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Neuron-Astrocyte models

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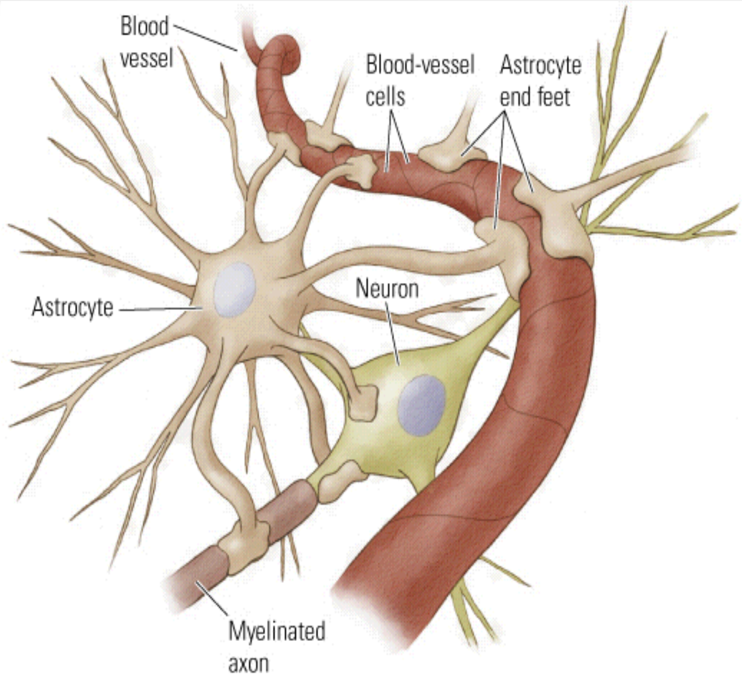
Cells in the Central Nervous Systems

Neuron
Electrical Activity

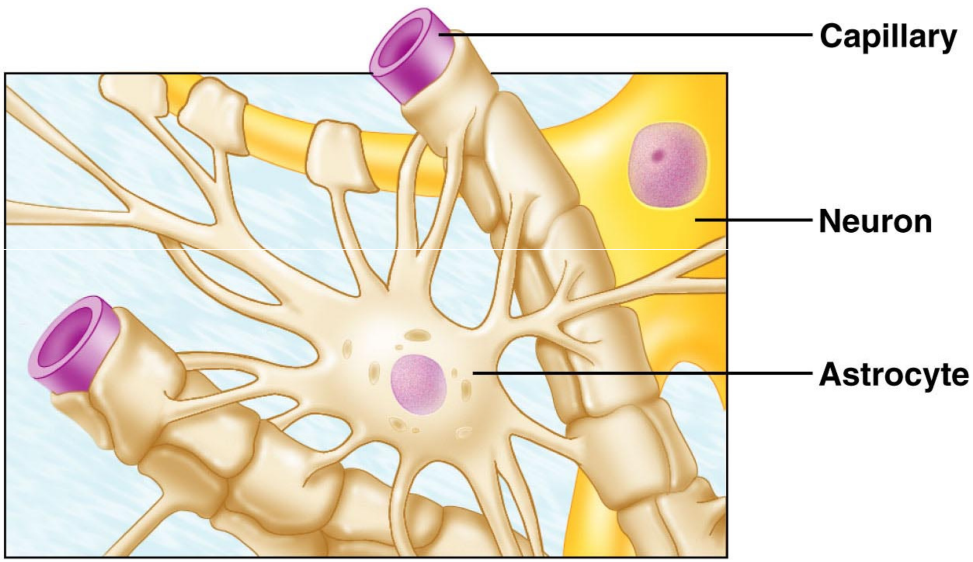


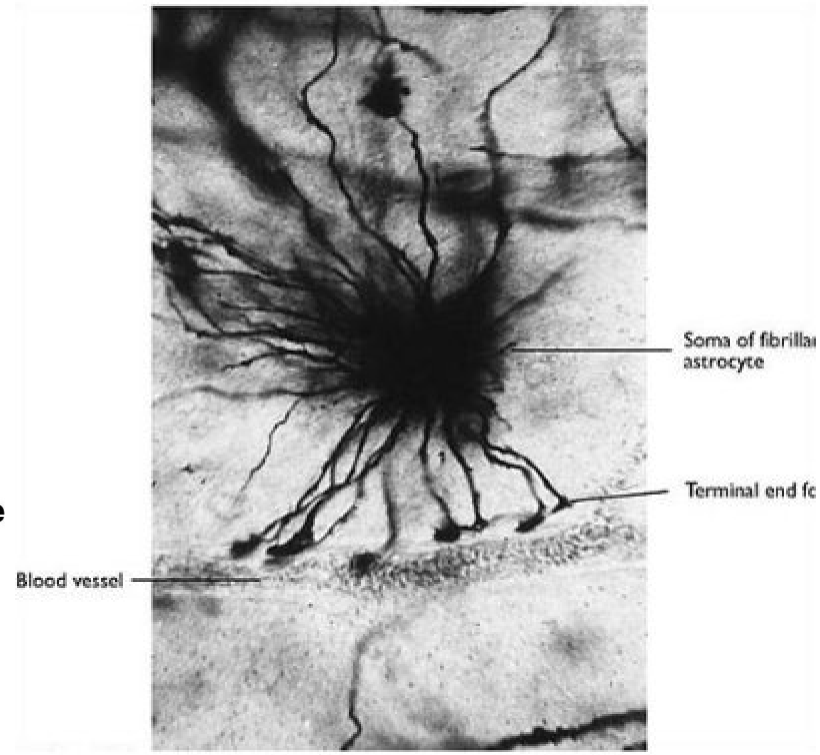
Glia
Biochemical Activity

- Astrocyte
- Oligodendrocytes
- Schwann Cell

Astrocytes.........most abundant glial cell type

Form anatomical link between neurons and arterioles





Radial astrocytes: surround ventricles
Protoplasmic astrocytes: in gray matter
Fibrous astrocytes: in white matter

Function

	AMPARs	NMDARs	P2XRs	Dopamine receptors	GABARs	Glycine receptors	MGluRs	P2YRs
Cortex	+	+	+	-	-	-	+	+
Hippocampus								
GluR cells	+	-	-	-	+	-	?	+
GluT cells	-	-	-	-	?	-	+	+
Cerebellum	+	-	-	-	+	-	+	+
Basal ganglia	?	-	-	+	-	-	?	?
Spinal cord	+	+	-	-	-	+	+	+

Development

Structural

BBB

Metabolic support

Homeostasis

Signal

(Before ~1990) Neurons are the only carriers of information in the brain.

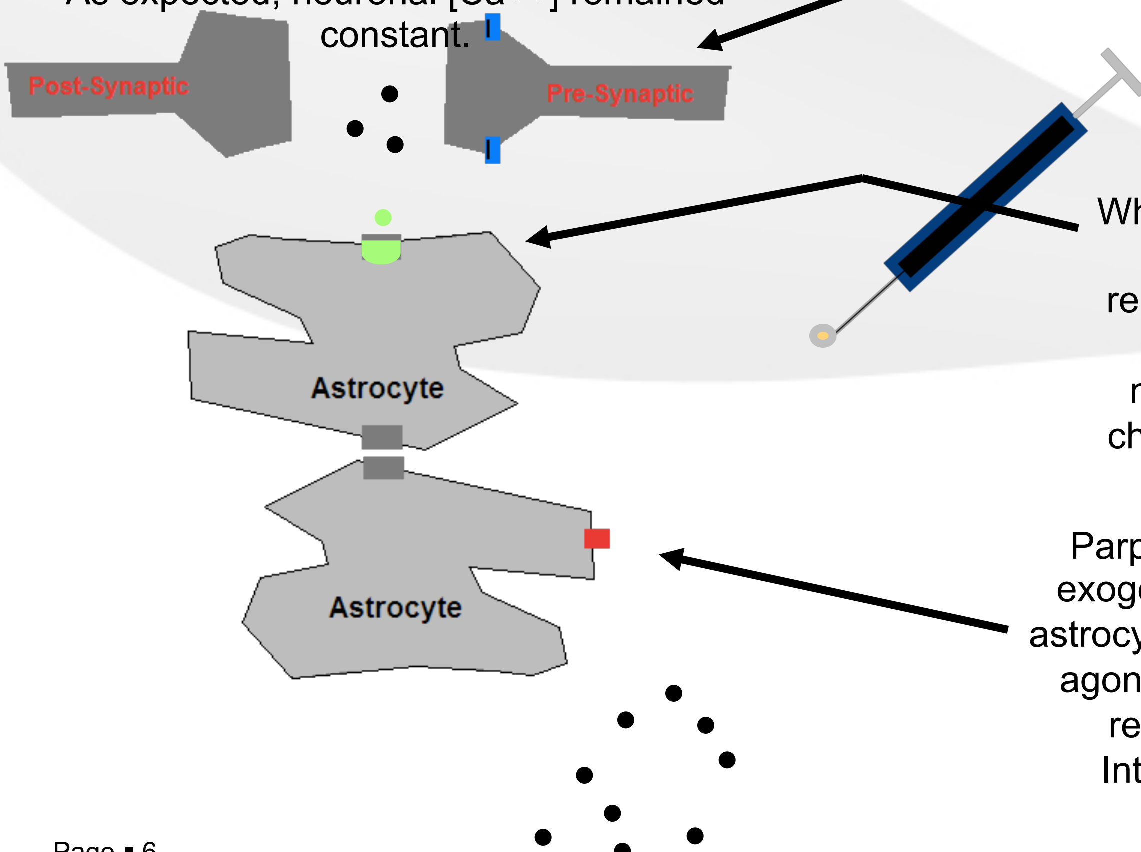
Glia cells exist only for metabolic support

