

Modeling/Data analysis/ Neuron-Glial interactions from network to protrusion

David Holcman

(November 8 2023)



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References

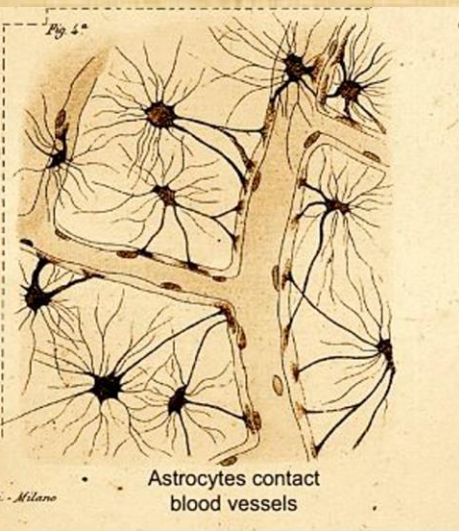
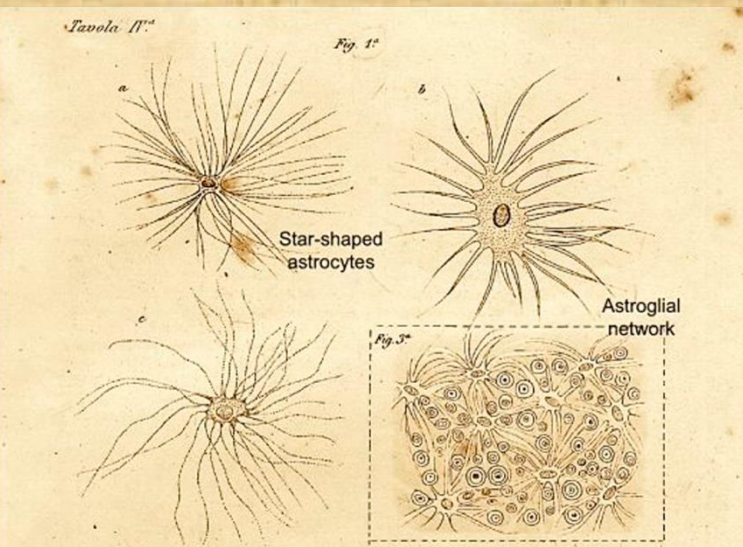
- D. Holcman Tsodyks, Plos Comp. Bio. 2006
- D. Freche et. al, Plos 1 2011
- U.Pannach et. al, Nat Neuro 2014
- K.Daoduc et. al, Opera Physiological, 2018
- J.Sibille et. al, Plos CB 2016
- E. Dossi L.Zonca et al., BioRxiv 2022

Plan of the Lecture

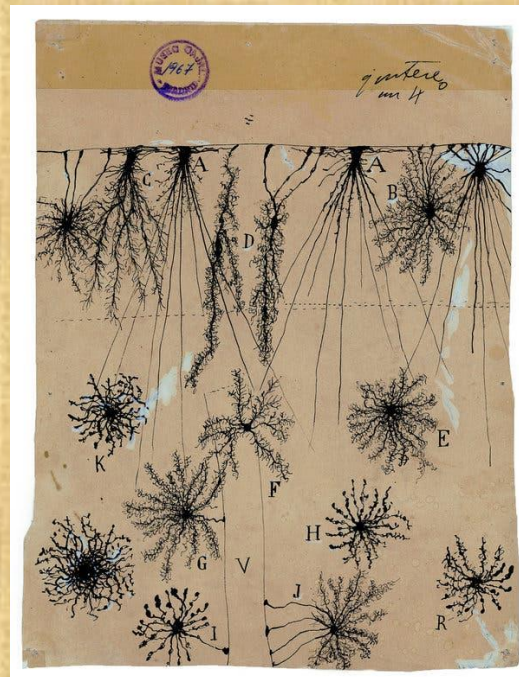
1. Introduction: Neuron-glia Interaction
2. Modeling synaptic dynamics: modeling, simulation, prediction of geometrical organization
3. Compartment model: regulation of ionic fluxes between astro and neuron
4. How glial cell regulate neuronal activity: bursting, AHP, synaptic depression facilitation model and mean-field model
5. Open question: BVI → model activity, pumping glutamate, potassium and activity

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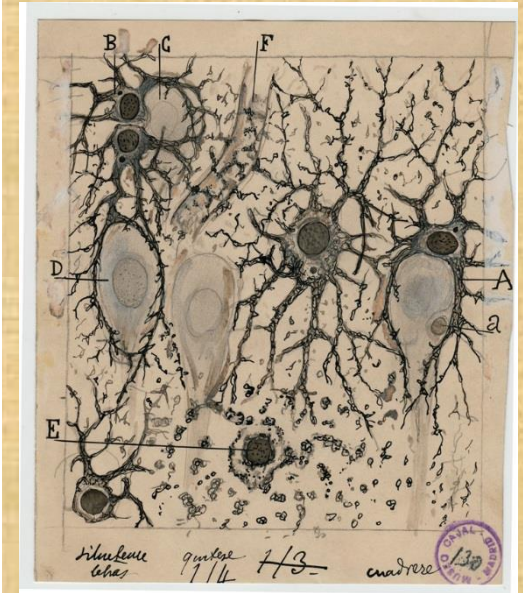
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Camillo
Golgi 1903



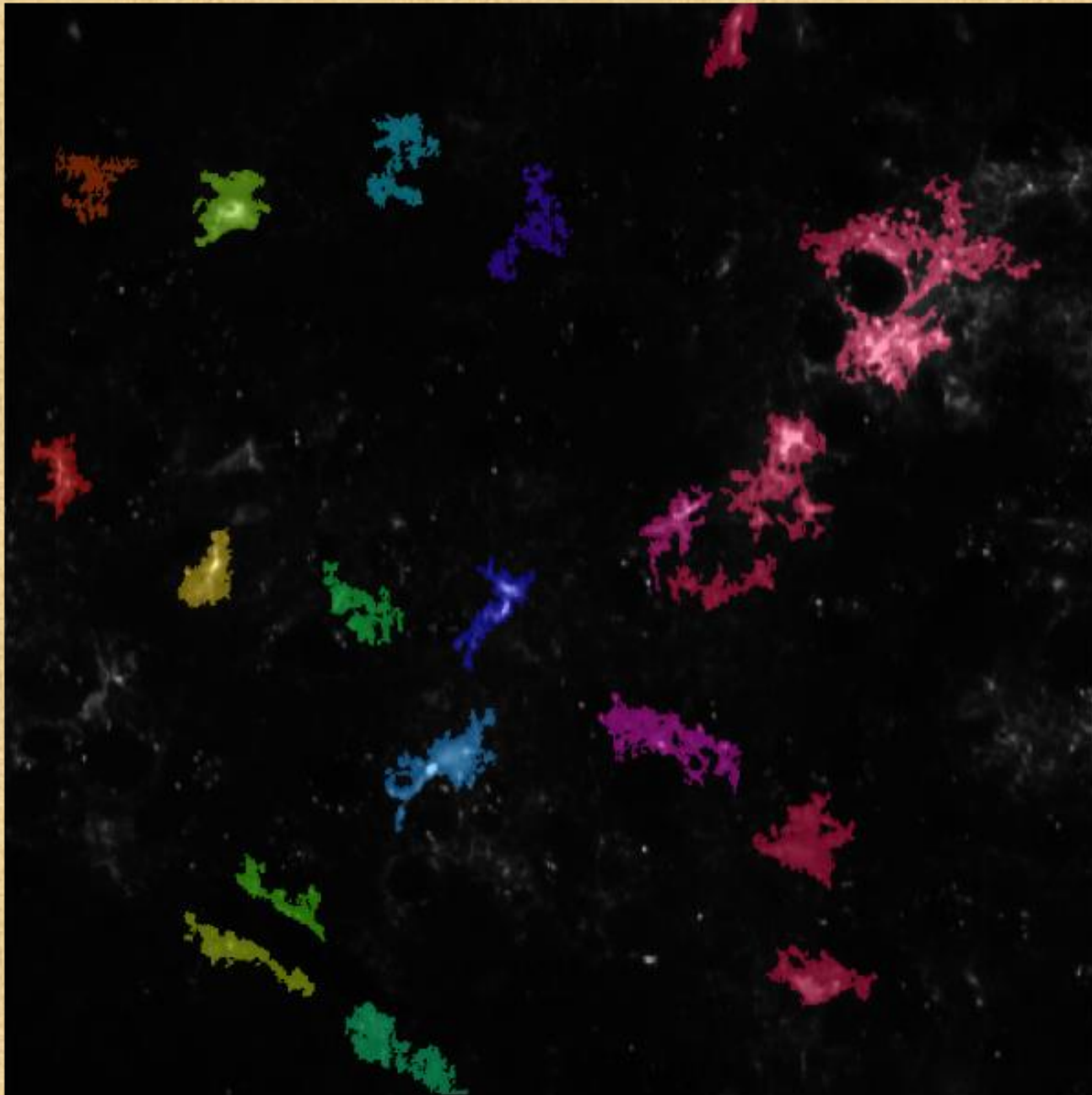
Astrocytes of the cerebral cortex of a child

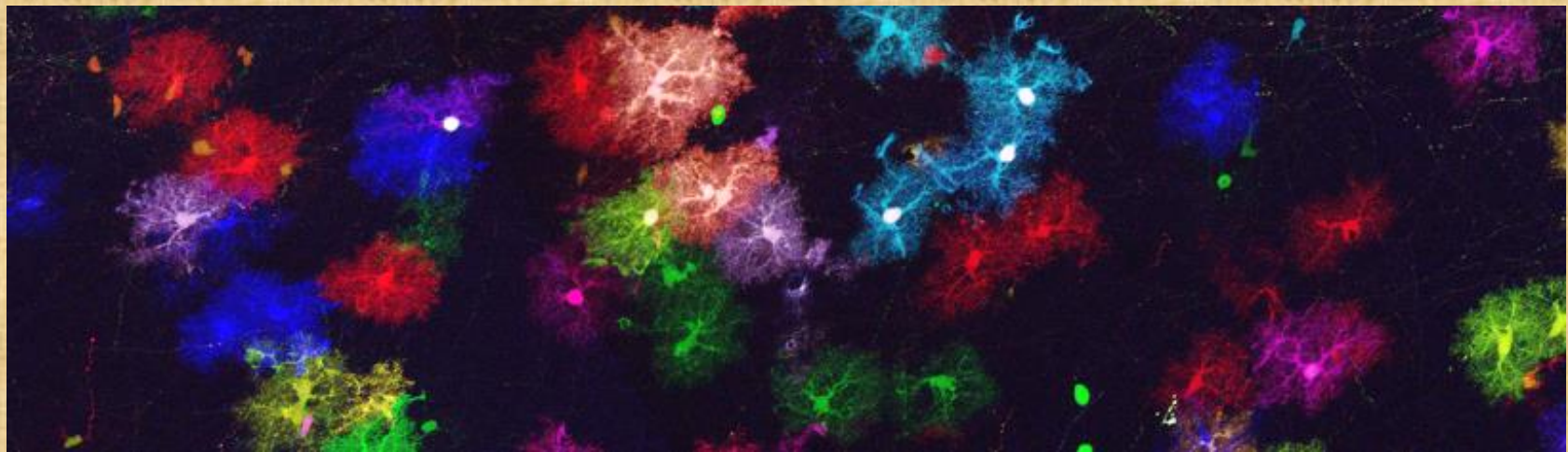


Astrocytes in the hippocampus
of the human brain

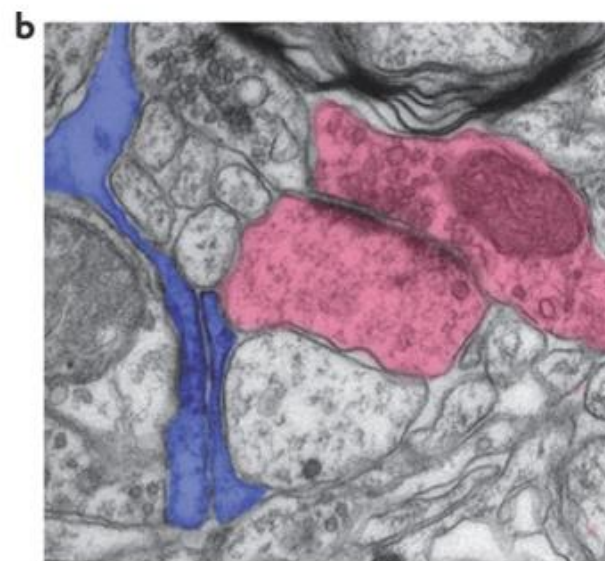
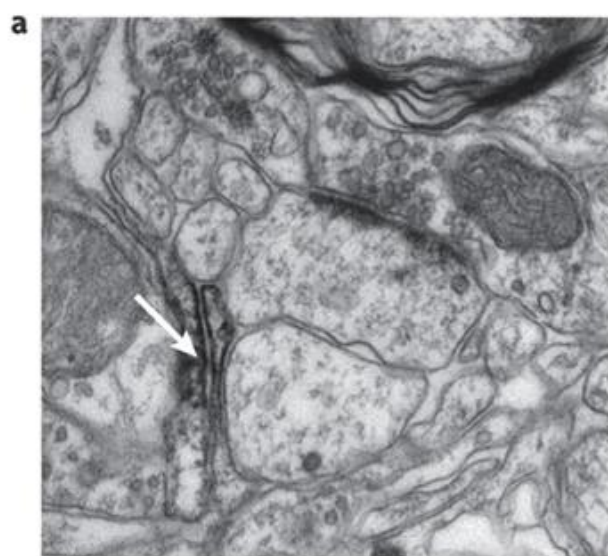
Santiago Ramon y Cajal

Astrocytic shapes

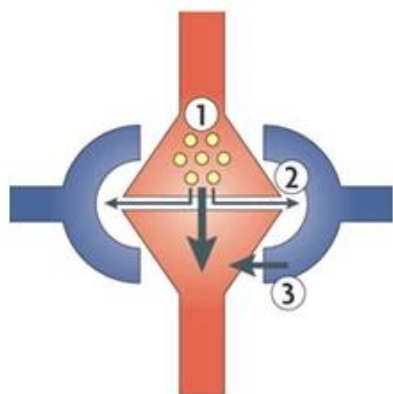




Clavreul et al 2019 Nat Com

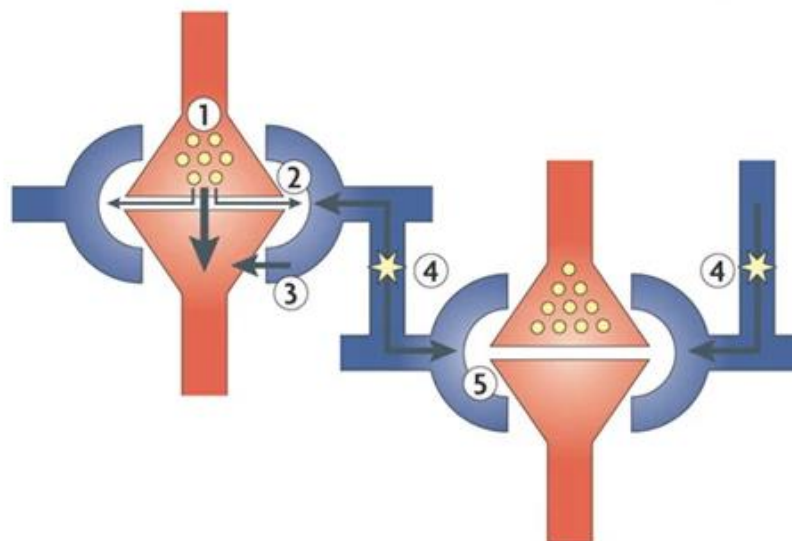


c Tripartite synapse

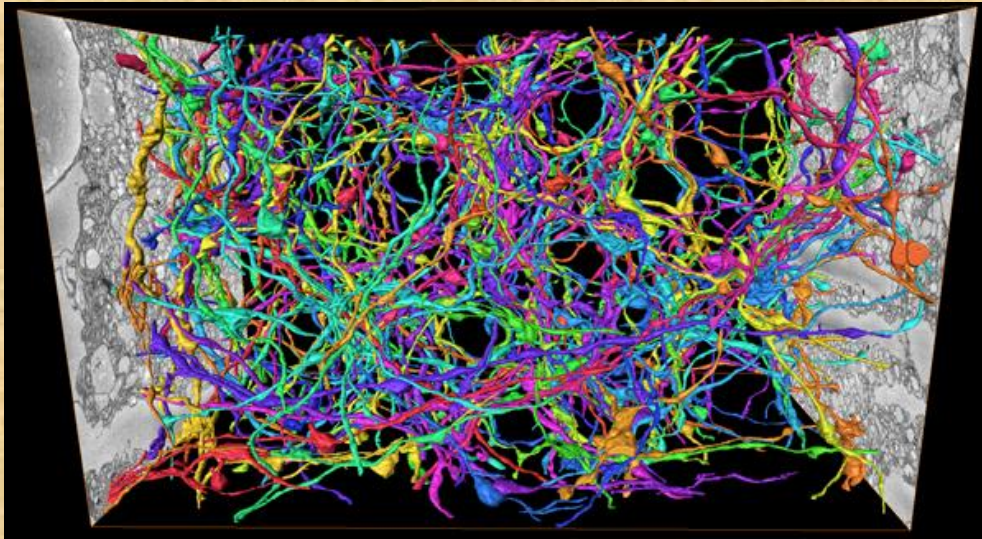


d

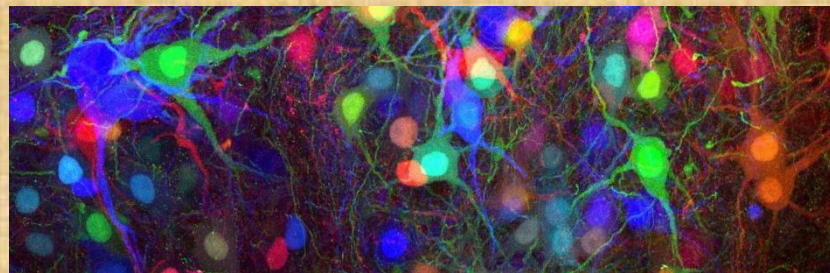
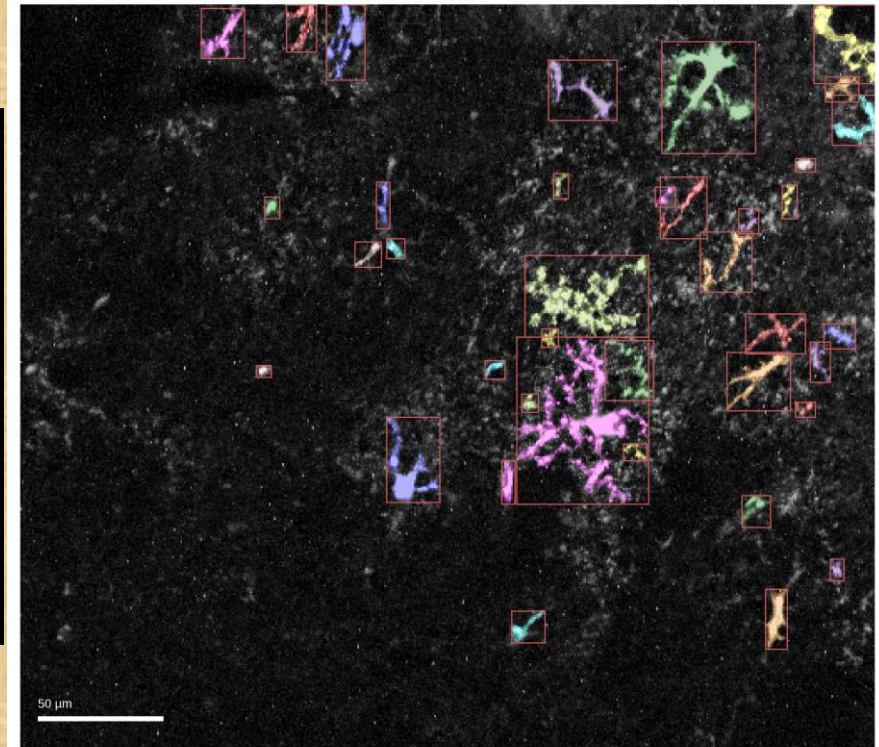
Synapses and neuroglial networking



Neuronal Network



Astrocyte Network



Network organization through astrocytic connexins



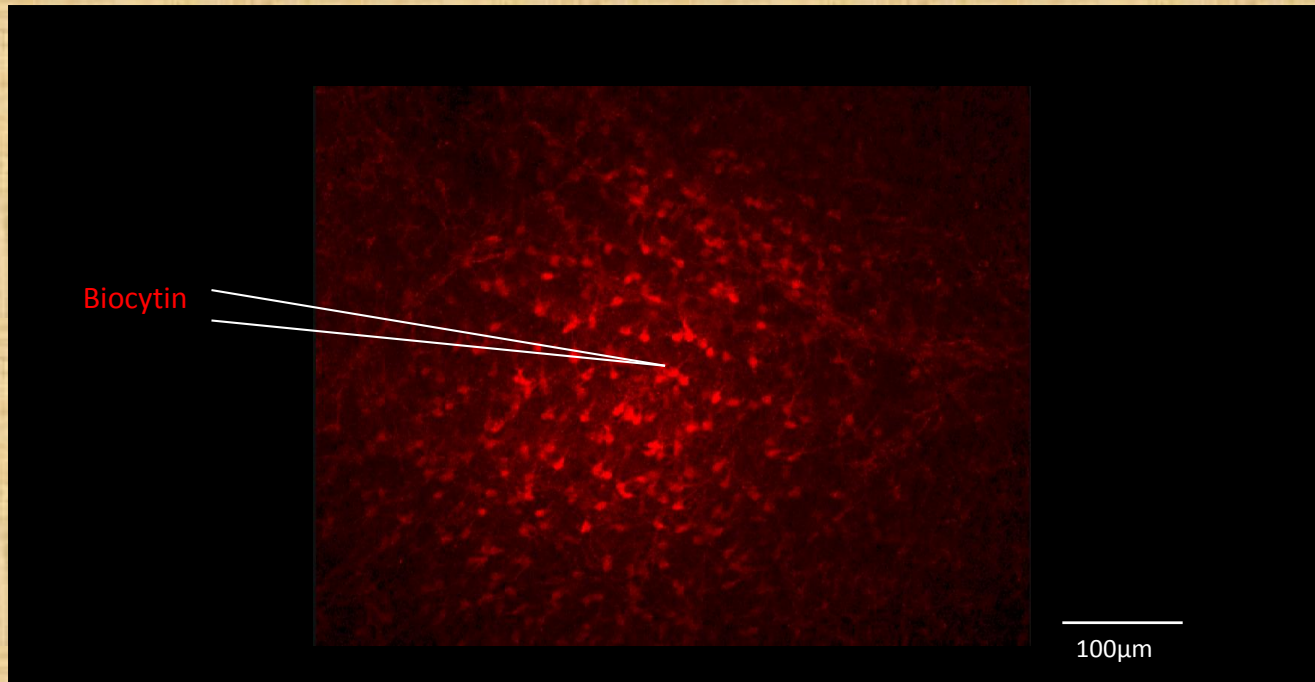
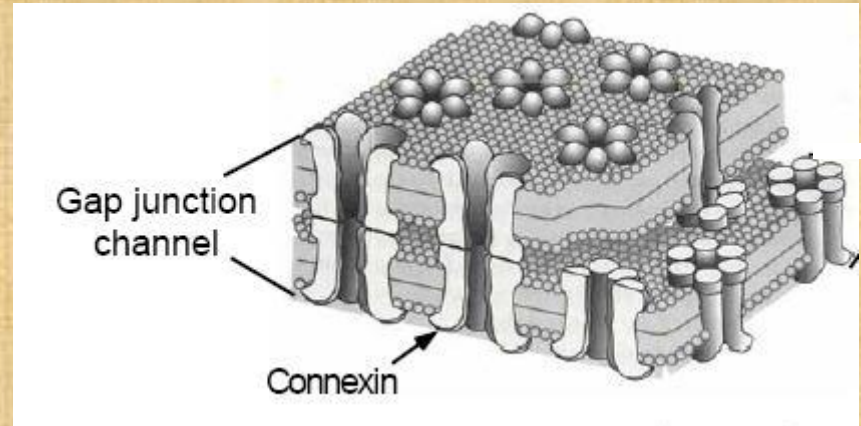
Connexin

Connexon

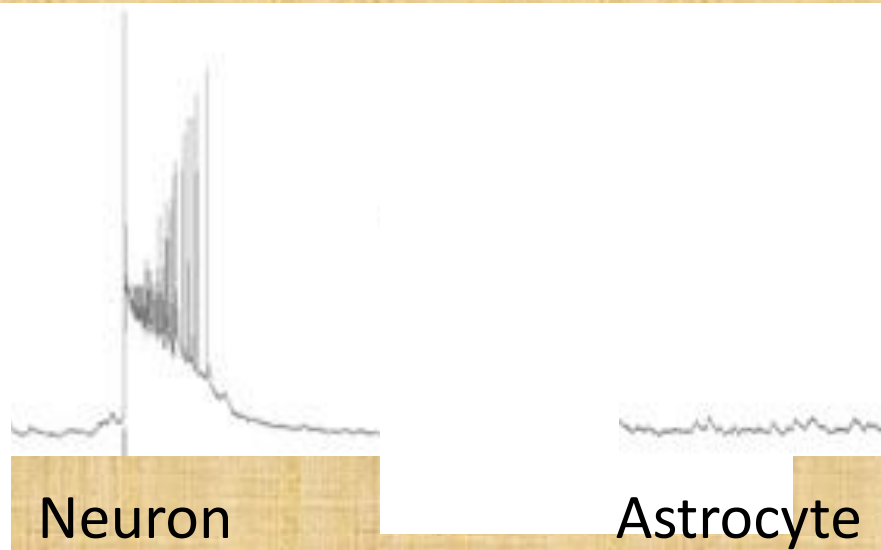
intracellular channel

Connexin 43

Connexin 30

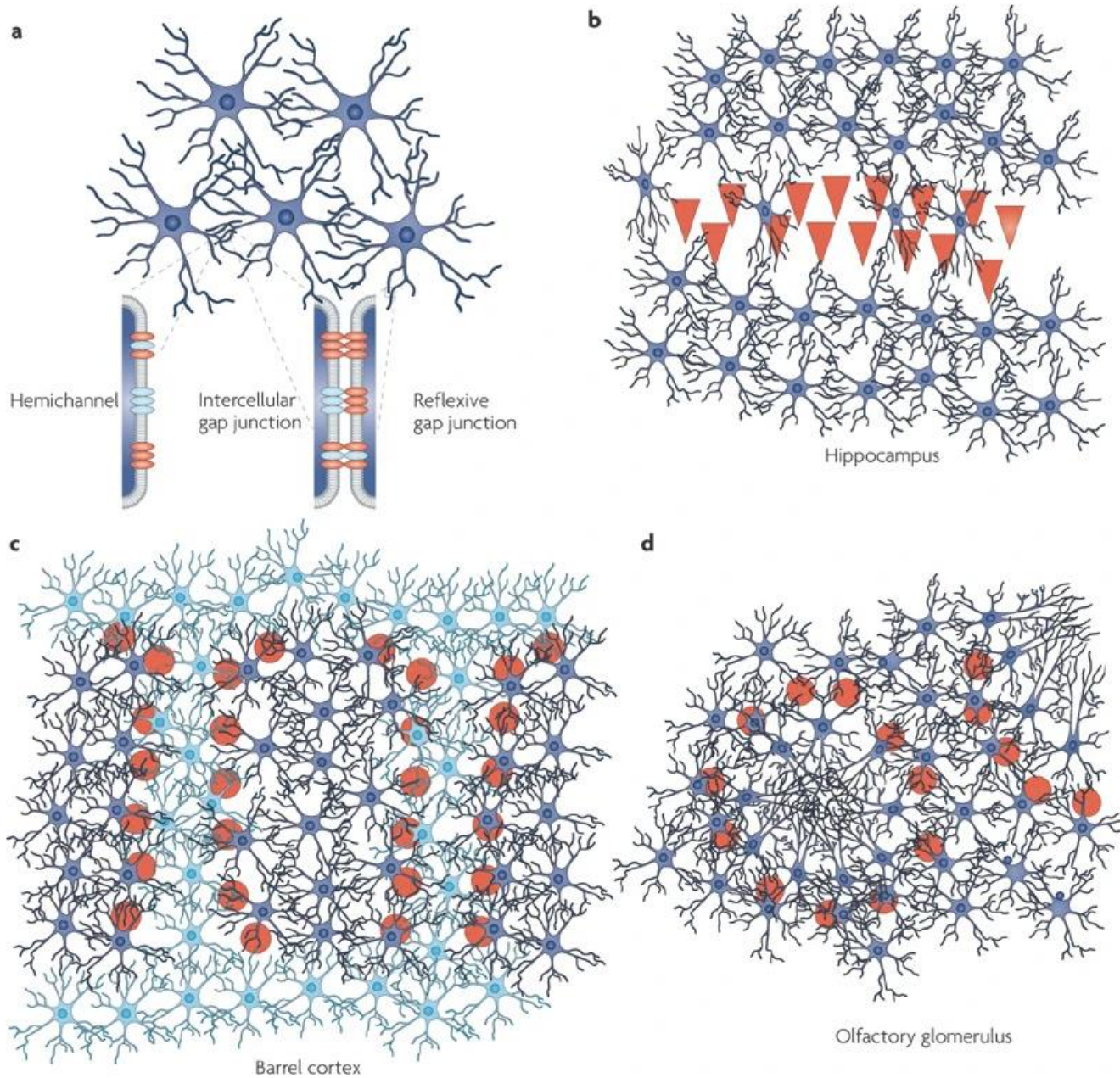


Astrocytes are electrically non excitable

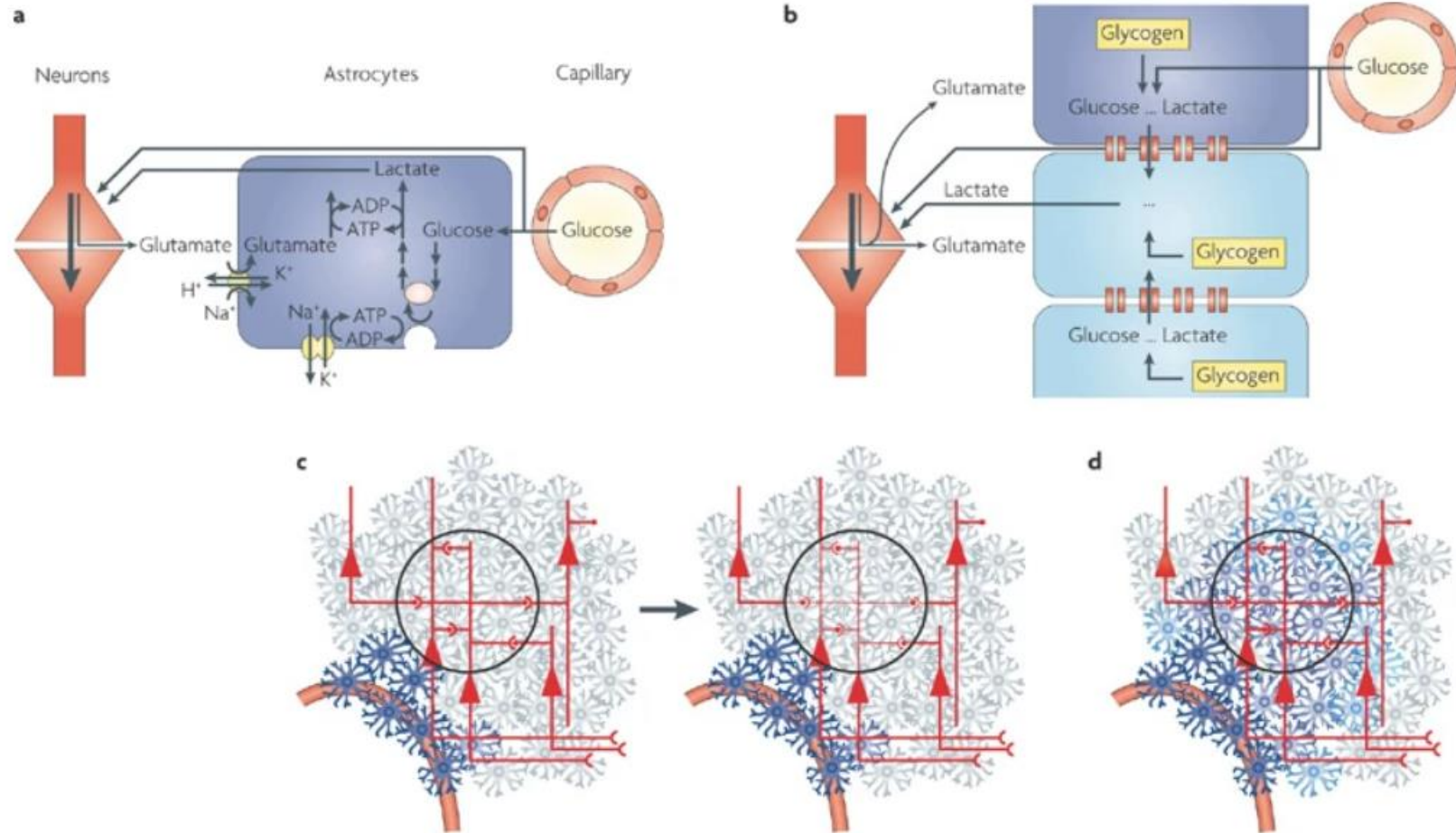


-80mV

Various network organization (different density, # neighbors...)

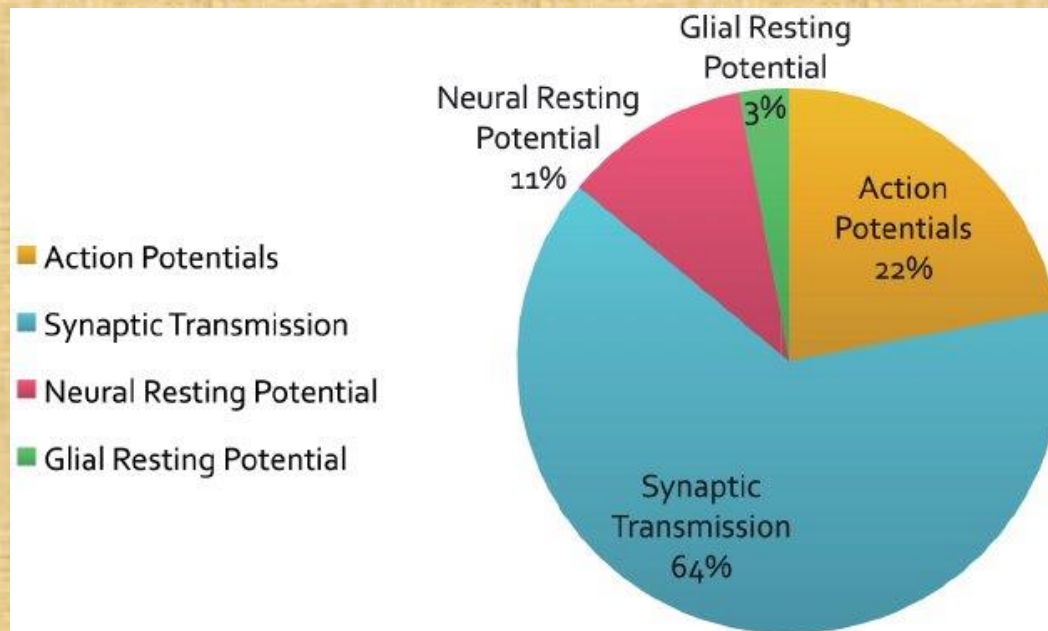
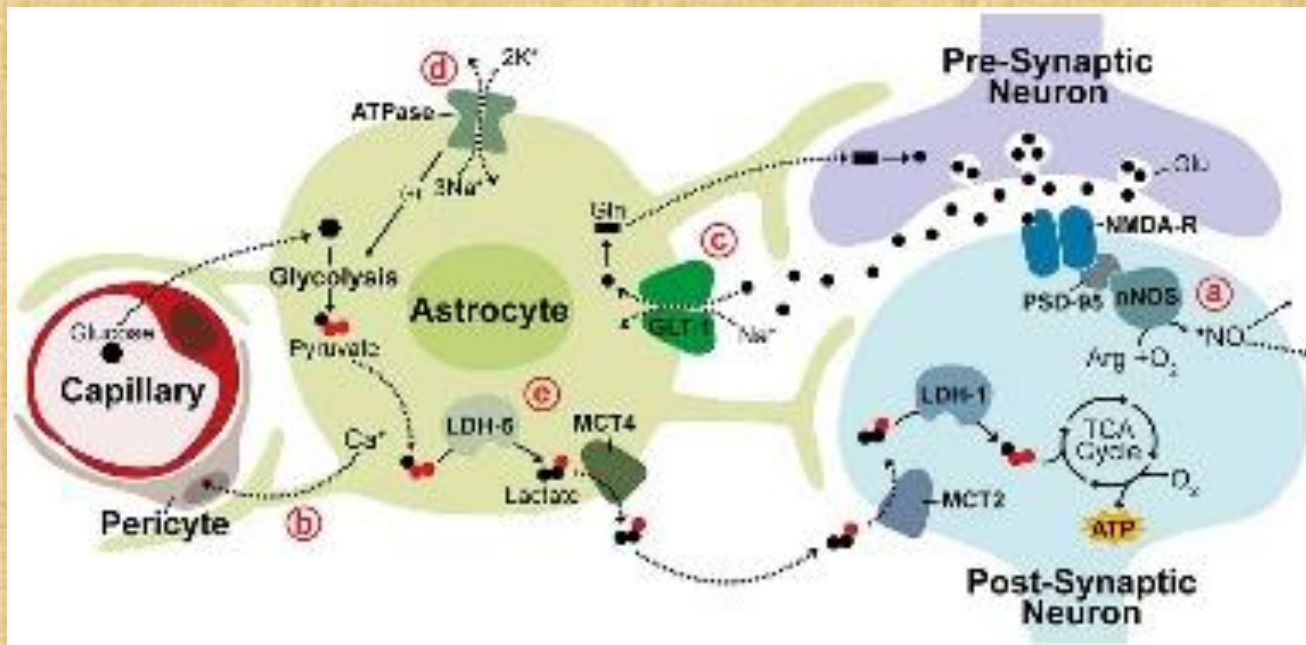


metabolism support in a network



Nature Reviews | Neuroscience

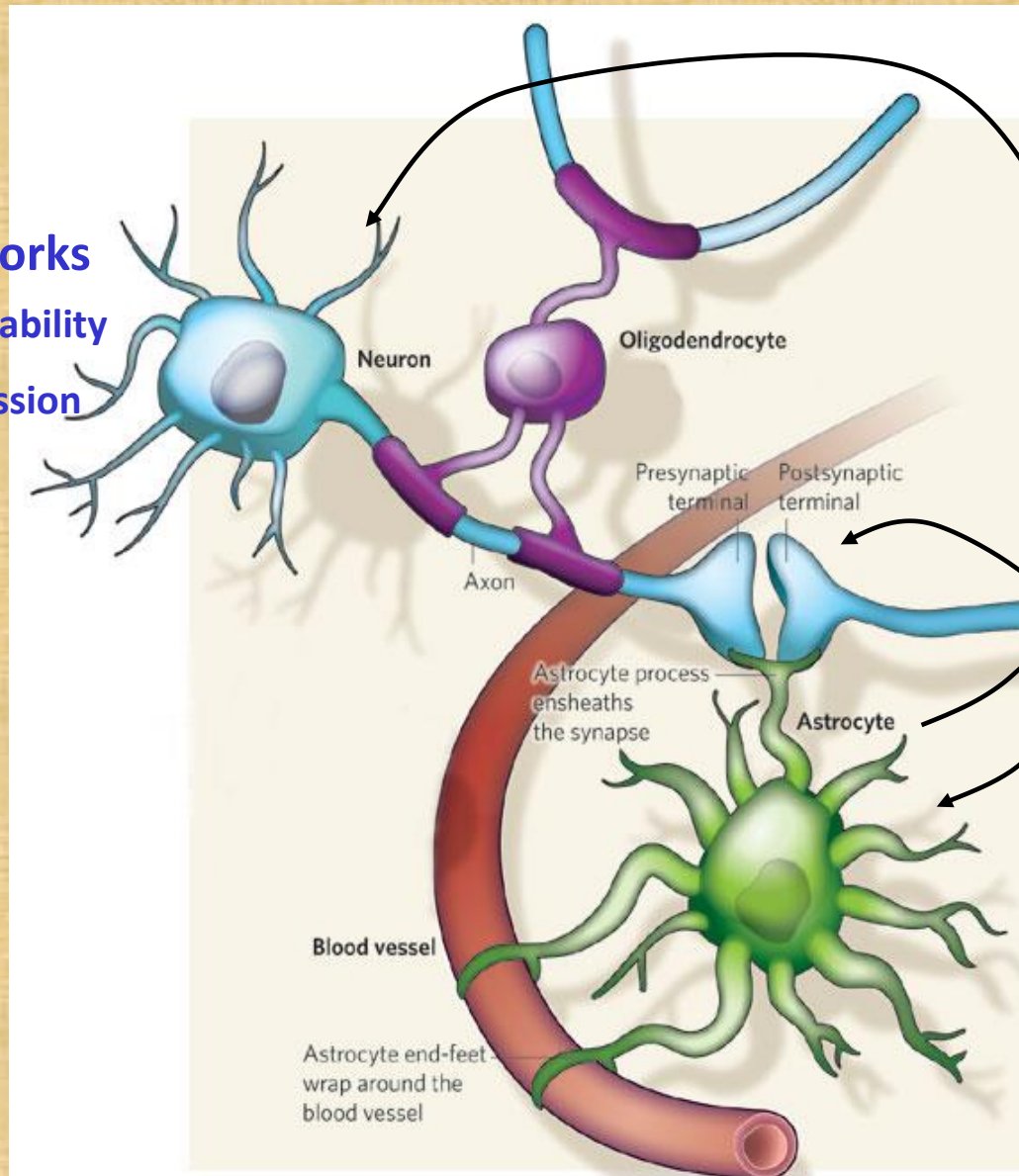
- Glutamate/Glutamine cycle
- Metabolism spread



