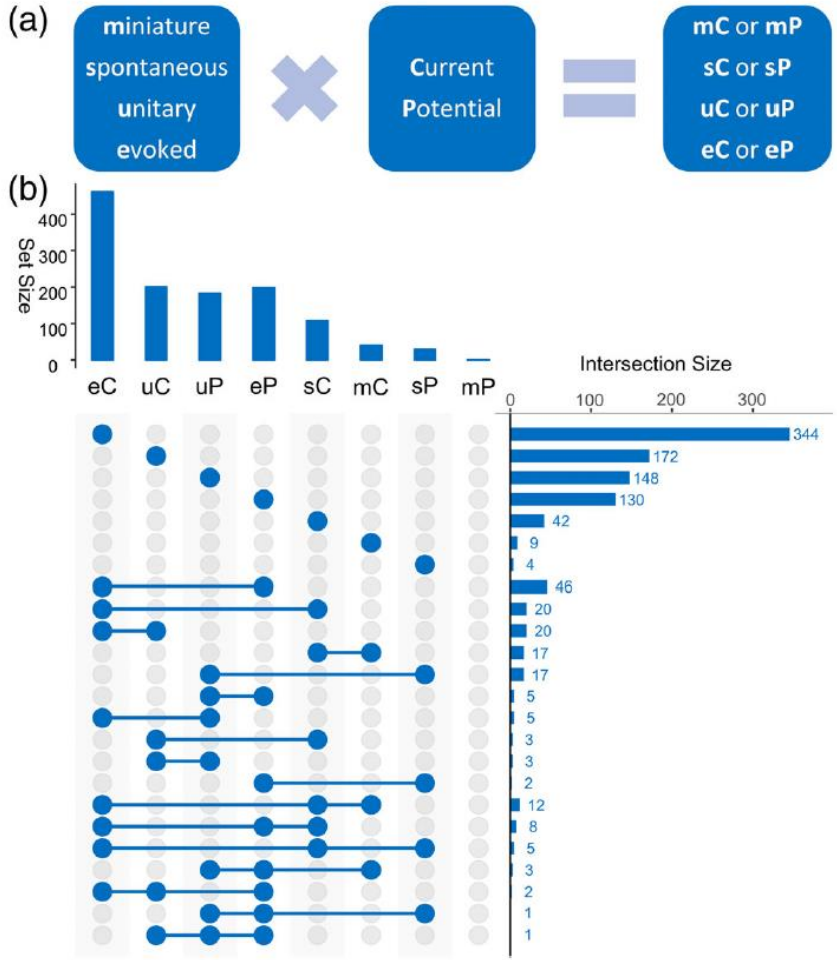
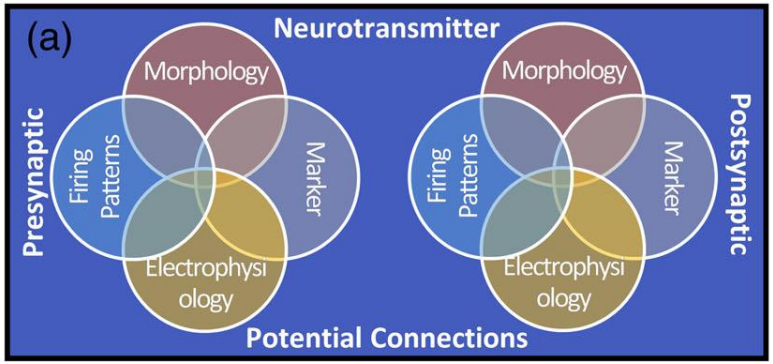


FIGURE 4 Data modalities. (a) Synaptic signals can be generated in eight different modalities depending on stimulation methods (e: evoked, u: unitary, s: spontaneous, and m: miniature) and response type (C: current or P: potential). (b) The most prevalent modality among all extracted data (upper chart) is eC and the most prevalent combination of multiple modalities in the same experiment (right chart) is between eC and eP [Color figure can be viewed at wileyonlinelibrary.com]



(b)

Potential Connections	
Presynaptic Cell Types	Postsynaptic Cell Types
DG Basket	DG Granule

Experiment IDs		
Proper	Fuzzy-High	Fuzzy-Low
66; 73; 75; 132; 165; 331	50; 105; 133; 144; 145; 146; 147; 148; 158; 182; 332	27; 39; 41; 86; 88; 111; 112;

We consider a mapping as "proper" only if the corresponding experiment matches a single potential connection. For all other "fuzzy" mappings that involve multiple potential connections, we assign high- and low-confidence to the more and less likely neuron type pair(s), respectively.