For many years it was thought that process of synaptogenesis, maintenance, and elimination of synaptic contacts was solely neural responsibility

Glutamate-dependent Astrocyte Modulation of Synaptic Transmission Between Cultured Hippocampal Neurons

To confirm that the increase in neuronal Ca++ was due to an astrocytic-dependant pathway (in contrast to synaptic), Parpura introduced a mGluR antagonist, d-glutamylglycine, into the cell co-culture. As expected, neuronal [Ca++] remained constant.

Parpura measured neuronal [Ca++] after Bradykinin injection, and found that Ca++ waves in astrocytes induced a neural Ca++ rise. This leads to a greater potential for synaptic activity.



When [Ca++] rises in astrocytes adjacent to the co-cultured neurons, glutamate is released (through exocytosis) and binds to ionotropic glutamate receptors on the neural membrane. This opens Ca++ ion channels to, and extrasynaptic Ca++ flows into the neuron.

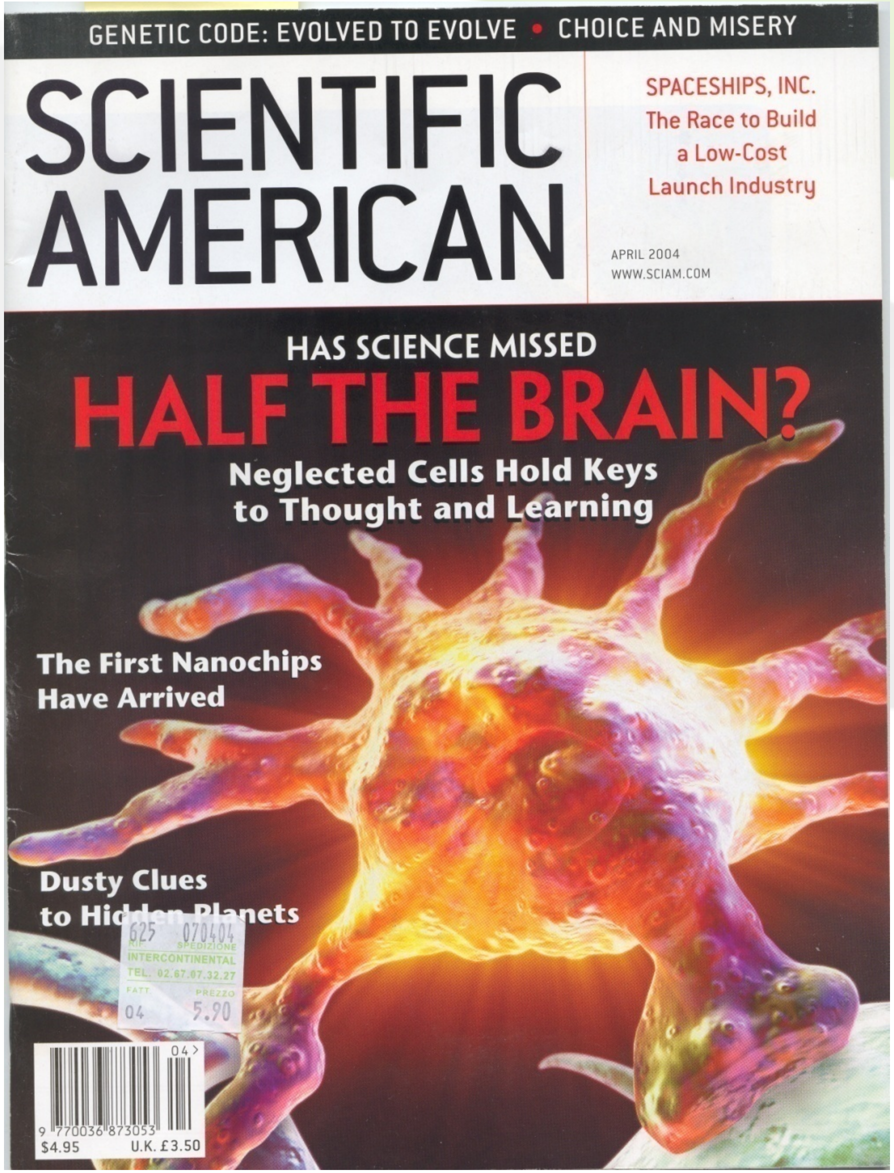
Parpura et al. introduced Bradykinin, an exogenous neuro-ligand, into the neuron-astrocyte co-culture. This glutamate receptor agonist bound to metabotropic glutamate receptor sites on a distal Astrocyte. Intracellular [Ca++] rises, eventually propagating into a global wave.

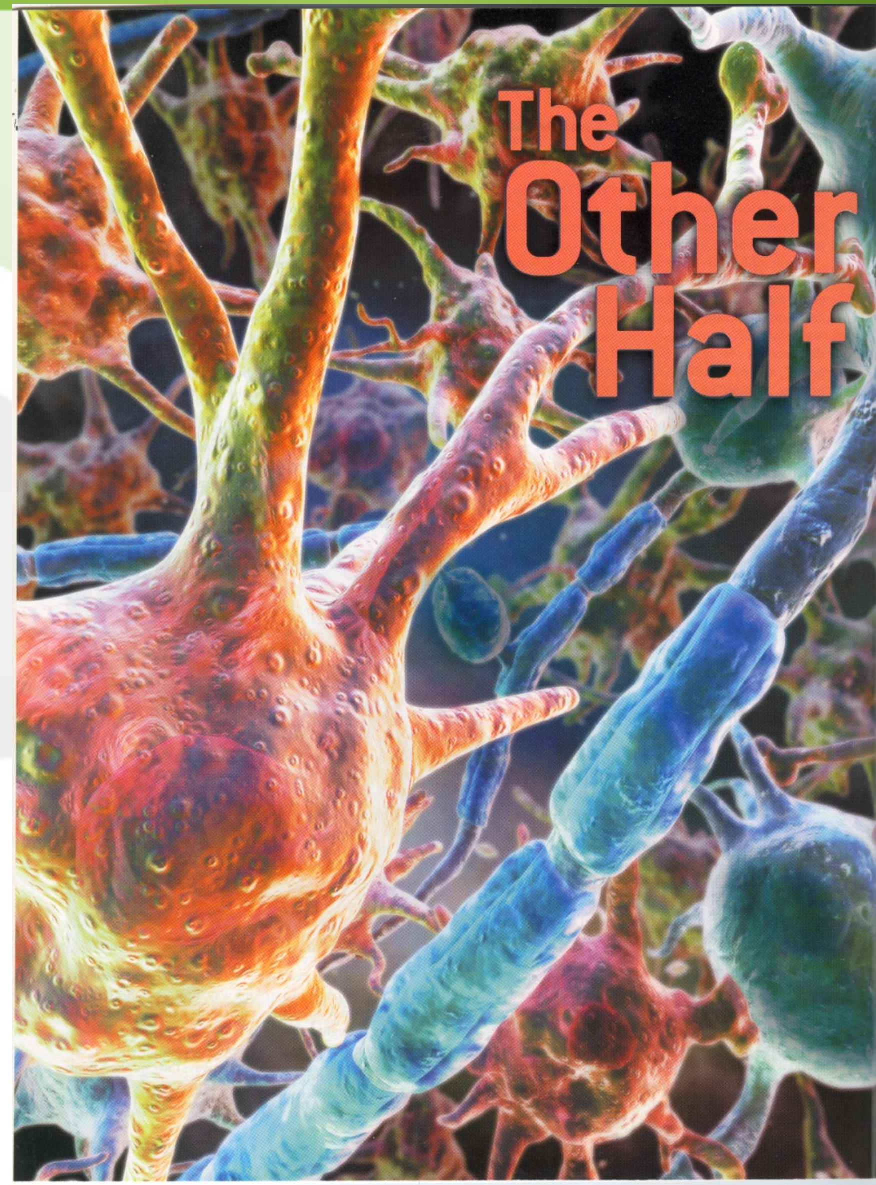
Before 1990: ***Structural support for neurons***

1990-2000: *"housekeeping" cells with active support roles*

- Buffering and siphoning of $[K^+]_{out}$ and $[Ca^{2+}]_{out}$ after excessive firing
- Uptake of neurotransmitters
  - glutamate (Pellerin and Magistretti, 1994), GABA,
- Release of gliotransmitters
  - glutamate (Parpura et al., 1994), ATP, D-serine, GABA, growth factors, , Ca^{2+}-binding buffers (2013)
- Respond to synaptic activity by increasing $[Ca^{2+}]_i$
- Glutamate-mediated modulation of synaptic transmission
  - Concept of tripartite synapse (Araque et al., 1999).