Neuron-Glia-Interactions

Neuronal networks

- Electrical excitability
- Neurotransmission



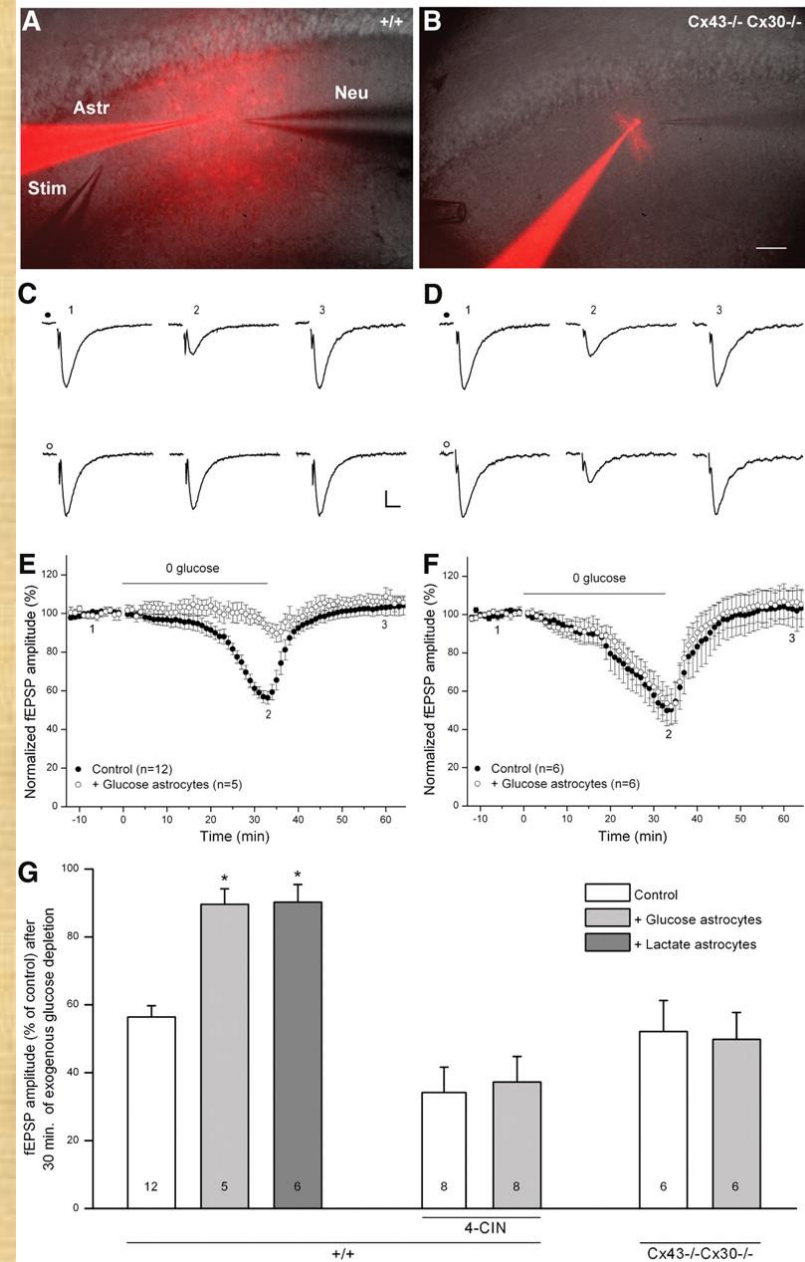
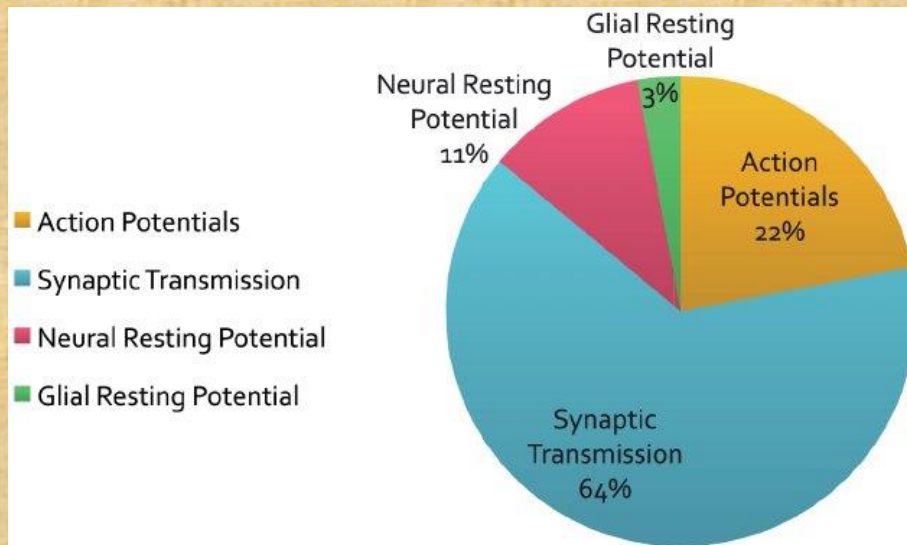
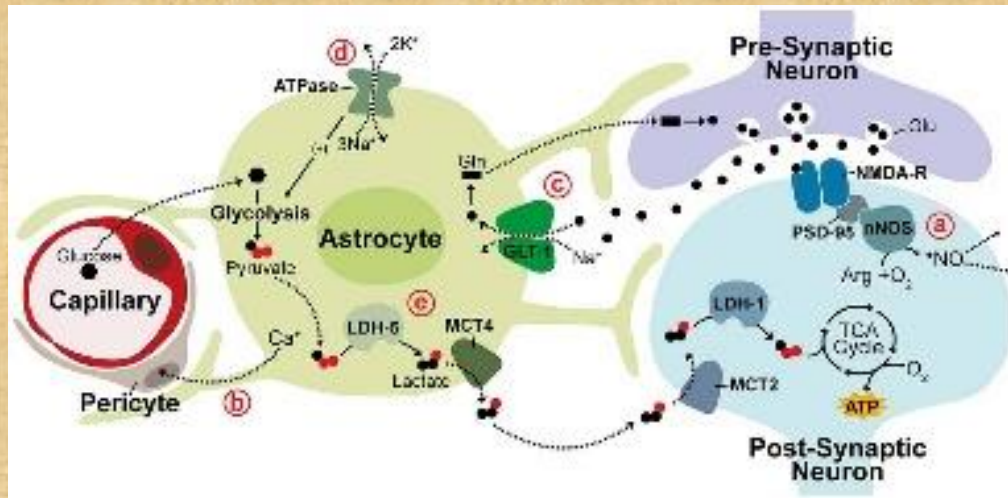
Classic concept:

Structural,
metabolic
and trophic
support

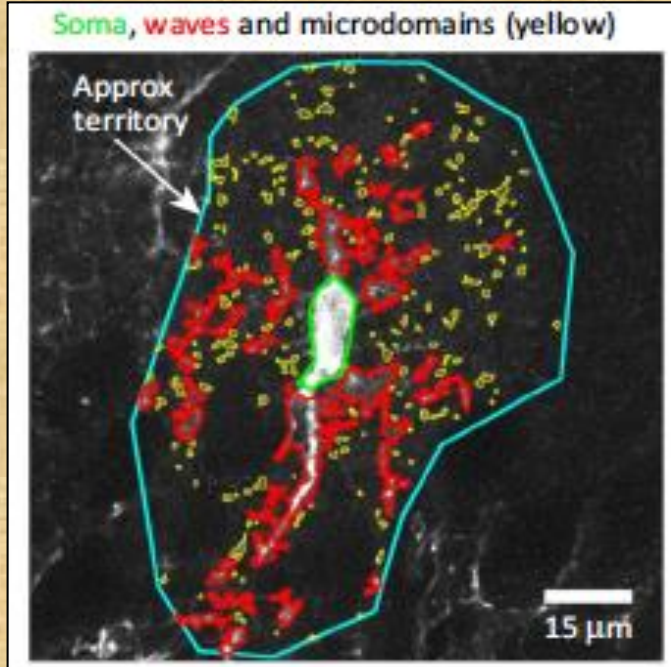
New concept:

Calcium excitability,
Gliotransmission

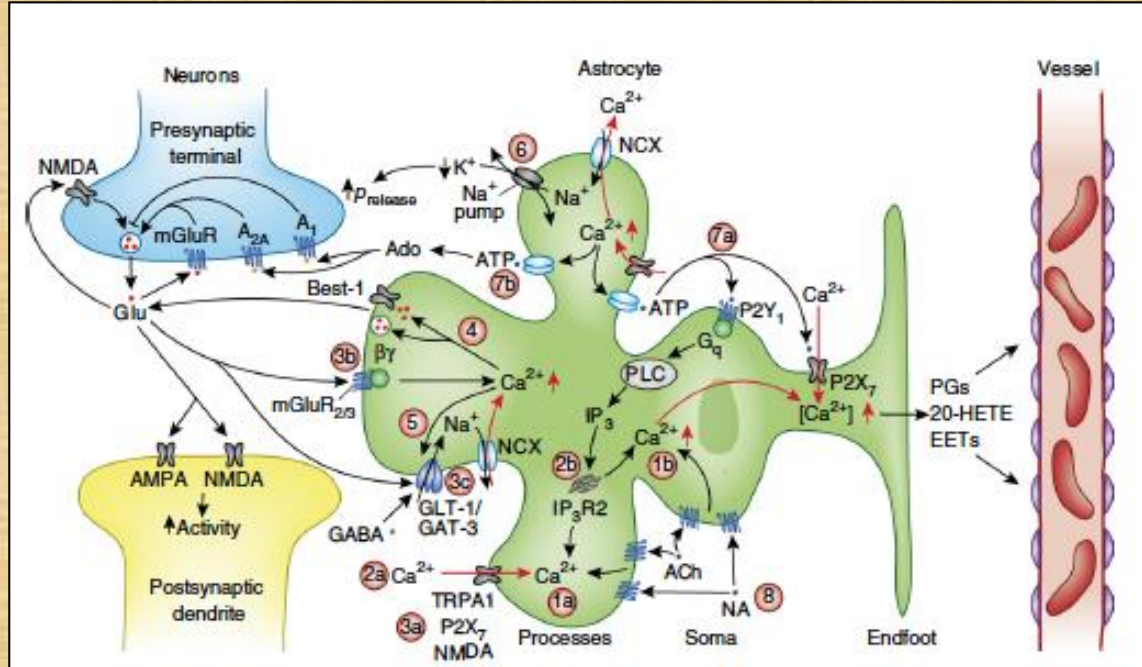
Astrocyte



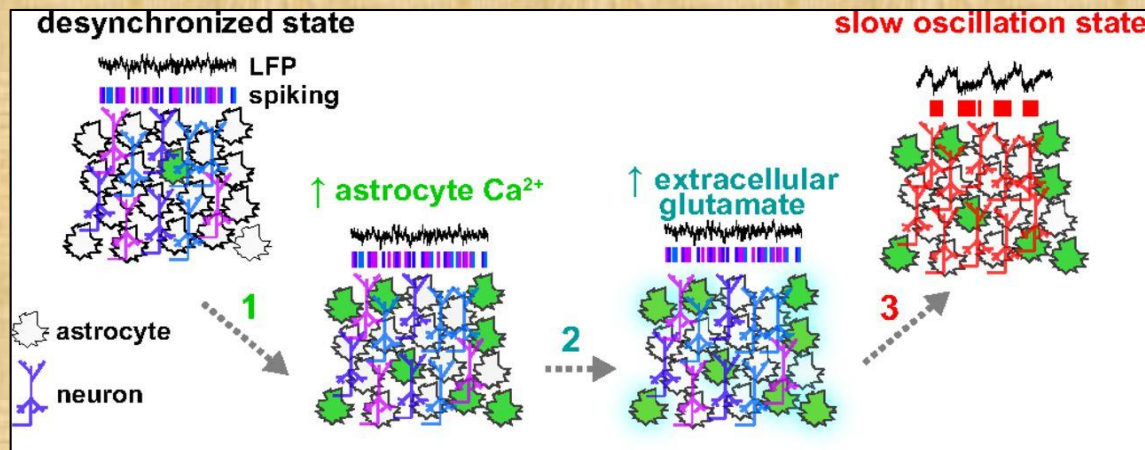
Astroglial Ca^{2+} controls neuronal activity



Srinivasan et al., 2015



Narges Bazargani & David Attwell, 2016



Kira Poskanzer and Rafael Yuste, 2016

Dopamine Elevates and Lowers Astroglial Ca^{2+} Through Distinct Pathways Depending on Local Synaptic Circuitry

Alistair Jennings,¹ Olga Tyurikova,^{1,2} Lucie Bard,¹ Kaiyu Zheng,¹ Alexey Semyanov,^{2,3} Christian Henneberger,^{1,4,5} and Dmitri A. Rusakov^{1,2}

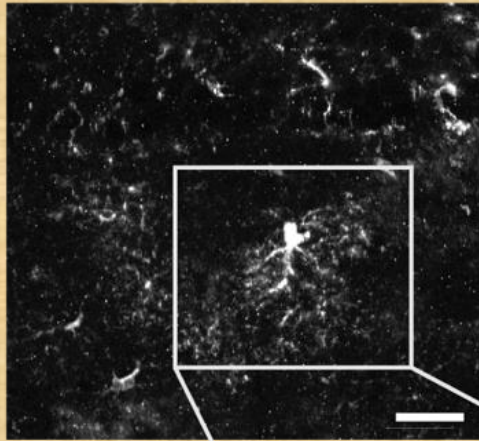
LETTER

doi:10.1038/nature20145

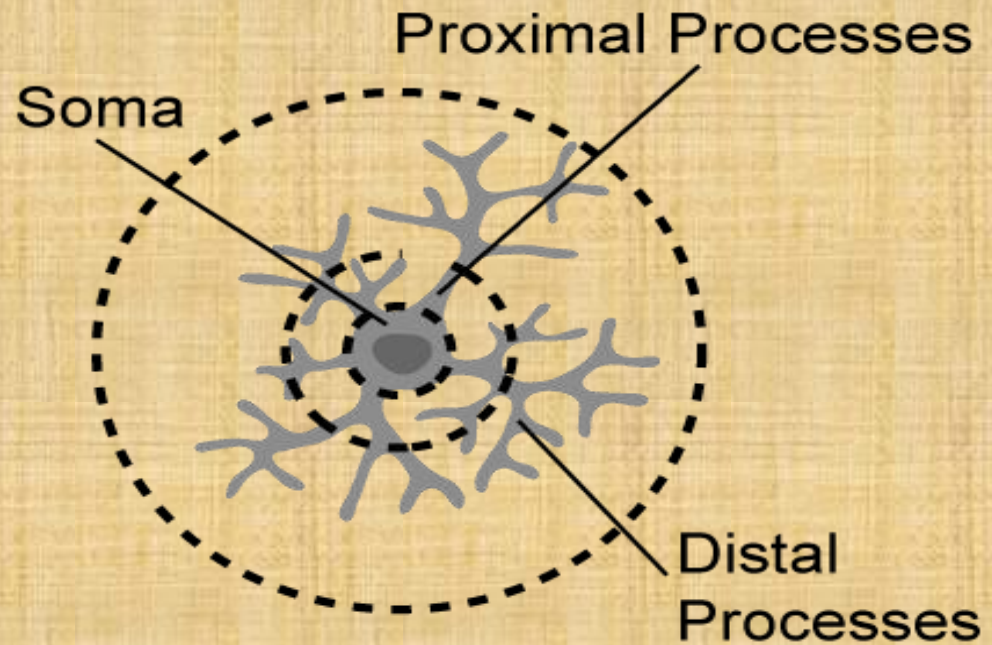
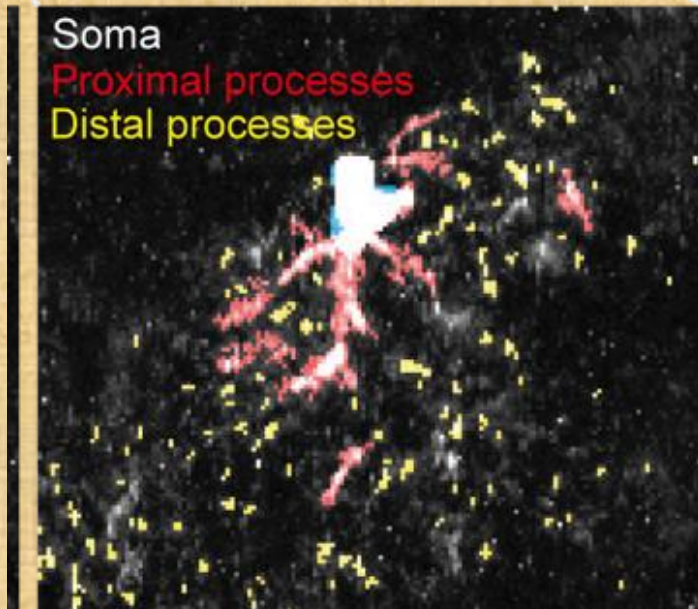
Neuromodulators signal through astrocytes to alter neural circuit activity and behaviour

Zhiguo Ma¹, Tobias Stork¹, Dwight E. Bergles² & Marc R. Freeman^{1†}

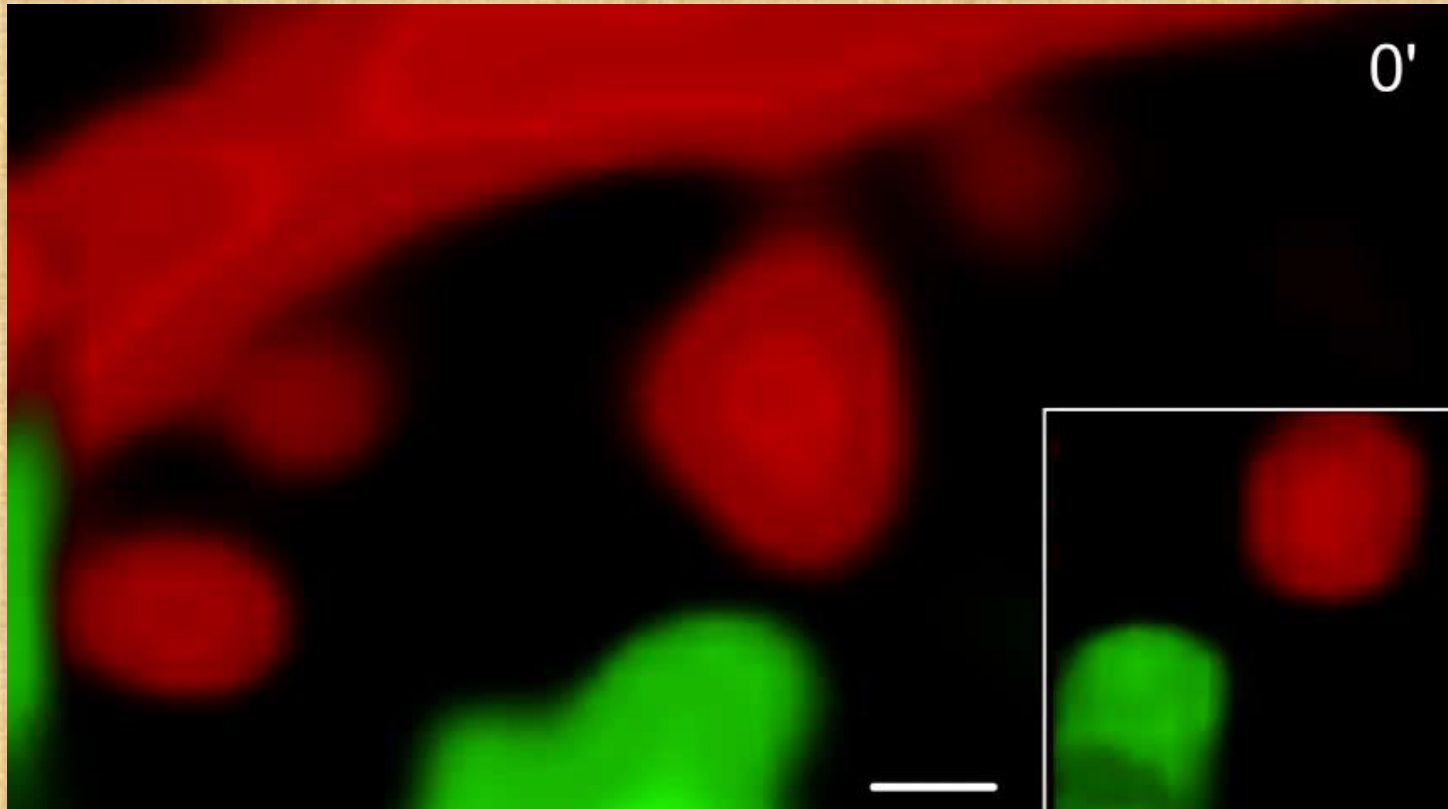
Multiscale astrocyte organization



Interactive segmentation



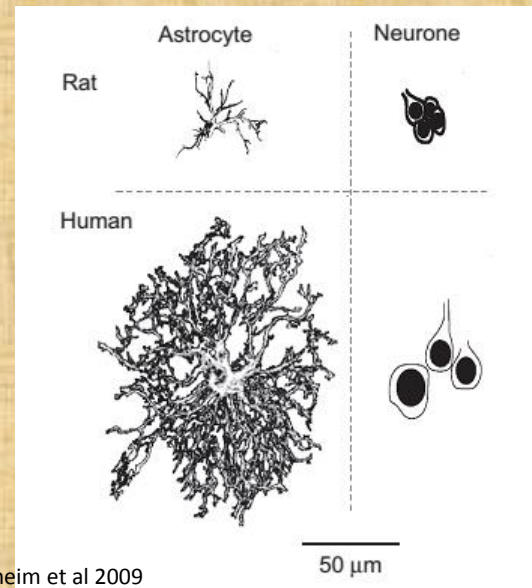
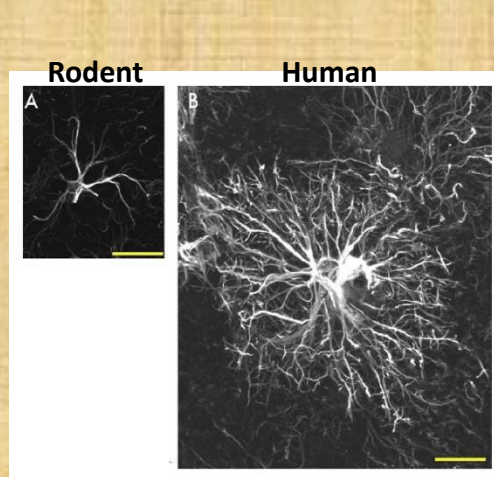
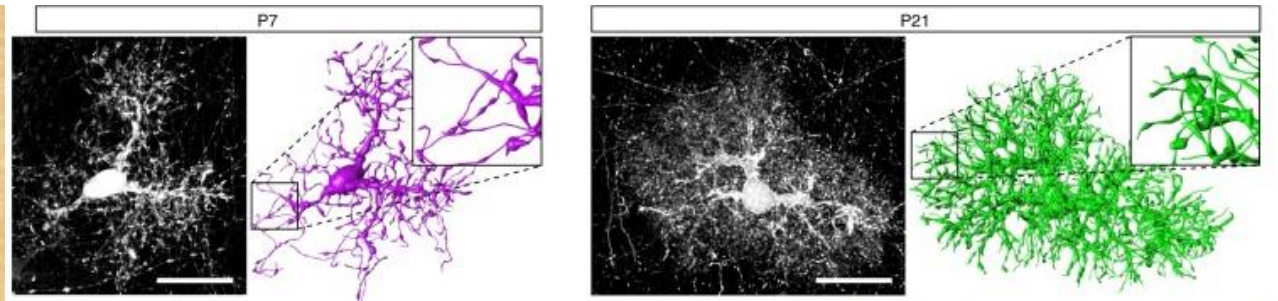
PAPs extending toward a dendritic spine



Astrocytes
Neurons

Haber M. et al 2006

Astrocytes during development and in humans

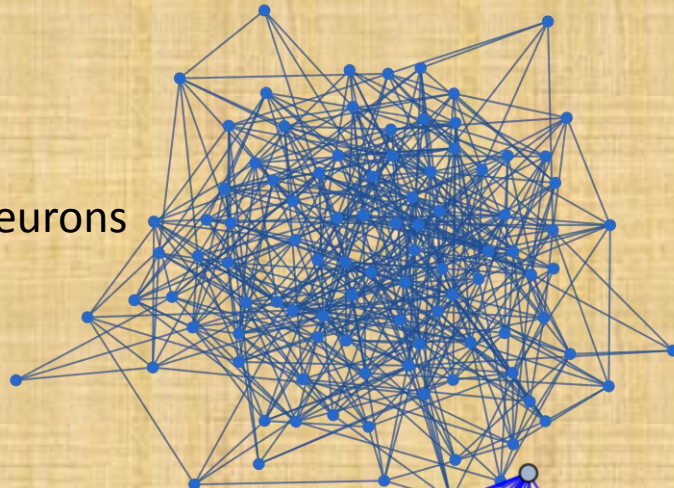


Oberheim et al 2009

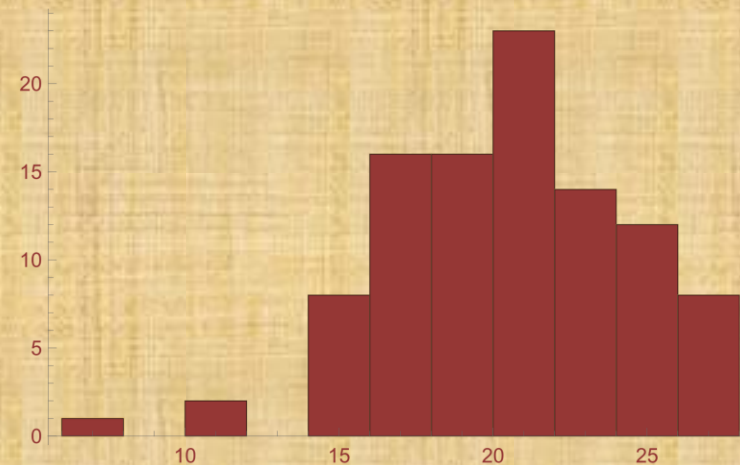
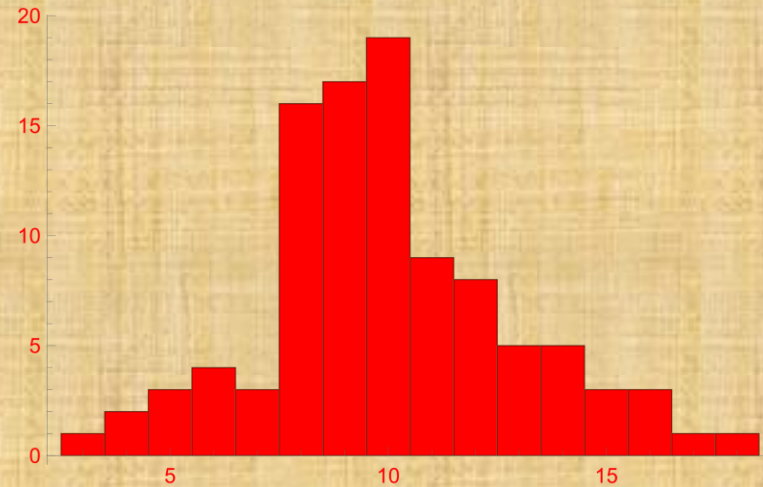
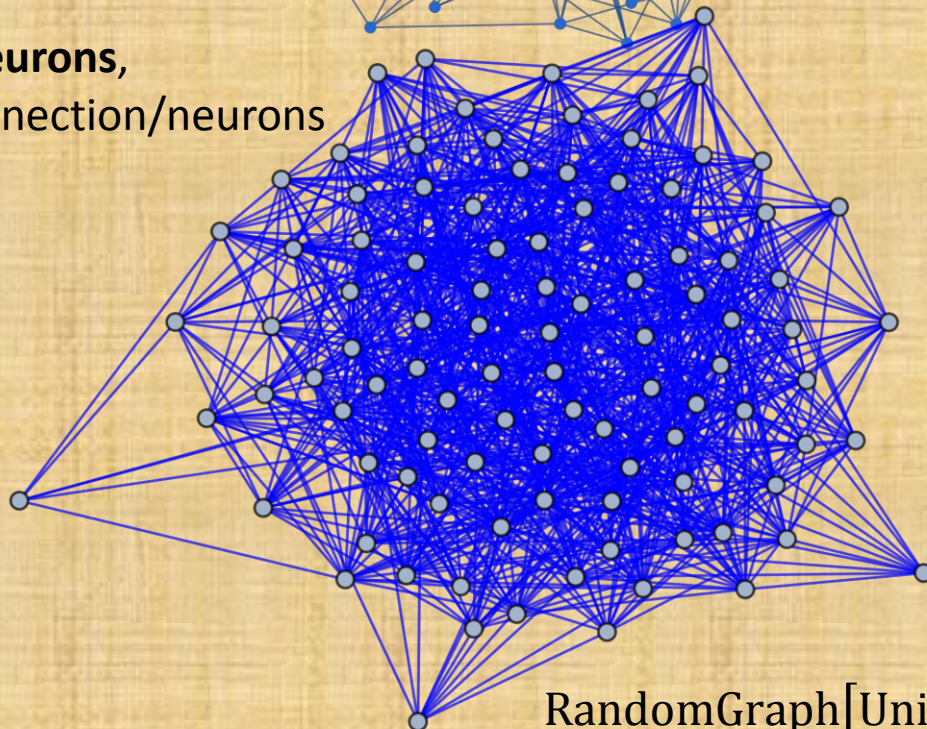
Generating network in Mathematica

Number of neurons/astrocyte (50 microns)

100 neurons,
5 connection/neurons



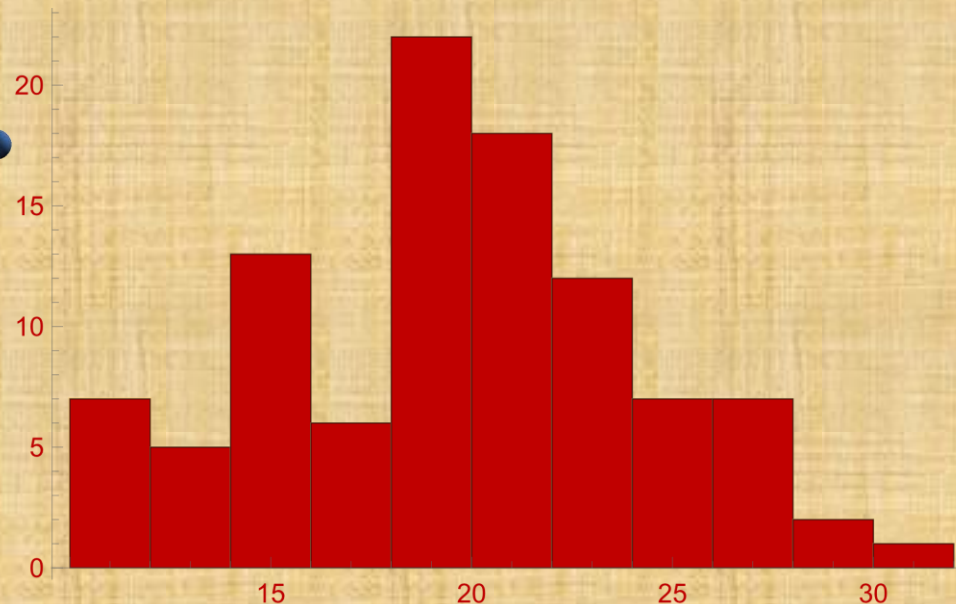
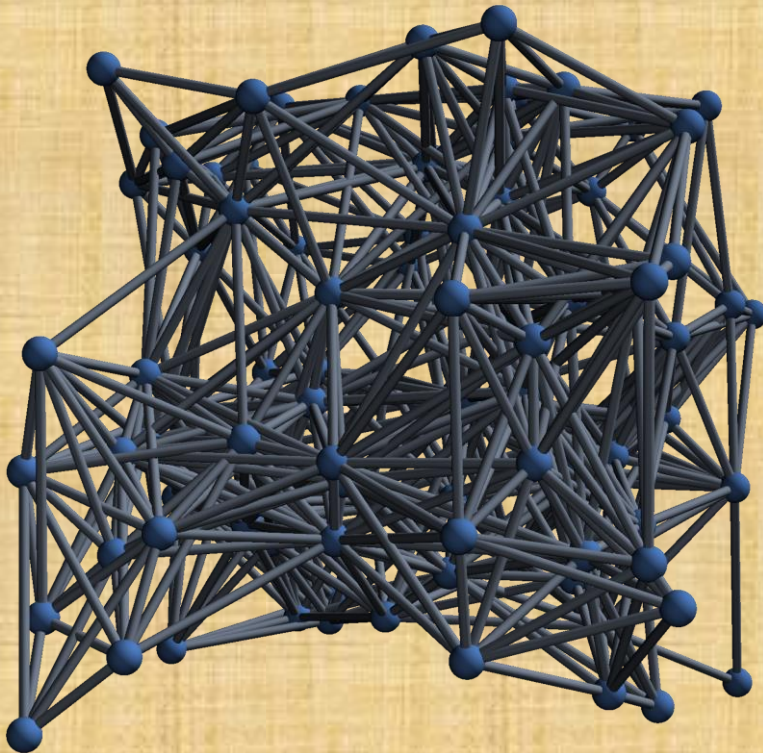
100 neurons,
10 connection/neurons



`RandomGraph[UniformGraphDistribution[100,2000]]`

Generating network in Mathematica

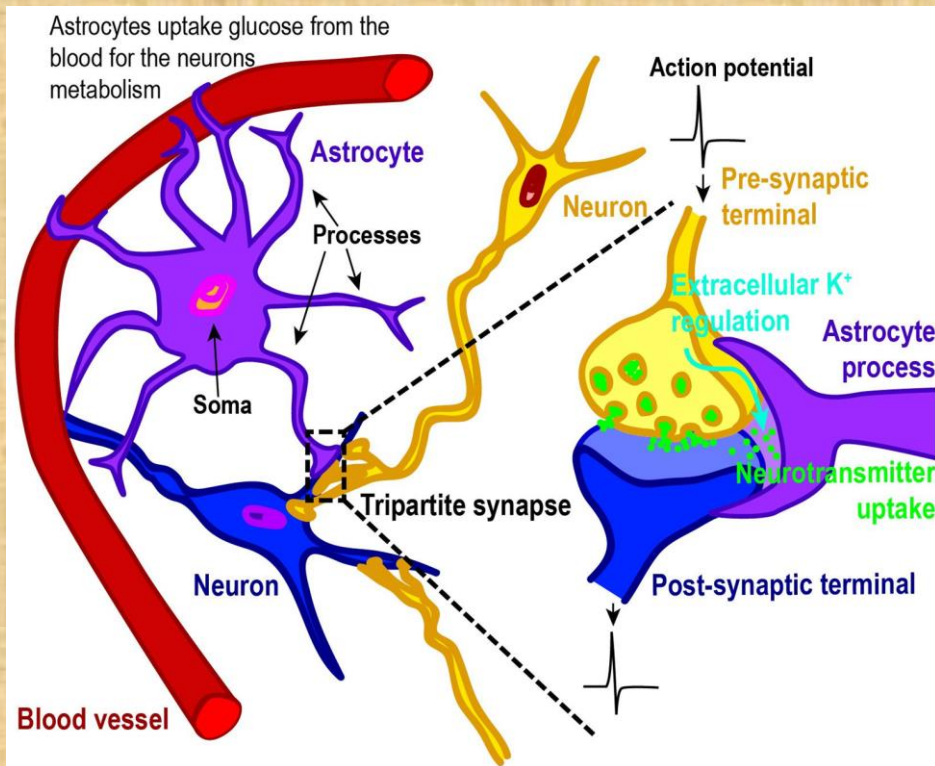
```
h=RandomGraph[SpatialGraphDistribution[100,.4,3]]
```



```
h=RandomGraph[SpatialGraphDistribution[100,.4  
VertexDegree[n]  
,3]] Histogram[%57]
```

Project: modeling 2 interacting networks: regulation of ions during BVI: stop blood flow on neuronal activity

Summary: astroglial networks



Astrocytes

-connected in a network by **gap junctions** (through proteins called Connexin 30-43)

regulate neuronal activity through:

- **Metabolism** (astrocyte-neuron lactate shuttle)
- **Neurotransmitters** uptake (Glutamate)
- **Extracellular K⁺** uptake (*Sibille et al, J Physiology, 2013*)[*shown later*]
- **influences bursting**, neuronal dynamics

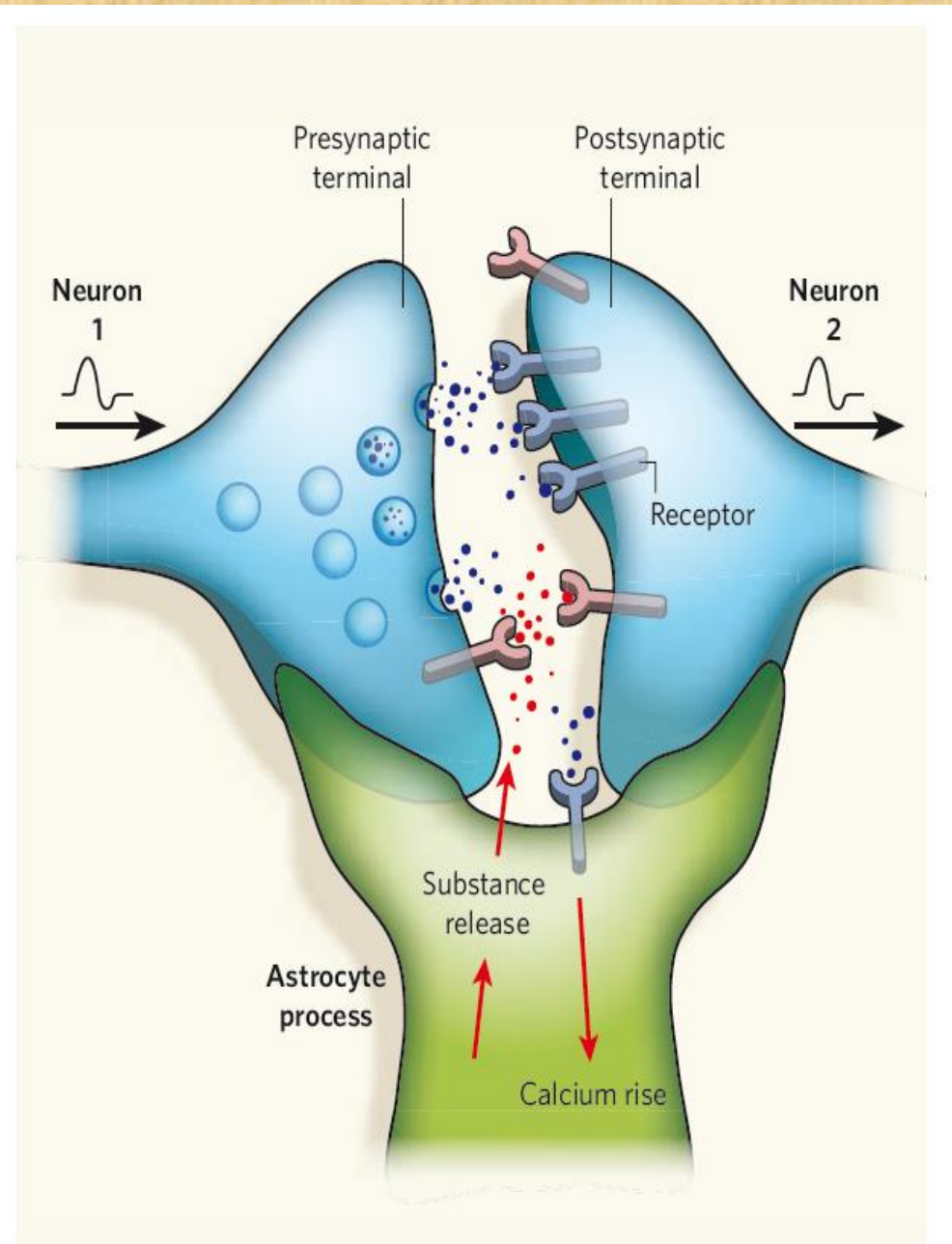
Why modeling astrocyte (individual and network)

1. Account for Astro neuronal interaction [not necessary specific tools].
2. Make sense of complex experiments and determine the role of each components
3. Modeling ion fluxes such Potassium regulation [Difficult: coarse-grained model—compartment: ECS/Neuron/Glia/Blood vessel/Microglia/..
4. Modeling at synaptic level [glutamate re-uptake: tripartite synapse (Freche, Plos 2011 & Nat Neuro2014)
5. Which component in astrocytes modulate burst activity (direct or indirect)
6. How astrocytic networks are really operating (are they specific paths? Or like a uniform sponges) --functional from time series--.
7. How astrocytes “sense” neuronal activity?→ astrocyte Protrusion Modeling Voltage [electrodiffusion] in thin domains.