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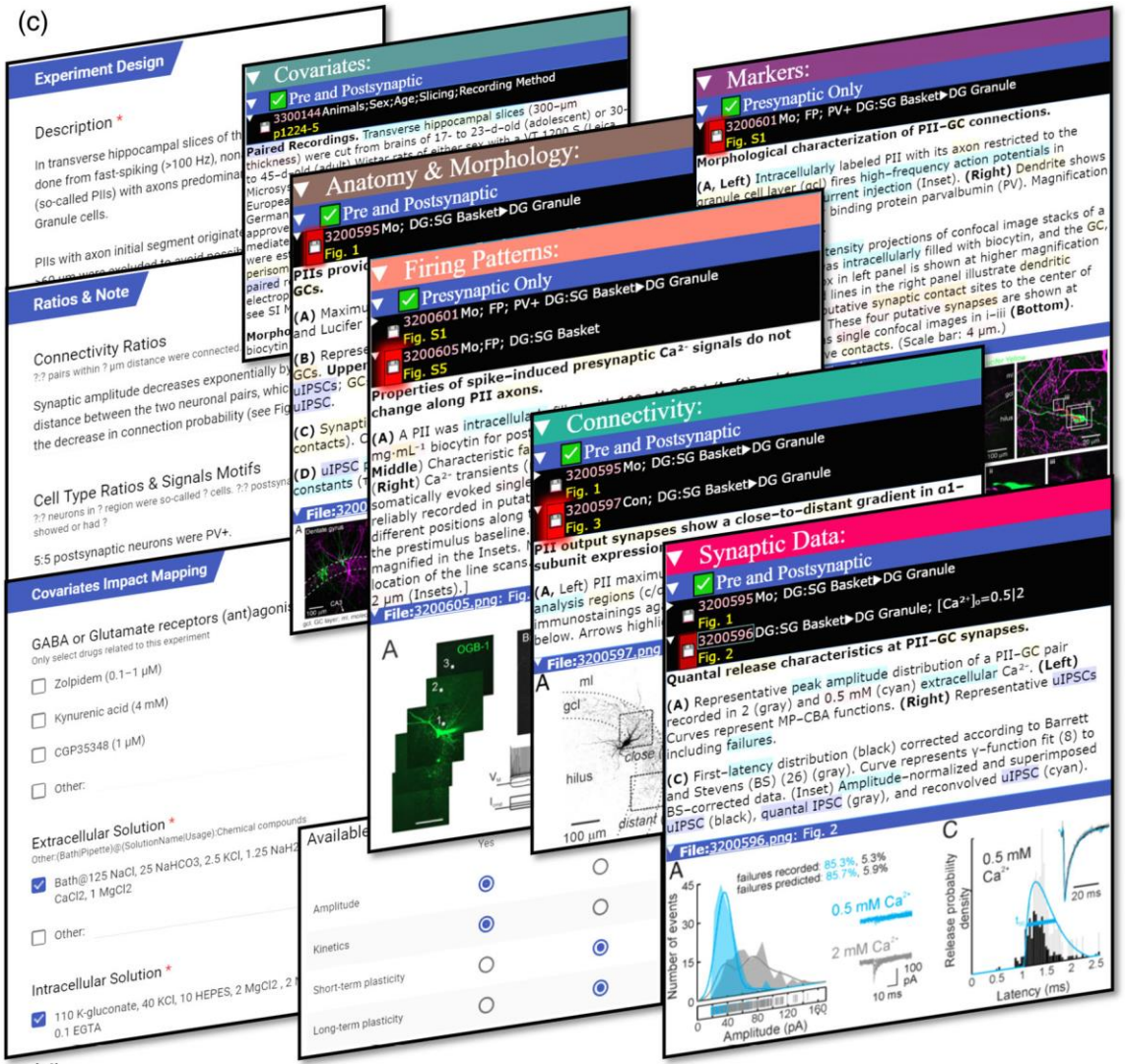

(c)
Experiment Design
Description *
Ratios & Note
Connectivity Ratios
Cell Type Ratios & Signals Motifs
Covariates Impact Mapping
GABA or Glutamate receptors (ant)agonis
Zolpidem (0.1–1 µM)
Kynurenic acid (4 mM)
CGP35348 (1 µM)
Other:
Extracellular Solution *
Bath@125 NaCl, 25 NaHCO3, 2.5 KCl, 1.25 NaH2
CaCl2, 1 MgCl2
Intracellular Solution *
110 K-gluconate, 40 KCl, 10 HEPES, 2 MgCl2 , 2
0.1 EGTA
Covariates:
Pre and Postsynaptic
3300144 Animals;Sex;Age;Slicing;Recording Method
p1224-5
Anatomy & Morphology:
Pre and Postsynaptic
3200595 Mo; DG:SG Basket▶DG Granule
Fig. 1
Firing Patterns:
Presynaptic Only
3200601 Mo; FP; PV+ DG:SG Basket▶DG Granule
Fig. S1
3200605 Mo;FP; DG:SG Basket
Fig. S5
Properties of spike–induced presynaptic Ca²⁺ signals do not change along PII axons.
Markers:
Presynaptic Only
3200601 Mo; FP; PV+ DG:SG Basket▶DG Granule
Fig. S1
Morphological characterization of PII–GC connections.
Connectivity:
Pre and Postsynaptic
3200595 Mo; DG:SG Basket▶DG Granule
Fig. 1
3200597 Con; DG:SG Basket▶DG Granule
Fig. 3
Synaptic Data:
Pre and Postsynaptic
3200595 Mo; DG:SG Basket▶DG Granule
Fig. 1
3200596 DG:SG Basket▶DG Granule; [Ca²⁺]o=0.5|2
Fig. 2
Quantal release characteristics at PII–GC synapses.
File:3200596.png: Fig. 2
Number of events
Amplitude (pA)
Release probability density
Latency (ms)
0.5 mM Ca²⁺
2 mM Ca²⁺
Available
Yes
Amplitude
Kinetics
Short-term plasticity
Long-term plasticity

(d)

Measure	Value	Reference ID	Note
1st Failure Rate (%)	4.36±8.54 [0 to 39.95] (n=32)	3200595	from 250 to 650 µm distance between pairs, adolescent P17-23
Average Amplitude (pA)	-146.16±22.23 [-552 to -8.75] (n=32)	3200595, 3200602	
Weighted Decay Time Constant (ms)	7.06±0.42 [3.18 to 12.74] (n=32)		
Latency (ms)	1.04±0.06 [0.79 to 1.3] (n=7)	3200595, 3200596	Linear change from 230 to 405 µm distance between pairs
20-80% Rise Time (ms)	0.31±0.02 [0.17 to 0.63] (n=31)	3200602	Calculated by Hippocampome.org
50-50% Rise-to-Decay Time (ms)	0.32±0.02 [0.24 to 0.42] (n=6)	3200596	

FIGURE 7 Data access. The described knowledge base of synaptic electrophysiology is freely available online. (a) Potential connections are searchable by the properties of the presynaptic and postsynaptic neuron types. (b) They are linked to experiment IDs categorized by mapping confidence. (c) The details and summaries of any experiment (e.g., experiment with eID 331) can be reviewed while checking excerpts as evidence and (d) the extracted data is directly accessible. This example is from Struber, Jonas, and Bartos (2015) [Color figure can be viewed at wileyonlinelibrary.com]

Synaptic Data Source: example 2

ALLEN INSTITUTE for BRAIN SCIENCE

https://portal.brain-map.org/explore/connectivity/synaptic-physiology.