Then…the other half of the brain



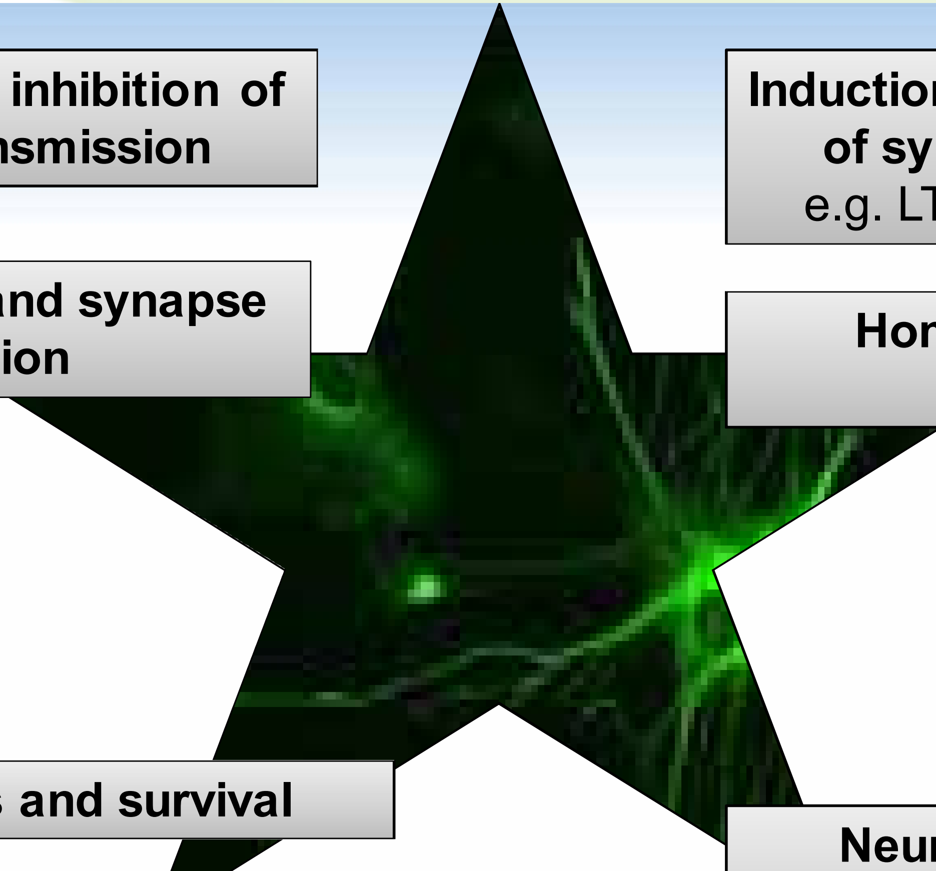


Stimulation and inhibition of synaptic transmission

Induction and maintenance of synaptic plasticity
e.g. LTP, LTD, STDP,

Neurogenesis and synapse formation

Homo/heterosynaptic plasticity



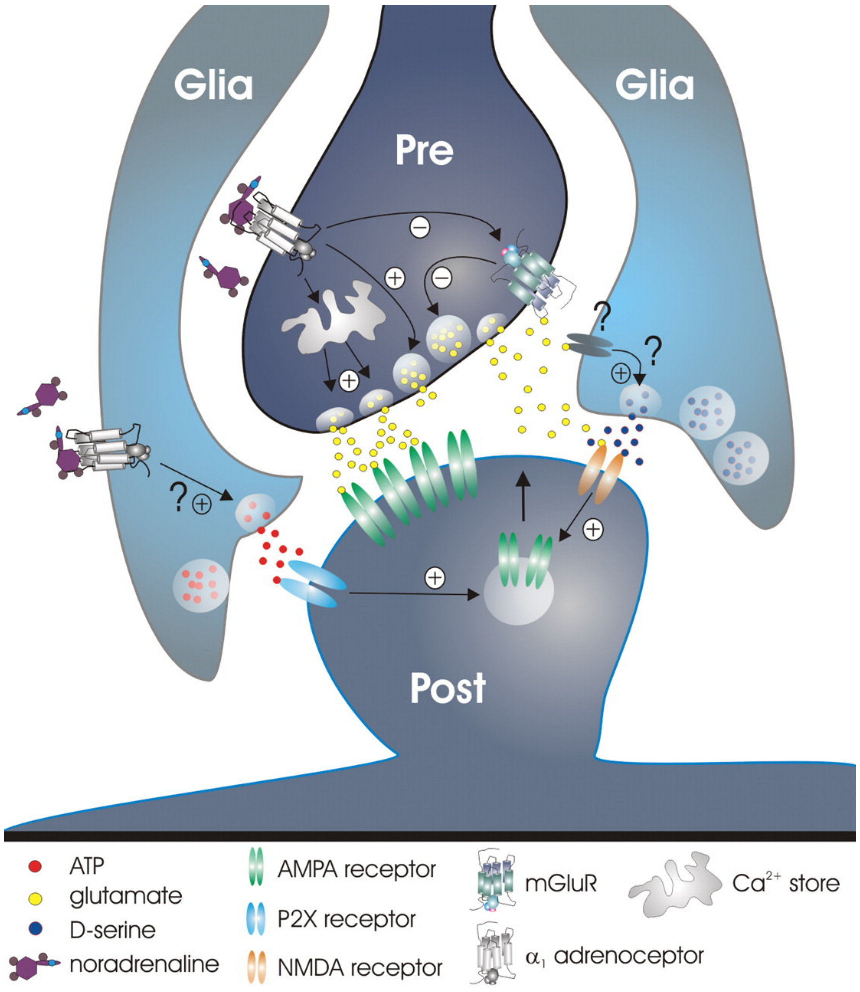
Homeostasis and survival

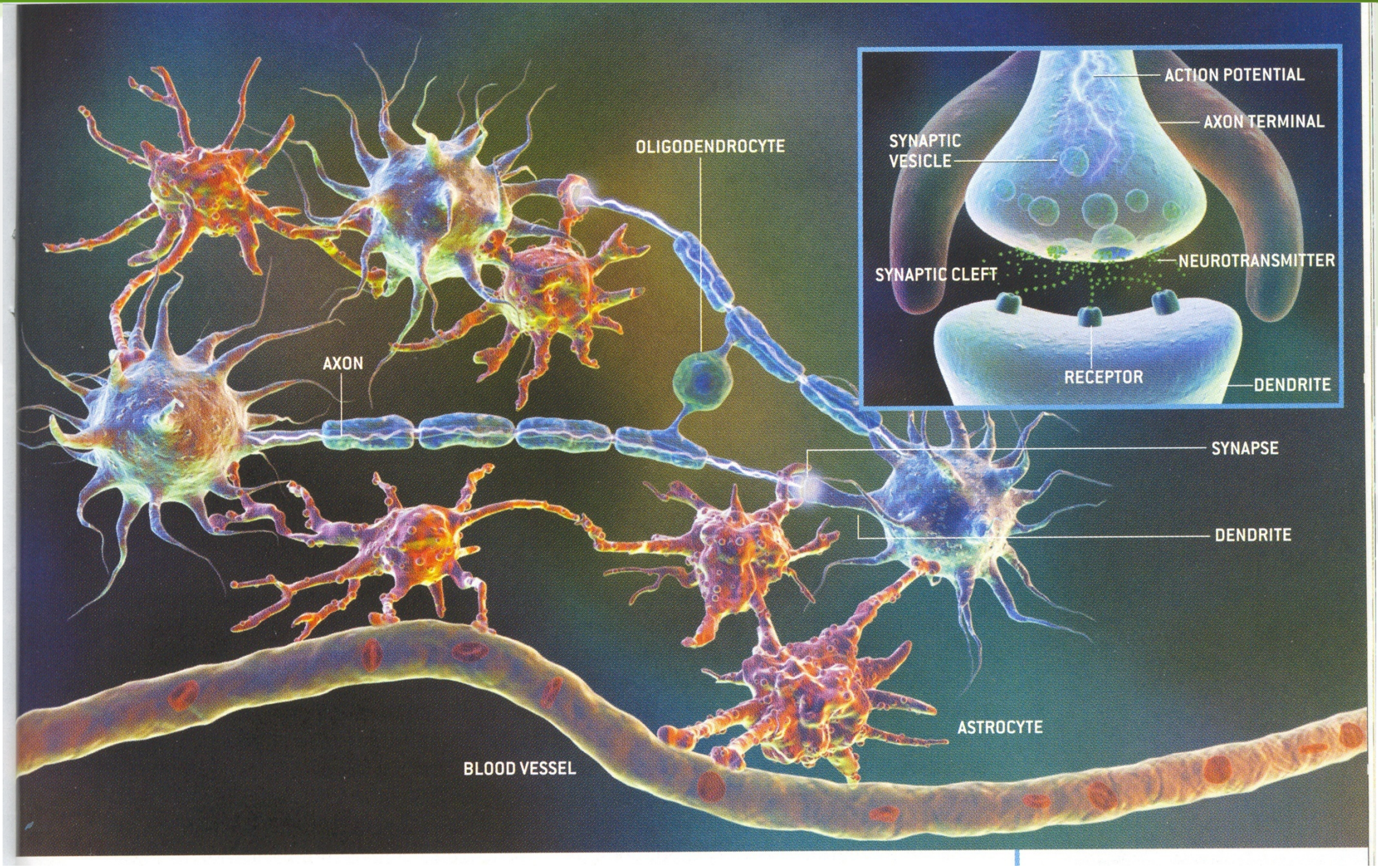
Control of CNS blood circulation

Neuronal metabolism

Neurological disorders and neurodegenerative diseases

Tripartate synapse

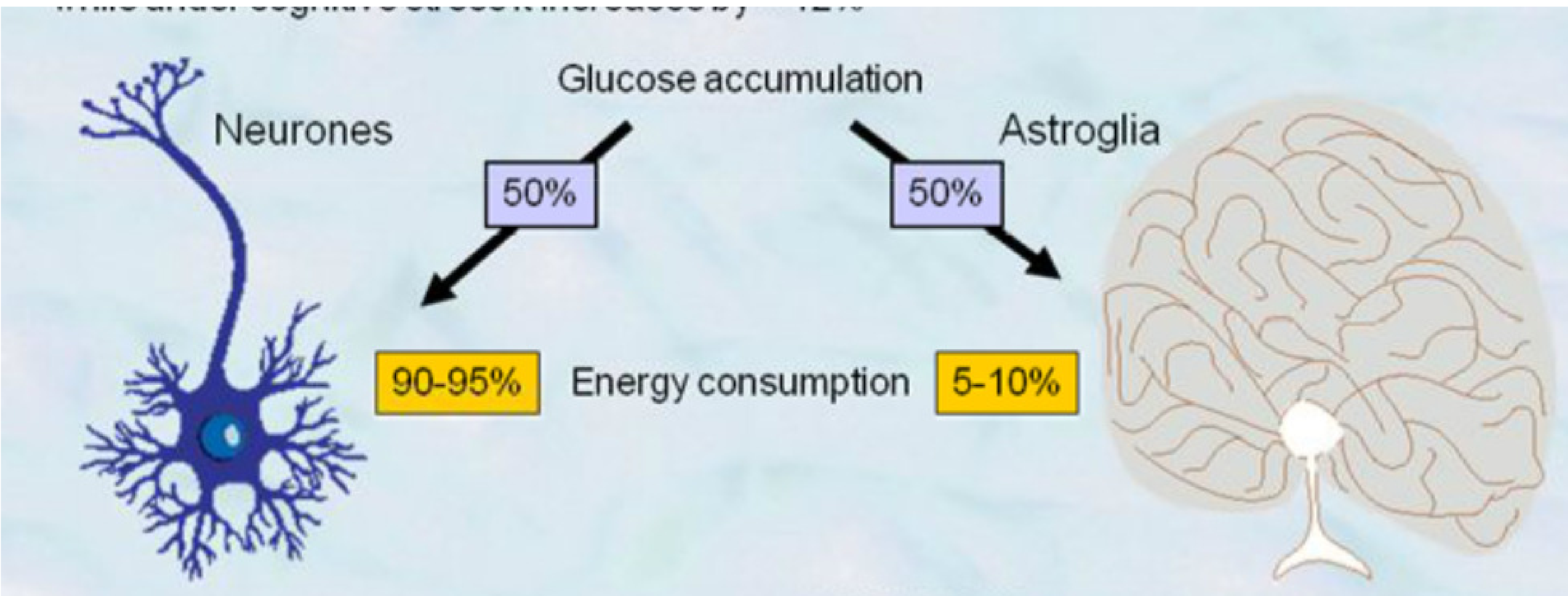



ACTION POTENTIAL
AXON TERMINAL
SYNAPTIC VESICLE
NEUROTRANSMITTER
SYNAPTIC CLEFT
RECEPTOR
DENDRITE
OLIGODENDROCYTE
AXON
SYNAPSE
DENDRITE
ASTROCYTE
BLOOD VESSEL

Ca^{2+} Role in the Intracellular and intercellular communication

Metabolism

Brain represents approx 2% of total body mass, but consumes 20% of total energy
-decreases by 40% during sleep
-increases by 12% under cognitive stress