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Modeling tripartite synapse

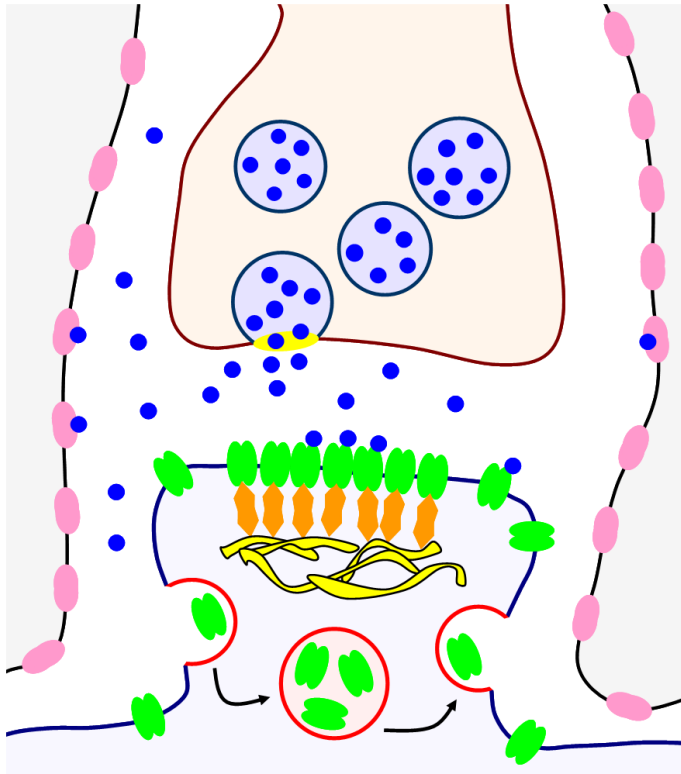


How to model synapses

What we take into account here:

- vesicle release
- AMPAR trafficking
- glutamate transport of glial cells
- endo/-/exocytosis of AMPARs

⇒ **computational model**



How to compute the synaptic current

$$I_{post}(t) = \int \sum_k \gamma_k(t) N_k(x, t) p(k, x, t) dx \Delta V$$

γ_k = Conductivity of type k-receptor

Depends on molecular interactions

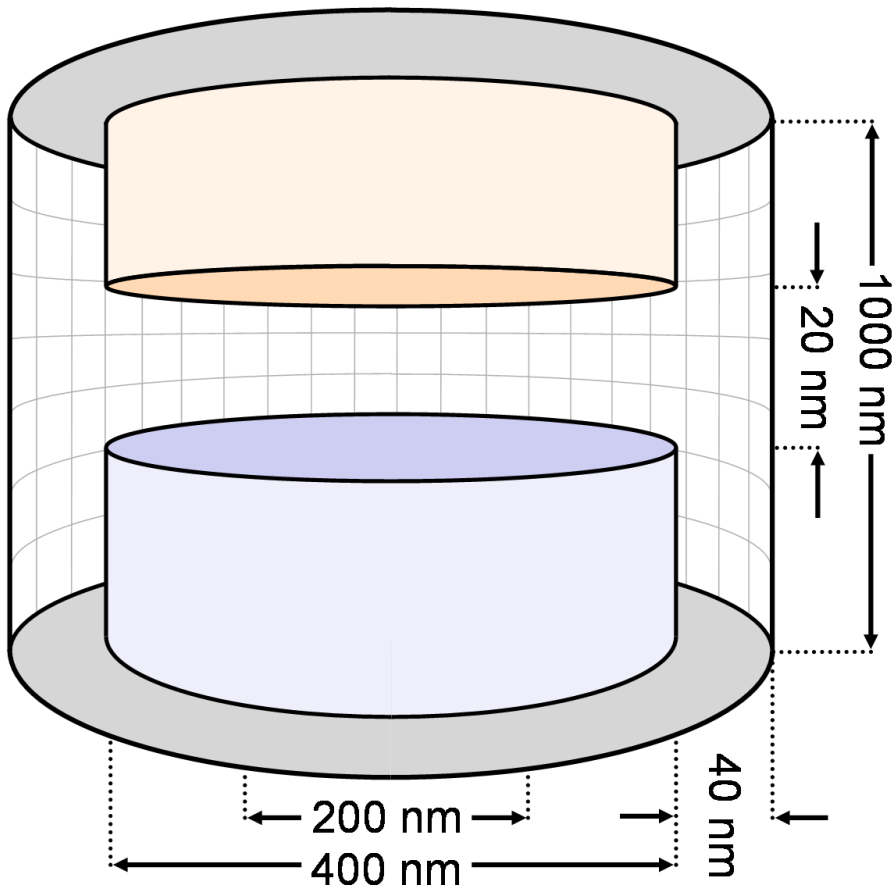
$N_k(x, t)$ = # k-receptors at position x

Continuously vary at different time scales

$p(k, x, t)$ = Pr{Receptor k at x opens at time t }

-diffusion in the cleft and intrinsic properties of receptors
-the organization of the PSD, Active Zone

Geometry



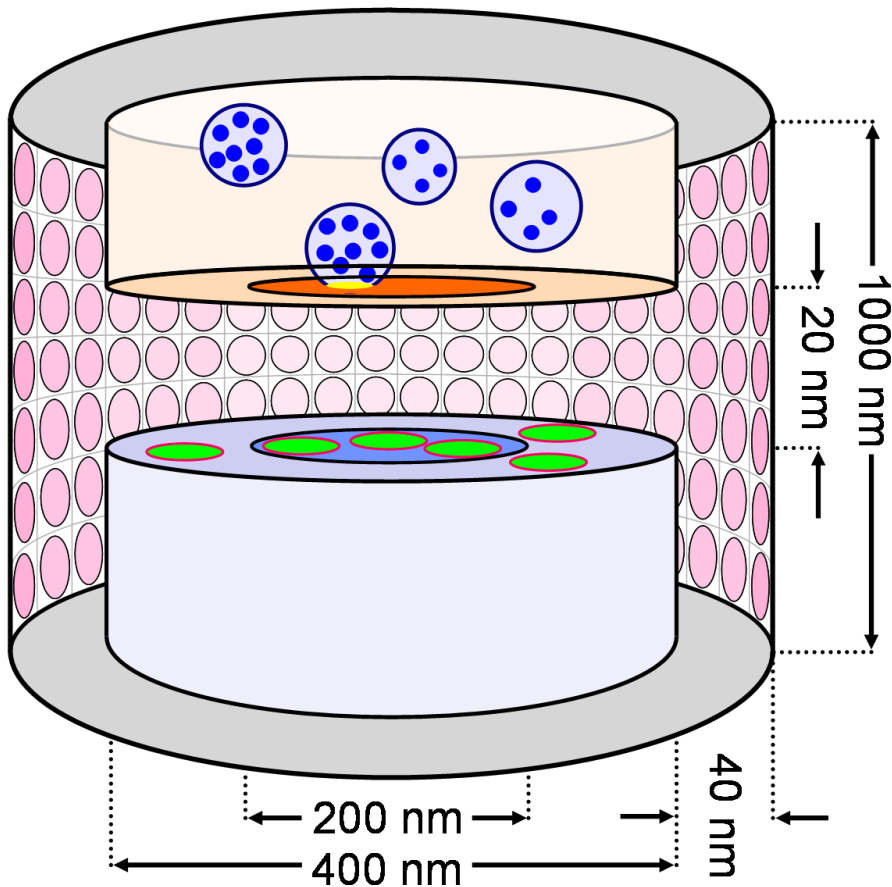
Presynaptic, postsynaptic terminal:
two coaxial cylinders

glial sheath:
surrounding coaxial cylinder surface

distance to glial sheath:
10 nm to 200 nm

cleft height:
10 nm to 40 nm

Functionality

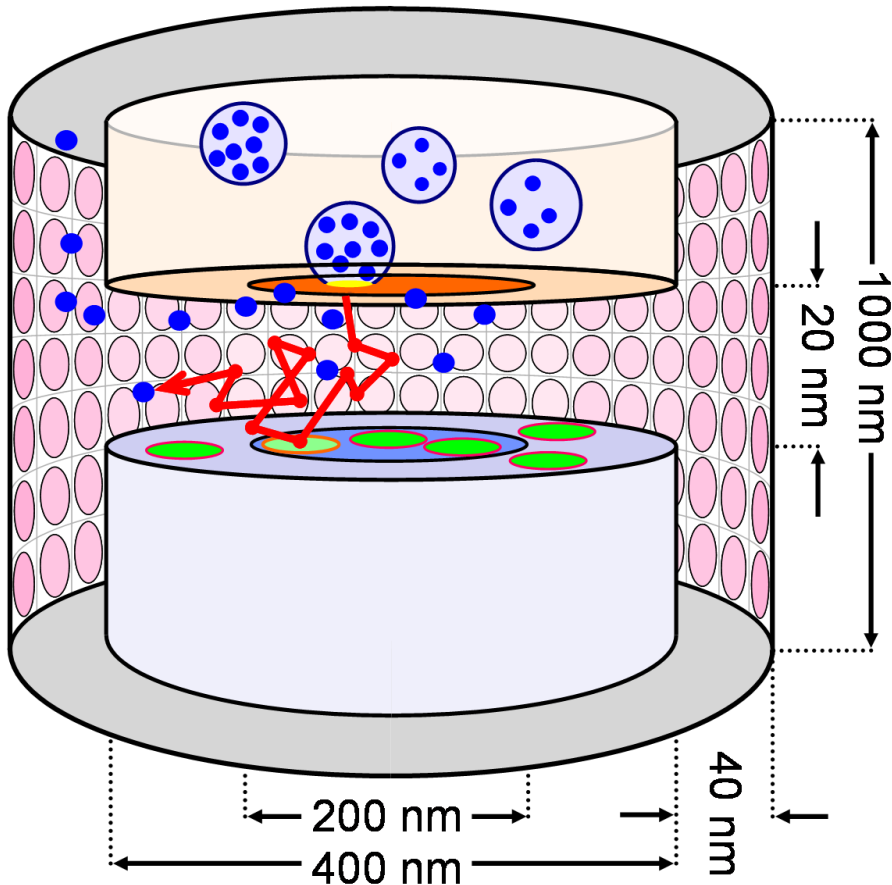


Vesicles, active zone

PSD with AMPARs

glial transporters

Monte-Carlo (stochastic) simulations



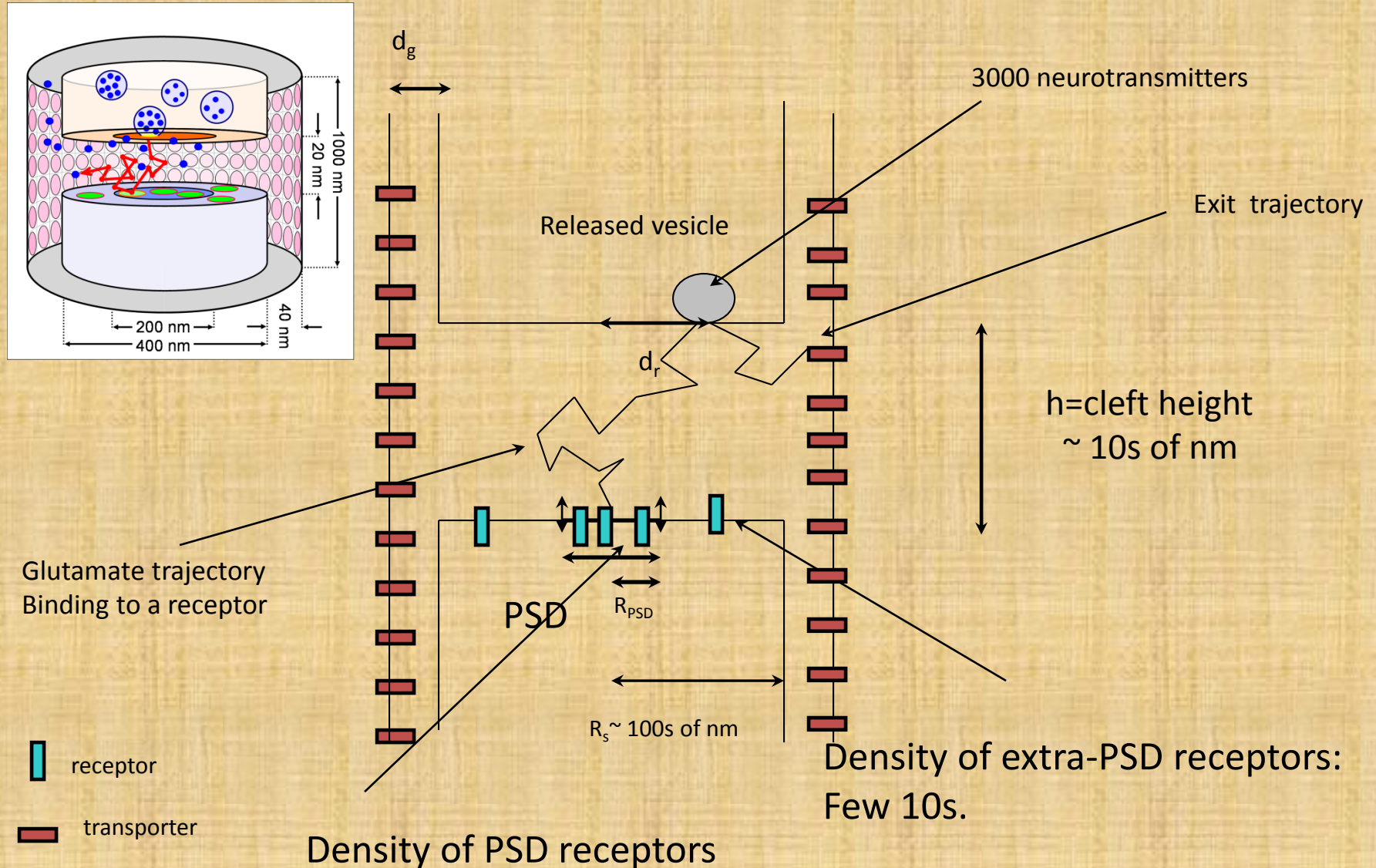
Sample single trajectories

Glutamate diffusion:

$$D = 0.2 \mu\text{m}^2 / \text{ms}$$

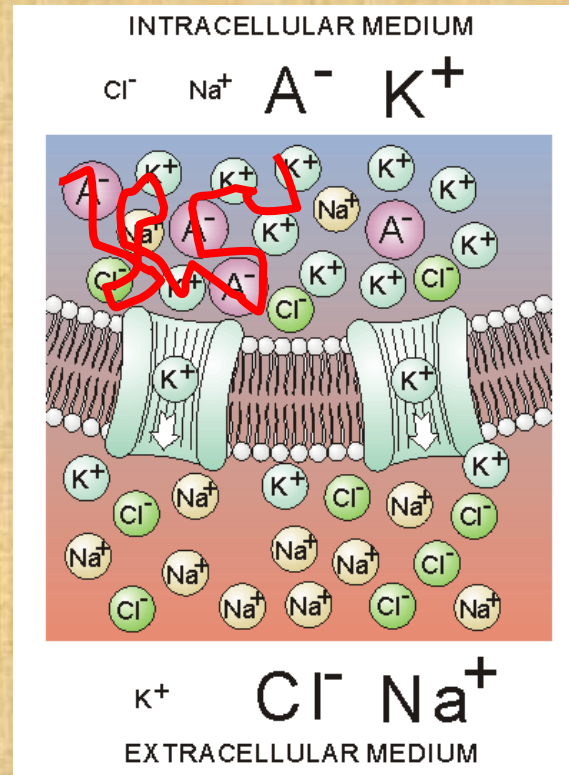
Glutamate molecules can interact with **receptors** and **transporters**

Detailed modeling of synaptic transmission



Langevin description of a particle (molecule)

Particle $X(x,t)$



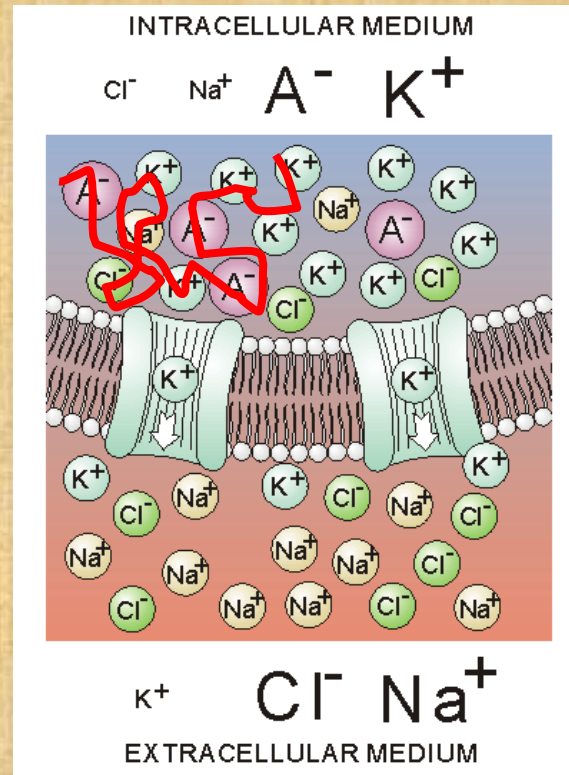
— trajectory

- electrostatic interaction $V'(x)$

Conclusion: Stochastic description of a single particle

Langevin description of a particle (molecule)

Particle $X(x,t)$



— trajectory

$$\ddot{x} + \gamma \dot{x} + V'(x) = \underbrace{\sqrt{2\varepsilon\gamma}}_{\text{Random noise modeled as Brownian}} \dot{w}$$

Acceleration Friction force Potential well or drift Random noise modeled as Brownian

- electrostatic interaction $V'(x)$

Conclusion: Stochastic description of a single particle

Modeling particle trafficking: using Langevin dynamics

$$\ddot{x} + \gamma \dot{x} + V'(x) = \sqrt{2\varepsilon\gamma} \dot{w} \quad 1908 \text{ Langevin}$$

$$\gamma \longrightarrow \infty$$

$$\dot{x} + \frac{V'(x)}{\gamma} = \sqrt{2\frac{\varepsilon}{\gamma}} \dot{w} \quad 1914 \text{ Smoluchowski}$$

$$\gamma = Cte$$

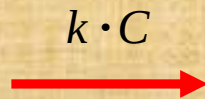
Conclusion: equation for a continuous stochastic particle

- Chandrasekar, RMP, 1945
- Z. Schuss, Stochastic Processes Wiley 1980
- Z. Schuss, Theory and Applications of Stochastic Processes Springer 2010
- D. Holcman Z. Schuss, Stochastic Narrow Escape, Springer 2015

AMPA-receptors finite-state Markov chains

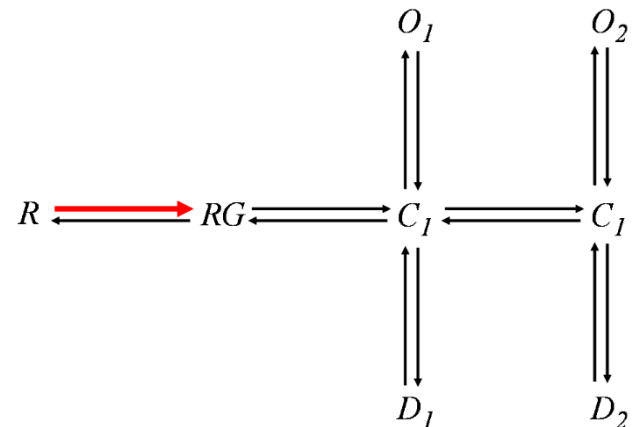
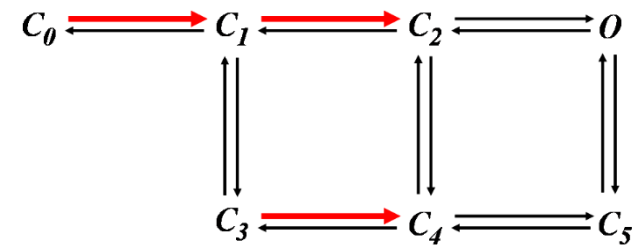
Kinetic schemes:

“good fit” of parameters for
finite-state Markov chains with
concentration-dependent rates

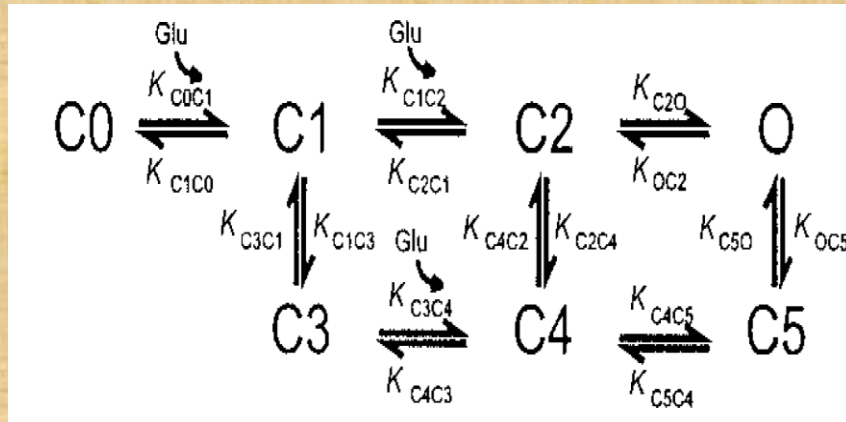


Jonas-Major-Sakmann 1993
CA3 pyramidal neurons

Milstein-Nicoll 2007
cerebellar granule cells



Markov description of AMPAR dynamics

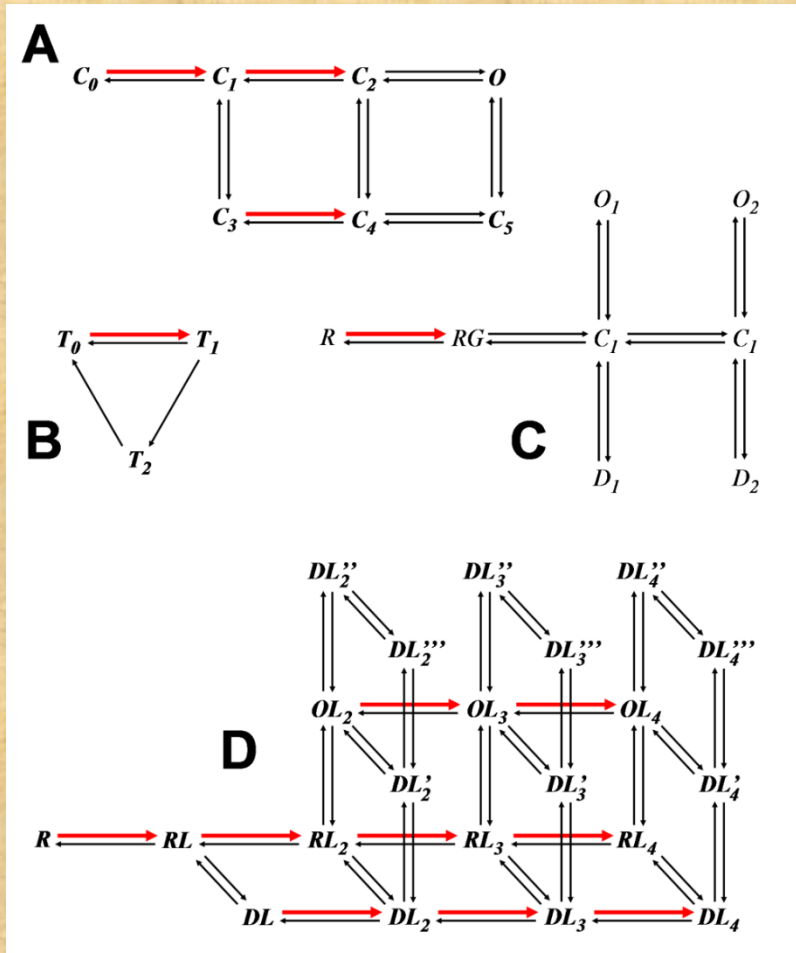


Jonas J. Physiol. 472 (1993), 615-663

Limitations:

- Need 2 glutamates only.
- Fitted constants.
- Concentration not # molecules:
problem of conversion

Examples of Markov'chains for receptors and transporters



A: The Jonas-Sakmann AMPAR scheme

B: The transporter scheme

C: The Milstein-Nicoll AMPAR scheme (no TARP ligation)

D: The Raghavachari-Lisman AMPAR scheme

Rates

Rates for the schemes:

JS scheme		MN scheme		Transporter scheme	
$k_{C_0C_1}$	$4.59 \cdot 10^6 M^{-1} s^{-1}$	$k_{R,RG}$	$1 \cdot 10^7 M^{-1} s^{-1}$	$k_{T_0T_1}$	$1.8 \cdot 10^7 M^{-1} s^{-1}$
$k_{C_1C_0}$	$4.26 \cdot 10^3 s^{-1}$	$k_{RG,R}$	$5 \cdot 10^4 s^{-1}$	$k_{T_1T_0}$	$1.8 \cdot 10^9 s^{-1}$
$k_{C_1C_2}$	$2.84 \cdot 10^7 M^{-1} s^{-1}$	k_{RG,C_1}	$3.65 \cdot 10^4 s^{-1}$	$k_{T_1T_2}$	$1.8 \cdot 10^9 s^{-1}$
$k_{C_2C_1}$	$3.26 \cdot 10^3 s^{-1}$	$k_{C_1,RG}$	$4.55 \cdot 10^3 s^{-1}$	$k_{T_2T_0}$	$2.57 \cdot 10^8 s^{-1}$
k_{C_2O}	$4.24 \cdot 10^3 s^{-1}$	$k_{C_1C_2}$	$3 \cdot 10^2 s^{-1}$		
k_{OC_2}	$9.00 \cdot 10^2 s^{-1}$	$k_{C_2C_1}$	$1 \cdot 10^4 s^{-1}$		
$k_{C_1C_3}$	$2.89 \cdot 10^3 s^{-1}$	$k_{C_1O_1}$	$1 \cdot 10^4 s^{-1}$		
$k_{C_3C_1}$	$3.92 \cdot 10^1 s^{-1}$	$k_{O_1C_1}$	$6 \cdot 10^3 s^{-1}$		
$k_{C_2C_4}$	$1.72 \cdot 10^2 s^{-1}$	$k_{C_2O_2}$	$1 \cdot 10^4 s^{-1}$		
$k_{C_4C_2}$	$0.727 s^{-1}$	$k_{O_2C_2}$	$6 \cdot 10^3 s^{-1}$		
k_{OC_5}	$1.77 \cdot 10^1 s^{-1}$	$k_{C_1D_1}$	$1.1 \cdot 10^3 s^{-1}$		
k_{C_5O}	$4.00 s^{-1}$	$k_{D_1C_1}$	$1 s^{-1}$		
$k_{C_3C_4}$	$1.27 \cdot 10^6 M^{-1} s^{-1}$	$k_{C_2D_2}$	$3 \cdot 10^2 s^{-1}$		
$k_{C_4C_3}$	$4.57 \cdot 10^1 s^{-1}$	$k_{D_2C_2}$	$10 s^{-1}$		
$k_{C_4C_5}$	$1.68 \cdot 10^1 s^{-1}$				
$k_{C_5C_4}$	$190.4 s^{-1}$				

7.2 Simulation of AMPA-receptors and glial transporters

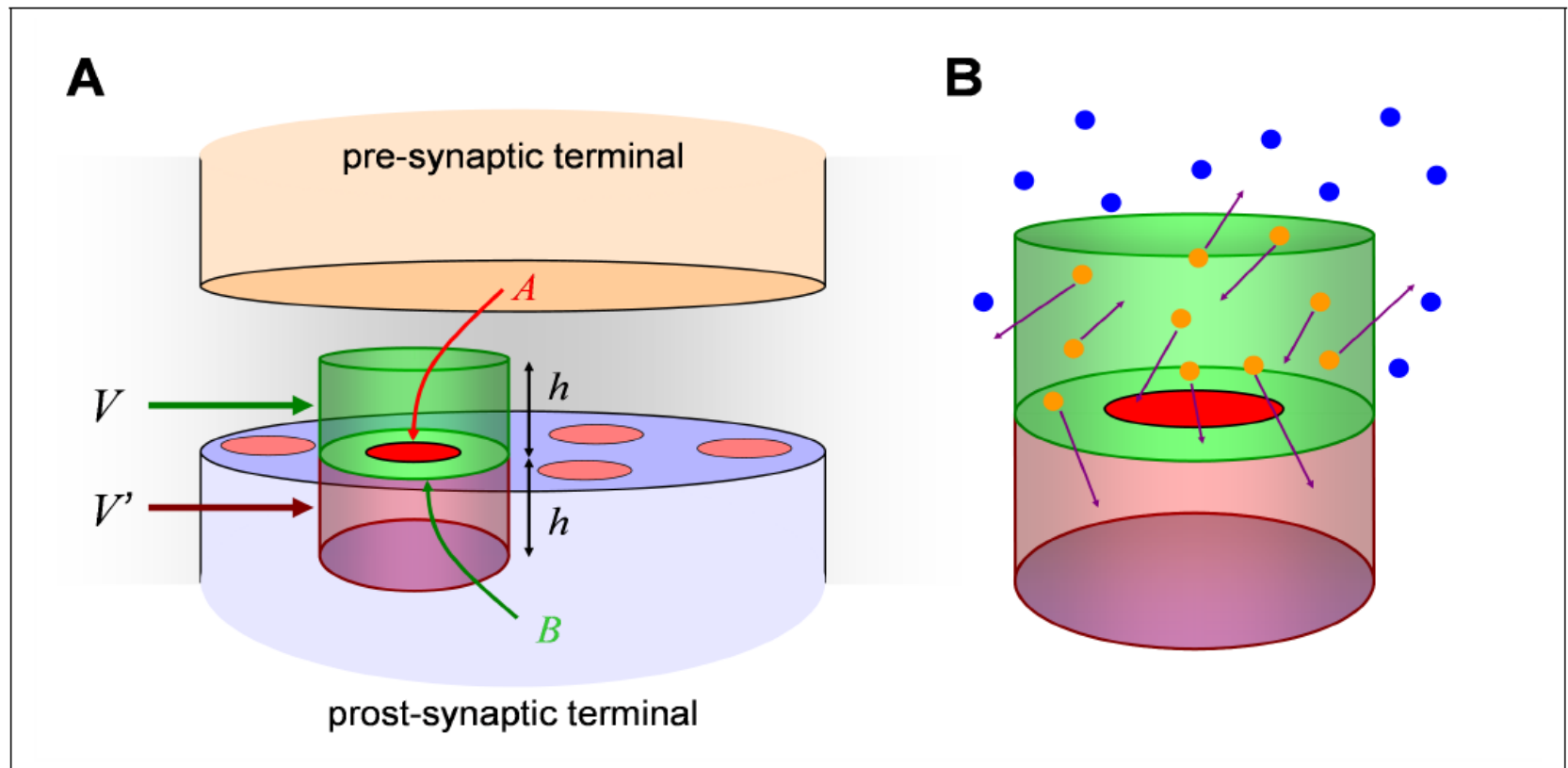
The dynamics of AMPARs and glutamate transporters were modelled by classical Markov chains. The glutamate dependence of the dynamics is taken into account in the transition rates which are proportional to the concentration in the neighborhood of the receptor. To every AMPAR or transporter, we use the probability vectors $p_i(t) := \text{Pr}(\text{state } i \text{ at time } t)$ for $i = 1, \dots, N$ where N is the total number of internal states. The transition probability function $\mathbf{p}(t) = (p_1(t), \dots, p_N(t))$ satisfies the Markov transition equation

$$\mathbf{p}'(t) = \mathbf{p}(t)\mathbf{Q}(C(t)) \quad (12)$$

$$\mathbf{p}(0) = \mathbf{p}_{initial} \quad (13)$$

where $\mathbf{p}_{initial}$ is the initial probability conditions and $\mathbf{Q}$ is the transition matrix which depends on the glutamate concentration $C(t)$. Because some transition rates depend on the glutamate concentration, we shall further characterize the local concentration (amount glutamate near the glutamate binding domain).

7.2.4 The local glutamate concentration



$$p_H = Pr(X_{t+\Delta t} \in V' \text{ and the trajectory hits } A | X_t \in V) \quad (14)$$

where V' is the mirror image of V on the bottom face B . For a molecule starting uniformly distributed in V ,

$$p_H = Pr(X_{t+\Delta t} \in V' \text{ and the trajectory hits } A | X_t \in V) \quad (15)$$

$$= \frac{A}{B} \int_{-\infty}^0 \frac{1}{h} \int_0^h p(2D\Delta t, x-y) dx dy \approx \frac{A}{V} \int_{-\infty}^0 \int_0^\infty p(2D\Delta t, x-y) dx dy = \frac{A}{V} \sqrt{\frac{D\Delta t}{\pi}}, \quad (16)$$

less than h (corresponding to $\Delta t < h^2/6D$). When there are N independent molecules, the number H_t of hits on A during Δt follows a binomial distribution with mean and variance

$$\langle H_t \rangle = N p_H = \frac{N Pr(X_t \in V)}{V} A \sqrt{\frac{D\Delta t}{\pi}} \quad (17)$$

$$\langle\langle H_t \rangle\rangle = N p_H (1 - p_H). \quad (18)$$

Surface calibration

Choosing the surface A for glial transporters. To determine the size of the surface A associated with glutamate binding to a transporter, we use the forward binding rate constant k_{on} for the glutamate molecules. The number of glutamate molecules hitting A during δt is

$$\langle H_t \rangle = k_{on} \langle C_t \rangle \Delta t. \quad (22)$$

which we evaluated using expression (17),

$$\langle H_t \rangle = \langle C_t \rangle A \sqrt{D \Delta t} / \sqrt{\pi}, \quad (23)$$

thus, we find that

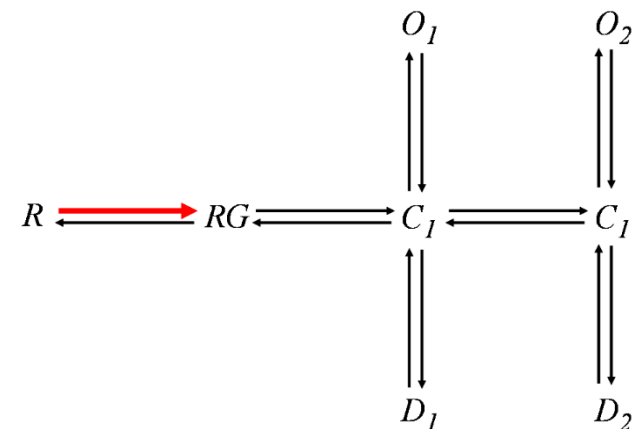
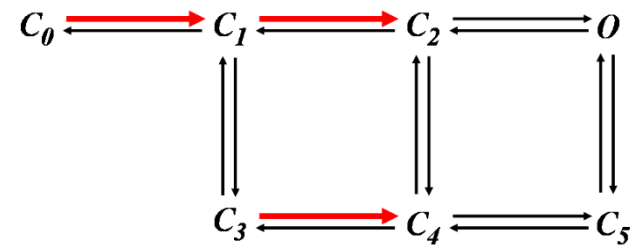
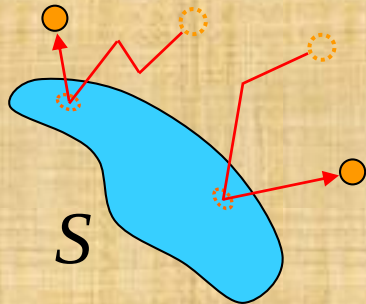
$$A = k_{on} \sqrt{\frac{\pi \Delta t}{D}}. \quad (24)$$

A similar formula was obtained in [2, Formulas (6a), (6b)], [3]. It may happen, however, that A can be too small compared to the mean square displacement of the discretization $\sqrt{2D\Delta t}$ of a single glutamate trajectory. In that case, A has to be enlarged to a disk $\tilde{A}$ with a radius larger than $\sqrt{2D\Delta t}$ and we have to use the rejection probability $A/\tilde{A}$ to single out the additional hits on $\tilde{A}$.