EPFL

RESEARCH ARTICLE

NEUROSCIENCE

Local connectivity and synaptic dynamics in mouse and human neocortex

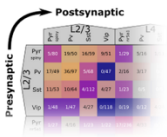
Luke Campagnola[1]†, Stephanie C. Seeman[1]†, Thomas Chartrand[1], Lisa Kim[1], Alex Hoggarth[1], Clare Gamlin[1], Shinya Ito[1], Jessica Trinh[1], Pasha Davoudian[1], Cristina Radaelli[1], Mean-Hwan Kim[1], Travis Hage[1], Thomas Braun[2], Lauren Alfiler[1], Julia Andrade[1], Phillip Bohn[1], Rachel Dalley[1], Alex Henry[1], Sara Kebede[1], Alice Mukora[1], David Sandman[1], Grace Williams[1], Rachael Larsen[1], Corinne Teeter[1]‡, Tanya L. Daigle[1], Kyla Berry[1]§, Nadia Dotson[1], Rachel Enstrom[1], Melissa Gorham[1], Madie Hupp[1], Samuel Dingman Lee[1], Kiet Ngo[1], Philip R. Nicovich[1], Lydia Potekhina[1], Shea Ransford[1], Amanda Gary[1], Jeff Goldy[1], Delissa McMillen[1], Trangthanh Pham[1], Michael Tieu[1], La'Akea Siverts[1], Miranda Walker[1], Colin Farrell[1], Martin Schroedter[1], Cliff Slaughterbeck[1], Charles Cobb[3], Richard Ellenbogen[4], Ryder P. Gwinn[5], C. Dirk Keene[6], Andrew L. Ko[4,7], Jeffrey G. Ojemann[4,7], Daniel L. Silbergeld[4], Daniel Carey[1], Tamara Casper[1], Kirsten Crichton[1], Michael Clark[1], Nick Dee[1], Lauren Ellingwood[1], Jessica Gloe[1], Matthew Kroll[1], Josef Sulc[1], Herman Tung[1], Katherine Wadhwani[1], Krissy Brouner[1], Tom Egdorf[1], Michelle Maxwell[1], Medea McGraw[1], Christina Alice Pom[1], Augustin Ruiz[1], Jasmine Bomben[1], David Feng[1], Nika Hejazinia[1], Shu Shi[1], Aaron Szafer[1], Wayne Wakeman[1], John Phillips[1], Amy Bernard[1], Luke Esposito[1], Florence D. D'Orazi[1], Susan Sunkin[1], Kimberly Smith[1], Bosiljka Tasic[1], Anton Arkhipov[1], Staci Sorensen[1], Ed Lein[1], Christof Koch[1], Gabe Murphy[1], Hongkui Zeng[1], Tim Jarsky[1]*

We present a unique, extensive, and open synaptic physiology analysis platform and dataset. Through its application, we reveal principles that relate cell type to synaptic properties and intralaminar circuit organization in the mouse and human cortex. The dynamics of excitatory synapses align with the postsynaptic cell subclass, whereas inhibitory synapse dynamics partly align with presynaptic cell subclass but with considerable overlap. Synaptic properties are heterogeneous in most subclass-to-subclass connections. The two main axes of heterogeneity are strength and variability. Cell subclasses divide along the variability axis, whereas the strength axis accounts for substantial heterogeneity within the subclass. In the human cortex, excitatory-to-excitatory synaptic dynamics are distinct from those in the mouse cortex and vary with depth across layers 2 and 3.

Synaptic Physiology

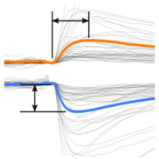
The Allen Institute for Brain Science aims to further our understanding of neuronal cell types by describing the patterns of connectivity among them and characterizing their synaptic signaling. The Synaptic Physiology project advances this goal by examining the intralaminar connectivity between neuronal subclasses[?] in human and mouse cortex via *in vitro* electrophysiology. This dataset is readily accessible and produced using standardized experimental methods and analysis. The applications of the dataset are wide-ranging, as the data are suited to parameterize synaptic modeling studies, address higher-order connectivity questions, and inform current comprehension of the cortical microcircuit.

synaptic connectivity



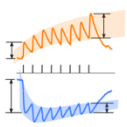
Measurements of connection probability between cortical cell subclasses and the relationship to intersomatic distance. more...

strength & kinetics

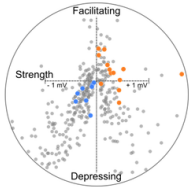


Synaptic strength, latency, and rise/decay kinetics derived from current and voltage clamp recordings. more...

short-term plasticity



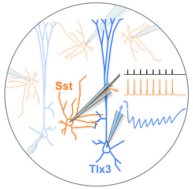
Short-term plasticity induced by stimulus trains with varying spike timing. more...



How to use the Synaptic Physiology Dataset

Explore the interplay of features such as synaptic strength, facilitation, depression, and more via online Jupyter notebooks or interactive desktop tools. Alternatively, access the data directly via our Python API.

More on how to access the data



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Connectivity among cell subclasses was investigated via multiple-patchclamp electrophysiology in human and mouse cortical slices. Transgenic mice enabled two cell subclass populations to be visualized in a single slice and to target connections among them.

More on experimental methods

Connections between recorded neuron pairs were identified and properties such as strength, kinetics, and short-term plasticity were characterized to identify how synaptic properties vary among different cell classes.

More on analysis methods

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Stay up-to-date on what's coming

Seeman, Campagnola et. al. eLife 2018

Campagnola, Seeman et. al. Science 2022

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Interact with the Synaptic Physiology Dataset

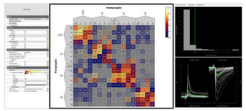
The Synaptic Physiology Dataset allows users to explore interactions between cell subclasses in mouse and human cortex. There are a variety of ways to access the data based on your interests.

Online Jupyter notebooks

Hosted by mybinder.org, these notebooks provide an interactive environment for accessing, analyzing, and visualizing results from the Synaptic Physiology Dataset. This provides a quick way to begin interacting with the data in your browser, but some Python experience is recommended.

Note: mybinder.org instances will shut down after 10 minutes of inactivity. These are great for quickly exploring the dataset, but not appropriate for prolonged data analysis.