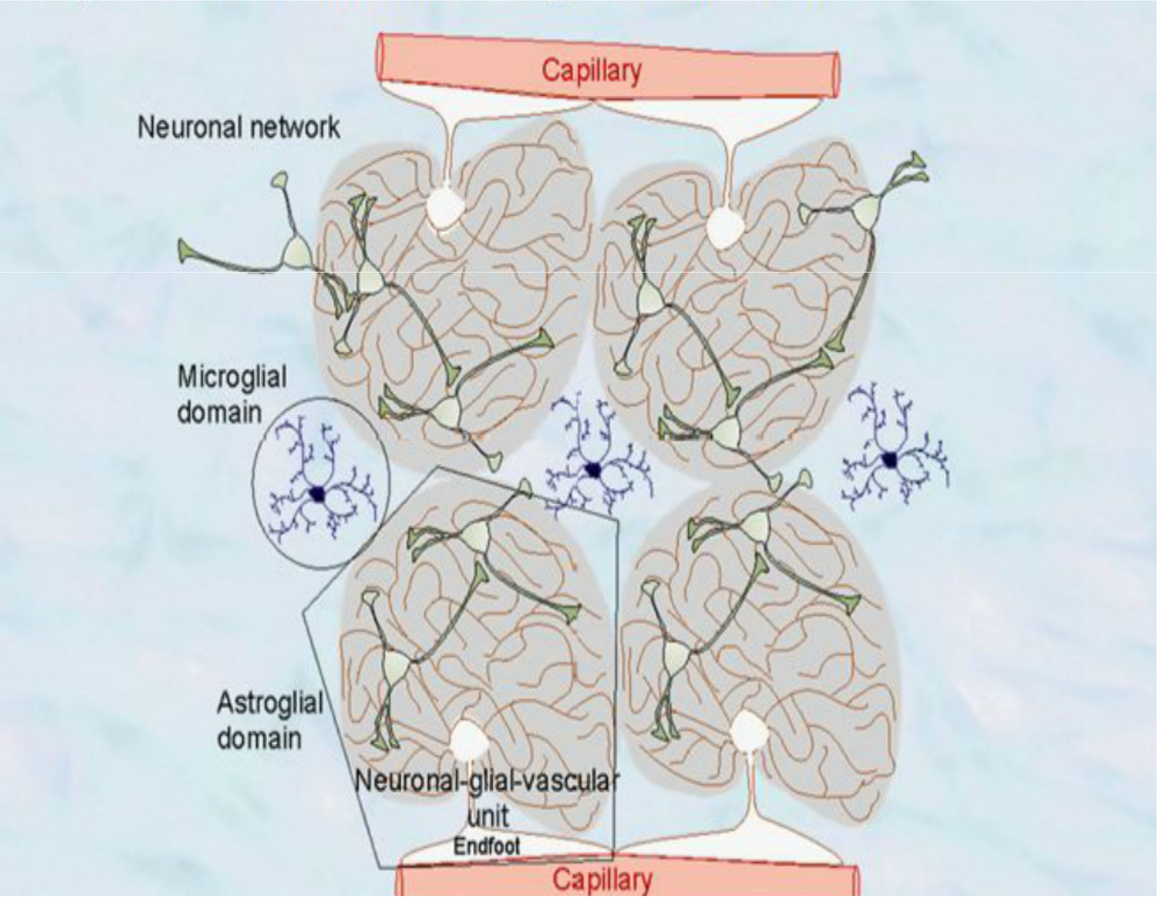


Energy for transmembrane ion gradients

Development	**Structural**	BBB
Metabolic support	Homeostasis	Signal

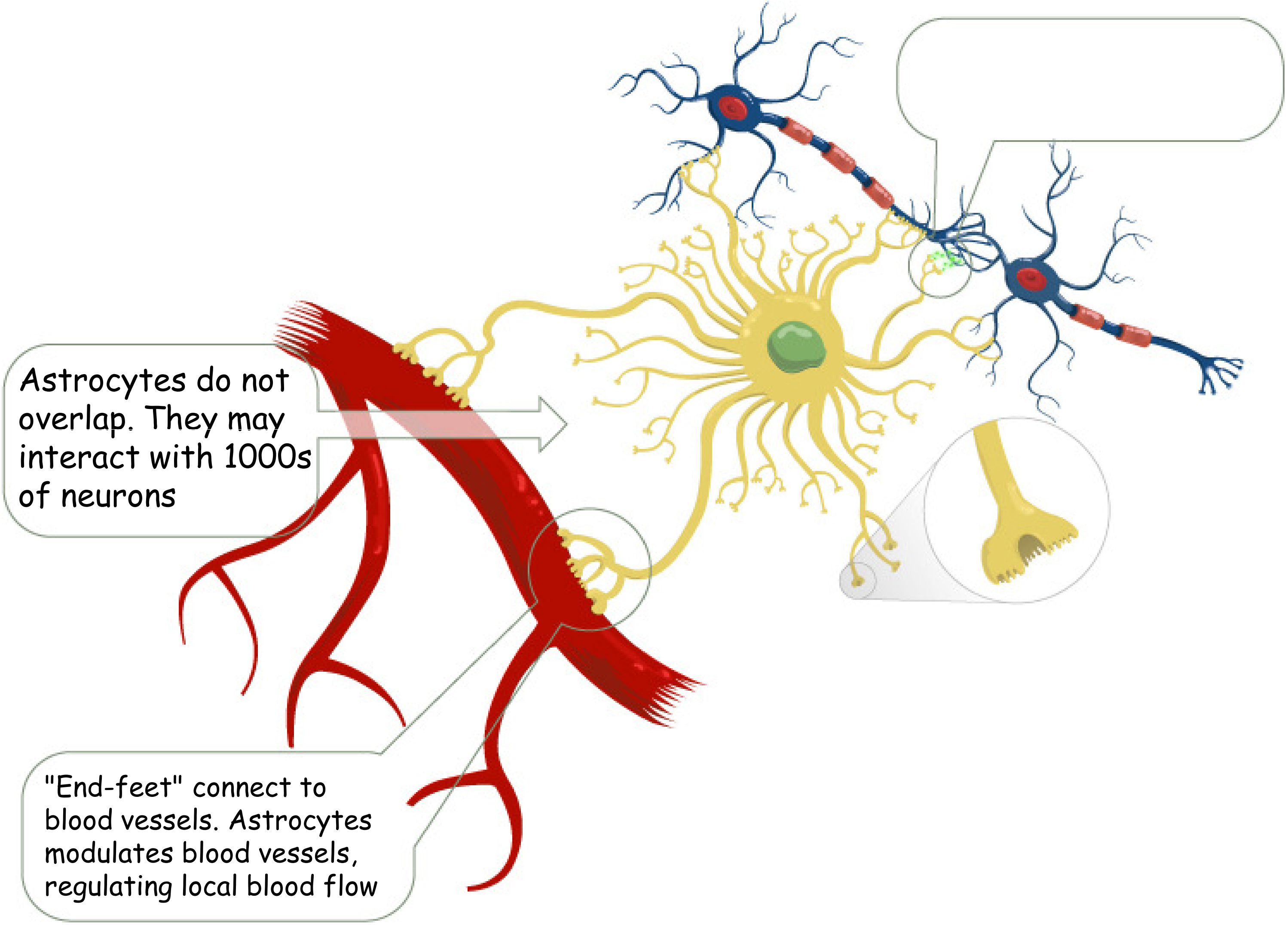
Structure of the grey matter

Maintain contacts with neurons, blood vessels and synapses residing in their anatomical domain



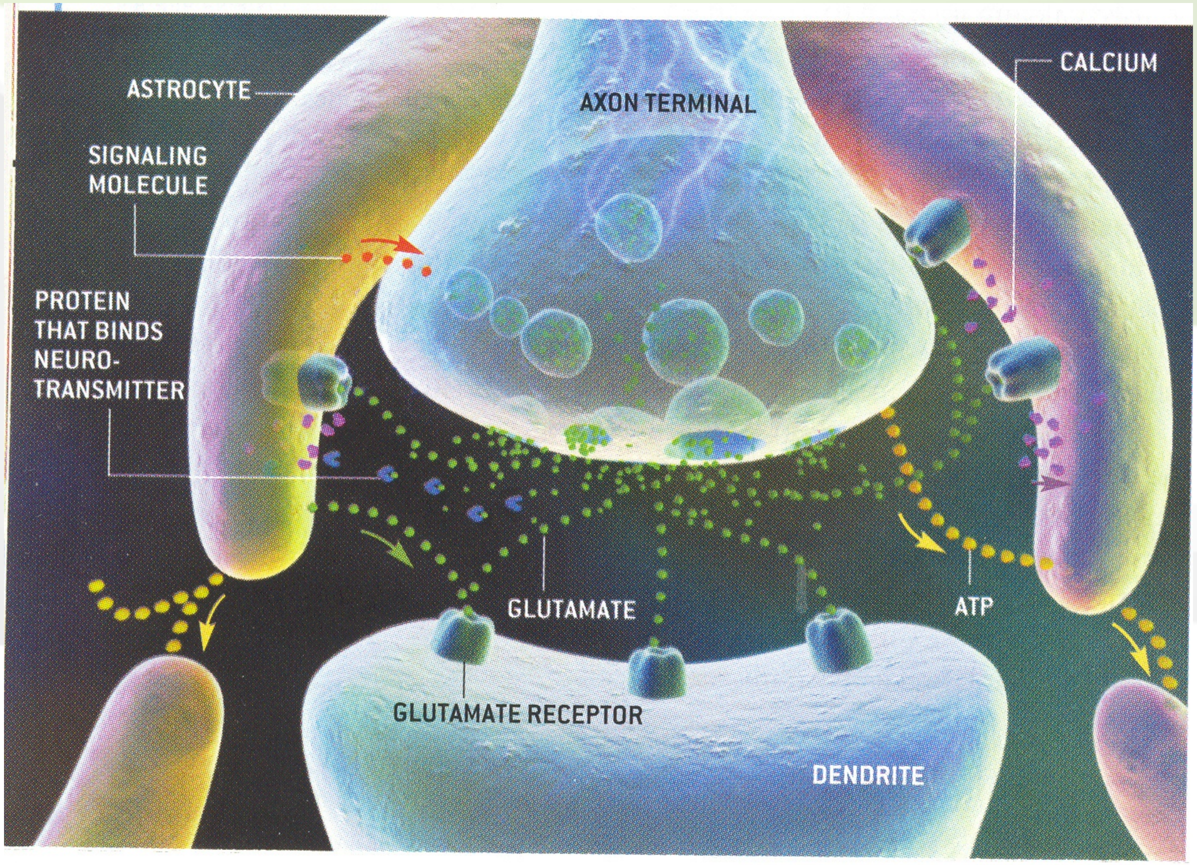
Structural

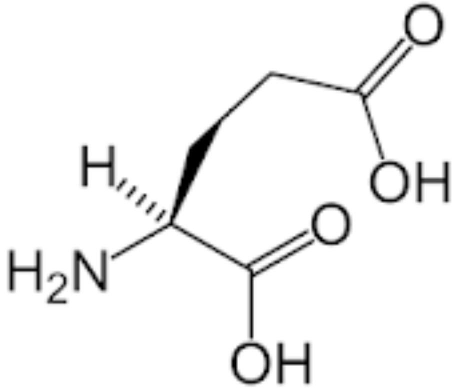
Astrocytes form an anatomical link between neurons and arterioles