AMPA-receptors

kinetic schemes:

- 1) get local concentration
- 2) update concentration-dependent rates
- 3) solve master equations for current time step
(neglect binding)

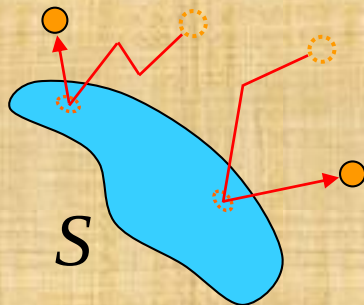


AMPA-receptors

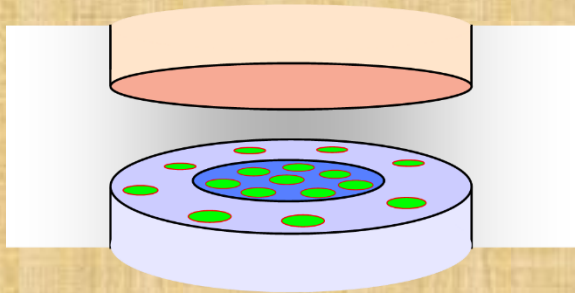
kinetic schemes:

- 1) get local concentration
- 2) update concentration-dependent rates
- 3) solve master equations for current time step
(neglect binding)

All simulated fluctuations
are solely due to
glutamate diffusion
not “channel noise”

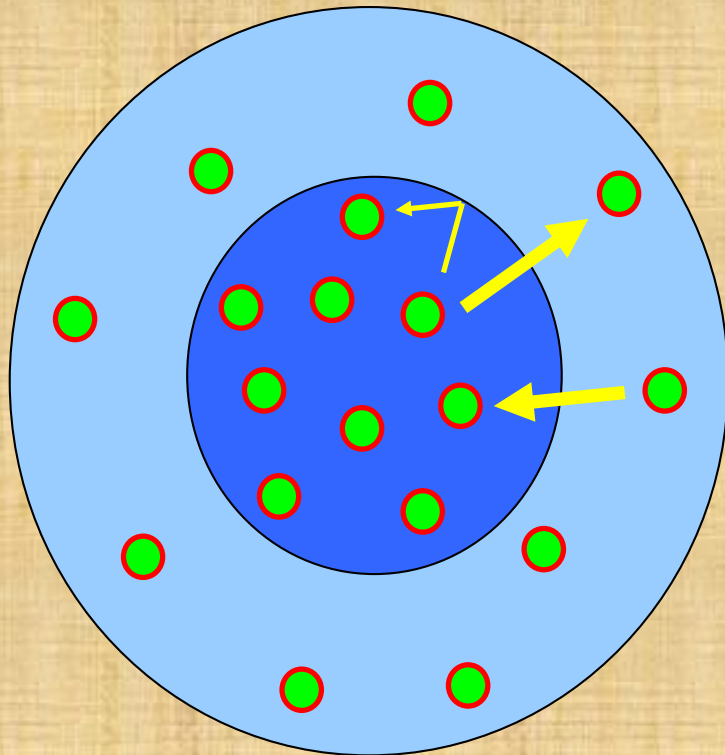


AMPA_Rs: trafficking



AMPA _R s on PSD	100
AMPA _R s outside (“reservoir”)	30

$$D_{\text{AMPA}_R} = 0.1 \mu\text{m}^2 / \text{s}$$



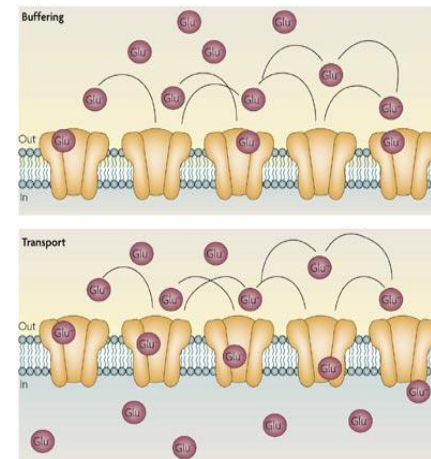
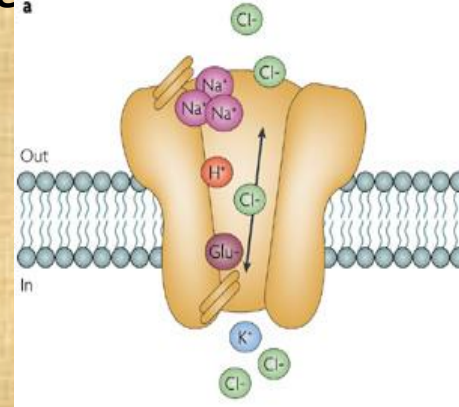
Keeping constant concentrations
== plain model for scaffolding molecules

$$C_{\text{PSD}} > C_{\text{outside}}$$

with passage probabilities

Glutamate transporters: properties conferring the ability to influence synaptic transmission

- High affinity for glutamate
- Fast binding of glutamate
- High density
- 75% hippocampal synapses contacted by GLT containing astrocytic processes
- Low cycling time but buffering of glutamate
- Extrasynaptic location: can alter activation of extrasynaptic GluRs



Nature Reviews | Neuroscience

FSS transporter model (Franks, Stevens, Sejnowski)

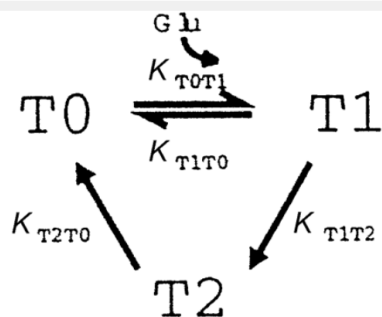
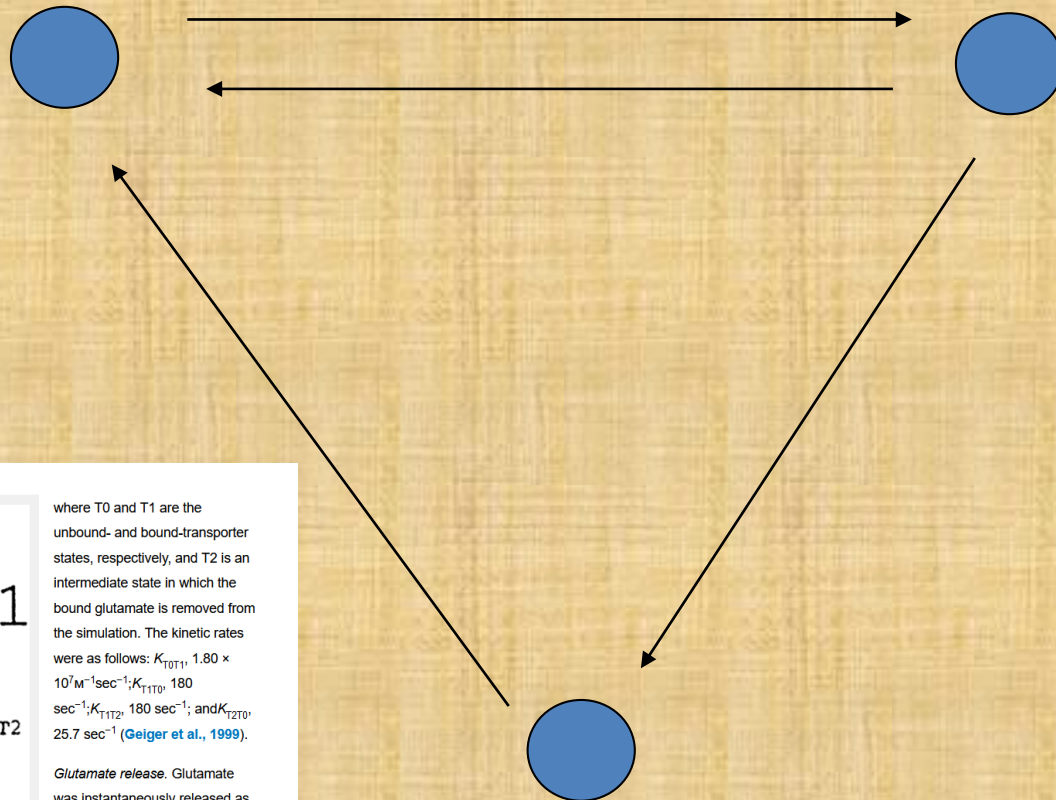
The Journal of Neuroscience, April 15, 2003 • 23(8)

“Independent Sources of Quantal Variability at Single Glutamatergic Synapses”

(3 states)

Free, ready to bind

Bound by glutamate

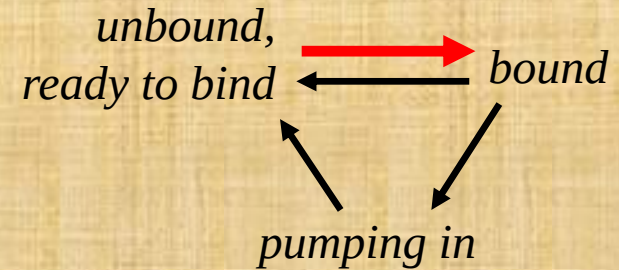
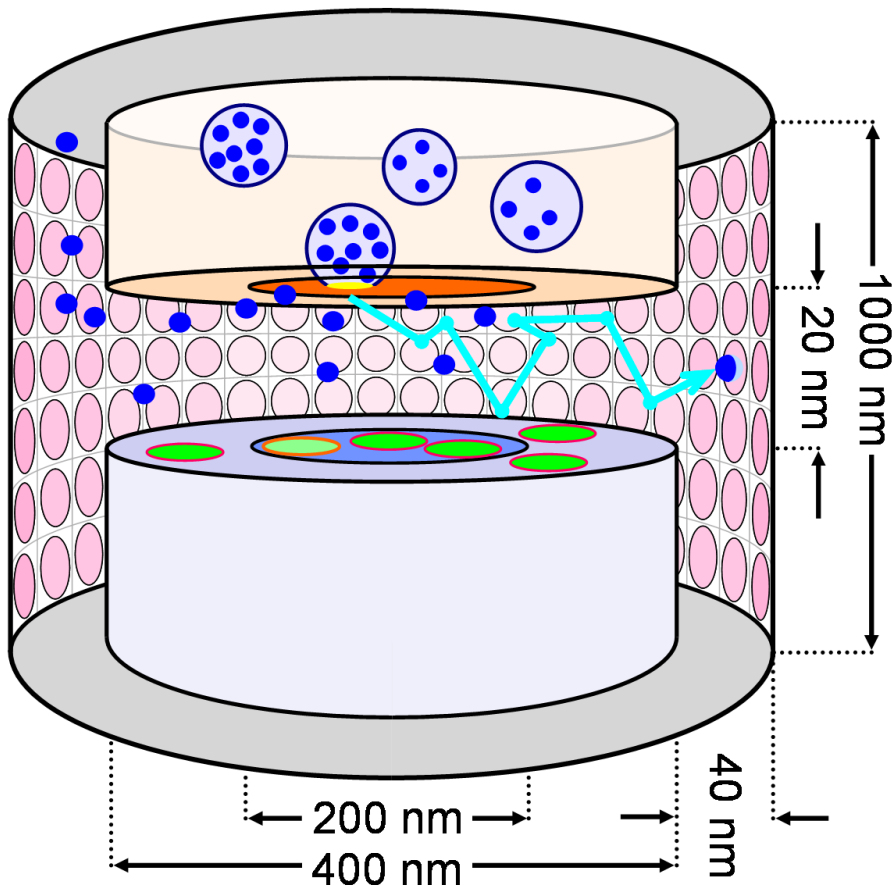


where T0 and T1 are the unbound- and bound-transporter states, respectively, and T2 is an intermediate state in which the bound glutamate is removed from the simulation. The kinetic rates were as follows: K_{T0T1} , $1.80 \times 10^7 \text{ M}^{-1} \text{ sec}^{-1}$; K_{T1T0} , 180 sec^{-1} ; K_{T1T2} , 180 sec^{-1} ; and K_{T2T0} , 25.7 sec^{-1} (Geiger et al., 1999).

Glutamate release. Glutamate was instantaneously released as a point source in the synaptic

Pumping the glutamate

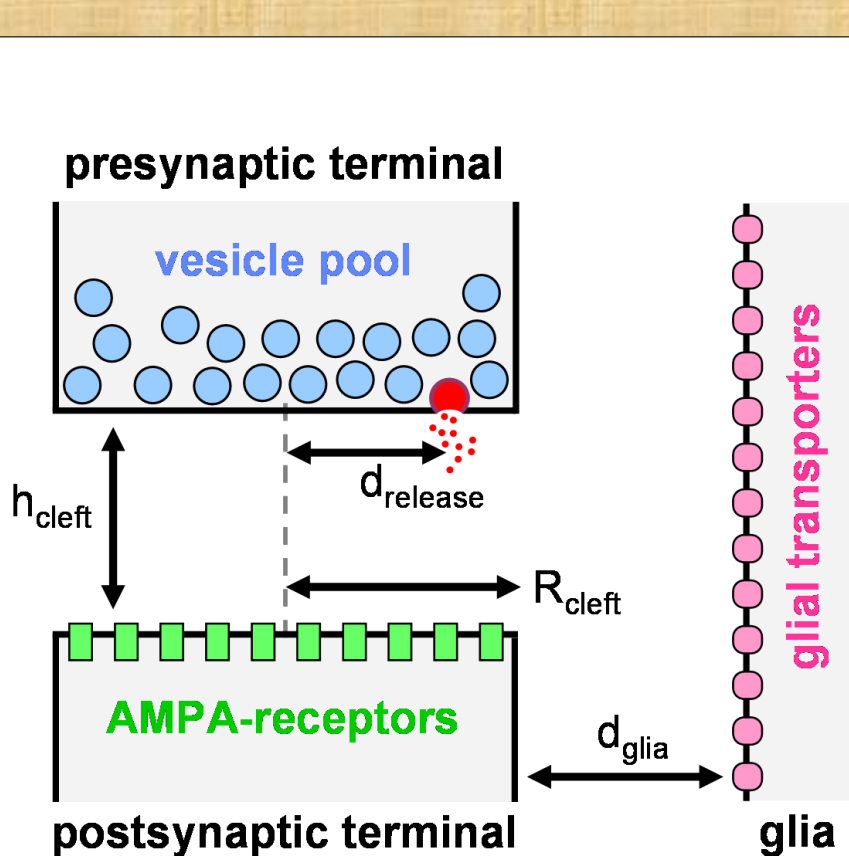
Glial glutamate transporters



(Franks, Stevens, Sejnowski 2003)

transporter density:
2,500 to 10,000 / μm^2

Synapse geometry influences transmitter diffusion



h_{cleft}

20 nm

R_{cleft}

200 nm

d_{glia}

40 nm

d_{release}

uniformly

$n_{\text{transporter}}$
vesicles
released

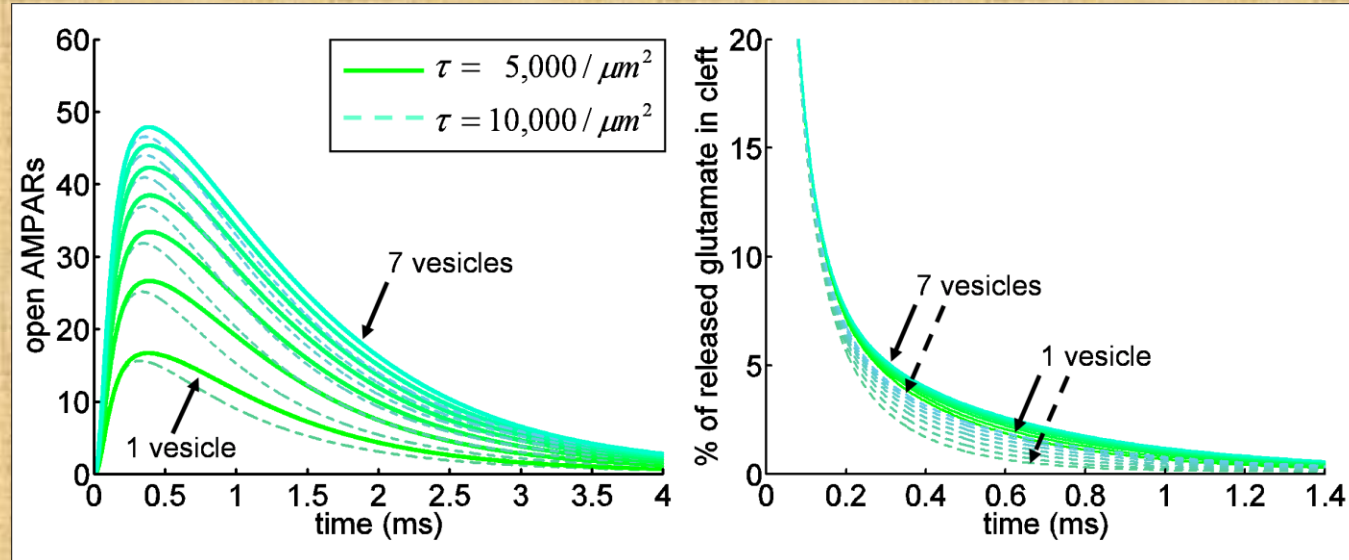
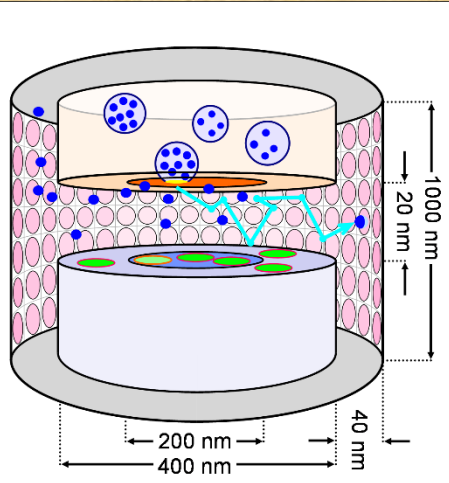
5,000 and 10,000 /
 μm^2
1 to 7

3000 molecules

AMPA 130 (uniformly distr.)

Starting simulations

Transporters: glutamate in cleft



h_{cleft}
 R_{cleft}
 d_{glia}
 d_{release}

20 nm
 200 nm
 40 nm
 uniformly

$n_{\text{transporter}}$
 vesicles released

5,000 and 10,000 / μm^2
 1 to 7

Transporters: extra-cleft glutamate

Clearance time

least time after release at which 90% of released glutamate has been taken up

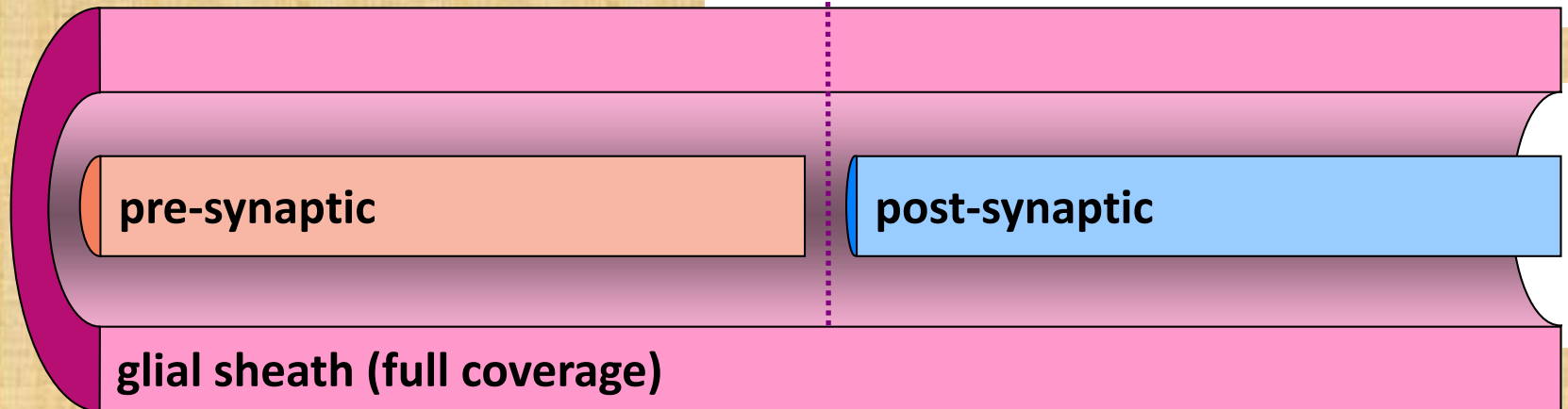
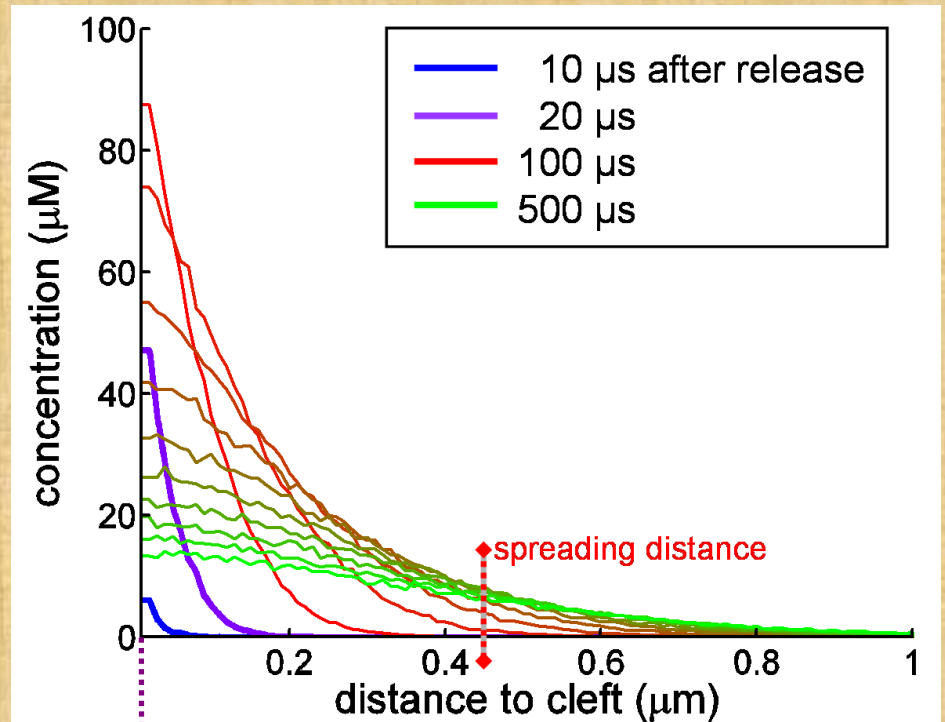
Spreading distance

largest distance from synaptic cleft beyond which only 10% of the released glutamate is found

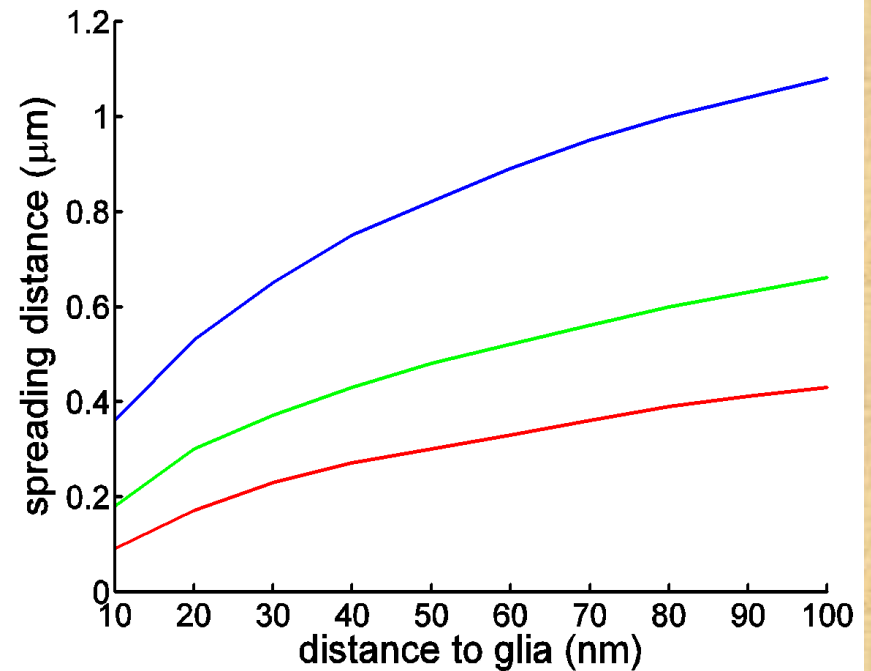
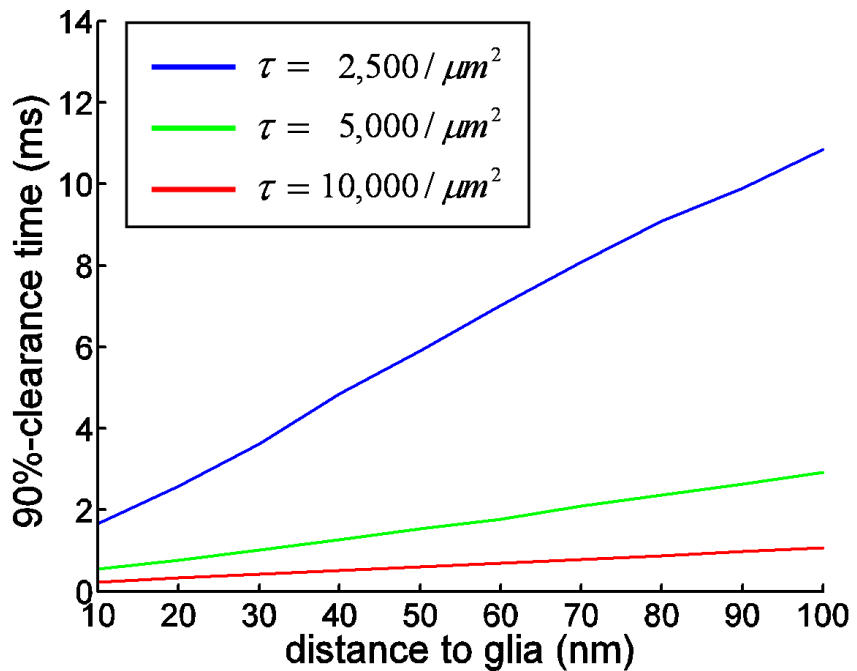
Transporters: extra-cleft glutamate

Example:

d_{glia} 40 nm
 $n_{\text{transporter}}$ 5,000 / μm^2



Transporters: extra-cleft glutamate



h_{cleft}

20 nm

R_{cleft}

200 nm

d_{glia}

10 ... 100 nm

d_{release}

center-top

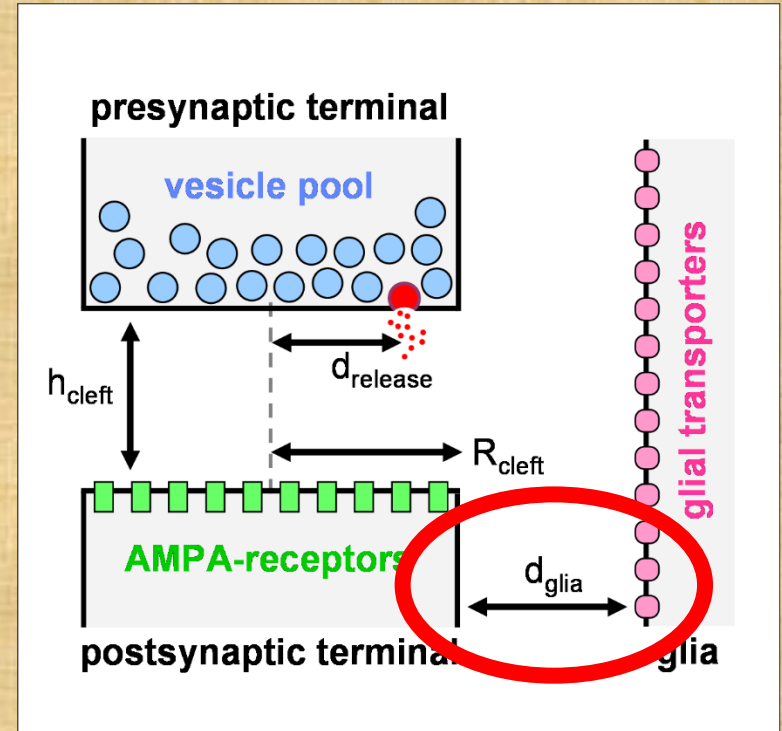
$n_{\text{transporter}}$

2,500 5,000 10,000 / μm^2

vesicles released

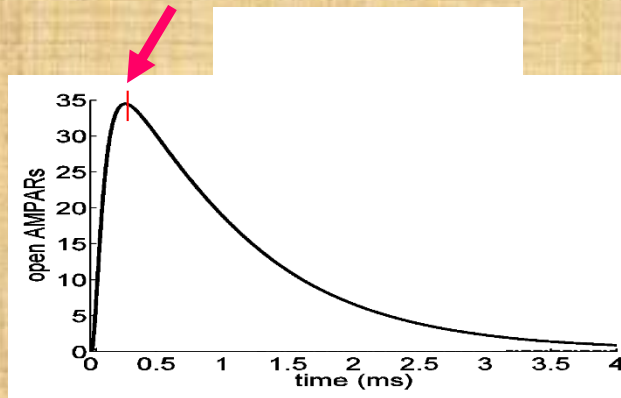
1

Glial distance

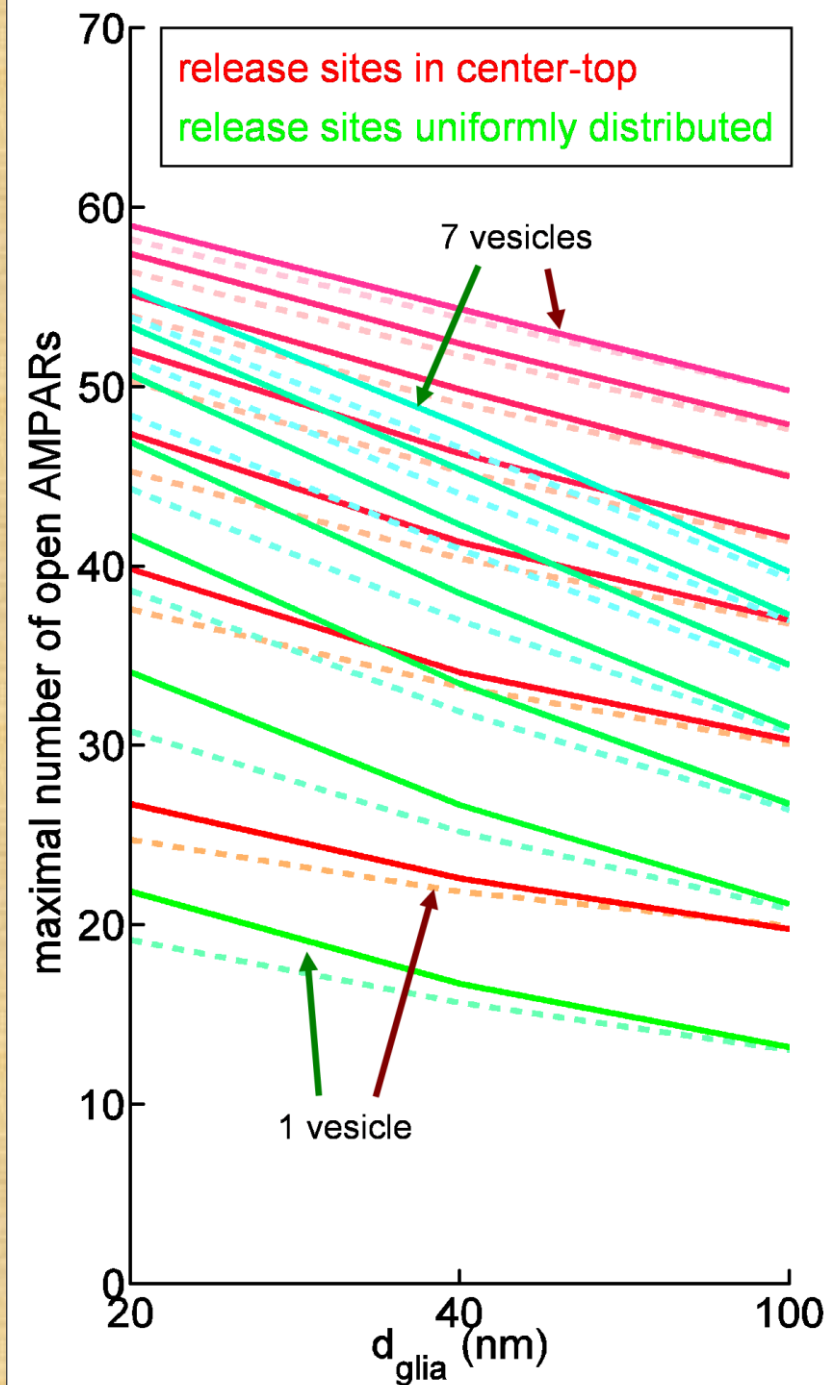


h_{cleft}	20 nm
R_{cleft}	200 nm
d_{glia}	20, 40, 100 nm
d_{release}	center-top, uniformly
$n_{\text{transporter}}$	5,000 and 10,000 / μm^2
vesicles	1 to 7

Glial distance



h_{cleft}	20 nm
R_{cleft}	200 nm
d_{glia}	20, 40, 100 nm
d_{release}	center-top, uniformly
$n_{\text{transporter}}$	5,000 and 10,000 / μm^2
vesicles	1 to 7

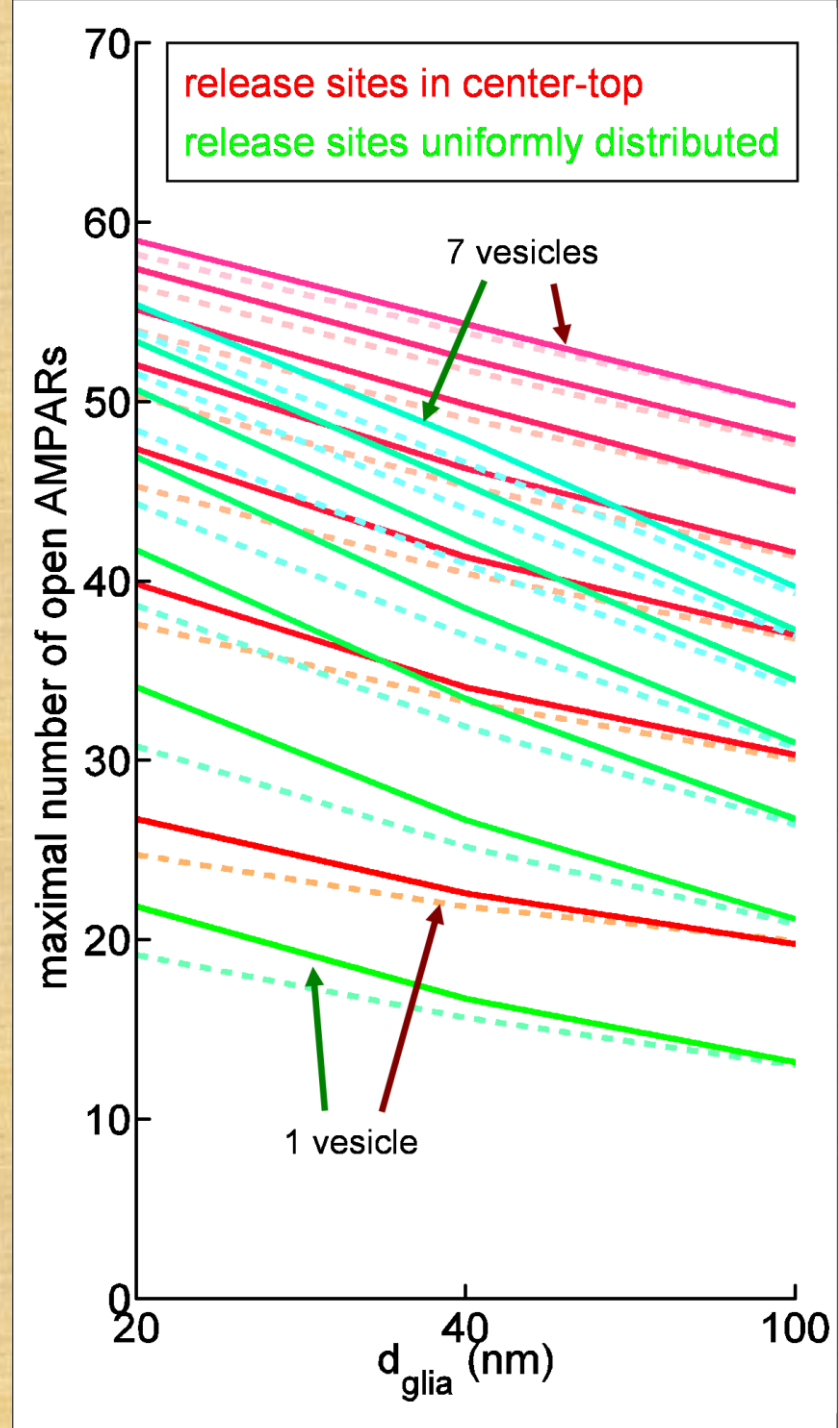


Glial distance

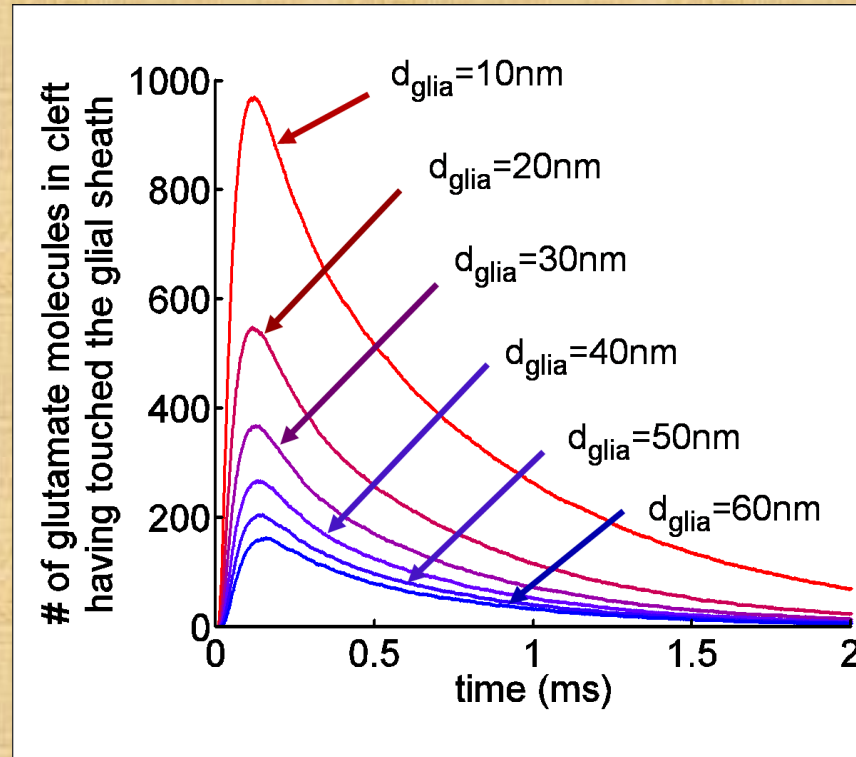
h_{cleft}	20 nm
R_{cleft}	200 nm
d_{glia}	20, 40, 100 nm
d_{release}	center-top, uniformly
$n_{\text{transporter}}$	5,000 and 10,000 / μm^2
vesicles	1 to 7