Explore notebooks in MyBinder



Interactive desktop tools

Explore the Synaptic Physiology Dataset with interactive tools. Choose cell classes of interest and synaptic metrics to see an overview of cortical synaptic physiology. Requires installation of a Python programming environment on your local machine.

Getting started with Synaptic Physiology tools

Access the data directly via our API

The Synaptic Physiology Python programming packages provide access to three sqlite databases, described below, as well as the original NWBv1 (HDF5) data files.

Getting started with the Synaptic Physiology API

Synaptic Physiology Database

The Synaptic Physiology Dataset is available as three different sqlite files, each increasing in content and size. It is recommended that you download the database files directly from our API or contact us for other options.

	Small (~170 MB)	Medium (~7 GB)	Full (>160 GB)
experiment metadata tissue source, experimental conditions	✓	✓	✓
chemical / electrical connections connection probability	✓	✓	✓
cell properties transgenic class, layer, morphology, intrinsic physiology	✓	✓	✓
per-connection average properties strength, kinetics, dynamics, averaged synaptic responses, electrical connection properties	✓	✓	✓
per-connection synaptic release models quantal release parameters, short-term plasticity	✓	✓	✓
per-stimulus response properties curve fits to individual synaptic responses		✓	✓
per-stimulus spike properties timing and measurements of individual presynaptic spikes		✓	✓
stimulus / recording metadata		✓	✓
per-stimulus response data time-series data for every presynaptic spike and corresponding postsynaptic recording			✓

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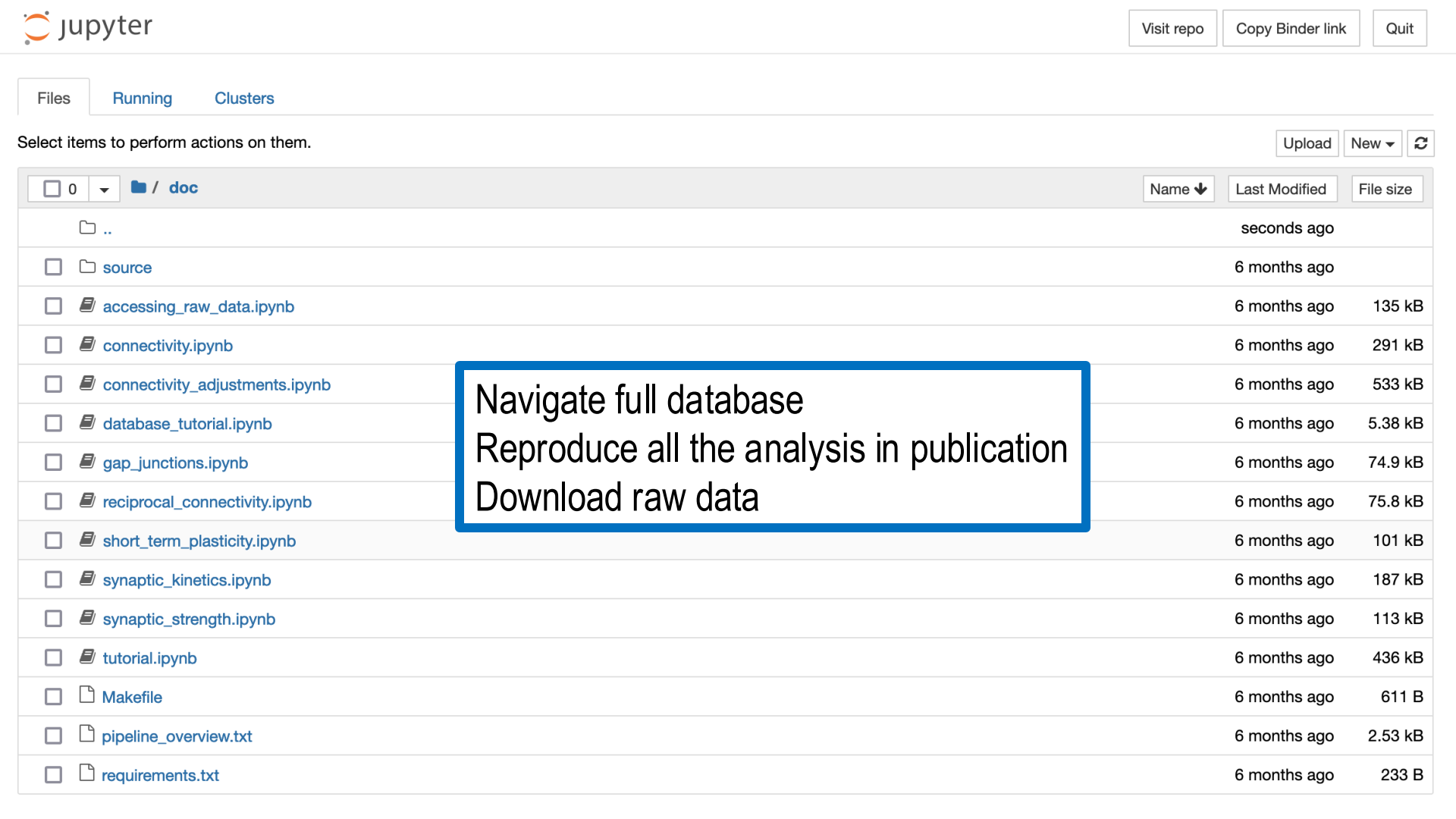
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Navigate full database
Reproduce all the analysis in publication
Download raw data

Synaptic Physiology

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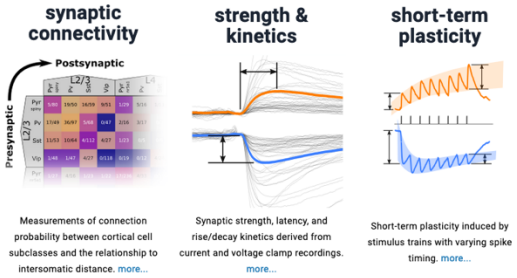

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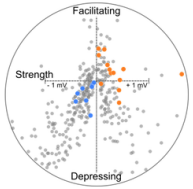

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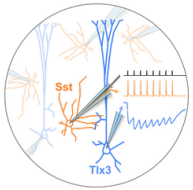