Glutamate

Glutamate (the conjugate base of glutamic acid) is abundant in the human body, but particularly in the nervous system and especially prominent in the human brain.
It is the brain's main excitatory neurotransmitter





Glutamate binds with receptor mGluR

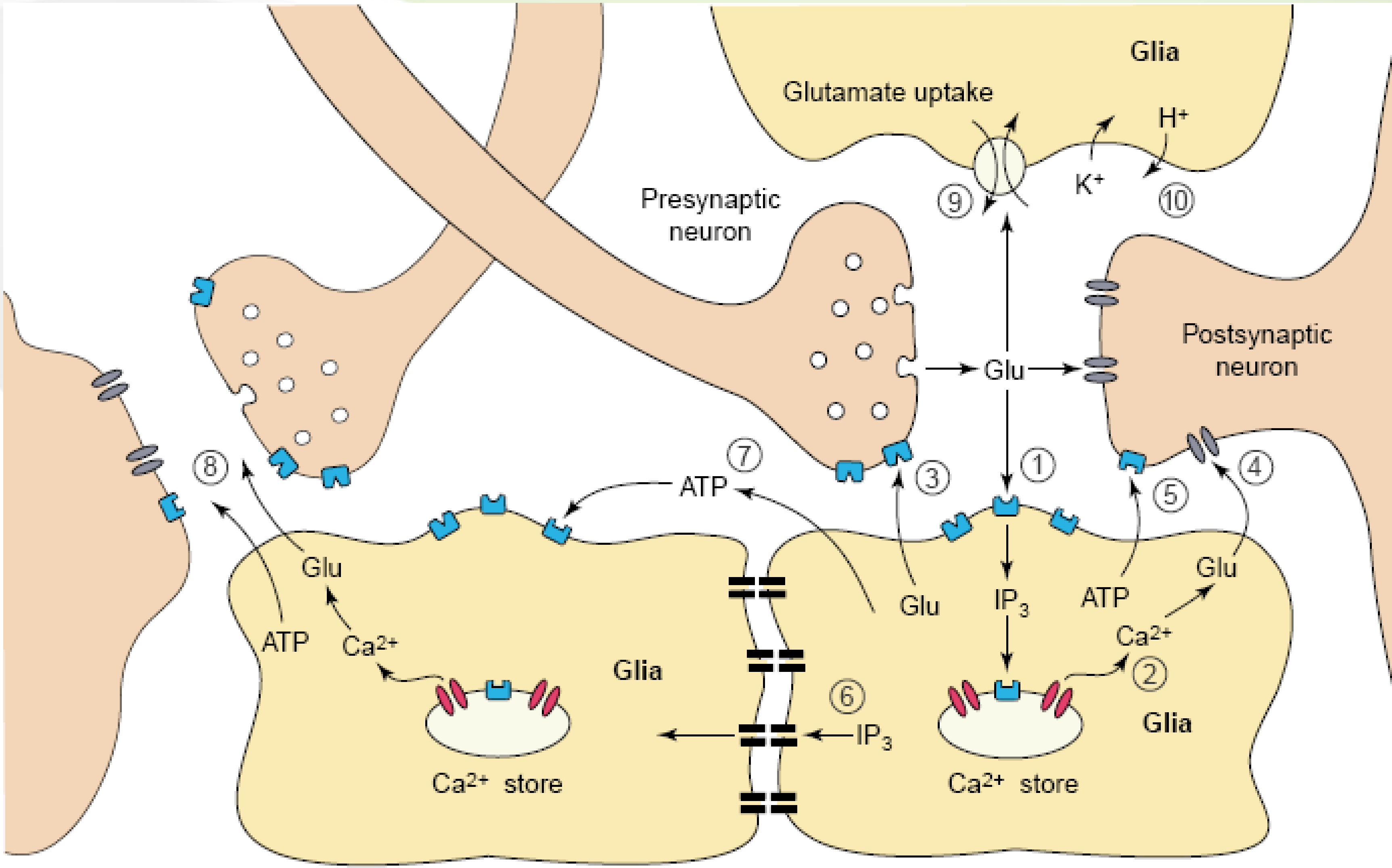
Series of chemical reactions

Production of IP_3 (inositol 1,4,5-trisphosphate)

IP_3 diffusion through cell cytoplasm

IP_3 binds with its receptors in the endoplasmic reticulum

The tripartite synapse



IP_3 receptors release Ca^{2+} in the endoplasmic reticulum

↓

Ca^{2+} in the endoplasmic reticulum create a gradient of Ca^{2+} concentration between the endoplasmic reticulum and the cell cytoplasm