16%, 28%

27%, 40%



Recurring glutamate



h_{cleft}

20 nm

R_{cleft}

200 nm

d_{glia}

40 nm

$d_{release}$

center-top

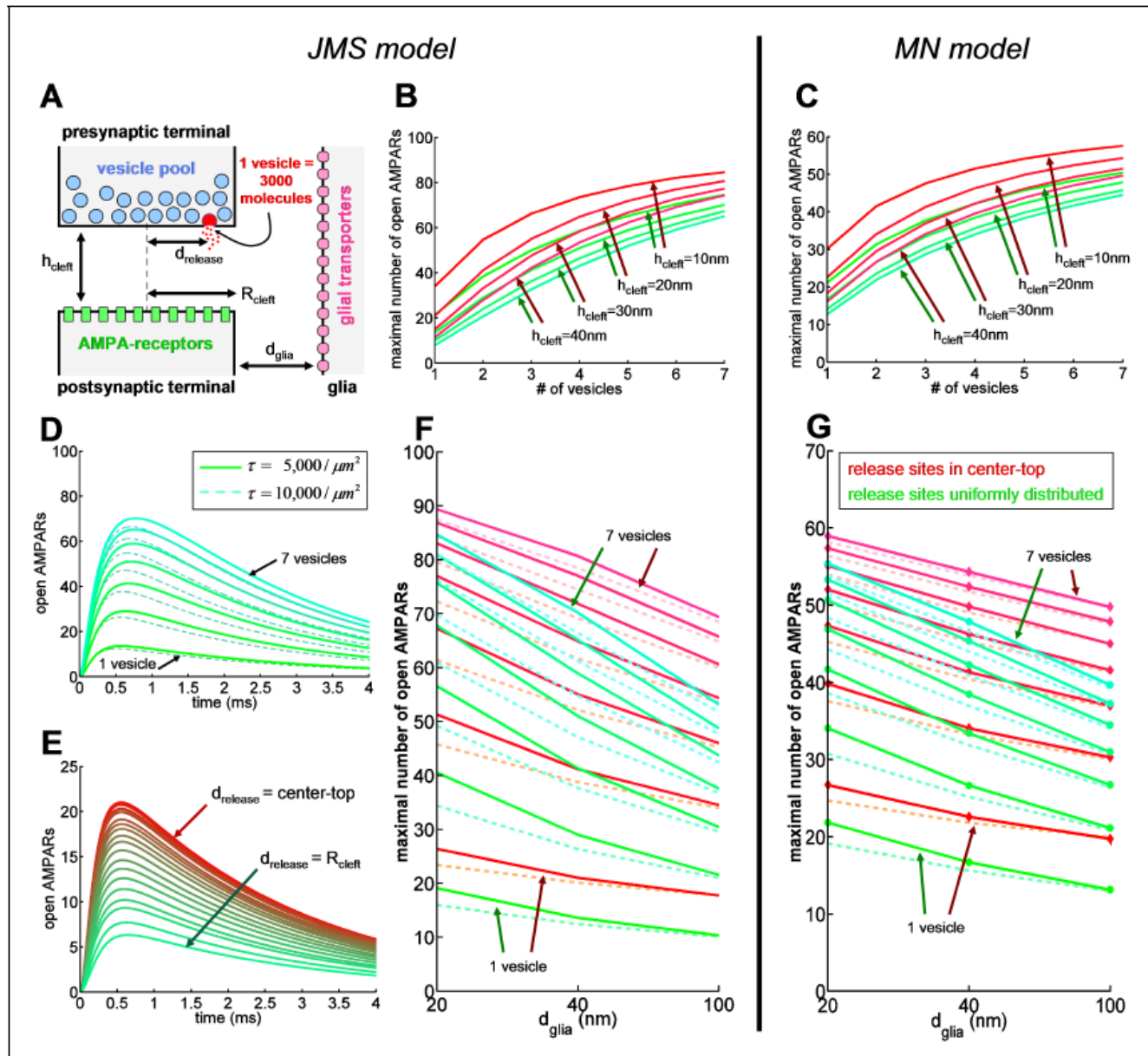
$n_{transporter}$

0 / μm^2

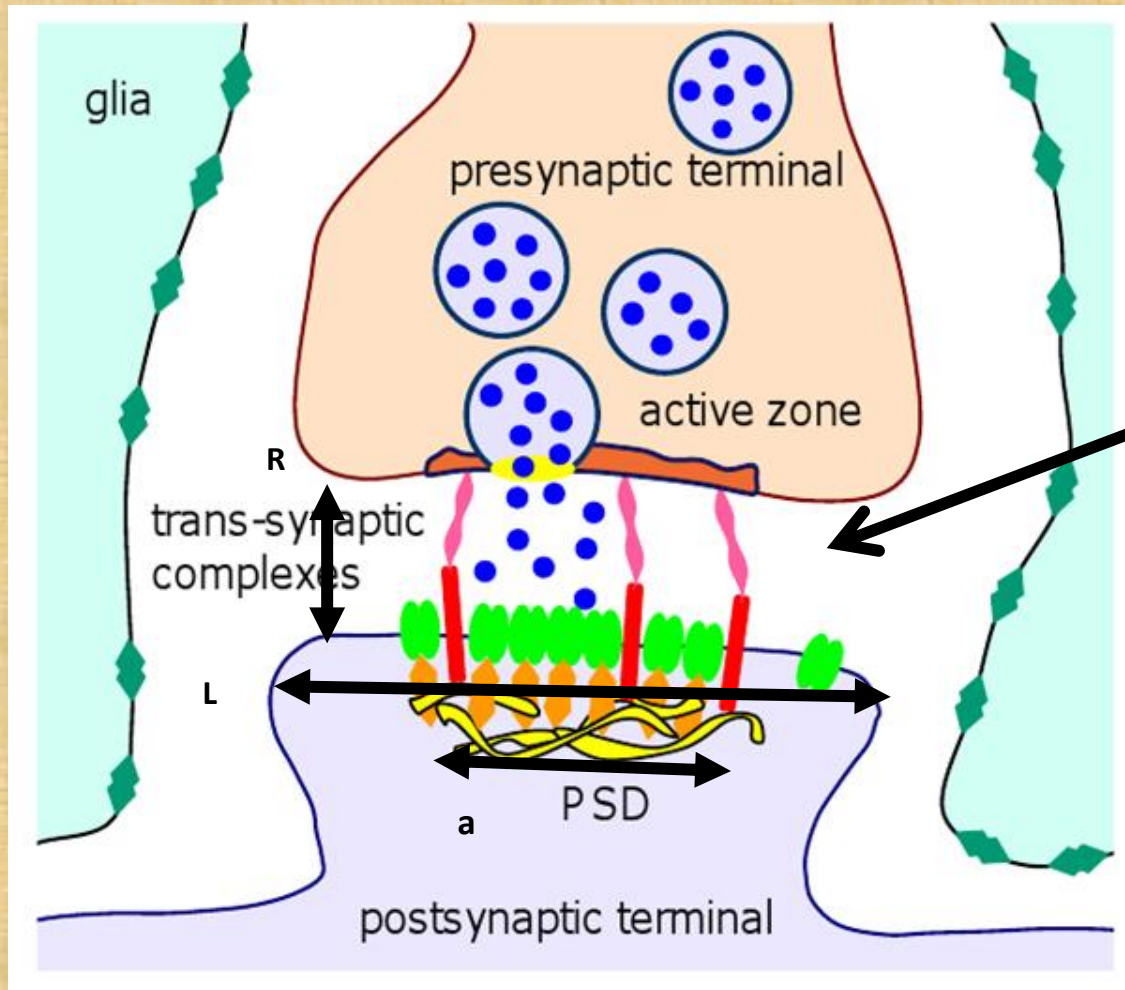
vesicles released

1 (3000 molecules)

Summary: stochastic simulations



Modeling synaptic transmission



Diffusion law in the synaptic cleft.
Probability of finding a receptor

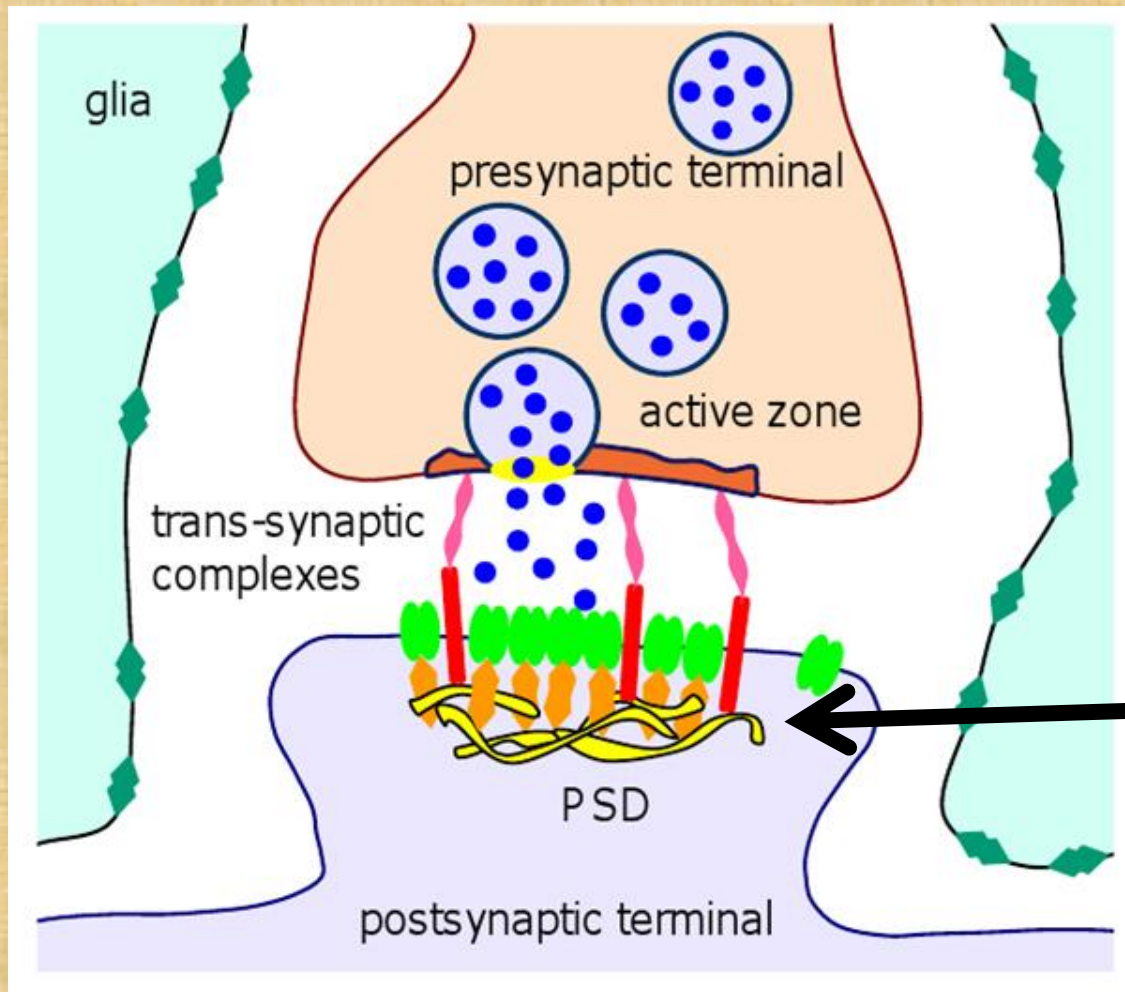
$$\Pr\{\tau_{\text{hole}} < \tau_{s_r}\} = \frac{4a}{\pi R} \sum_{m=1}^{\infty} \frac{1}{\gamma_{0,m} J_0'^2(\gamma_{0,m}) \sinh \frac{\gamma_{0,m} L}{R}} + O\left(\frac{a^2}{L^2} \log \frac{a}{L}\right).$$

-Reingruber et al ,
*SIAM Multiscale
Modeling Simulation.*
9, pp. 793-816 (2011)

Conclusion: the number of bound receptors is independent of the diffusion coefficient

-Holcman, Rep Prog
Phys 2013

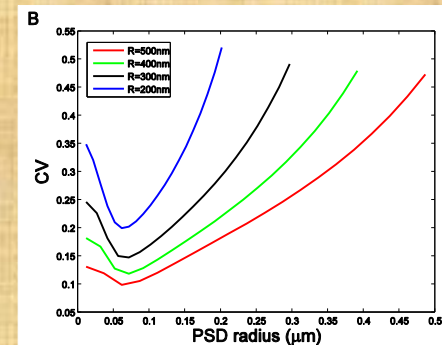
Modeling synaptic transmission



-Number of receptors

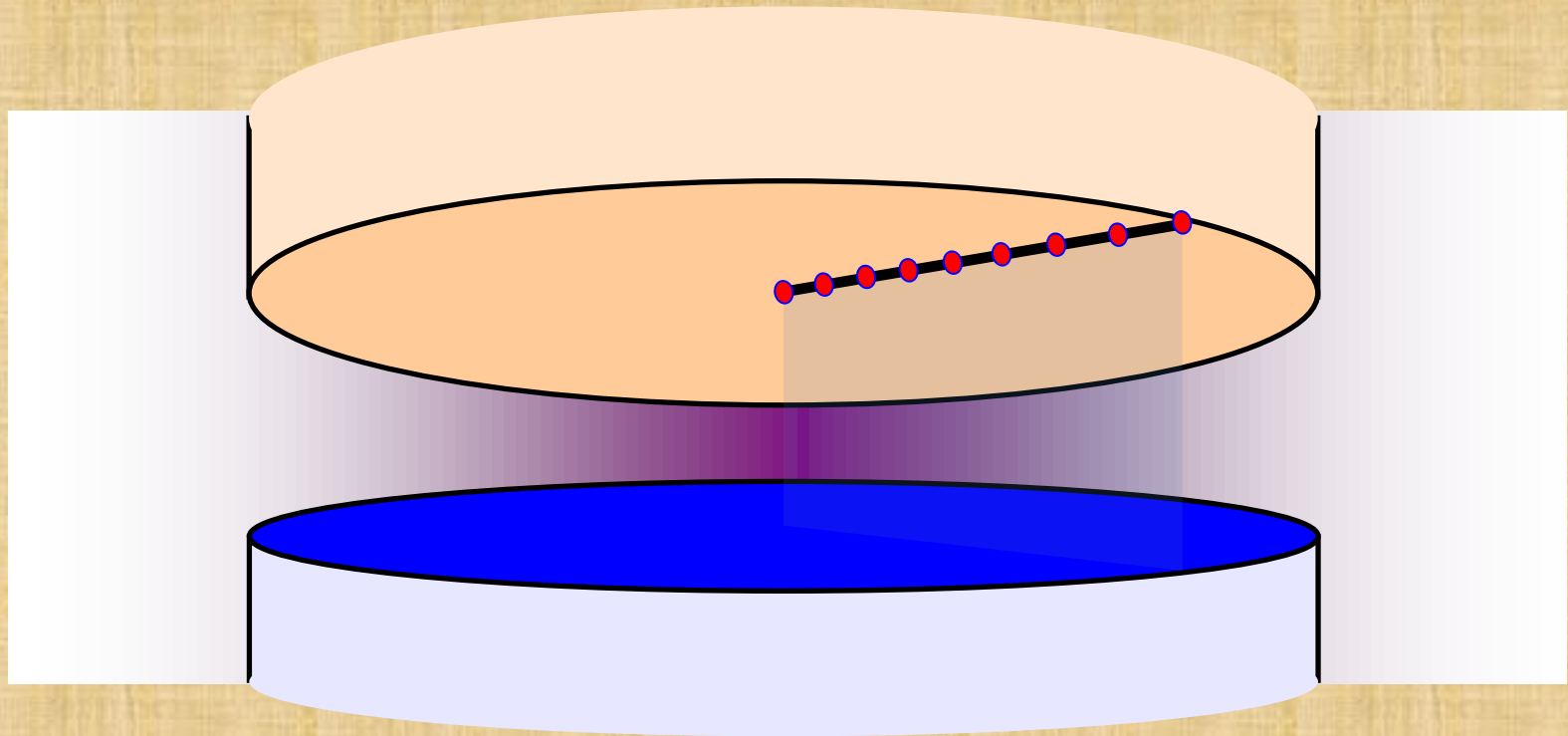
-Organization at the PSD

-Optimal PSD for a given AZ to maximize
The $CV = SD / \text{Mean}$ of the current



-D. Holcman, *AMS Contemporary Mathematics (CONM) book series:*
1, 26 (2000)

Release location



h_{cleft}

20 nm

R_{cleft}

200 nm

d_{glia}

40 nm

d_{release}

0 ... 200 nm (1 step = 10nm)

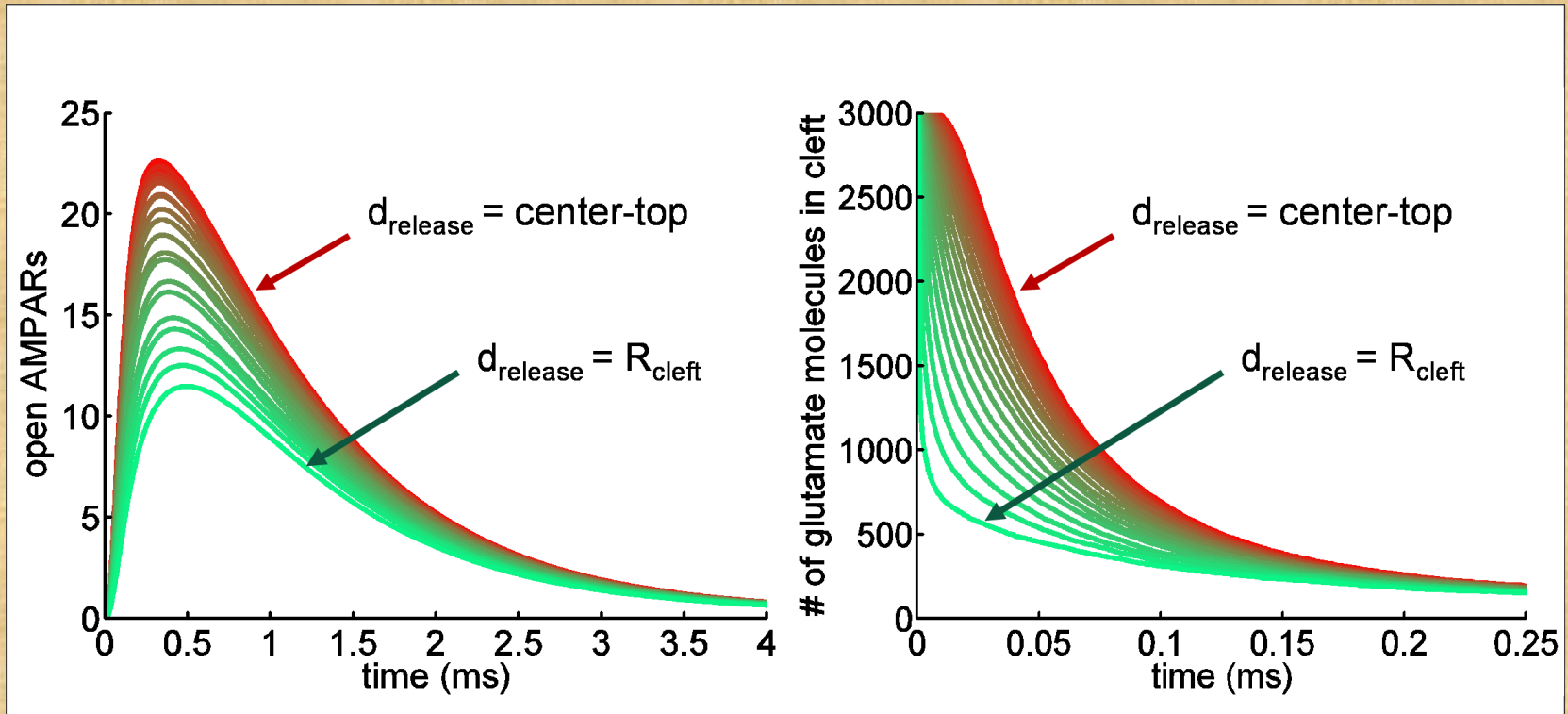
$n_{\text{transporter}}$

5,000/ μm^2

vesicles released

1

Release location



h_{cleft}

20 nm

R_{cleft}

200 nm

d_{glia}

40 nm

d_{release}

0 ... 200 nm (1 step = 10nm)

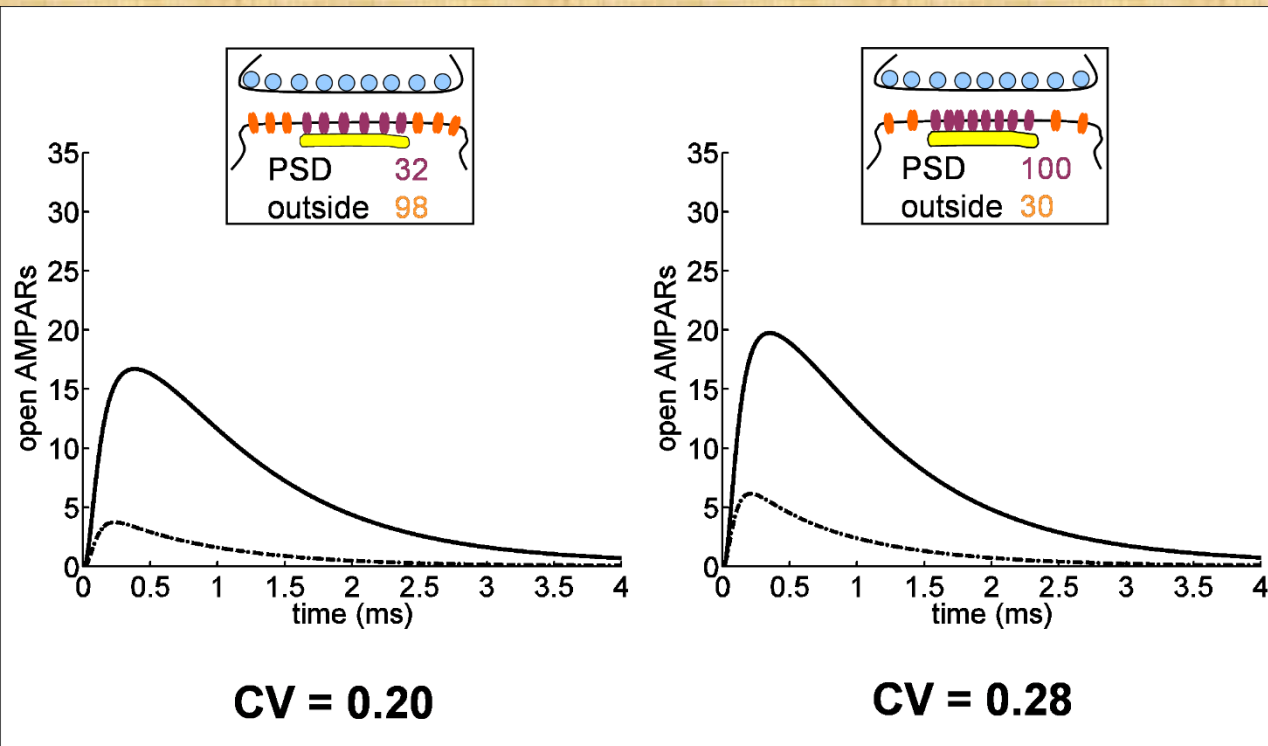
$n_{\text{transporter}}$

5,000/ μm^2

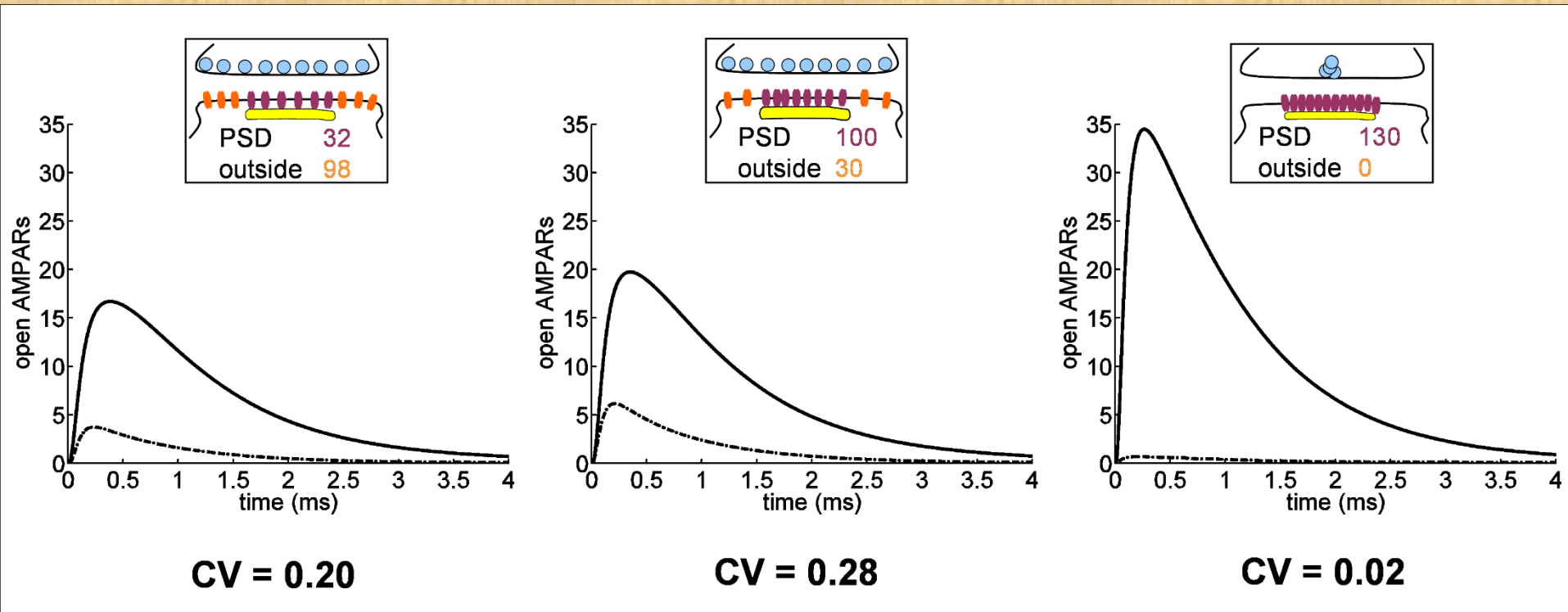
vesicles released

1

Clustering AMPARs

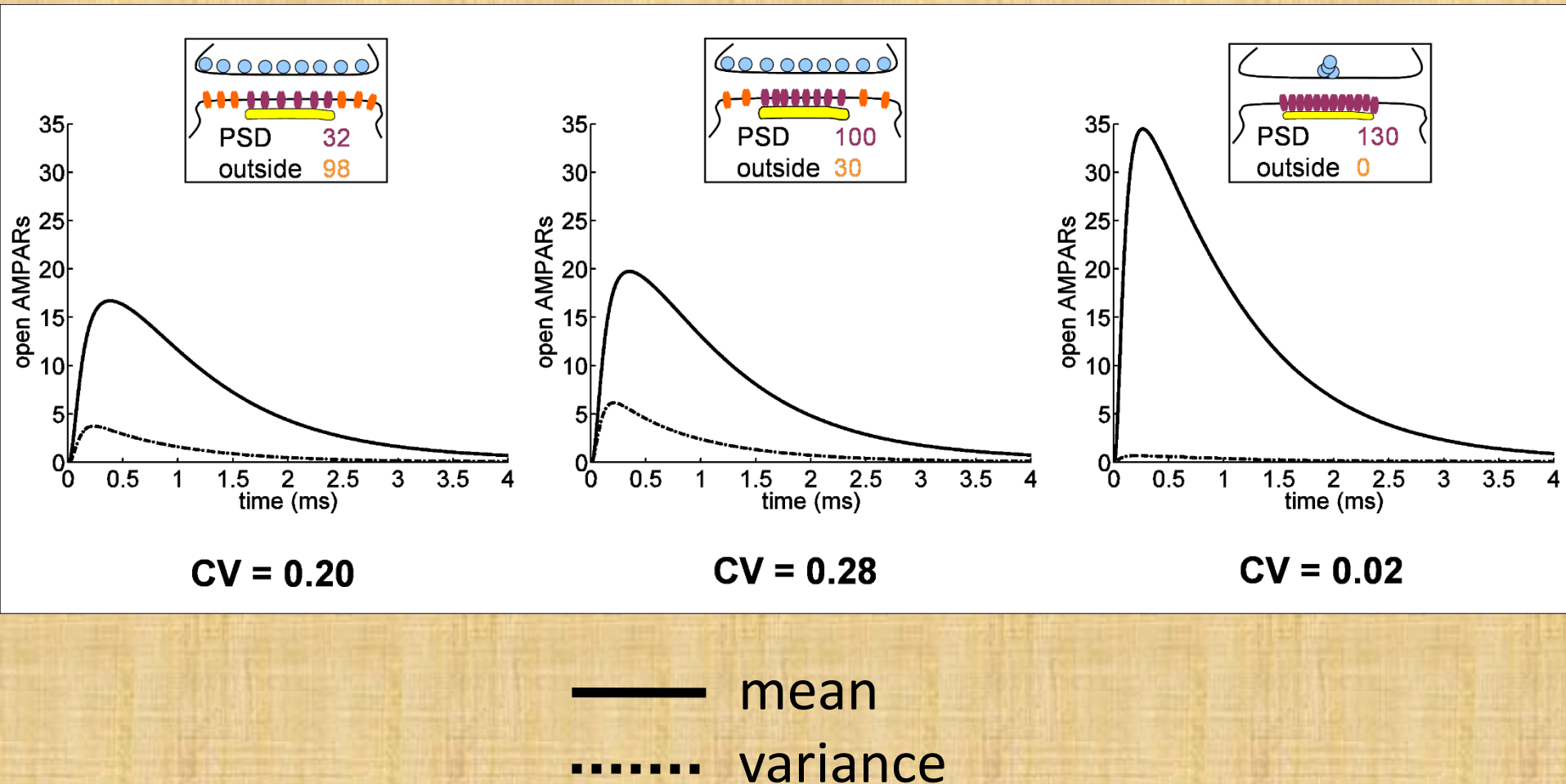


Clustering AMPARs, release sites

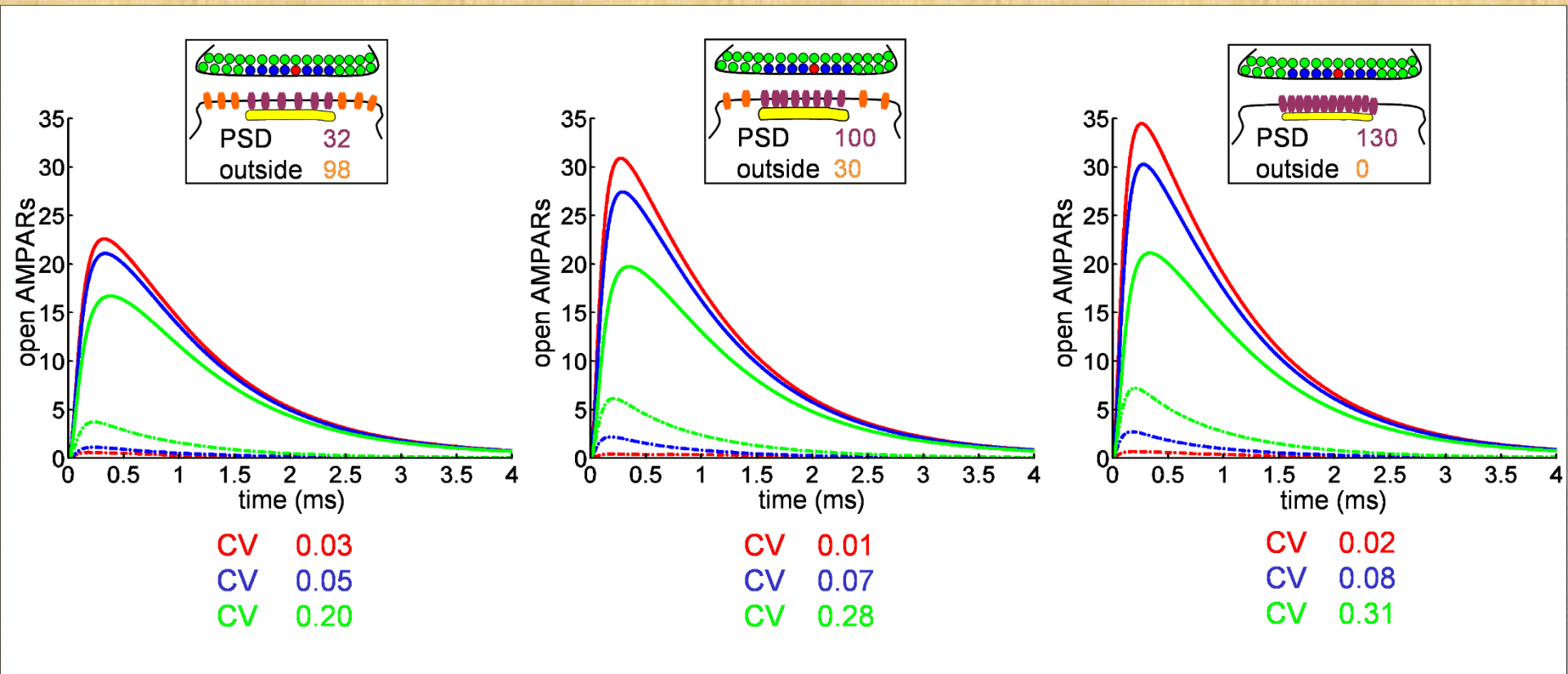


— mean
..... variance

Model for synapse development ?



Clustering AMPARs, release sites



release site distributions:

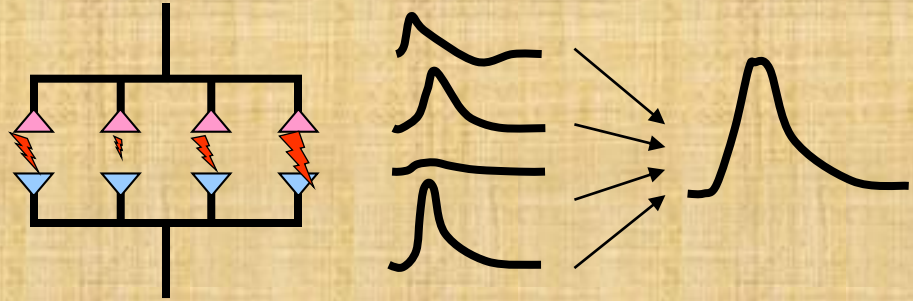
center-top

UD over PSD

UD over PT

Modes of **reliable** communication

- Integration *in space* (over several synapses)

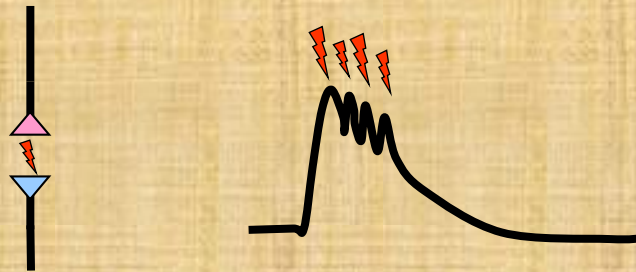


Modes of **reliable** communication

- Integration *in space* (over several synapses)



- Integration *in time* (over several bursts)

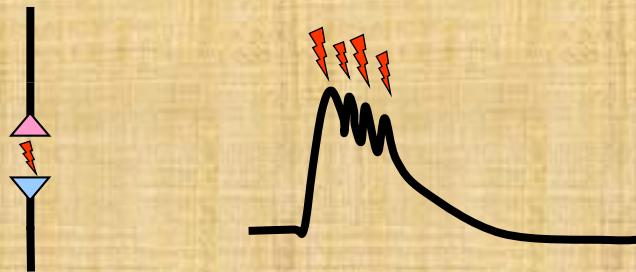


Modes of **reliable** communication

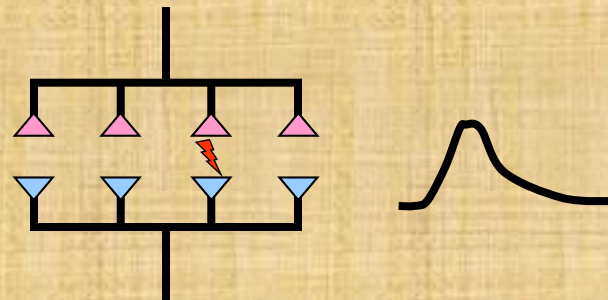
- Integration *in space* (over several synapses)



- Integration *in time* (over several bursts)



- Distribution over several *robust* synapses



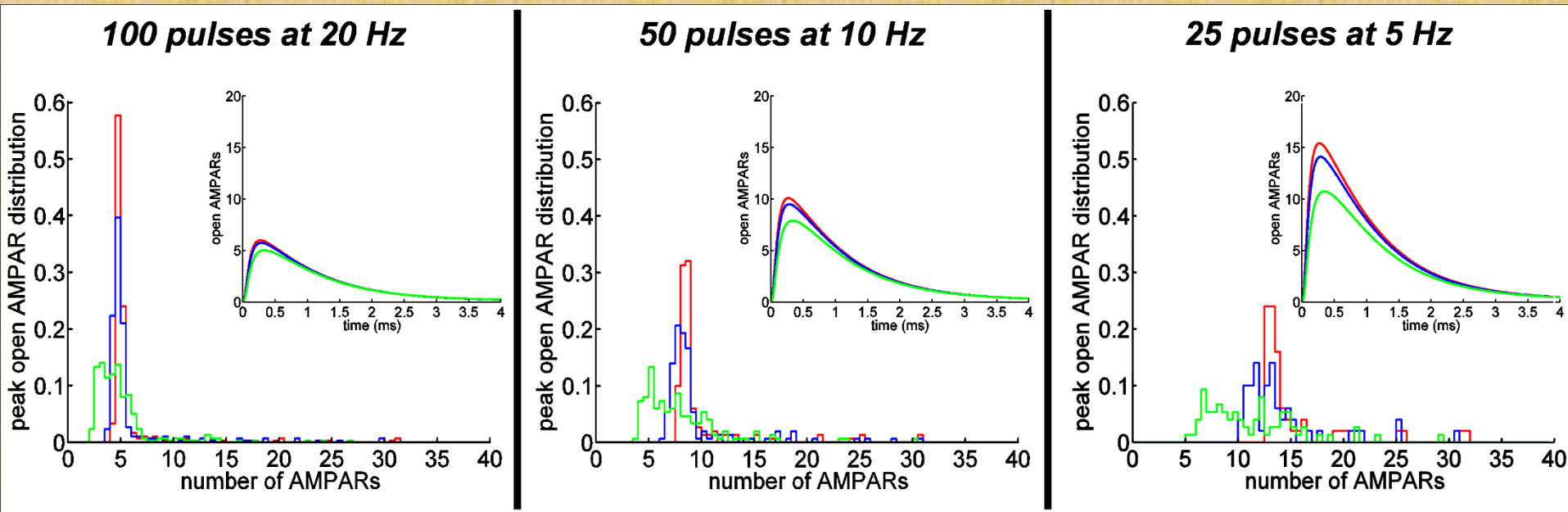
Modes of **reliable** communication: decoupling spikes