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scseeman Mar 15

Hi Natali,

I'm not sure why that is happening, but it appears to be the way `filter_exprs` is working. I can assure you that there are data with STP in the dataset. While we investigate that you can do this same filtering but outside of the query. To do this I would use your query here but remove the `filter_exprs` (also note that there should be no underscore in `standard multipatch`). Then you can use a list comprehension to get just pairs from that query which have STP data like so:

```
query = db.pair_query(
    experiment_type='standard multipatch',    # filter: just multipatch experiments
    species='human',                          # filter: only human data
    synapse=True,                             # filter: only cell pairs connected by
)
pairs = query.all()
print(len(pairs))
>>329
pairs_with_stp = [p for p in pairs if p.dynamics.stp_induction_50hz is not None]
print(len(pairs_with_stp))
>> 185
```

How to apply to research

frontiers in Synaptic Neuroscience

ORIGINAL RESEARCH
published: 15 October 2019
doi: 10.3389/fnsyn.2019.00029

Check for updates

Estimating the Readily-Releasable Vesicle Pool Size at Synaptic Connections in the Neocortex

Natalí Barros-Zulaica[1], John Rahmon[1], Giuseppe Chindemi[1], Rodrigo Perin[2], Henry Markram[1,2], Eilif Muller[1†] and Srikanth Ramaswamy[1*†]*

[1] Blue Brain Project, École Polytechnique Fédérale de Lausanne, Geneva, Switzerland, [2] Laboratory of Neural Microcircuitry, Brain Mind Institute, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland

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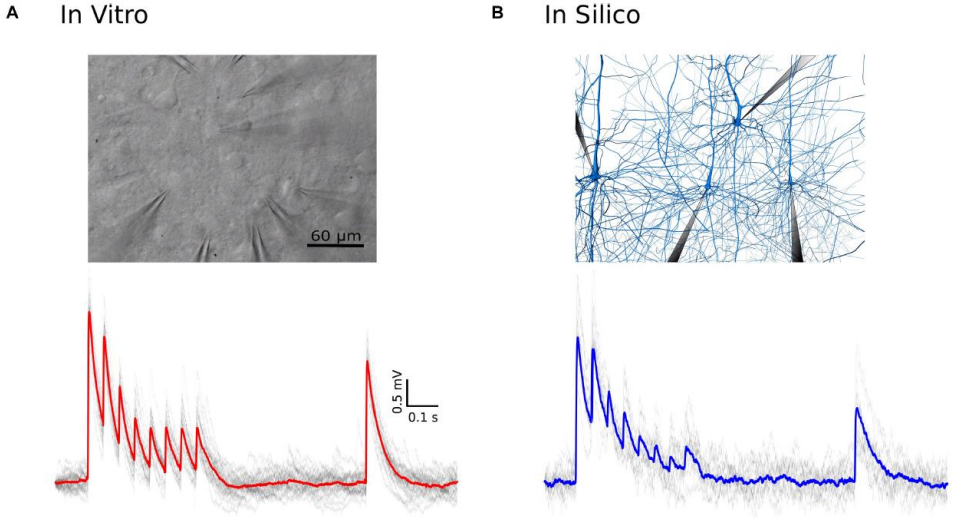
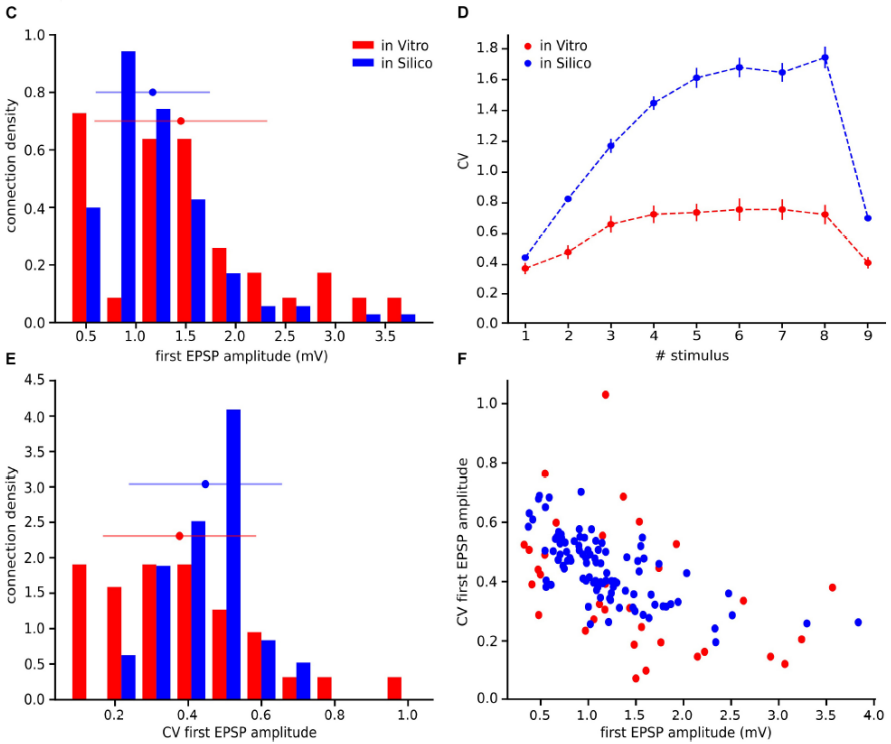
The problem

- Model synapses → univesicular (Nrrp = 1)
- Univescicular release could capture the average behavior of the synapse
- It did not capture the variability of the following EPSP (CV)
- Hypothesis → implement multivesicular release