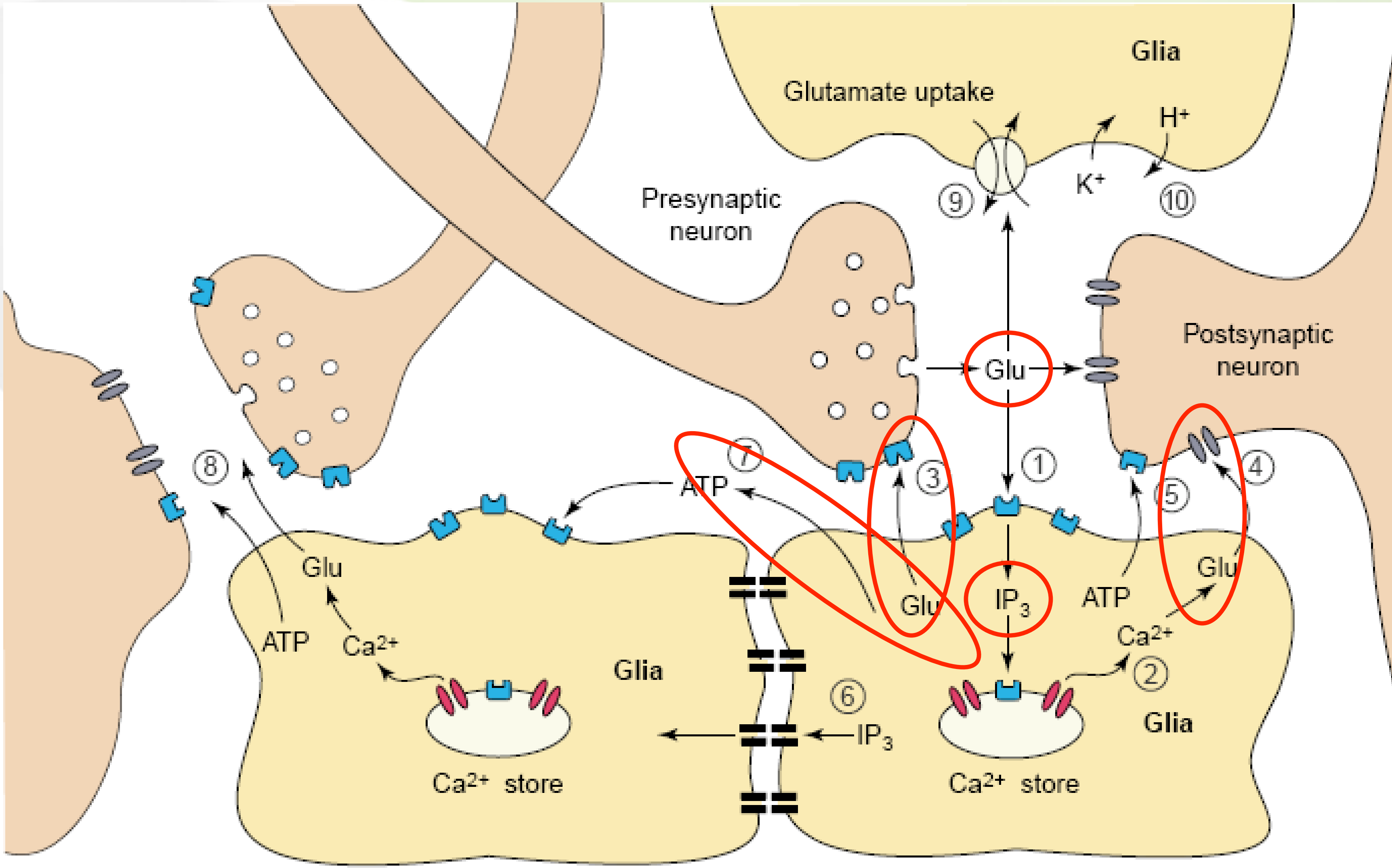
↓

IP_3 receptors are then re-activated and release Ca^{2+} in the cell cytoplasm

↓

An auto-catalytic process starts

The tripartite synapse

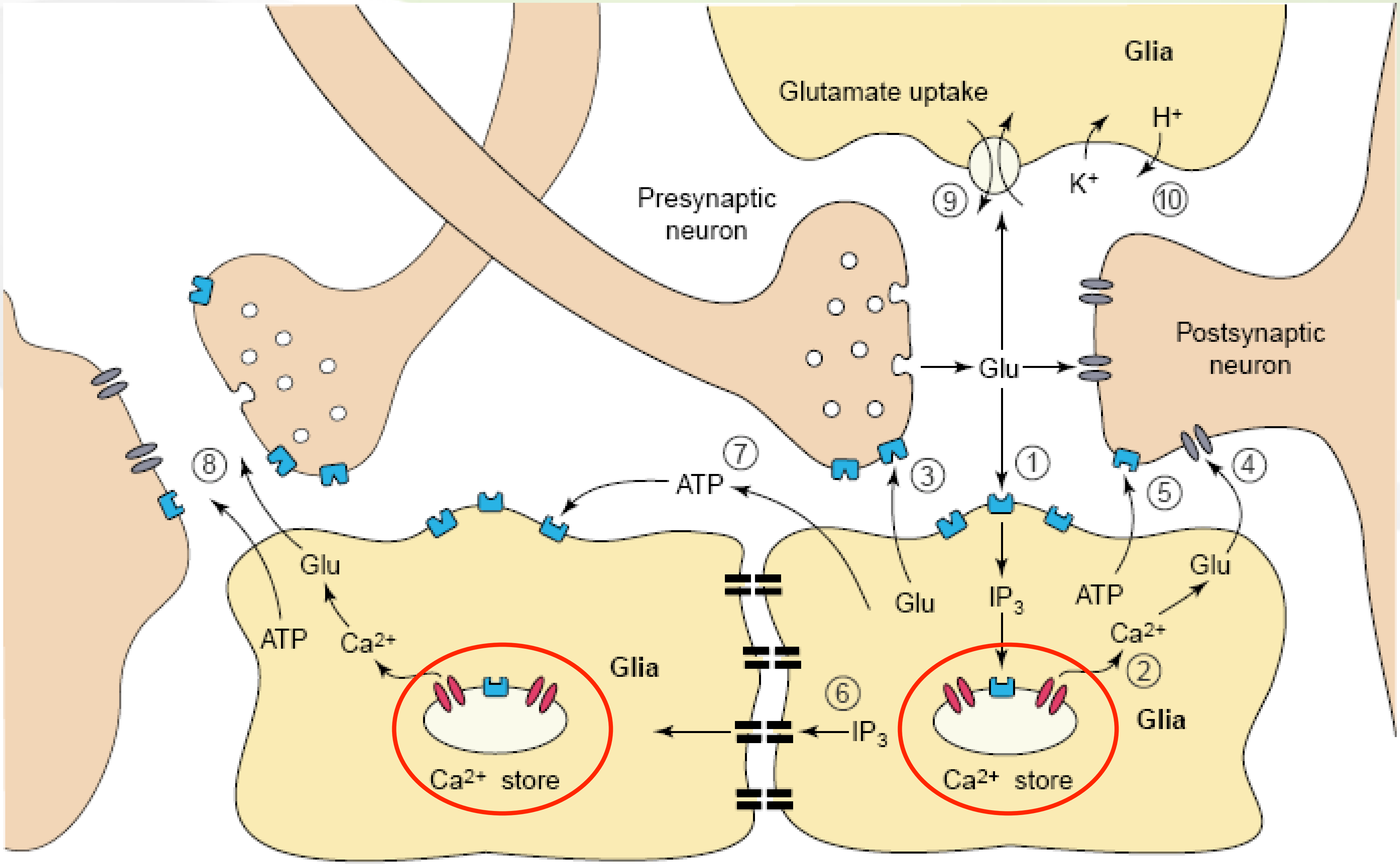


Over a certain threshold, [Ca^{2+}] in the cell cytoplasm activates pumps bringing Ca^{2+} in the endoplasmic reticulum and outside cells.