Distribute **100** pulses over

1 synapse

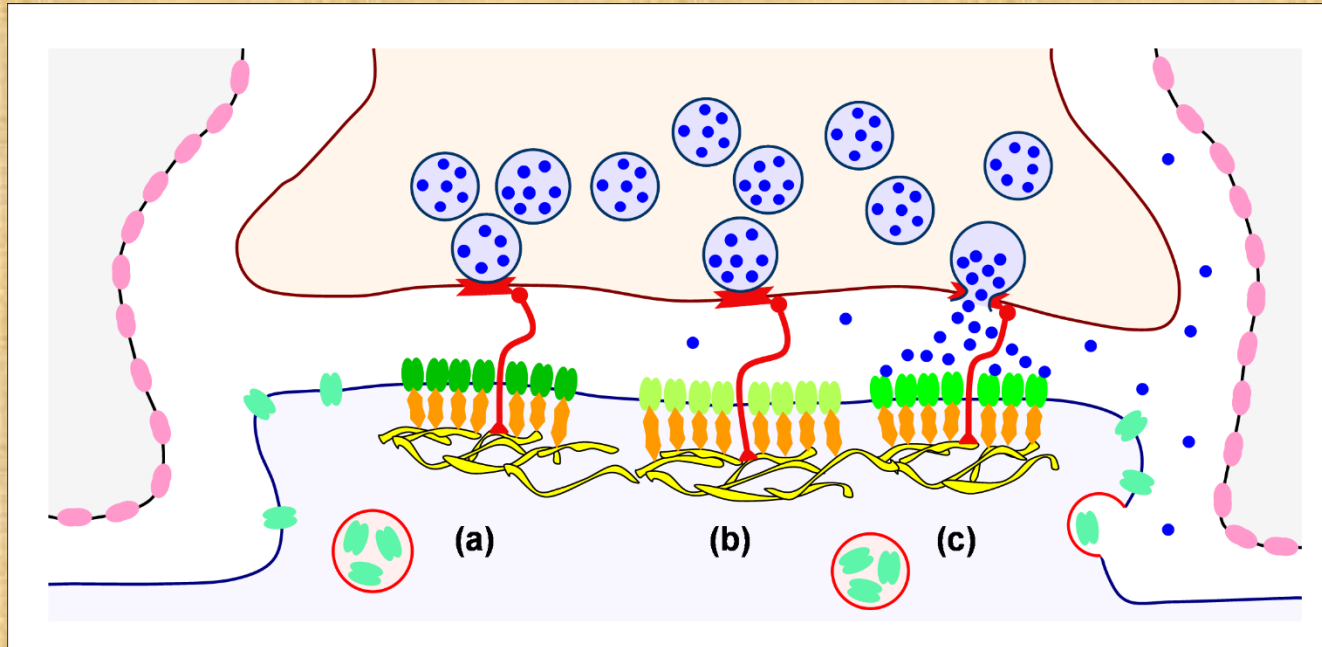
2 synapses

5 synapses

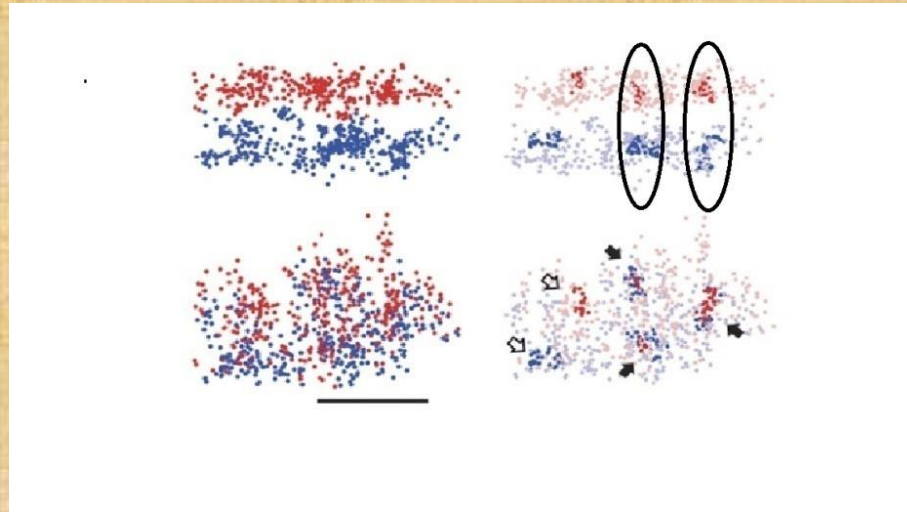


fewer pulses, longer inter-spike-time

Hypothesis: nanocolumn organization (Plos 1 2011)



Experimental proof 2016

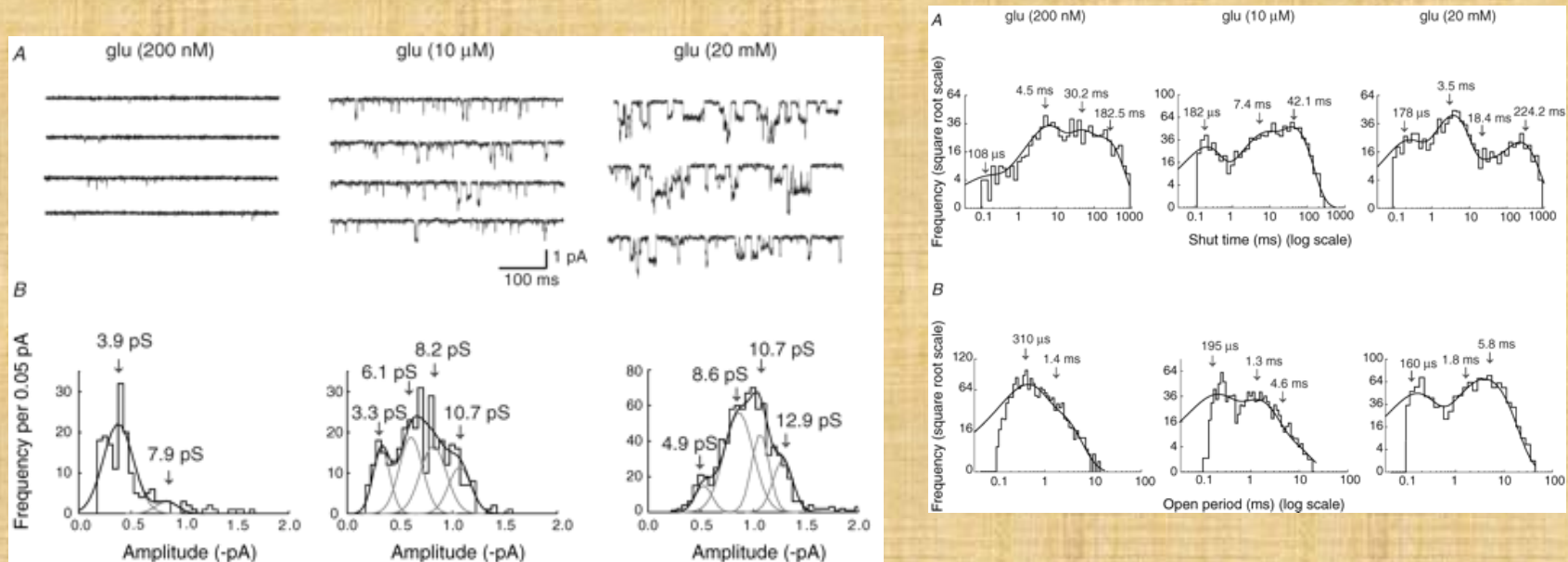


Optional

Computing the number of activated
receptors

AMPA dynamics

No direct information about conductances:
(many possible state due to the 4 subunits)



Gebhardt, C. Cull-Candy, S.G. (2006) *J. Physiol.*, pp. 371-394.

$$I_s(t) = (\gamma_2(t)N_2 + \gamma_3(t)N_3 + \gamma_4(t)N_4)\Delta V,$$

$$\gamma_2 = 4 \text{ pS} \quad \gamma_3 = 10 \text{ pS} \quad \gamma_4 = 13 \text{ pS} \quad \Delta V_m = -100 \text{ mV}$$

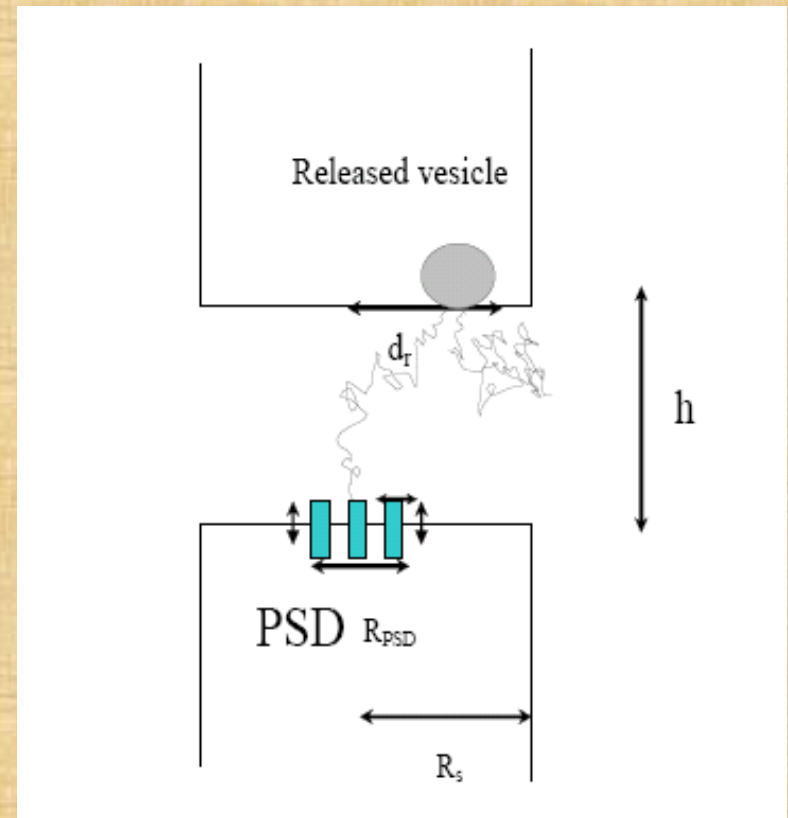
No real information about the dynamics:

What is the conductance associated with k-binding?

Tafliar et al Biophysical J, 2011

Model.

- A fixed voltage drop $\Delta V = 100mV$
- Conductance levels depend on the number of bound Glu.
- The synapse has a cylindrical geometry.
- The receptors are located in the PSD.
- Glu is released from the active zone (AZ).
- Glu has Brownian dynamics.
- PSD and the AZ are centered.



$$\gamma_1 = 0pS, \gamma_2 = 4pS, \gamma_3 = 10pS, \gamma_4 = 13pS$$

What we had to calculate?

- The current is given by

$$I_s(t) = (\gamma_2(t)N_2 + \gamma_3(t)N_3 + \gamma_4(t)N_4)\Delta V,$$

- The probability of glu to bind a binding site. Solve diffusion equation.
- The probability of a configuration: If we have 3 receptors and 10 glu are bound. We can have

$$(n_4, n_3, n_2, n_1) = (2, 0, 1, 0)$$

$$(n_4, n_3, n_2, n_1) = (1, 2, 0, 0)$$

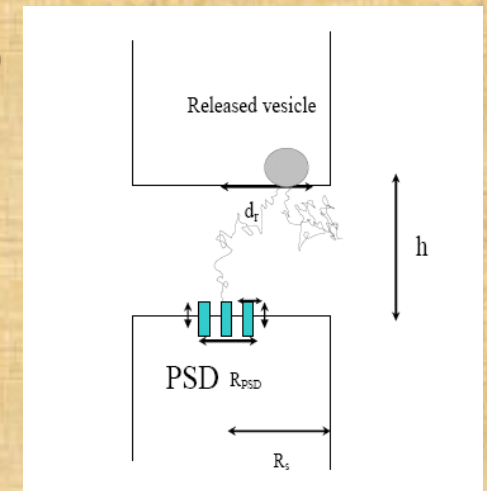
Modeling diffusion in the cleft

$$\frac{\partial p(x, t | x_0)}{\partial t} = D \Delta p(x, t | x_0), \quad x \in \Omega, t > 0$$

$$p(x, 0) = \delta(x - x_0)$$

$$\left. \frac{\partial p(x, t | x_0)}{\partial \nu} \right|_{\partial \Omega_r} = 0, \quad p(x, t | x_0)|_{\partial \Omega_{Lat}} = 0$$

$$\left. -D \frac{\partial p(x, t | x_0)}{\partial \nu} \right|_{\partial \Omega_{PSD}} = -\kappa p(x, t | x_0),$$



Homogenization partial
absorption

$$\kappa = \frac{D}{2\pi R_{PSD}^2} \frac{1}{\frac{f(\sigma)}{N_a a} + \frac{D}{\kappa_a 2\pi a^2 N_a}}$$

$$\sigma = Na^2/R_{PSD}^2$$

$$f(\sigma) = 1 - \sigma,$$

The mean and variance of the synaptic current . I_s

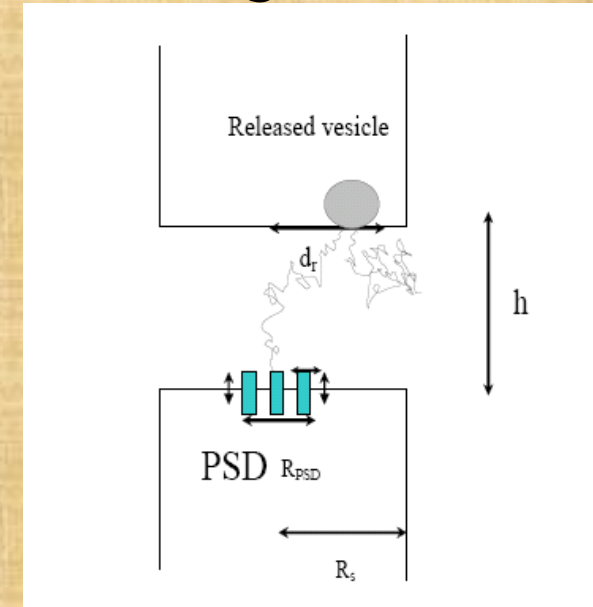
Probability distribution to have k sites of AMPAR bound, when a vesicle is released at position x_0

$$Pr_k(x_0) = C_{4N_a}^k p(x_0)^k (1 - p(x_0))^{4N_a - k},$$

$$p(x_0) = \kappa \int_{\partial\Omega_{PSD}} u(x | x_0) dS(x)$$

$$D\Delta u(x | x_0) = -\delta(x - x_0) \quad \text{for } x \in \Omega \quad u(x | x_0)|_{\partial\Omega_{Lat}} = 0 \quad \frac{\partial u(x | x_0)}{\partial \nu} \Big|_{\partial\Omega_r} = 0,$$

$$M(x_0) = N_g p(x_0) \quad \sigma^2(x_0) = N_g p(x_0)(1 - p(x_0))$$



$$D \frac{\partial u(x | x_0)}{\partial \nu} \Big|_{\partial\Omega_{PSD}} = \kappa u(x | x_0),$$

One vesicle is released at the center of the synapse, PSD and a synaptic radius

300nm 500nm

the effective surface area of a single AMPAR is

2.25nm² $\kappa_a = 1.6$

20 AMPARs, a probability of ,

$p(0) = 8 \cdot 10^{-3}$ $I_s = 54 \pm (17) pA$

Taflia et al Biophysical J, 2011

Combinatory of the Synaptic Current

The probability of a given configuration to have n_1 AMPARs bound to 1 glutamate, n_2 AMPARs bound to 2 glutamates and so on, when there are N_a AMPA receptors, for bound glutamate molecules, is given by

$$\vec{n} = (n_4, n_3, n_2, n_1) \quad k < 4N_a \quad \Pr\{\vec{n} | k\} = \frac{N_a!}{n_4!n_3!n_2!n_1!(N_a - (n_4 + n_3 + n_2 + n_1))!} \frac{1}{F(k, N_a)},$$

$F(k, N_a)$ is the total number of possibilities to decompose the number k as a sum of 4, 3, 2, 1, 0 on the integer.

$$\langle I_s(x_0) \rangle = \sum_{k=1}^{N_g} \sum_{n \in S_k} \vec{n} \cdot \vec{\gamma} \Pr\{\vec{n} | k\} Pr_k(x_0) = \sum_{k=1}^{4N_a} \sum_{n \in S_k} \vec{n} \cdot \vec{\gamma} \Pr\{\vec{n} | k\} Pr_k(x_0) + Na\gamma_4 \left(1 - \sum_{k=0}^{4N_a} Pr_k(x_0) \right)$$

$$\langle I_s^2(x_0) \rangle = \sum_{k=1}^{N_g} \sum_{n \in S_k} (\vec{n} \cdot \vec{\gamma})^2 \Pr\{\vec{n} | k\} Pr_k(x_0) - \langle I_s(x_0) \rangle^2 = \sum_{k=1}^{4N_a} \sum_{n \in S_k} (\vec{n} \cdot \vec{\gamma})^2 \Pr\{\vec{n} | k\} Pr_k(x_0) + (Na\gamma_4)^2 \left(1 - \sum_{k=0}^{4N_a} Pr_k(x_0) \right) - \langle I_s(x_0) \rangle^2$$

Estimation of the probability $p(x_0=0)$

$$D\Delta u(r, z) = -\delta(r)\delta(z - z_0) \quad \text{for } \{(r, z) \mid r \in [0, R), z \in (0, h)\}$$

$$\bar{u}(r) = \frac{1}{h} \int_0^h u(r, z) dz$$

$$D \left(\bar{u}''(r) + \frac{1}{r} \bar{u}'(r) - \frac{1}{h} \frac{\partial}{\partial z} u(r, 0) \chi_{[0, L]}(r) \right) = -\frac{1}{rh} \delta(r - r_0),$$

$$D \left(\bar{u}''(r) + \frac{1}{r} \bar{u}'(r) - \frac{2\kappa}{h(2D + \kappa h)} \bar{u} \chi_{[0, L]}(r) \right) = -\frac{1}{rh} \delta(r - r_0).$$

$$\bar{u}(r) = \begin{cases} \frac{1}{2\pi D} K_0(\alpha r) + A I_0(\alpha r) & 0 < r < L \\ C \log \frac{r}{R} & L < r < R \end{cases},$$

$$\begin{aligned} \frac{1}{D} K_0(\alpha L) + A I_0(\alpha L) &= C \log \frac{L}{R} \\ -\frac{1}{D} \alpha K_1(\alpha L) + A \alpha I_1(\alpha L) &= C \frac{1}{L}. \end{aligned}$$

$$J_{PSD} = \kappa \int_{\partial\Omega_{PSD}} u dS = 2\pi\kappa \int_0^L \frac{1}{D} K_0(\alpha r) r dr + 2\pi\kappa \int_0^L A I_0(\alpha r) r dr$$

$$J_{Lat} = -2\pi D R h \bar{u}'(R) = -2\pi D h C.$$

$$p = \frac{J_{PSD}}{J_{PSD} + J_{Lat}}.$$

Taflia et al Biophysical J, 2011

Homogenization of the PSD

How to replace a collection of partial absorbing AMPA receptors by a uniform one?

$$-D \frac{\partial p(x, t | x_0)}{\partial \nu} \Big|_{\partial \Omega_{\text{PSD}}} = -\kappa p(x, t | x_0),$$

$$\kappa = \frac{D}{2\pi R_{\text{PSD}}^2} \frac{1}{\frac{f(\sigma)}{N_a a} + \frac{D}{\kappa_a 2\pi a^2 N_a}}$$

Solve Small hole problem:

$$D\Delta u = -1 \text{ on } \Omega \quad \frac{\partial u}{\partial n} = 0 \text{ on } \partial \Omega_r \quad -D \frac{\partial u}{\partial n} = -\kappa_p u \text{ on the PSD}$$

$$u(x) \approx \frac{|\Omega|}{D} \left(\frac{1}{4R_{\text{PSD}}} + \frac{D}{2\pi\kappa_p R_{\text{PSD}}^2} \right)$$

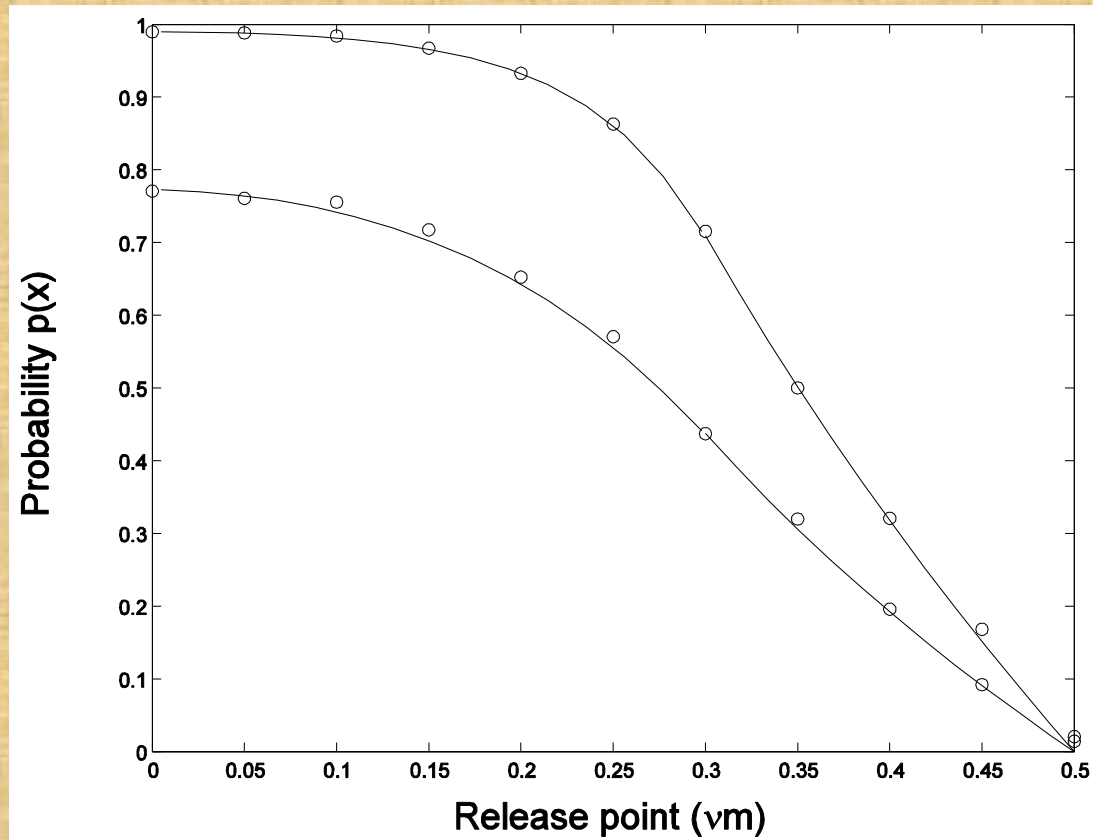
$$J = \frac{1}{u(x)} \approx \frac{D}{|\Omega|} \frac{1}{\frac{1}{4R_{\text{PSD}}} + \frac{D}{2\pi\kappa_p R_{\text{PSD}}^2}}$$

Criteria

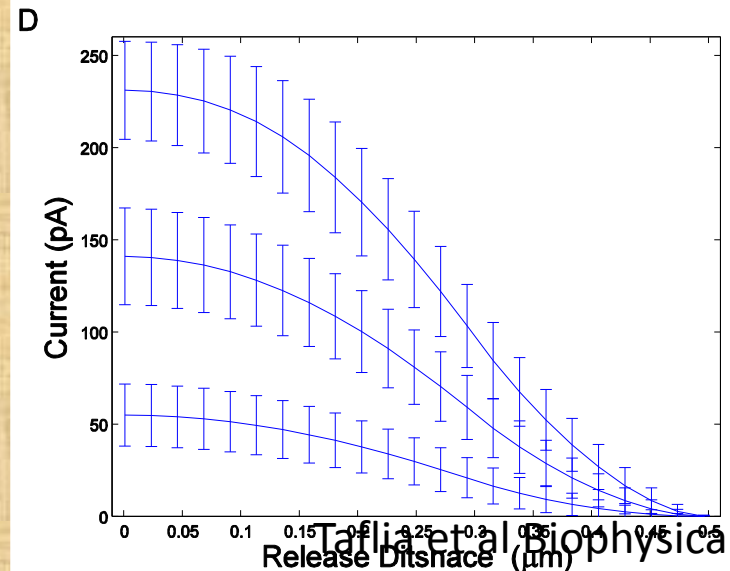
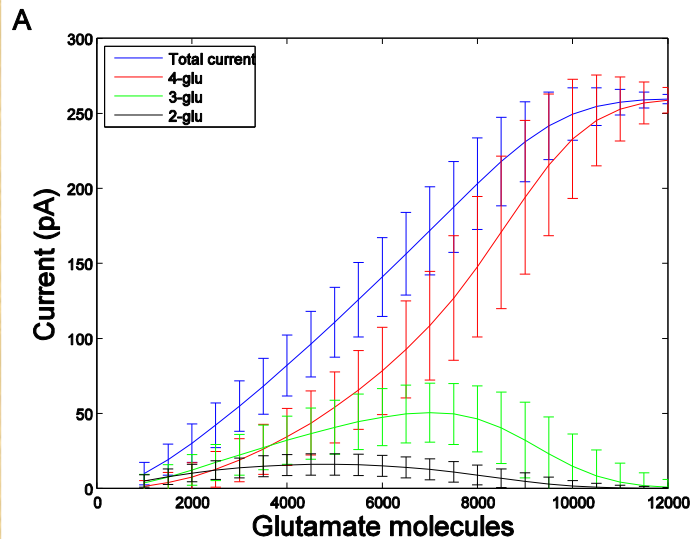
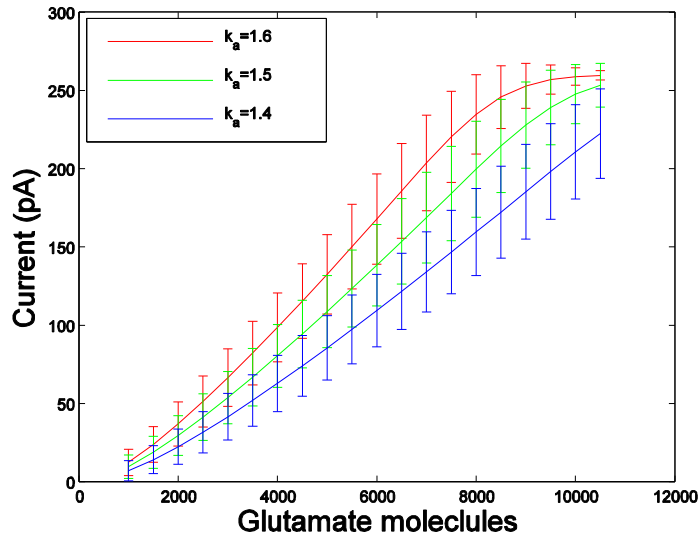
$$\frac{|\Omega|}{D} \left(\frac{1}{4R_{\text{PSD}}} + \frac{D}{2\pi\kappa_p R_{\text{PSD}}^2} \right) = \frac{|\Omega|}{4R_{\text{PSD}} D} \frac{Na + f(\sigma)R_{\text{PSD}}}{Na}$$

Taflija et al Biophysical J, 2011

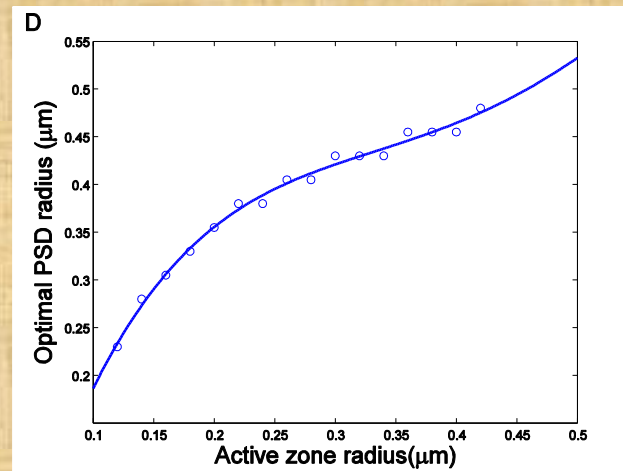
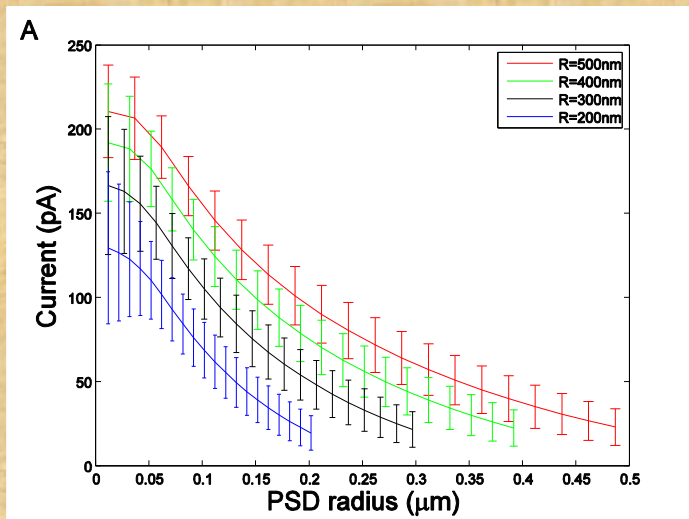
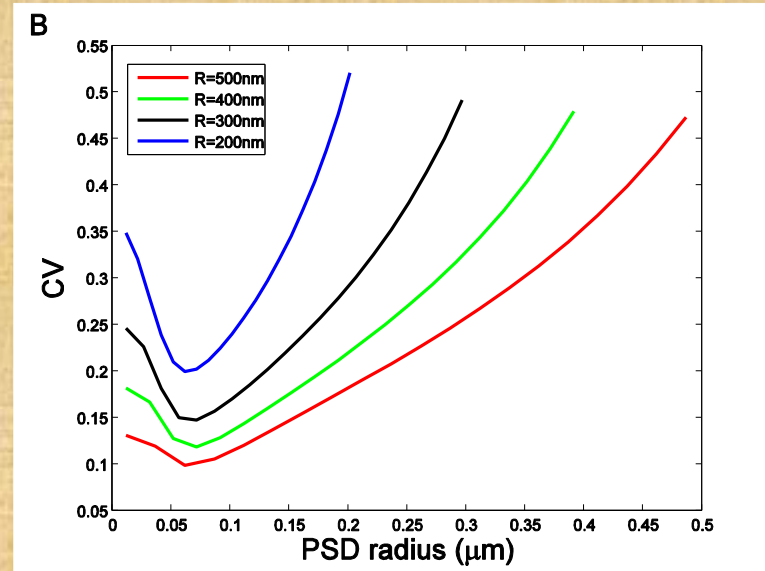
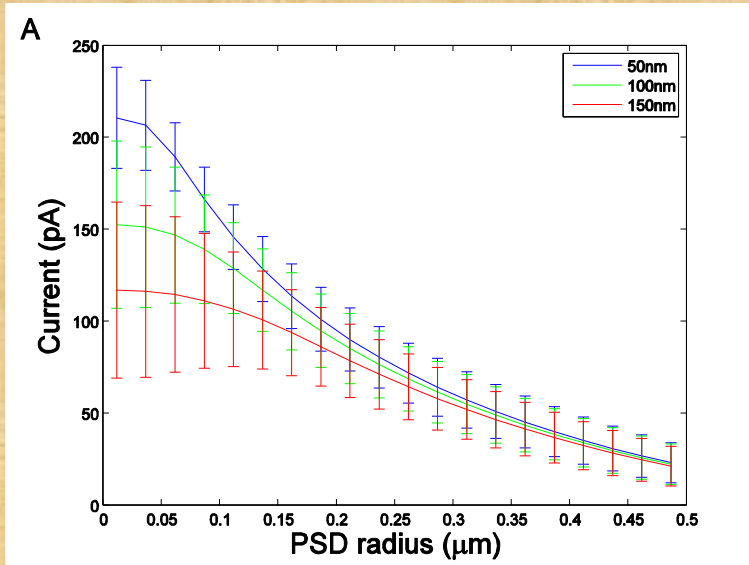
Brownian simulation/Analytical solution



Current properties



Optimal current



Plan of the Lecture

1. Introduction: Neuron-glia Interaction
2. Modeling synaptic dynamics: modeling, simulation, prediction of geometrical organization
3. Compartment model: regulation of ionic fluxes between astro and neuron
4. How glial cell regulate neuronal activity: bursting, AHP, synaptic depression facilitation model and mean-field model
5. Open question: BVI → model activity, pumping glutamate, potassium and activity

Investigating the role of astrocytic Cx30 in neuronal transmission and plasticity

Role of Connexin30 in mice behaviour and cognitive processes

Effects of environmental enrichment on gene expression in the brain

12880–12884 | PNAS | November 7, 2000 | vol. 97 | no. 23

Claire Rampon*, Cecilia H. Jiang[†], Helin Dong^{†‡}, Ya-Ping Tang*, David J. Lockhart[†], Peter G. Schultz[†], Joe Z. Tsien^{*§}, and Yinghe Hu[§]

Accession no.	Gene name	2 days	14 days
Neuronal signaling			
D50621	PSD-95/SAP90A	7	2.3
M19380	Calmodulin	2.5	2.4
U06670	Apolipoprotein-E receptor	2.3	2.2
ET63385	Connexin-30, a gap junction protein	4	2.8

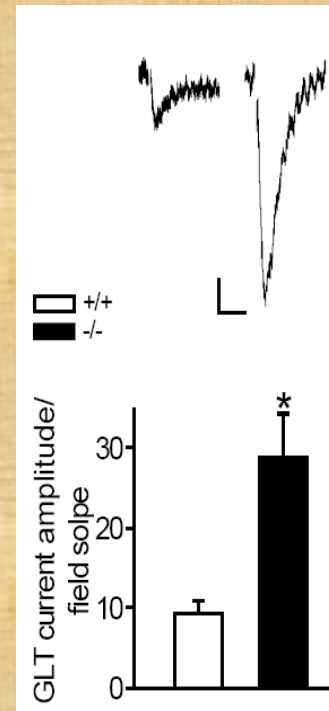
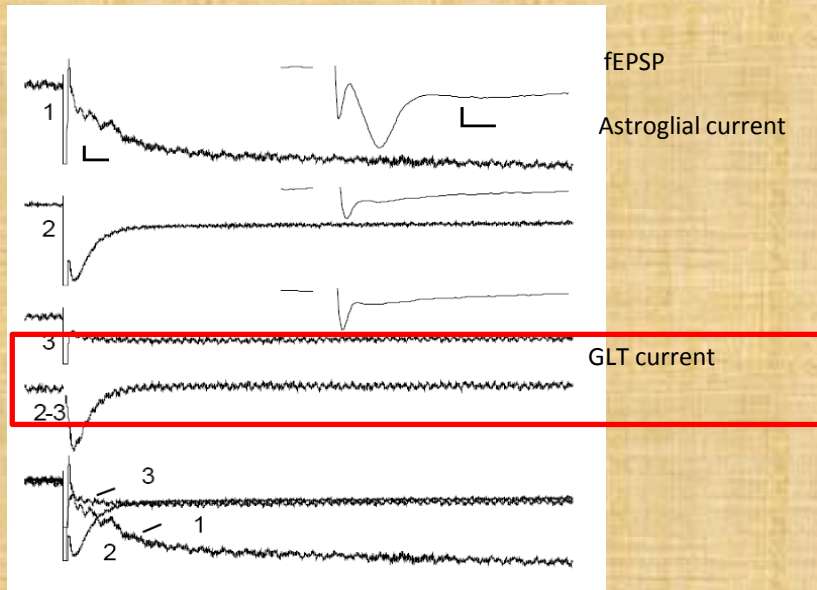
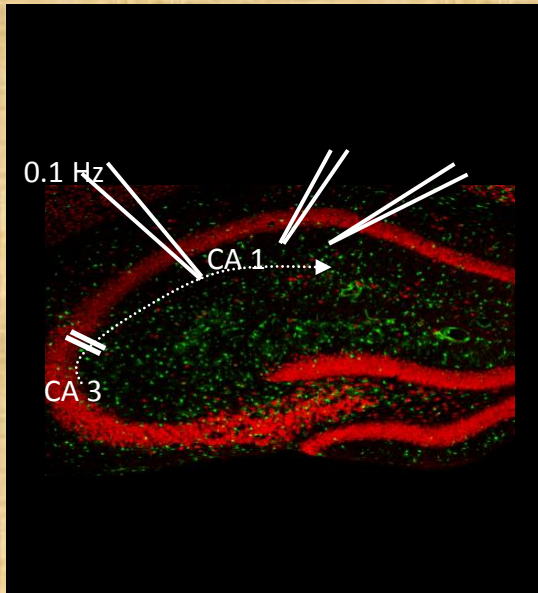
Connexin30-deficient mice show increased emotionality and decreased rearing activity in the open-field along with neurochemical changes

E. Dere,¹ M. A. De Souza-Silva,¹ C. Frisch,¹ B. Teubner,² G. Söhl,² K. Willecke² and J. P. Huston¹

European Journal of Neuroscience, **18**, 629–638

Due to increased astroglial glutamate transport

Synaptically-evoked astrocytic GLT currents



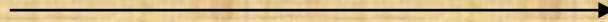
Pannasch et al., 2014 Nature Neuroscience

Summary of experimental evidences

1. 35-50% reduction in synaptic transmission in Cx30^{-/-} mice
2. AMPA/NMDA ratio was unchanged
3. Reduction in **frequency** of miniature EPSCs
 - Cx30^{+/+}, 0.9 ± 0.1 Hz n = 8,
 - Cx30^{-/-}, 0.4 ± 0.1 Hz n = 8, P < 0.01**and Amplitude**
 - Cx30^{+/+}, - 14.1 ± 0.5 pA n = 8,
 - Cx30^{-/-}, - 11.6 ± 0.7 pA n = 8, P < 0.05
- 4- change in synaptic glutamate concentration in Cx30^{-/-}
 - (γ -DGG inhibition of evoked AMPAR EPSCs was stronger in pyramidal cells from Cx30^{-/-} mice)
- 5-No significant change in pyramidal cell mIPSC frequency

Cx30

?