UVR vs MVR

N_{RRP} = number of readily releasable vesicle pool

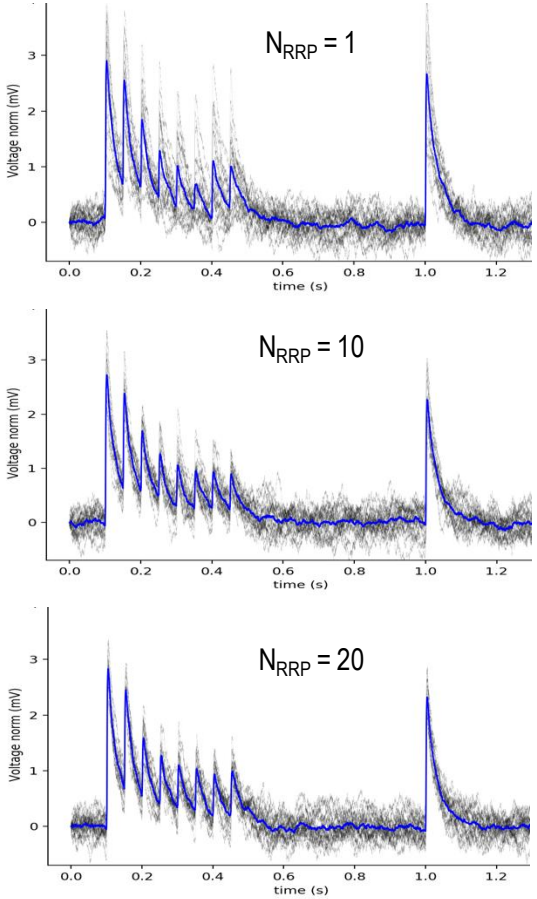
Importance:

1. Synaptic transmission is the bases of neuronal communication

2. Synaptic variability (noise) plays an important role in information coding in the cortex. (Nolte et al., 2019)

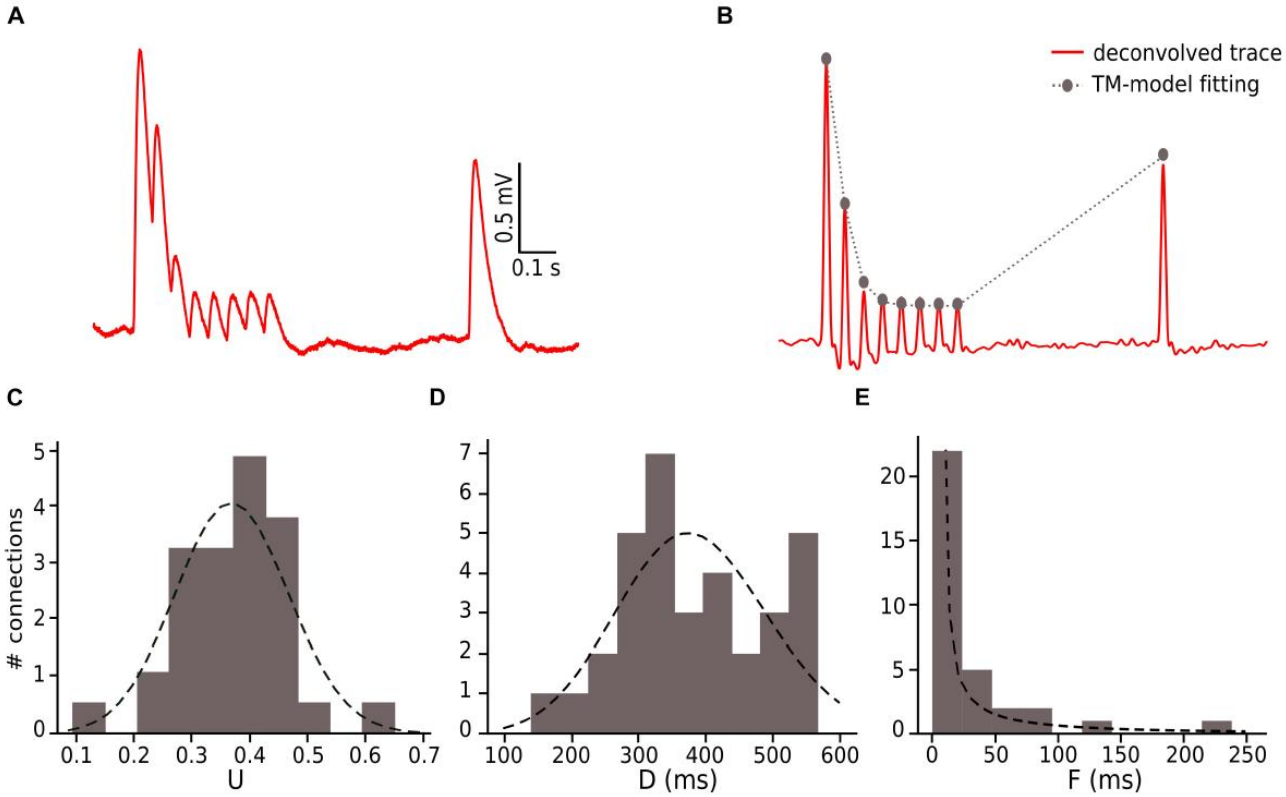
UVR (Univesicular release) :
N_{RRP} = number of connections

MVR (Multivesicular release):
several vesicles per active zone
-Increase the dynamics range of the synapse