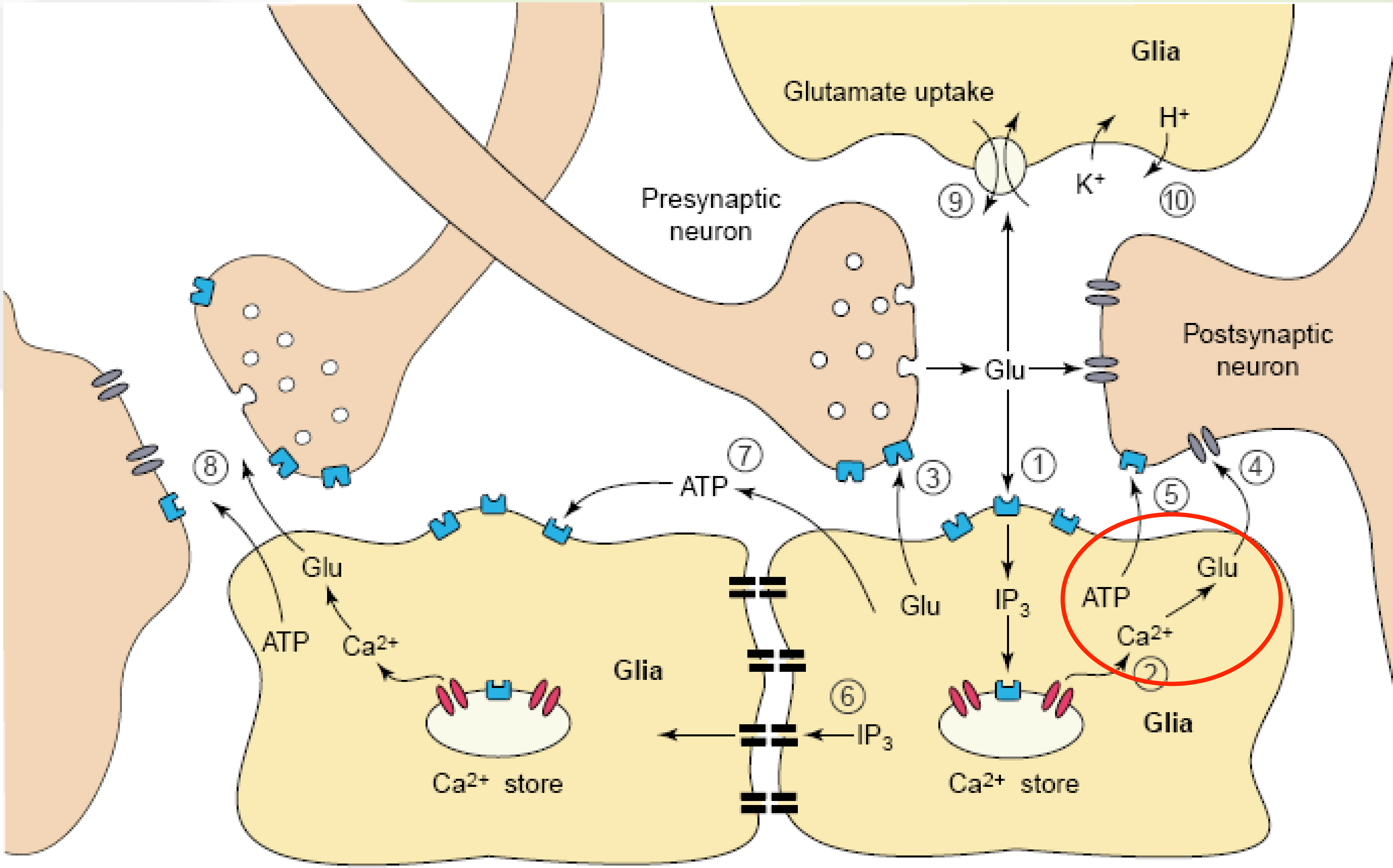
INTERcellular waves

INTRAcellular waves

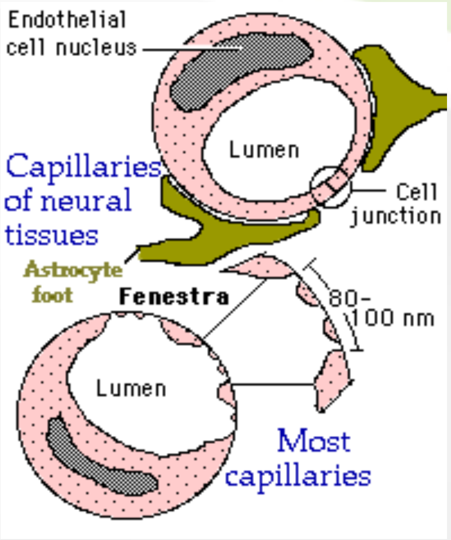
The tripartite synapse

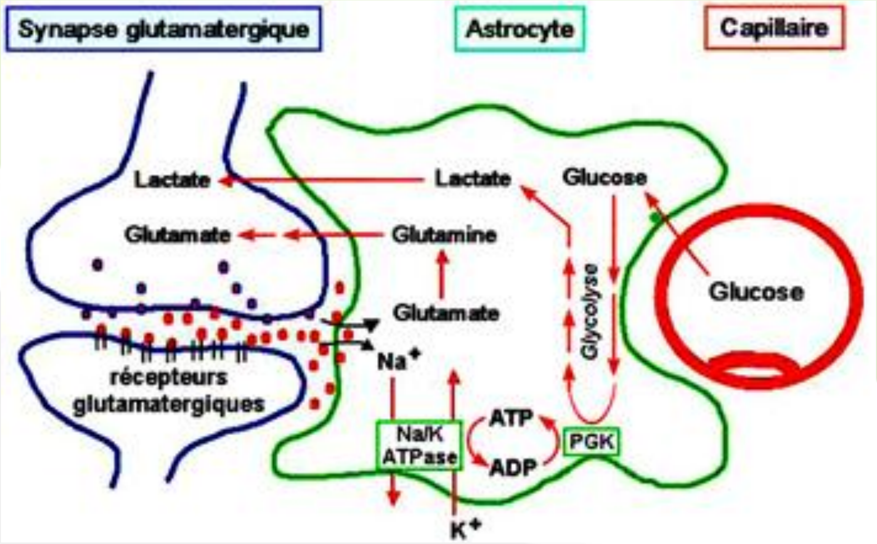


The tripartite synapse



Cerebral Circulation





As **Neural activity** ↑ there is an ↑ **Energy requirement**

To solve this…

↑ Astrocytic uptake of Glutamate leads to> ↑ADP leads to> ↑Glycolysis within Astrocytic endfeet **which finally leads to> ↑Lactate delivered to neuron**

But what about OXYGEN? Waste? Other nutrients?

With increased neural activity, there MUST be an increase in **LOCAL CIRCULATION OF BLOODFLOW**