GLT

Astrocytic Connexins



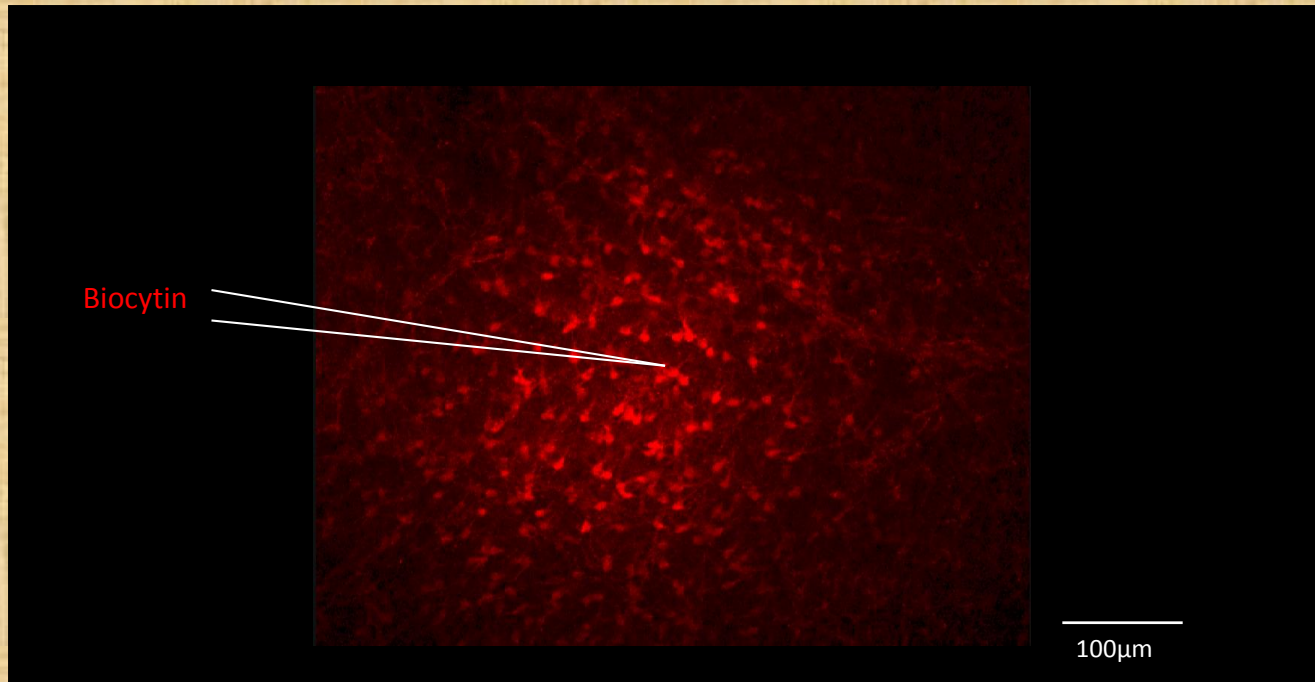
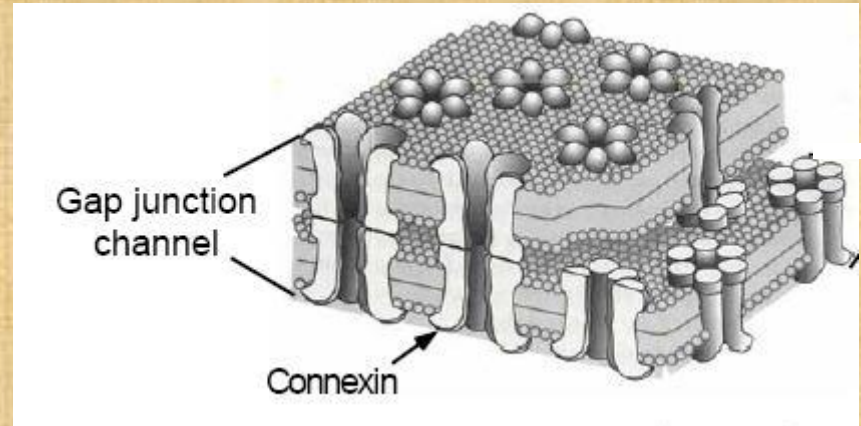
Connexin

Connexon

intracellular channel

Connexin 43

Connexin 30

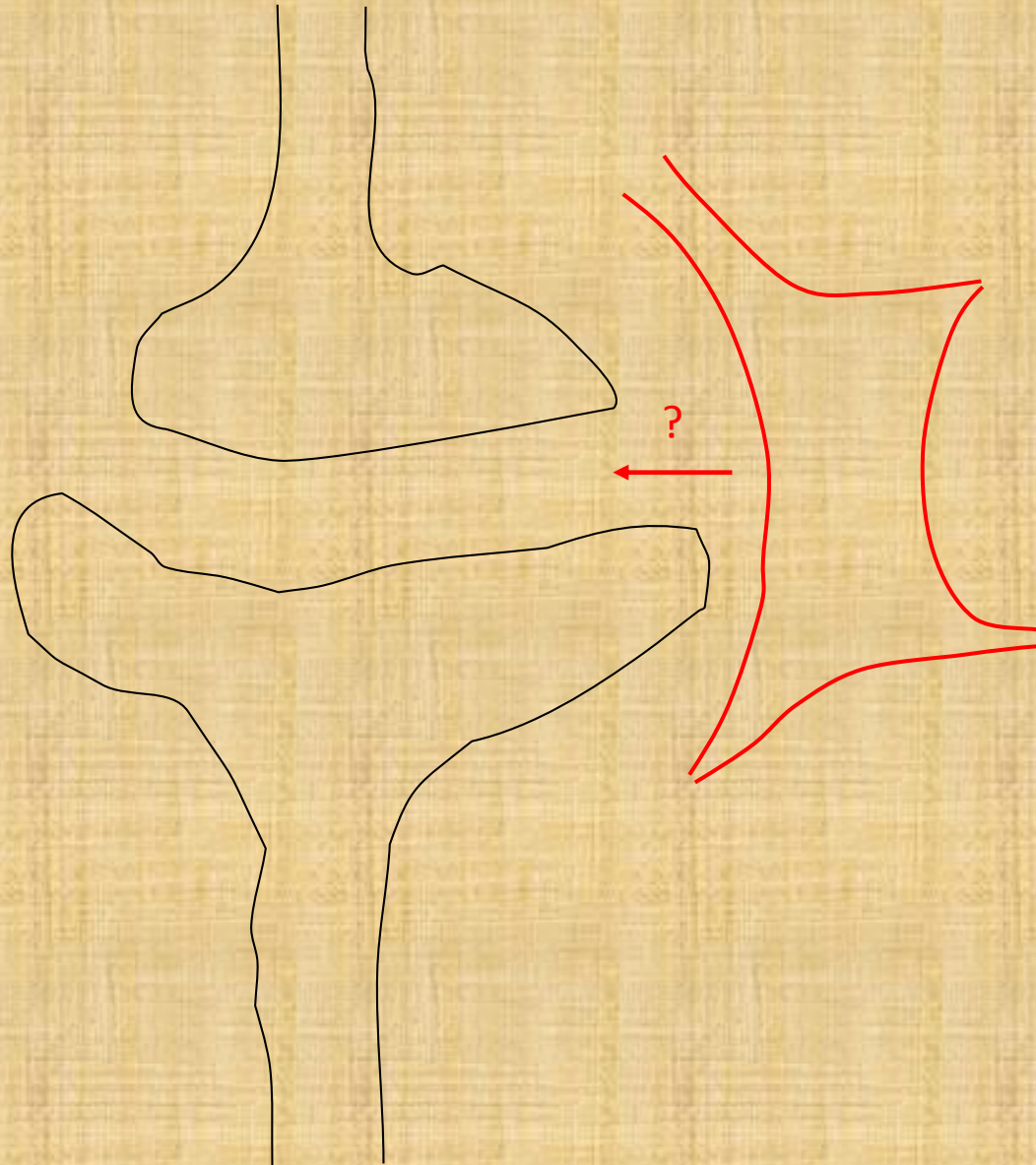


So how does this work ?

Have GLTs a direct role in regulating synaptic glutamate levels ?

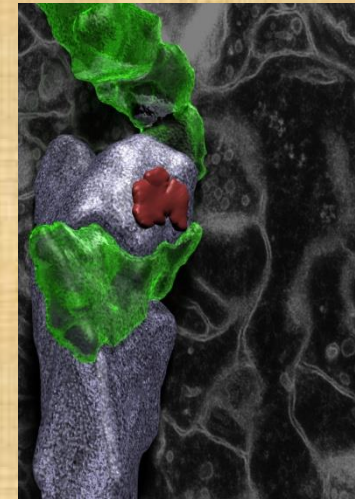
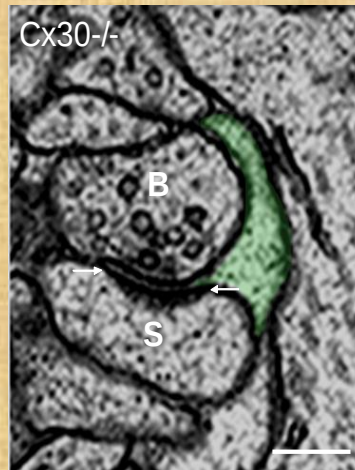
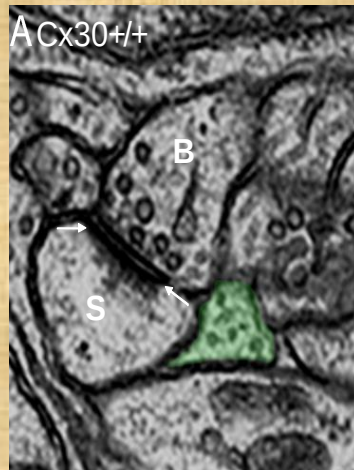
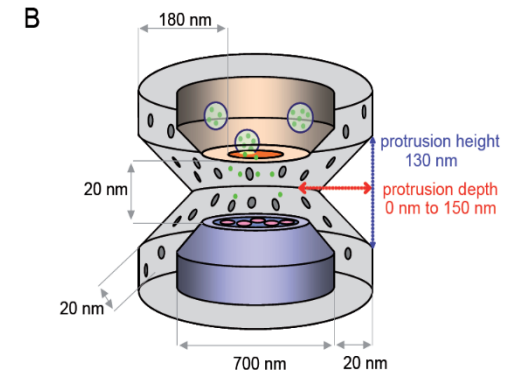
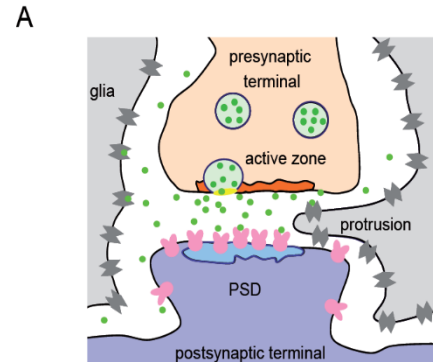
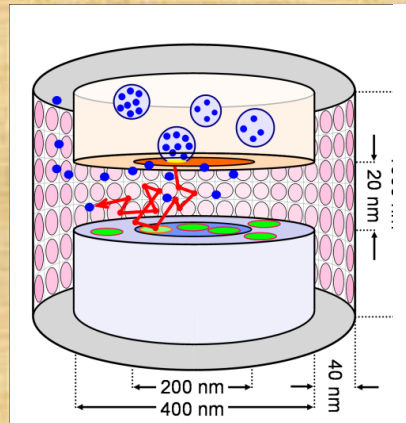
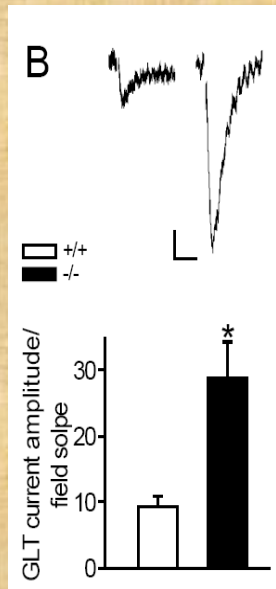
How neuronal transmission can be affected, while GluT in glial cells is x3?

How can astrocytes influence neuronal activity?

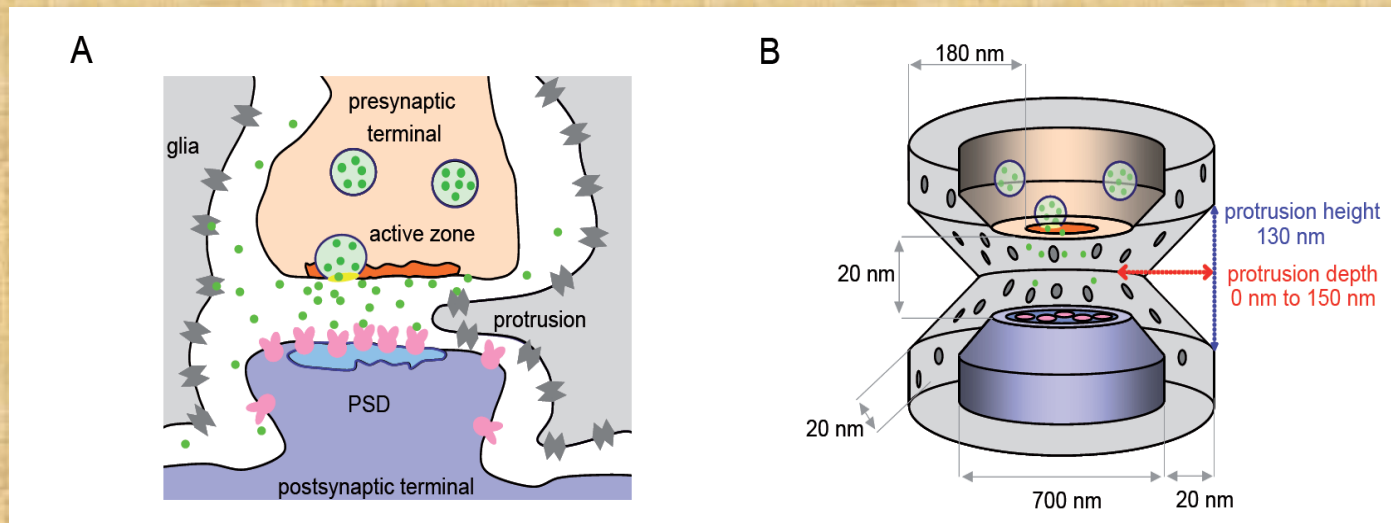


3-Non-channel role of Cx30 of in synaptic transmission predicted from stochastic simulations

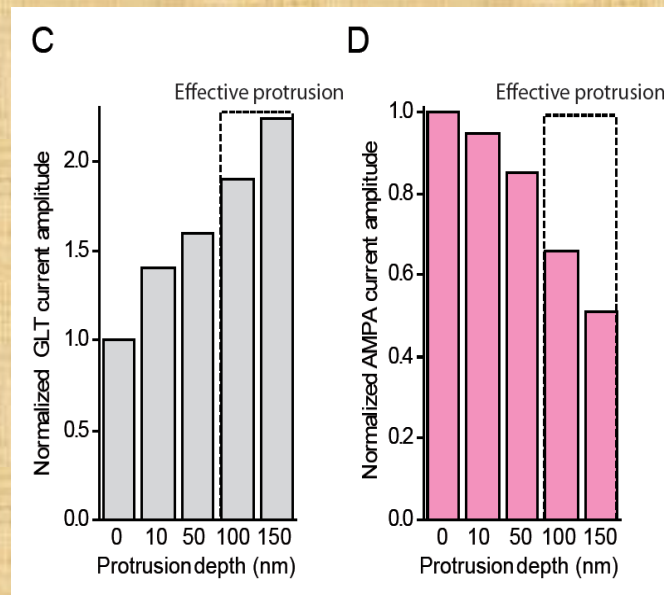
25% reduction in synaptic transmission in Cx30^{-/-} mice



Geometrical model of the tripartite synapse



Decreasing astrocyte distance to synapses decreases AMPA transmission



Plan of the Lecture

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2. Modeling synaptic dynamics: modeling, simulation, prediction of geometrical organization
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4. How glial cell regulate neuronal activity: bursting, AHP, synaptic depression facilitation model and mean-field model
5. Open question: BVI → model activity, pumping glutamate, potassium and activity

Ionic regulation: Potassium cycle during neurotransmission

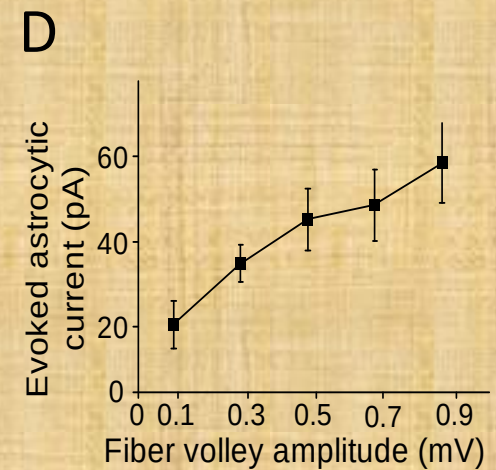
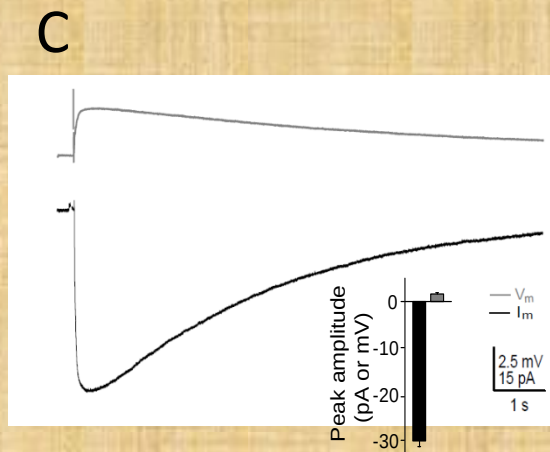
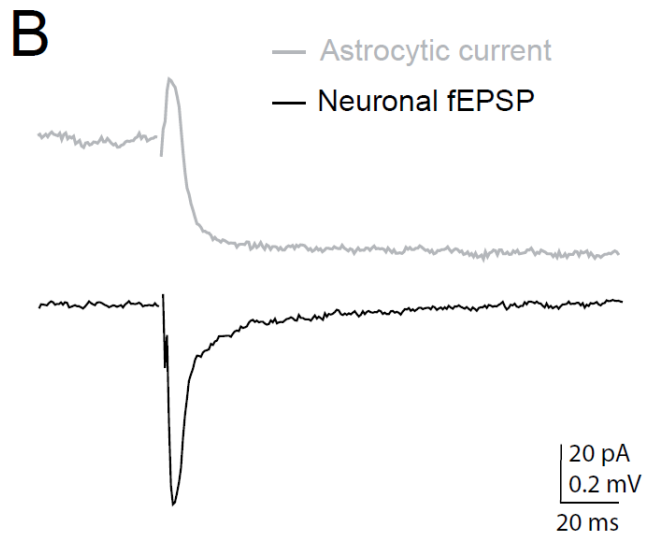
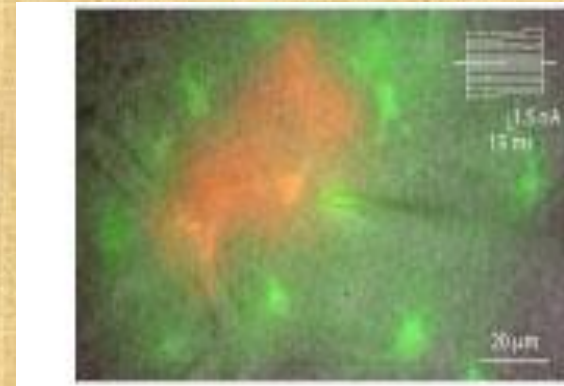
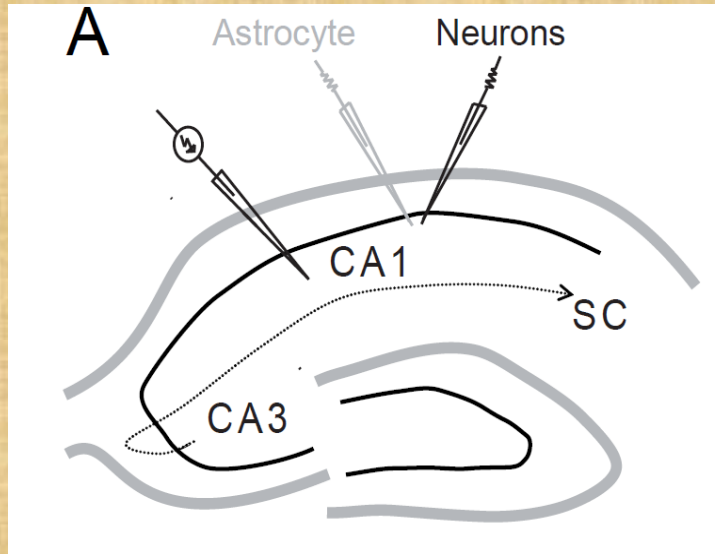
J Physiol 592.1 (2014) pp 87–102

Astroglial potassium clearance contributes to short-term plasticity of synaptically evoked currents at the tripartite synapse

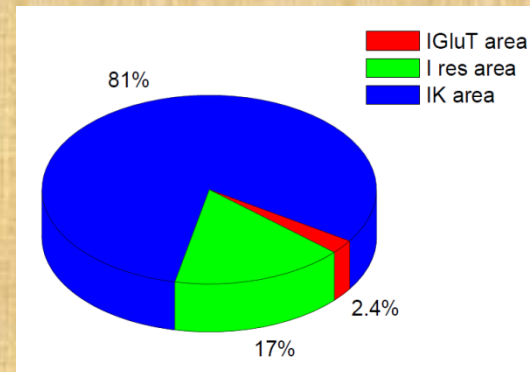
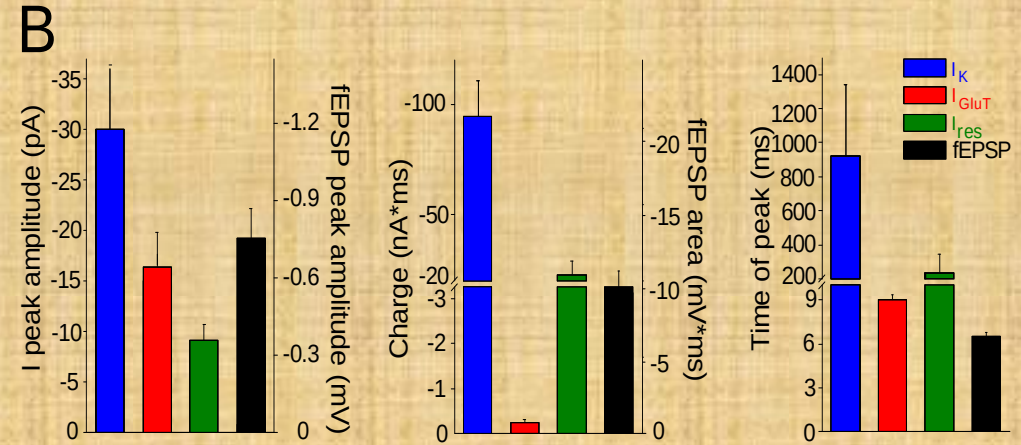
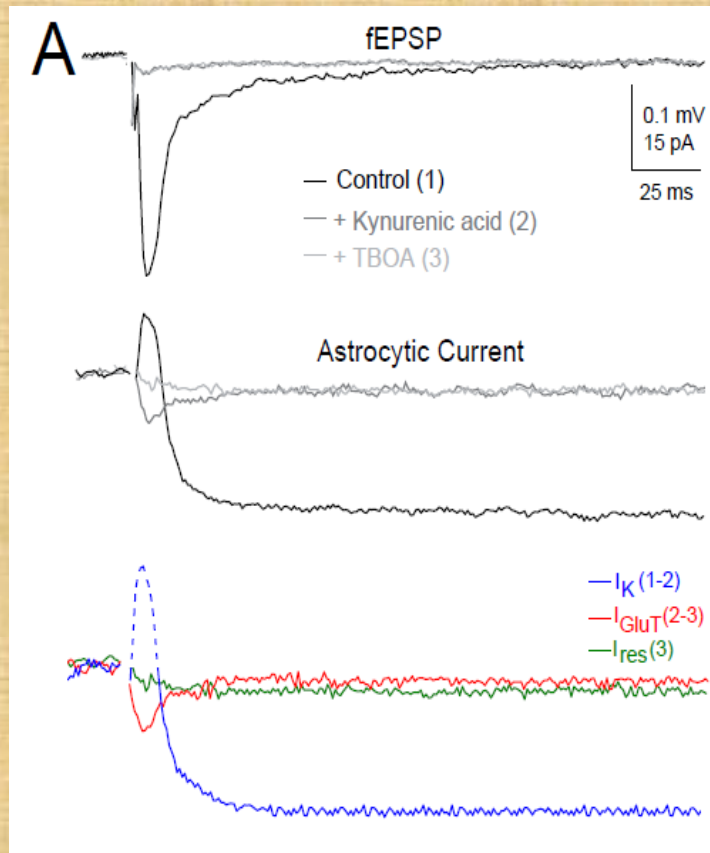
Jérémie Sibille^{1,2}, Ulrike Pannasch¹ and Nathalie Rouach¹

Pattern of synchronous responses evoked-synaptically in hippocampal neurons and astrocytes

Simultaneous recordings of neurons and astrocytes



Identification of the synaptically-evoked astroglial currents: a tripartite response with 2 dynamics

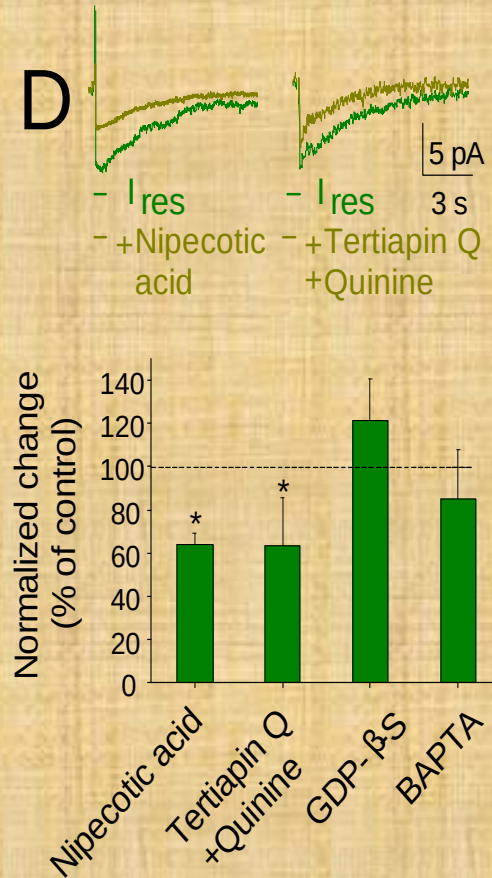
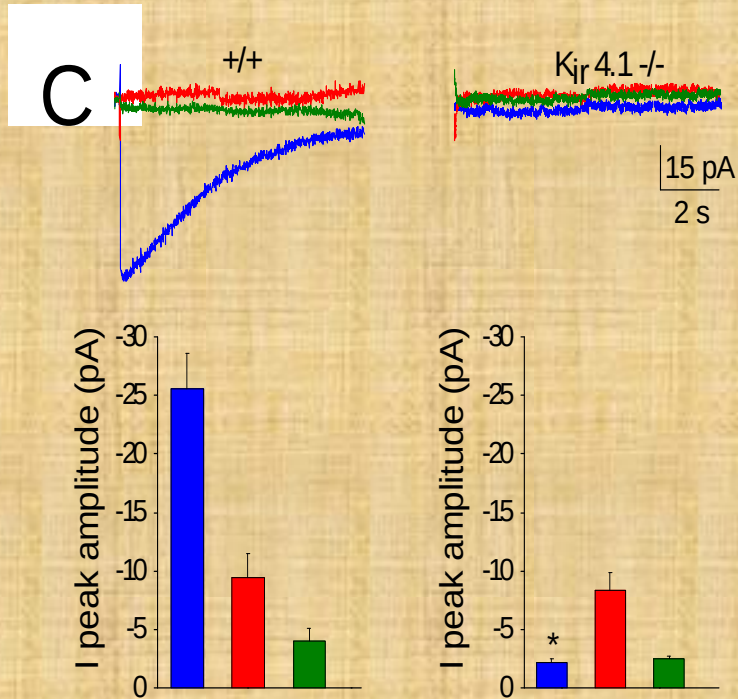


Astroglial modulation of neurotransmission at the tripartite synapse

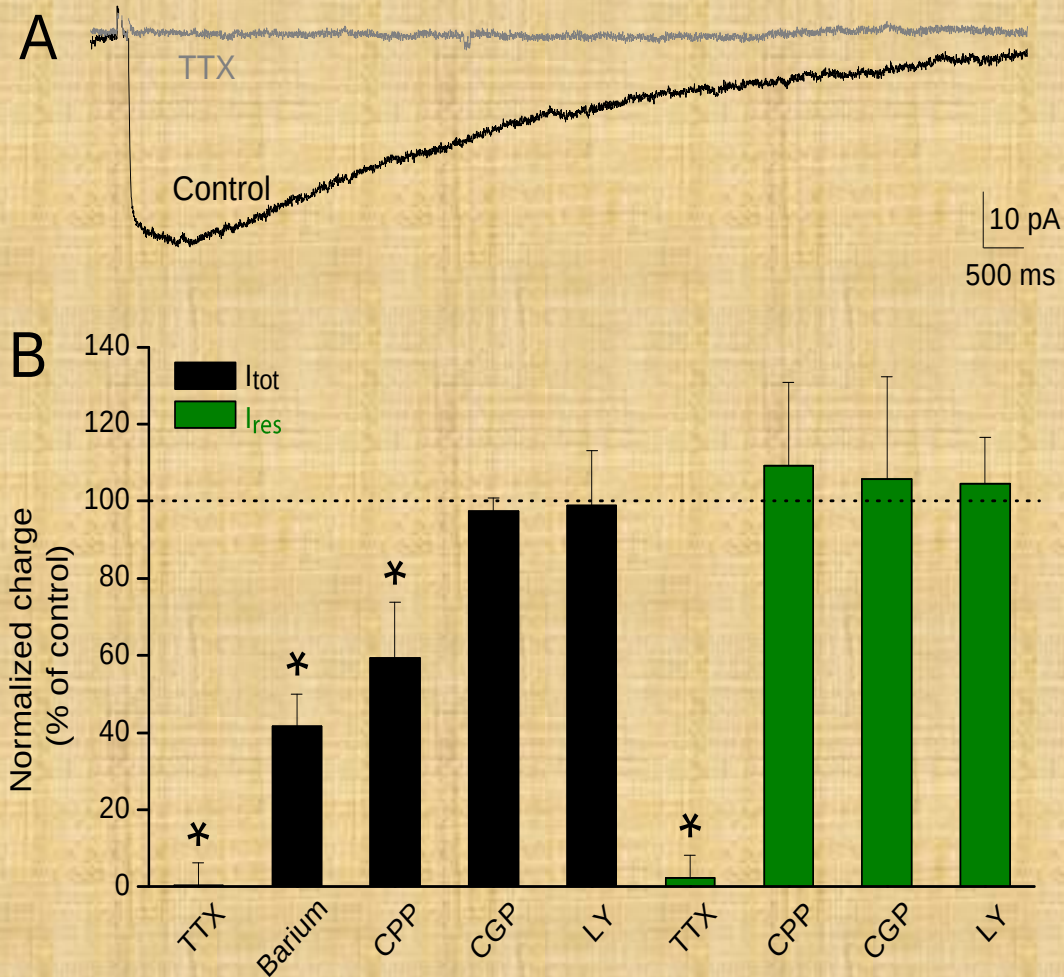
What happens to the potassium after it is released from neurons?

What is the contribution of astrocytes to Potassium clearance?

Identification of the potassium and residual currents



Astroglial total and residual currents are activity-dependent



Conclusions

1) Synaptic activity evokes a tripartite current response in hippocampal astrocytes:

- . a predominant long-lasting K^+ current
- . a transient glutamate transporter current
- . a slow residual current, partially mediated by GABAT and $K_{ir}4.1$ independent K^+ channels

2) Astroglial K^+ clearance through $K_{ir}4.1$ channels down-regulates hippocampal short-term synaptic plasticity

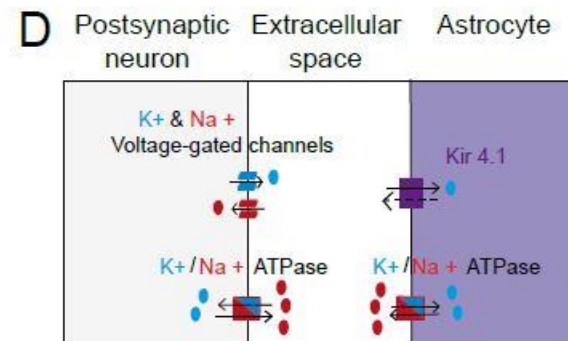
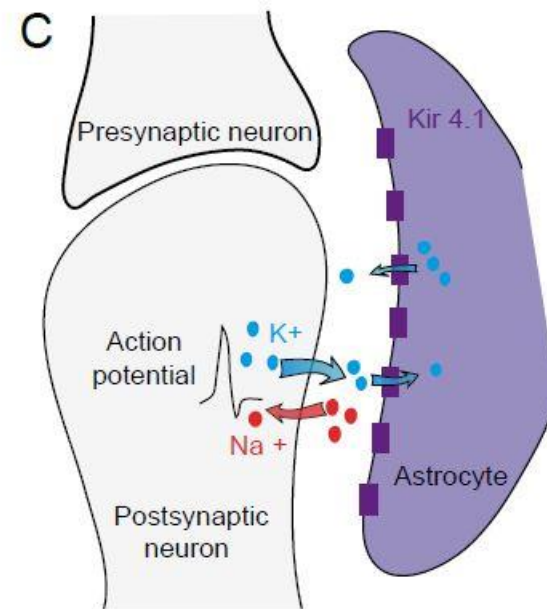
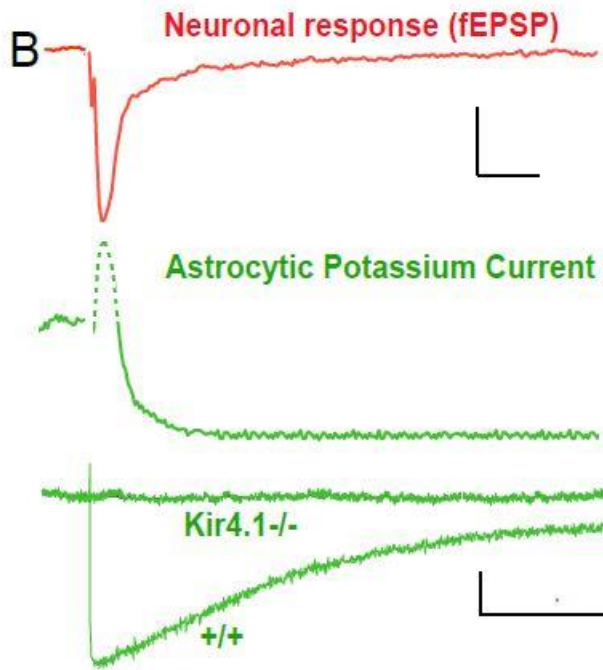
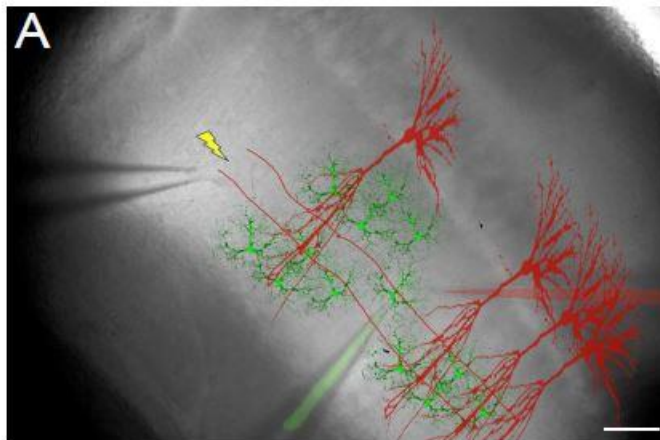
3) Limit $K_{ir}4.1^{-/-}$ mice:

- . $K_{ir}4.1$ deletion induces epilepsy and premature death
- . Conditional approach: deletion in GFAP $^+$ cells: oligodendrocytes also targeted
- . Chronic deletion possibly inducing compensations

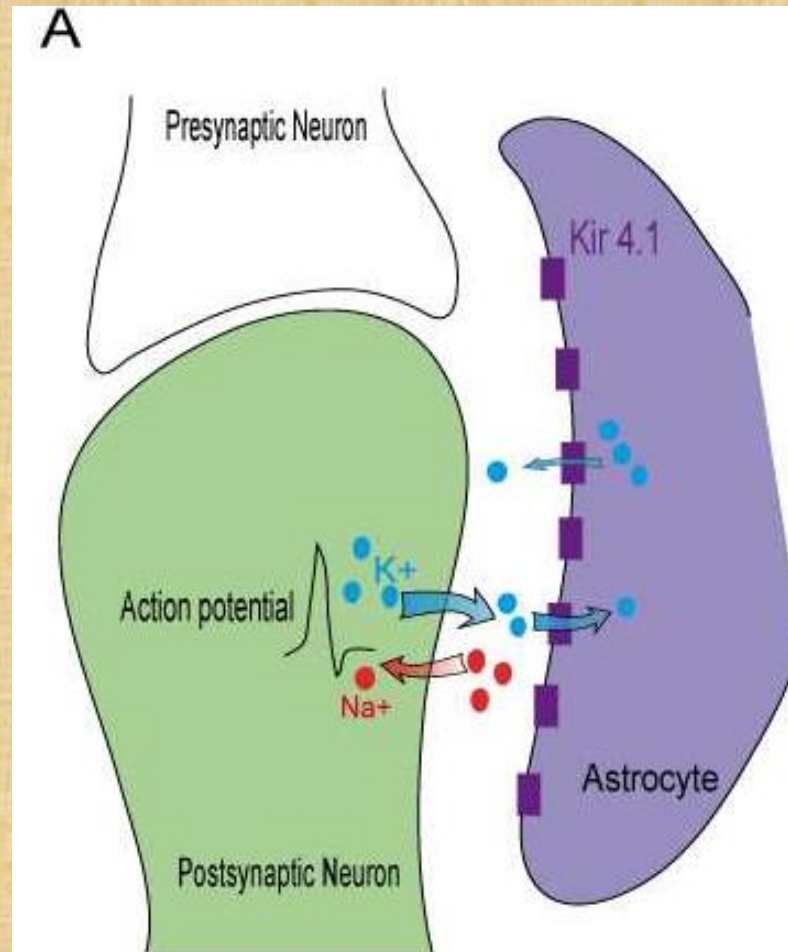
→ **Alternative approach:**

Theoretical model of K^+ neuroglial interactions to test the effect of astroglial $K_{ir}4.1$ channels acute inhibition and its role in neurotransmission

Modeling tri-compartment ionic exchange



Modelling the ionic coupling between neurons and astrocytes



Hodgkin-Huxley model for Na⁺ and K⁺ channels

$$I_{Na} = g_{Na} m^3 h (V_N - V_{rest} + V_{NaN})$$

$$I_K = g_K n^4 (V_N - V_{rest} + V_{KN})$$

$$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n \quad \beta_n(V_N) = 0.125 \exp(V_N/80) \quad (13)$$

$$\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m \quad \alpha_h(V_N) = 0.07 \exp(V_N/20) \quad (16)$$

$$\frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h \quad \alpha_n(V_N) = \frac{0.01(V_N + 10)}{\exp(0.1(V_N + 10)) - 1} \quad (12)$$

$$\beta_h(V_N) = \frac{1}{\exp(0.1(V_N + 30)) - 1} \quad (17)$$

$$\beta_m(V_N) = 4 \exp(V_N/18) \quad (15)$$

$$\alpha_m(V_N) = \frac{0.1(V_N + 25)}{\exp(0.1(V_N + 25)) - 1} \quad (14)$$

$$V_{NaN} = \frac{RT}{F} \ln \left(\frac{Na_o}{Na_N} \right)$$

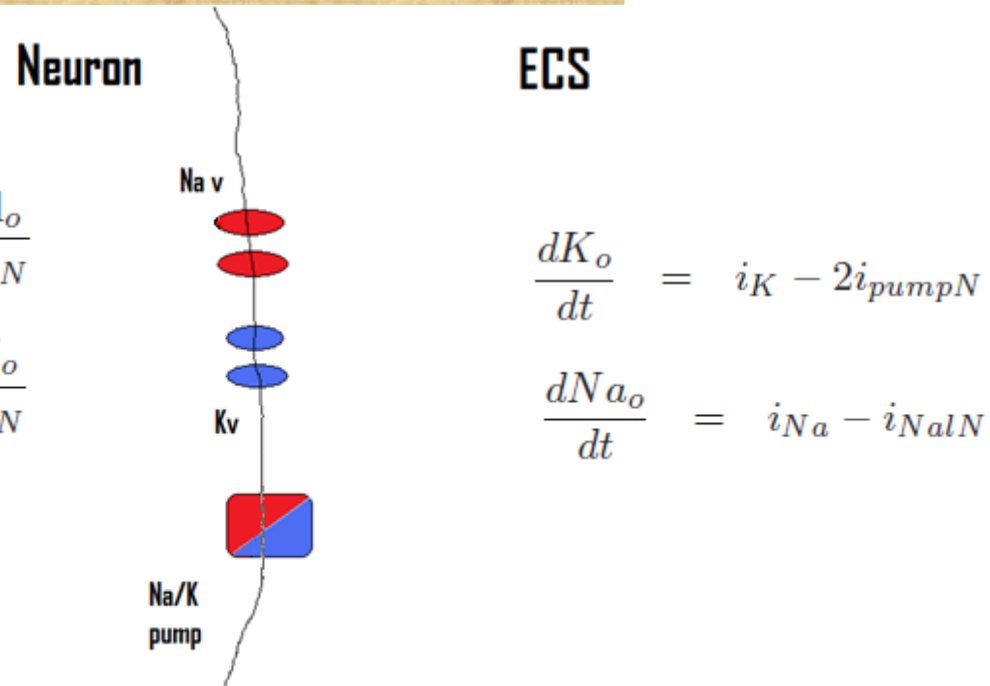
$$V_{KN} = \frac{RT}{F} \ln \left(\frac{K_o}{K_N} \right)$$

Modelling the ionic coupling between neurons and the extracellular space

$$C_N \frac{dV_N}{dt} = -(I_{Na} + I_K + I_{lN} + I_{app}),$$

$$\frac{dK_N}{dt} = (-i_K + 2i_{pumpN}) \frac{vol_o}{vol_N}$$

$$\frac{dNa_N}{dt} = (-i_{Na} + i_{lNaN}) \frac{vol_o}{vol_N}$$



$$\frac{dK_o}{dt} = i_K - 2i_{pumpN}$$

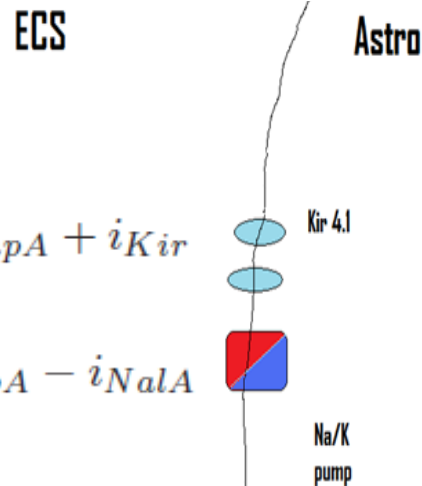
$$\frac{dNa_o}{dt} = i_{Na} - i_{NaIN}$$

$$i_{pumpN} = i_{maxN} \left(1 + \frac{7.3}{K_o}\right)^{-2} \left(1 + \frac{10}{Na_N}\right)^{-3}$$