Method: step 1

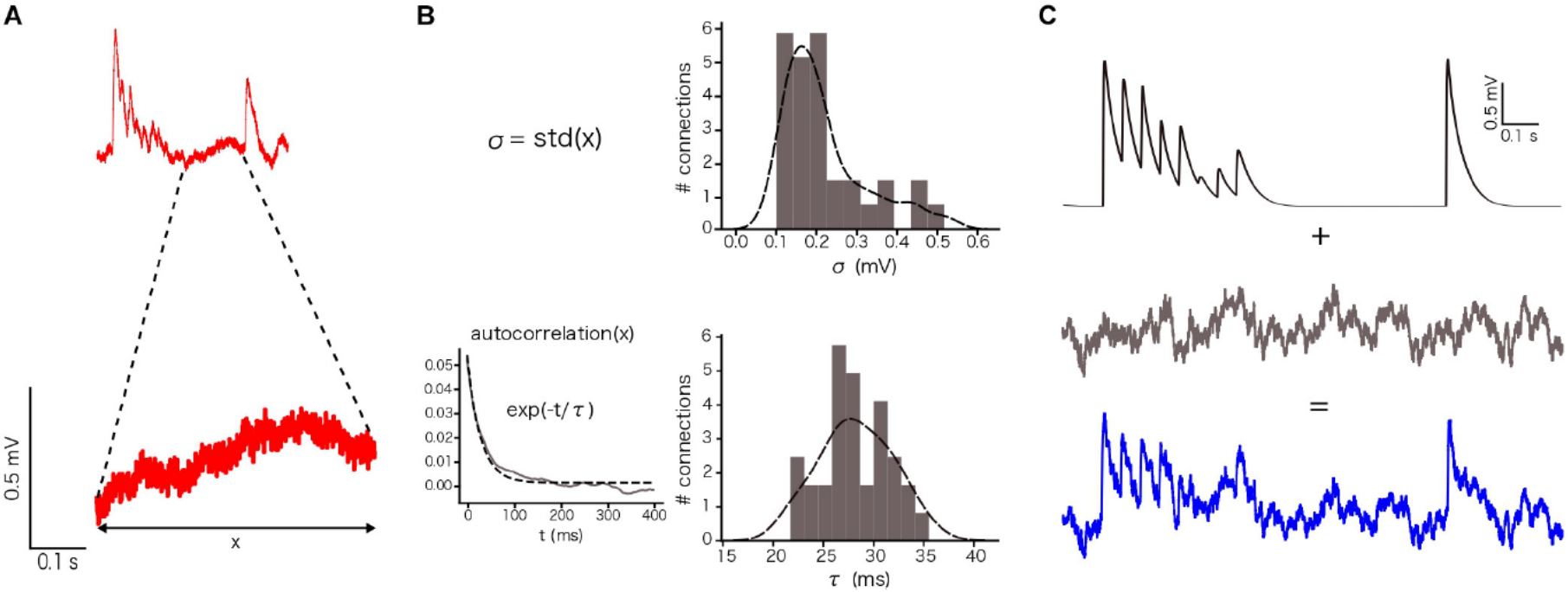
U, D, F parameters for the TM model obtained from 33 in vitro connections



Method: step 2

Model membrane voltage noise to completely capture synaptic variability:

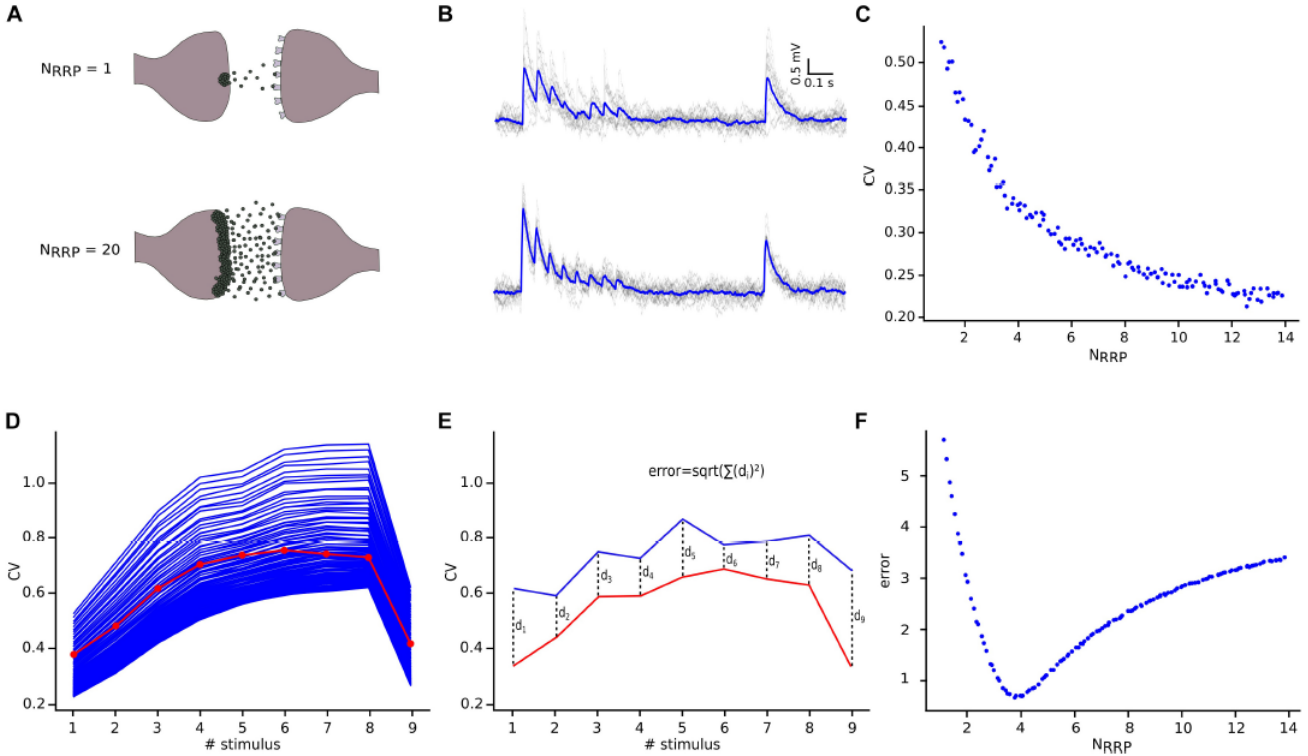
Ornstein-Uhlenbeck Process



Method: step 3

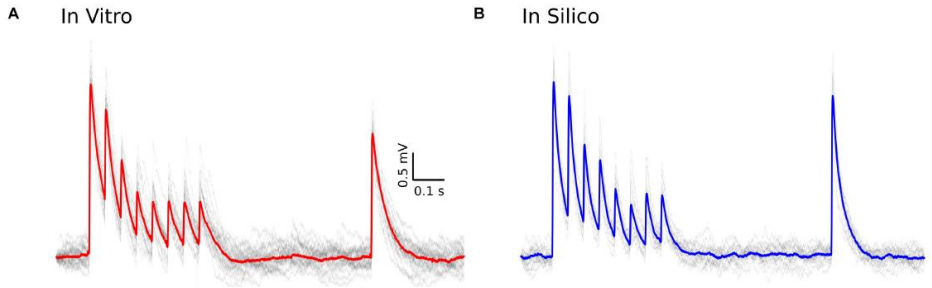
Simulations with different N_{RRP}

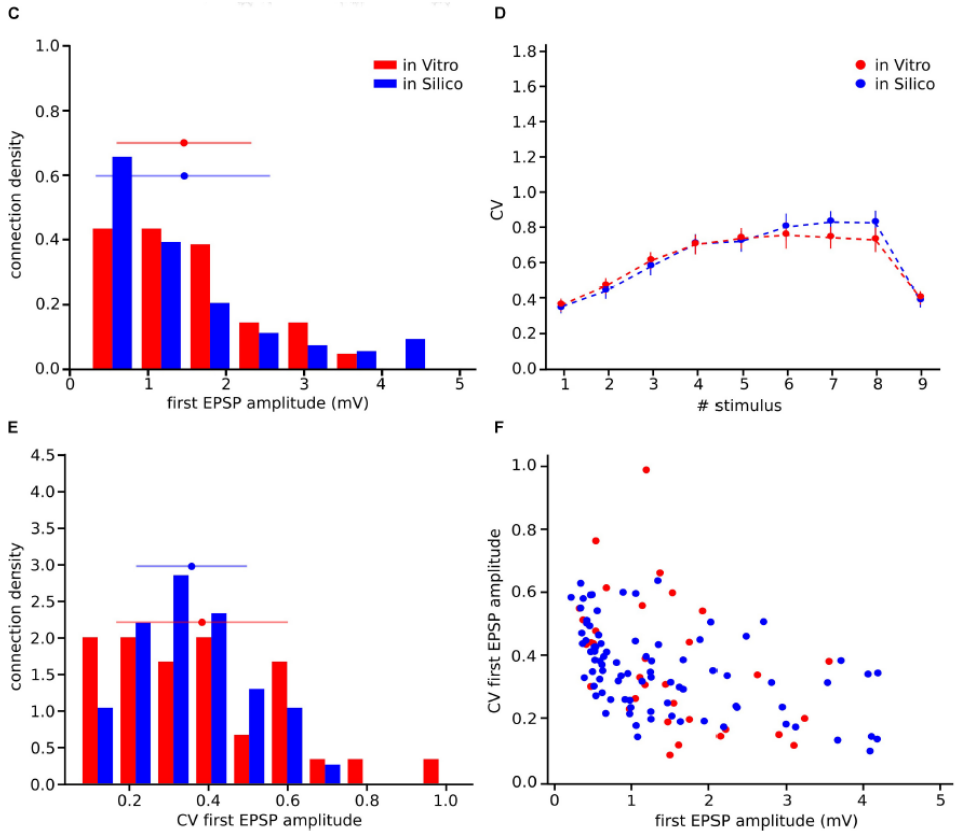
Increasing N_{RRP} → the synapse become more reliable or less variable (smaller CV)



Result

After optimizing the N_{RRP}, the CV of the following EPSPs are matched





Predictions for other connections →Eureka moment!

Connection type	Literature data	Jack-Knife conversion	Prediction
	CV	CV	N_{RRP}
L23_NBC_LBC-L23_PC	0.40 @ 0.09 (Wang et al., 2002)	0.38 ± 0.21	1.96 ± 0.98
L23_PC-L23_PC	0.33 @ 0.18 (Feldmeyer et al., 2006)	0.48 ± 0.23	2.60 ± 1.28
L4_SSC-L23_PC			1.81 ± 0.37
L4_SSC-L5_TPC:C			1.26 ± 0.50
L5_TTPC-L5_SBC			1.82 ± 0.90
L5_TTPC-L5_TTPC			2.84 ± 1.34

Article

Structure and function of a neocortical synapse

https://doi.org/10.1038/s41586-020-03134-2
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Accepted: 24 November 2020
Published online: 13 January 2021
Check for updates

Simone Holler[1], German Köstinger[1], Kevan A. C. Martin[1], Gregor F. P. Schuhknecht[1]✉ & Ken J. Stratford[1]

In 1986, electron microscopy was used to reconstruct by hand the entire nervous system of a roundworm, the nematode *Caenorhabditis elegans*[1]. Since this landmark study, high-throughput electron-microscopic techniques have enabled reconstructions of much larger mammalian brain circuits at synaptic resolution[2,3]. Nevertheless, it remains unknown how the structure of a synapse relates to its physiological transmission strength—a key limitation for inferring brain function from neuronal wiring diagrams. Here we combine slice electrophysiology of synaptically connected pyramidal neurons in the mouse somatosensory cortex with correlated light microscopy and high-resolution electron microscopy of all putative synaptic contacts between the recorded neurons. We find a linear relationship between synapse size and strength, providing the missing link in assigning physiological weights to synapses reconstructed from electron microscopy. Quantal analysis also reveals that synapses contain at least 2.7 neurotransmitter-release sites on average. This challenges existing release models and provides further evidence that neocortical synapses operate with multivesicular release[4–6], suggesting that they are more complex computational devices than thought, and therefore expanding the computational power of the canonical cortical microcircuitry.

Key points

- Estimating the number of independent release sites (N_{RRP}) experimentally is very challenging
- A modeling approach is used to quantify N_{RRP} on existing traces
- It shows that N_{RRP} has an impact on the synaptic transmission making it more or less reliable (‘noisy’)
- Model ‘baseline’ noise

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Summary 3

- Given the diversity of synapses even within the same brain region, public data repositories are often region-specific
- The number of synaptic types in the brain is extremely high and each of them is potentially unique
- Considering the cost of fully characterize one single synapse, it is clear how public resources and modeling tools are essential to move the research forward

Lecture Summary

- The huge number of synapses in the brain, their high diversity, and their complex machinery challenge researchers
- Biophysical models are only possible for few synapses, while we have adopt phenomenological models once the number of synapses grows in our models
- Even phenomenological models can be characterized by many parameters
- We have to deal with very sparse data
- In the next lecture, we will see how the synapses can change for long periods of time even forever

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What you have learnt:

- Definitions: electrical synapse, chemical synapse, axonal boutons, receptors
- AMPA, NMDA and GABA receptors
- Synaptic plasticity: STP (short term plasticity)
- Three ways of modelling synapses: understand the three models, their bases and their parameters, no need to know exactly the equations.
  - Equivalent circuit
  - Quantal release model
  - Tsodyks-Markram model

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