This first part of the model accounts for the different fluxes of ions between the neurons and the extracellular space

Modelling the ionic coupling between astrocytes and the extracellular space

$$C_A \frac{dV_A}{dt} = -(I_{Kir} + I_{lA}).$$



$$\frac{dK_o}{dt} = i_K - 2i_{pumpN} - 2i_{pumpA} + i_{Kir}$$

$$\frac{dNa_o}{dt} = i_{Na} - i_{NaIN} + 3i_{pumpA} - i_{NaIA}$$

$$\frac{dK_A}{dt} = (-i_{Kir} + 2i_{pumpA}) \frac{vol_o}{vol_A},$$

$$\frac{dNa_A}{dt} = (i_{NaIA} - 3i_{pumpA}) \frac{vol_o}{vol_A}.$$

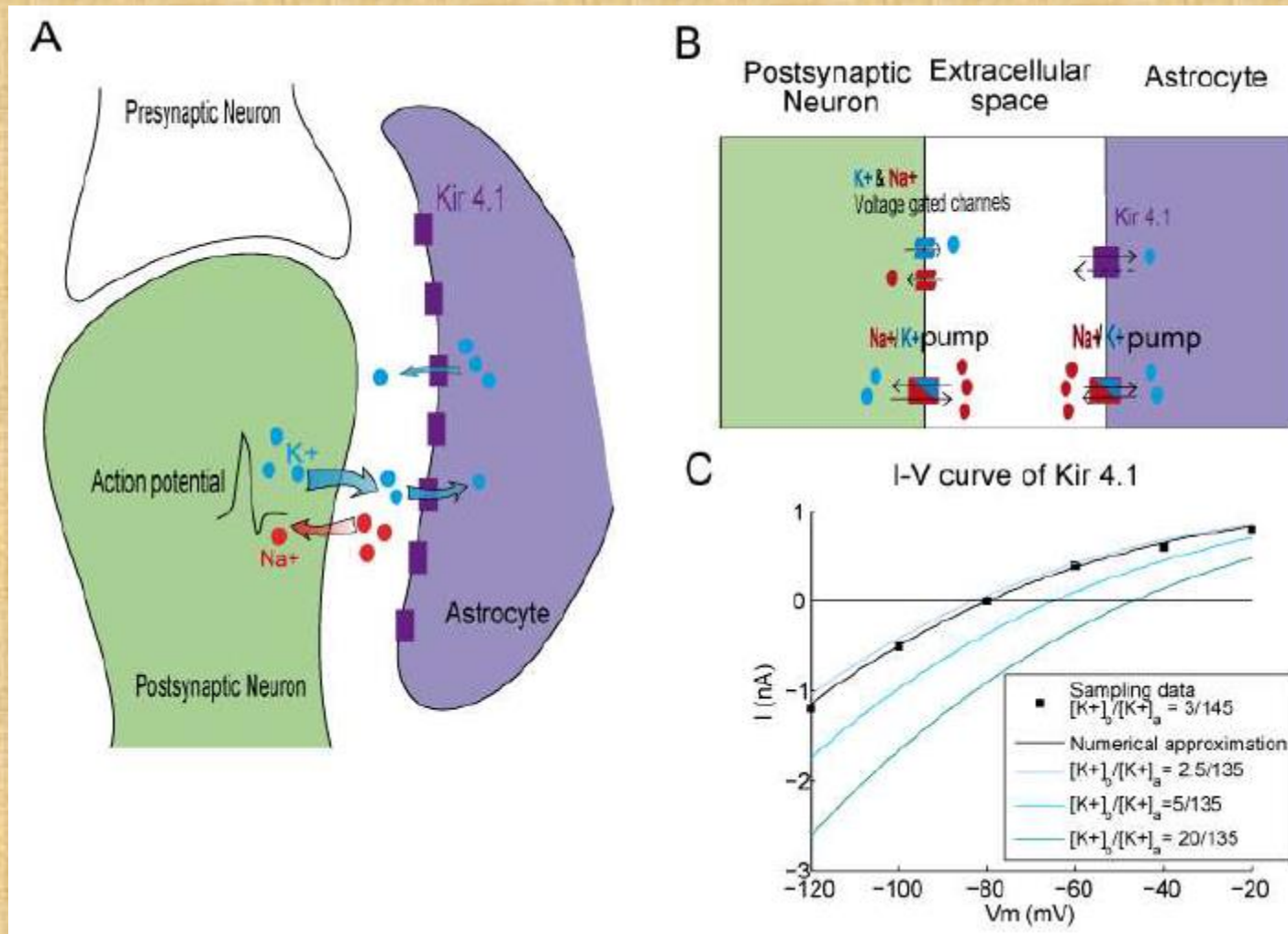
$$i_{pump,A} = i_{maxA} \left(1 + \frac{7.3}{K_o}\right)^{-2} \left(1 + \frac{10}{Na_A}\right)^{-3}$$

$$I_{Kir} = G_{maxA}(V_A - V_{KA} - V_{1A}) \left(\frac{\sqrt{K_o}}{1 + \exp\left(\frac{V_A - V_{KA} - V_{2A}}{V_{3A}}\right)} \right)$$

Modified from Siegenbeek Van Heukelom, J BioPhys. 1994

Astrocytes handle the variations of extracellular potassium together with membrane potential changes

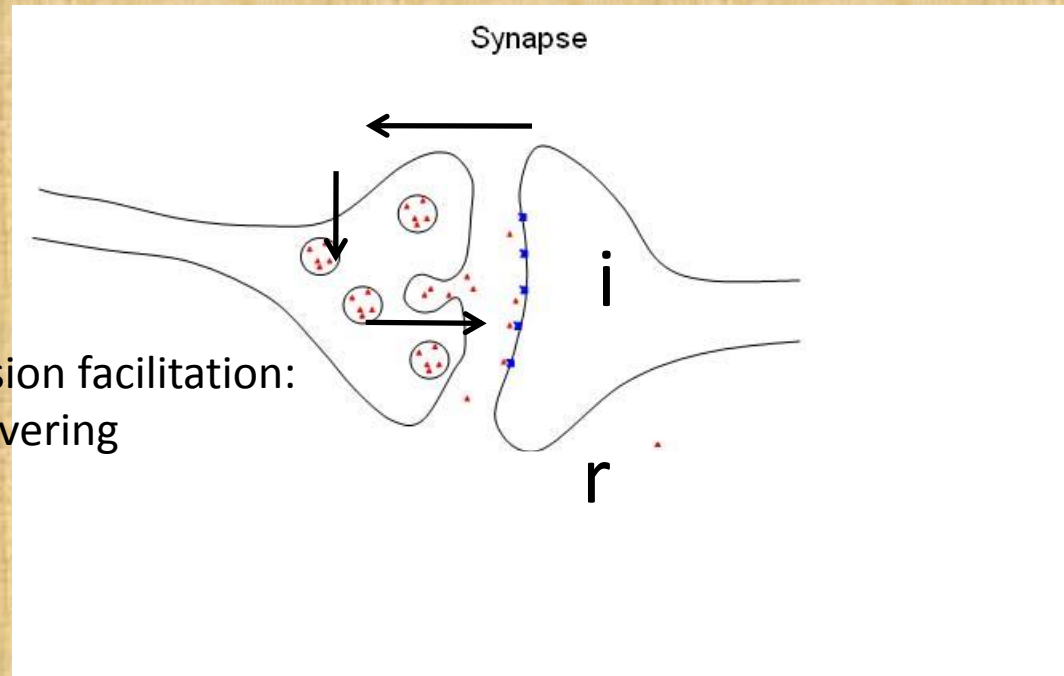
Summary of the tri-compartment model



We obtained a tri-compartment model based on mass action law that accounts for the main exchanges of ions

Modeling synaptic Short-term plasticity

Depression facilitation model



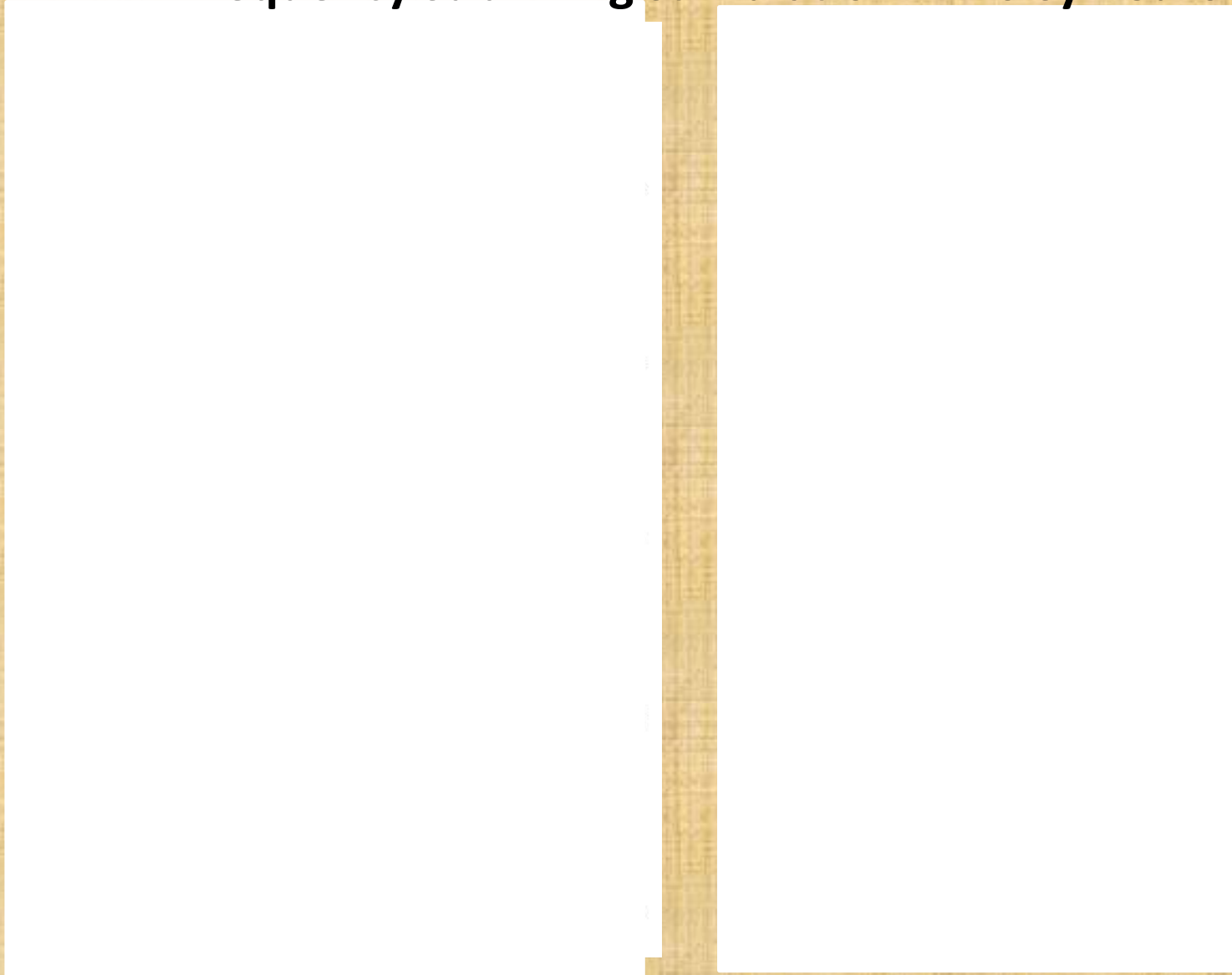
Modelling synaptic depression facilitation:
i inactive, e effective, r recovering

$$\begin{aligned}\frac{dr}{dt} &= \frac{i}{\tau_{rec}} - U_{se}r\delta(t - t_{AP}) \\ \frac{de}{dt} &= -\frac{e}{\tau_{inact}} + U_{se}r\delta(t - t_{AP}) \\ i &= 1 - r - e,\end{aligned}$$

Using the depression facilitation model allows us to simulate the responses of neurons to the stimulations that we used and compare it with our electrophysiological data.

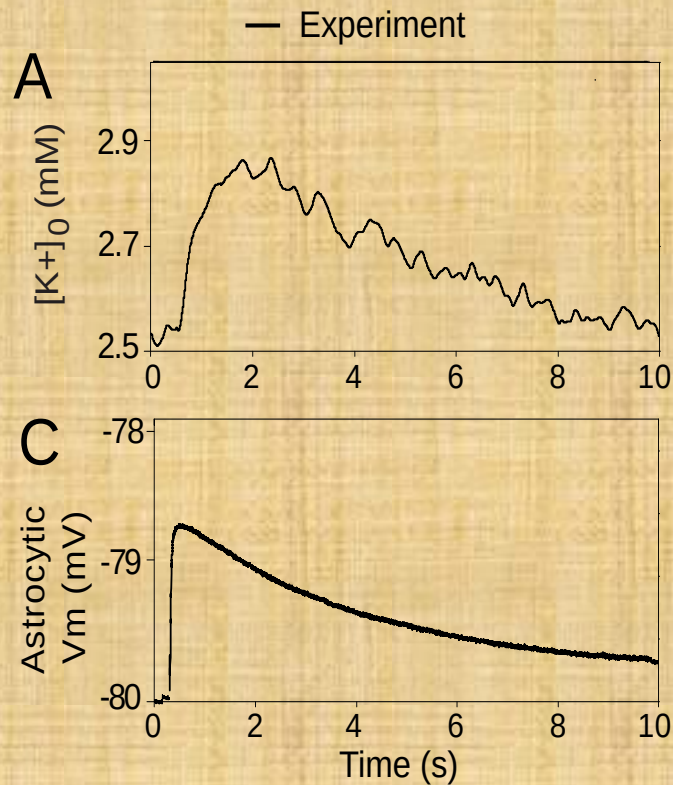
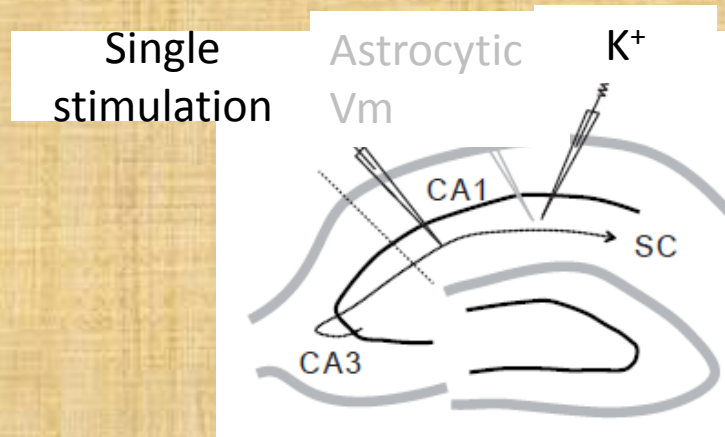
**Does Kir4.1 channels alone accounts for
proper extracellular K⁺ dynamics?**

Effect of K_{ir} 4.1 inhibition on firing probability induced by low frequency sub-firing stimulation in noisy neurons



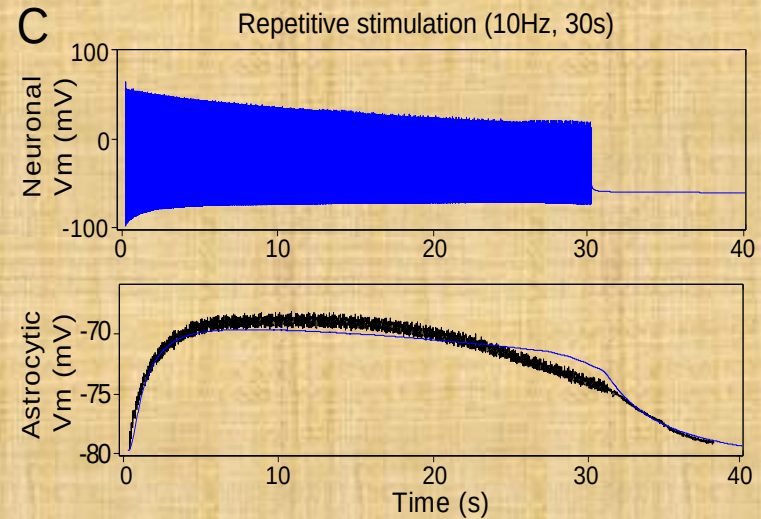
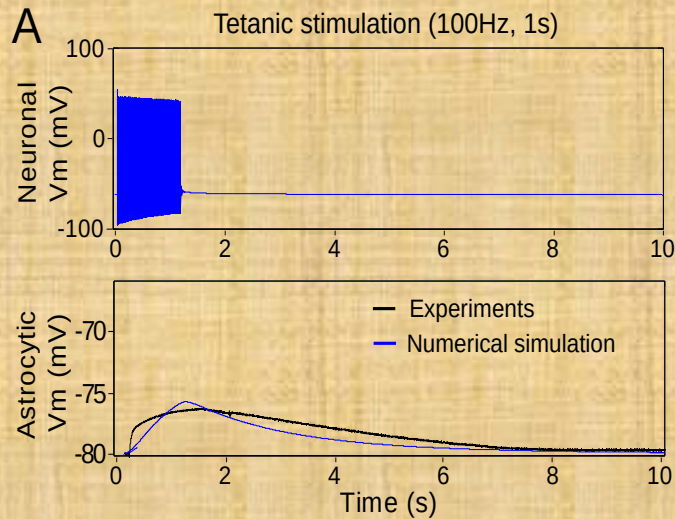
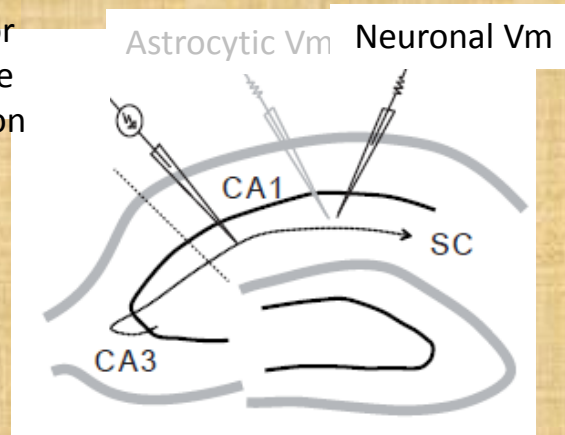
Prominent and specific involvement of astroglial K_{ir} 4.1 channels in theta rhythmic activity

Do K_{ir} 4.1 channels alone account for proper extracellular K^+ and astroglial membrane potential dynamics?



Dynamics of neuronal and astroglial membrane potential induced by trains of stimulations

Tetanic or
repetitive
stimulation



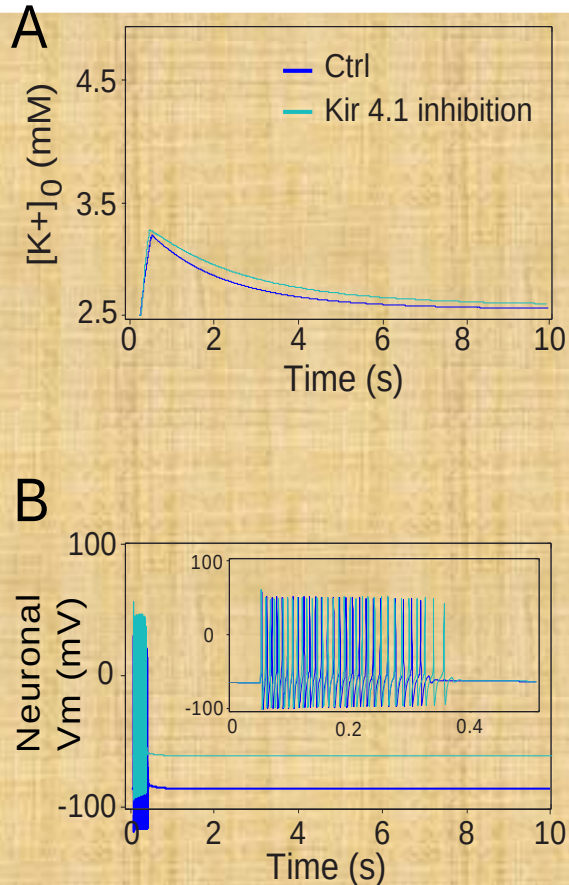
The potassium cycle between neuronal, astroglial and extracellular space compartments: timescale?

→ slow, but dynamic and efficient astroglial K^+ clearance capacity

How K_{ir} 4.1 channels acutely contribute to extracellular K^+ dynamics and neuronal firing?

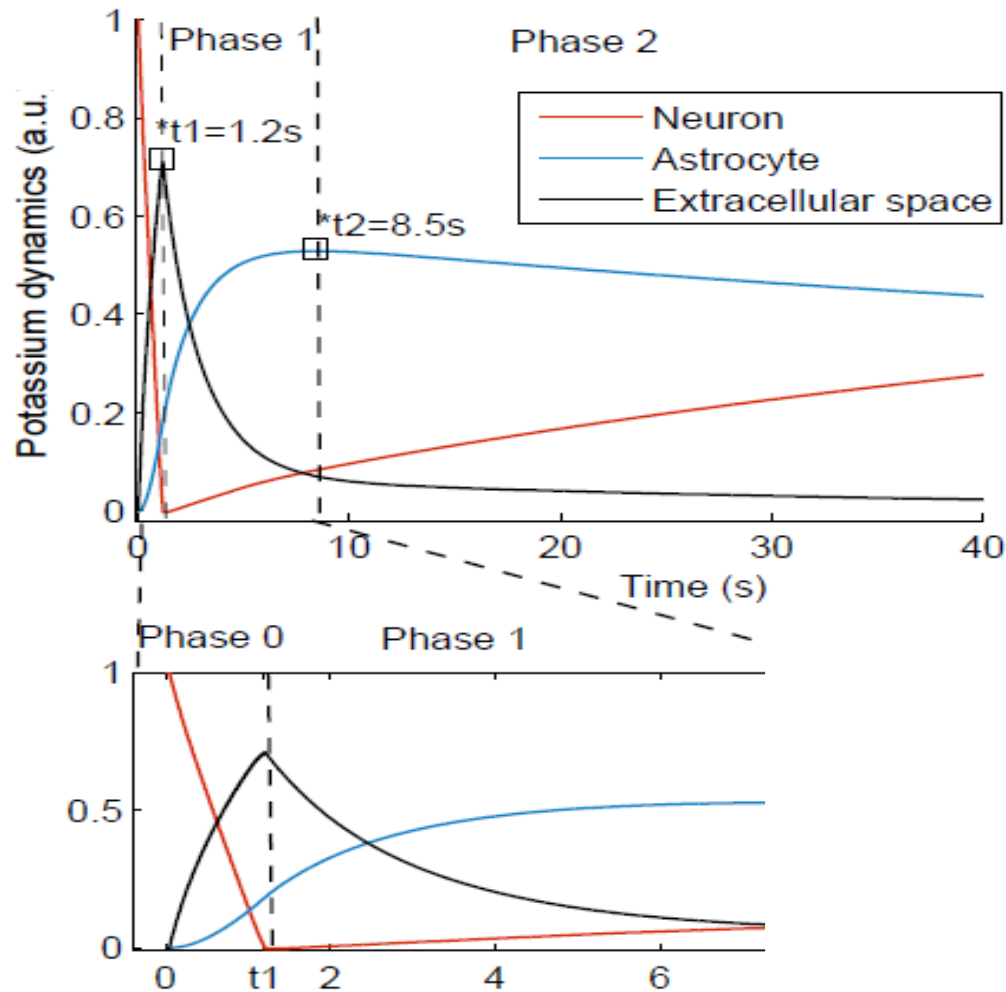
Acute inhibition of $K_{ir}4.1$ channels in the model

Single stimulation

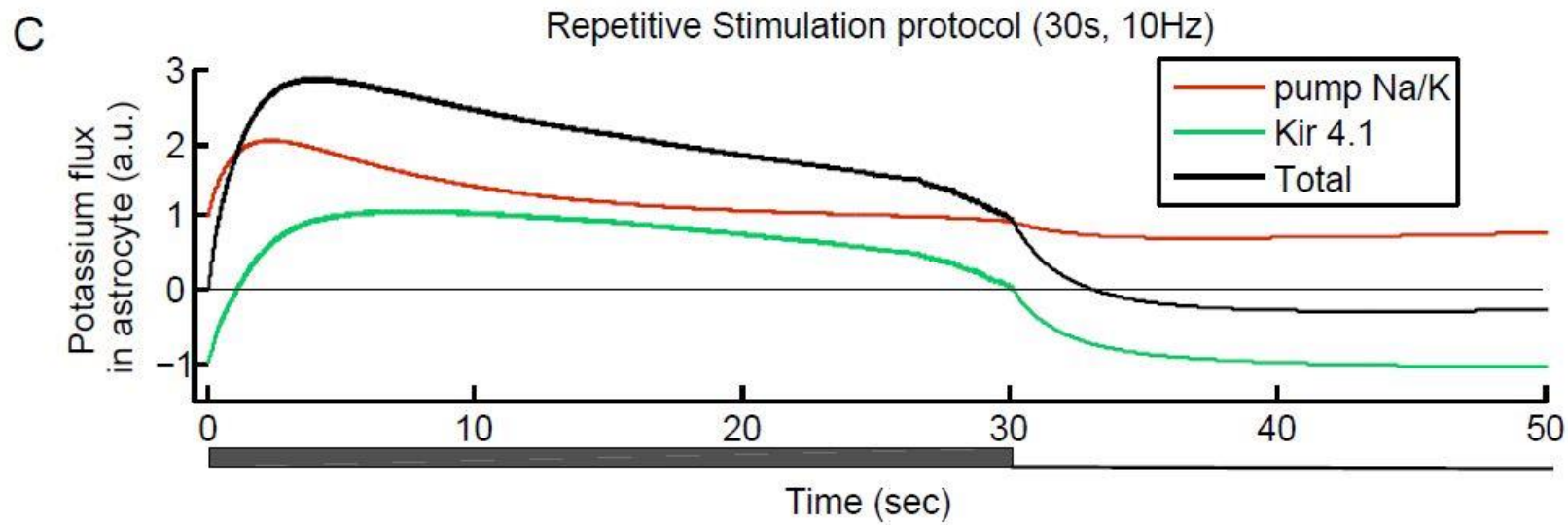
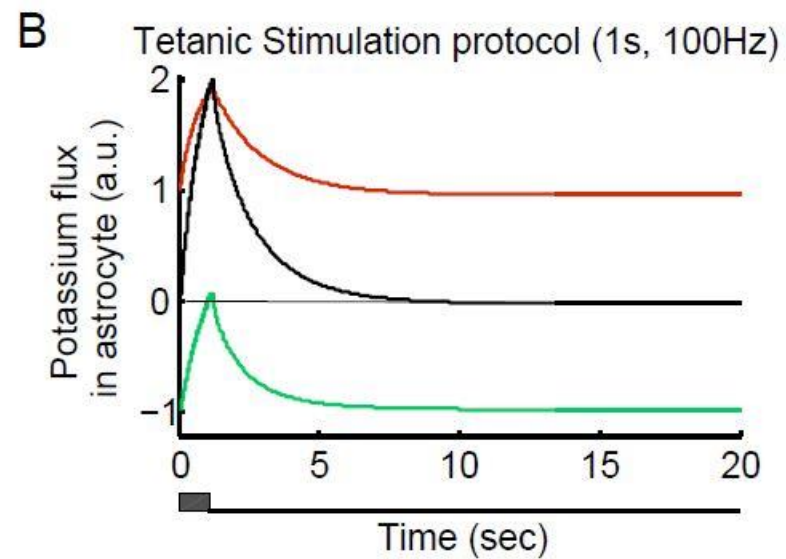
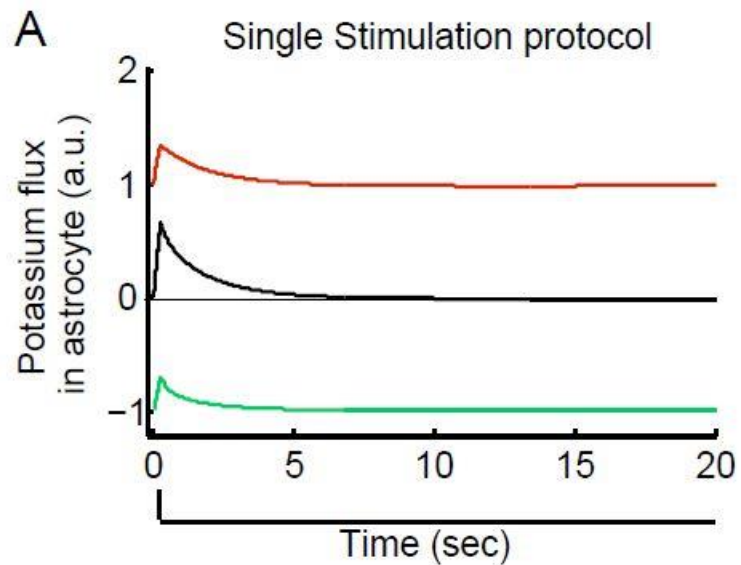


Kir4.1 channels: prominently involved in K^+ uptake during high level of activity
→ major impact on neuronal resting V_m , controlling firing during trains of stimulations

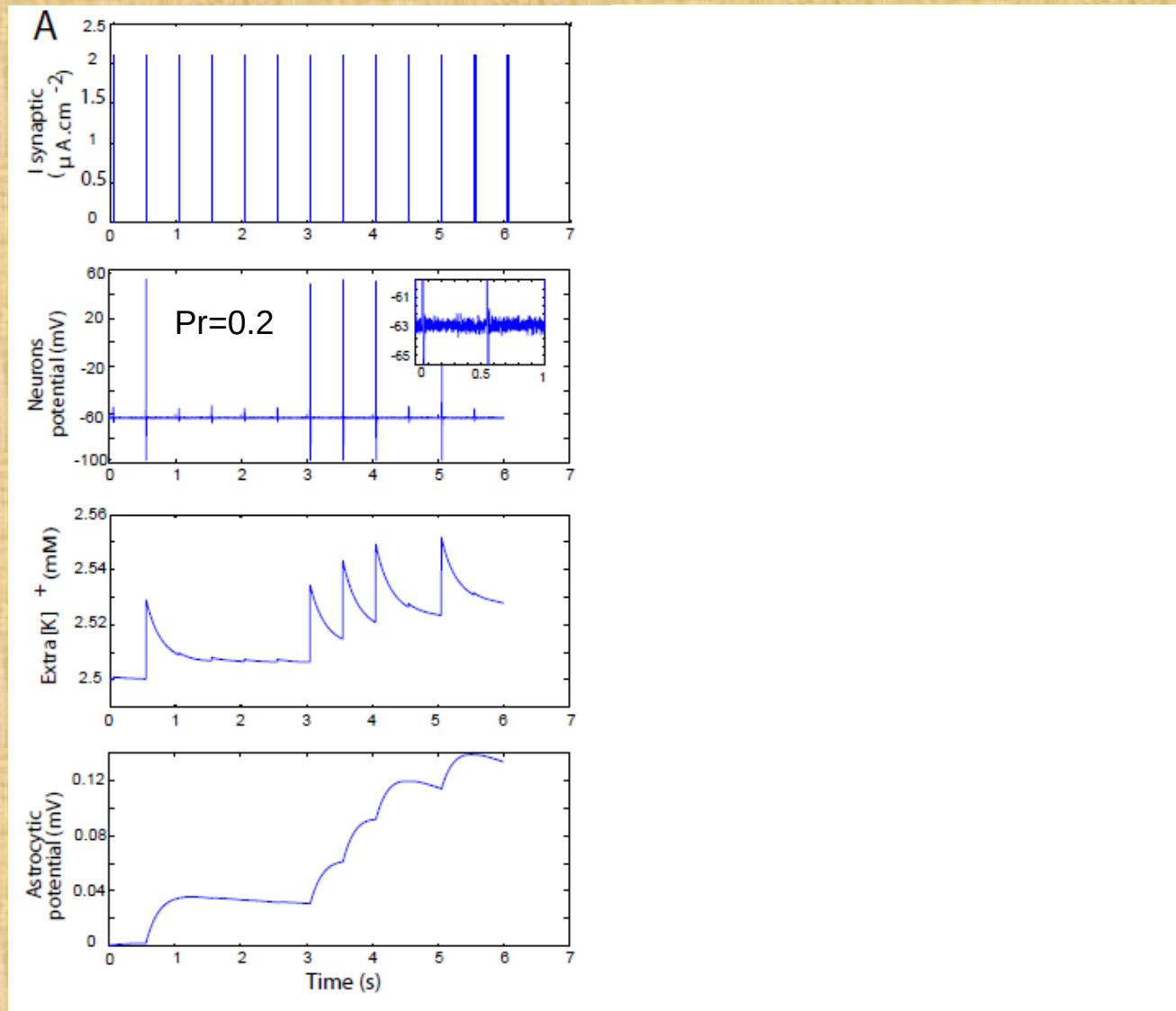
What is time scale of the potassium cycle?



The return to steady state in astrocytes after tetanic stimulations is in the order of 40s



Effect of Kir 4.1 inhibition at low neuronal activity



Kir 4.1 channels in astrocytes regulate the firing probability for frequency in the range of delta waves

Conclusions

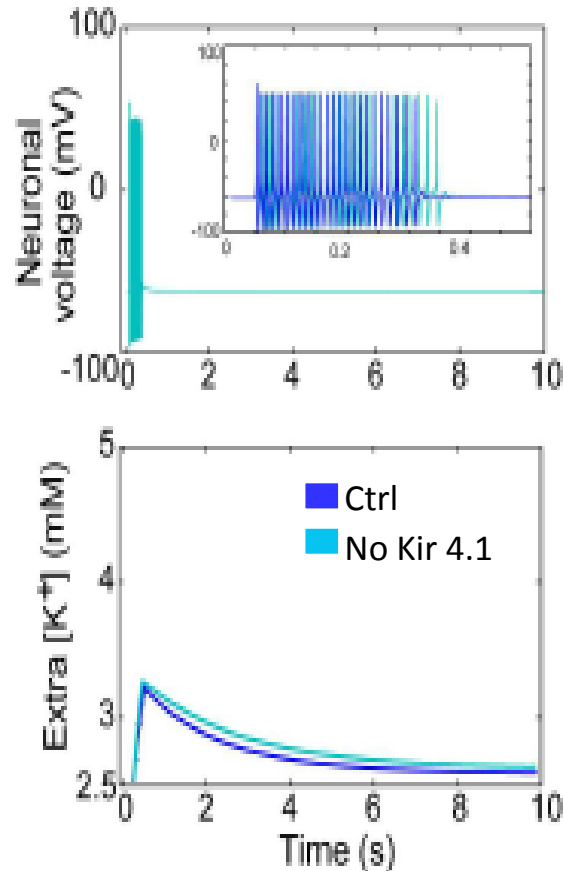
Astroglial Kir4.1 channels, key role in:

- 1) extracellular K^+ clearance
(**clear in 6-9 s** > 80% of K^+ released by neurons in response to basal or high activity)
- 2) activity-dependent astroglial and neuronal membrane potential dynamics, especially during trains of stimulation
- 3) regulating neuronal excitability for slow θ rhythmic activity (3-10 Hz)

**How Kir 4.1 channels acutely change
extracellular K⁺ dynamics ?**

Acute inhibition of Kir 4.1 channels in the model

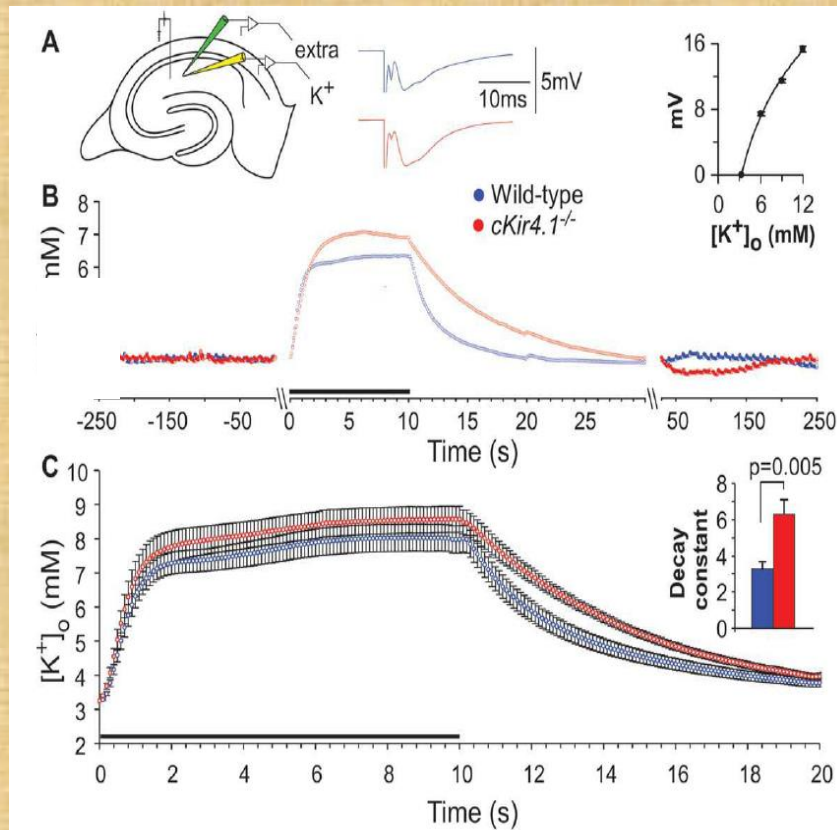
Single stimulation



Our model predicts no significant change for a single stimulation while we observed significant changes in the transient regimes after the tetanus and changes of the steady state of extracellular potassium during the repetitive stimuli

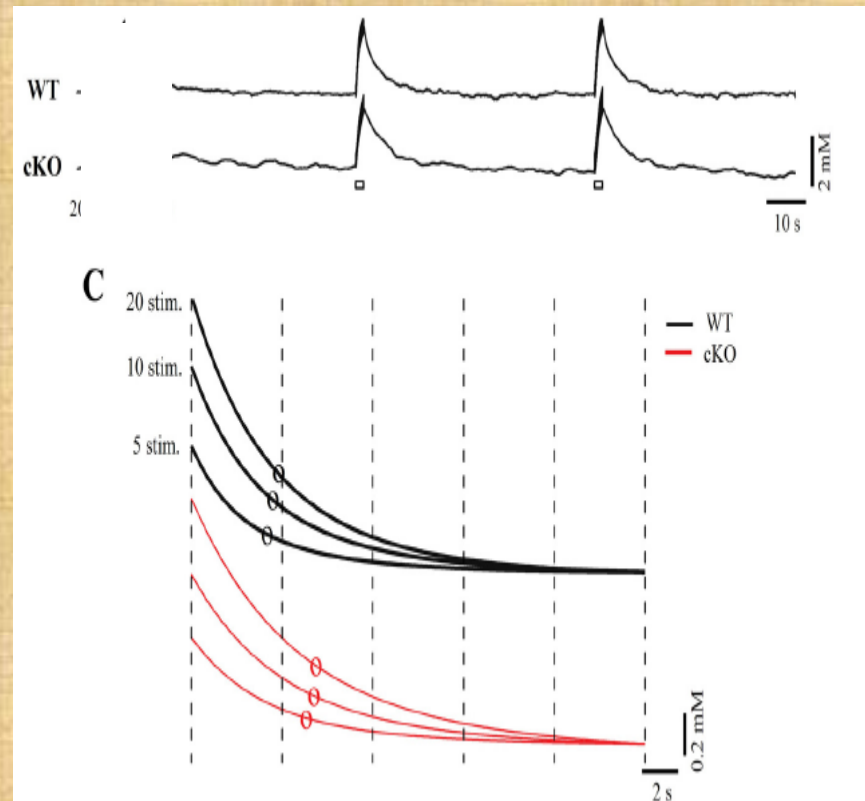
Validation of the model

On acute slice



Haj-Yasein et al. 2011, Glia

In vivo



Chever et al, 2011, J Neurosci.

In vivo and on acute slice, astroglial Kir4.1 channels deletion increases the decay time of extracellular K^+ transients following trains of stimulations