Neuron-to-astrocyte signaling is central to the dynamic control of brain microcirculation

Zonta et al., 2003

↑ Neural Activity

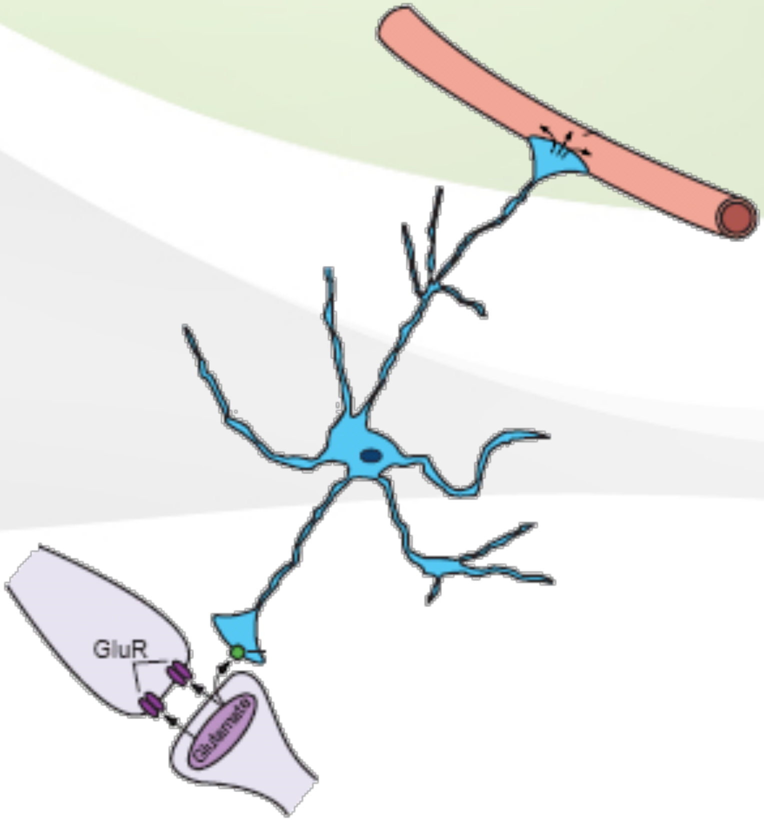
↑ Ca++ propagation throughout astrocytic syncytium

↑ [Ca++] at endfeet attached to endothelial cells

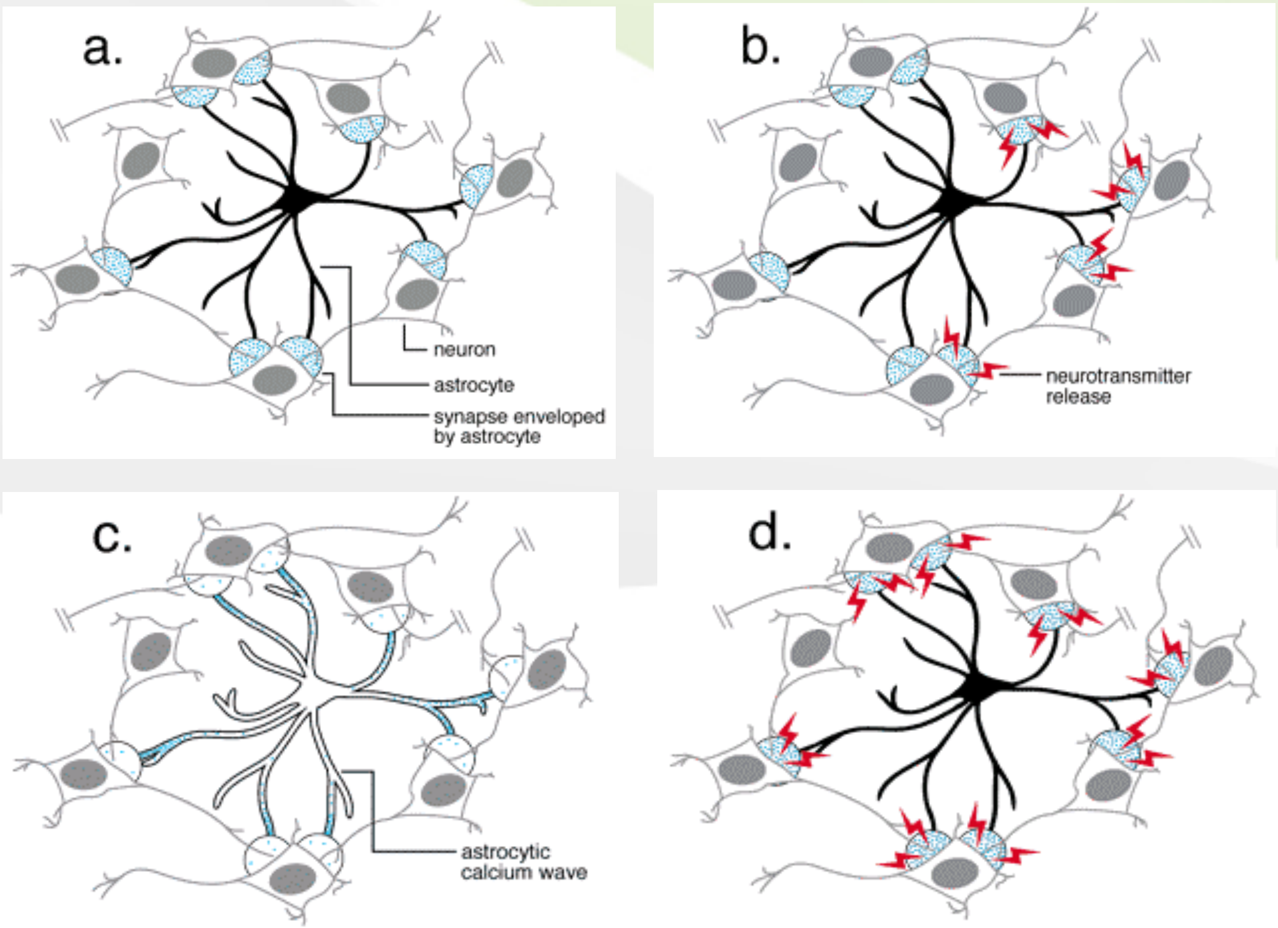
↑ Vesicular release of prostanoids

↑ Relaxation of capillary walls; decrease in vascular tone

↑ **Bloodflow**



Synchronous Firing Groups- Astrocytic Regulation of Neural Networks



Onde spirali di calcio

Onde spirali di calcio sono state osservate in fette di tessuto ippocampale

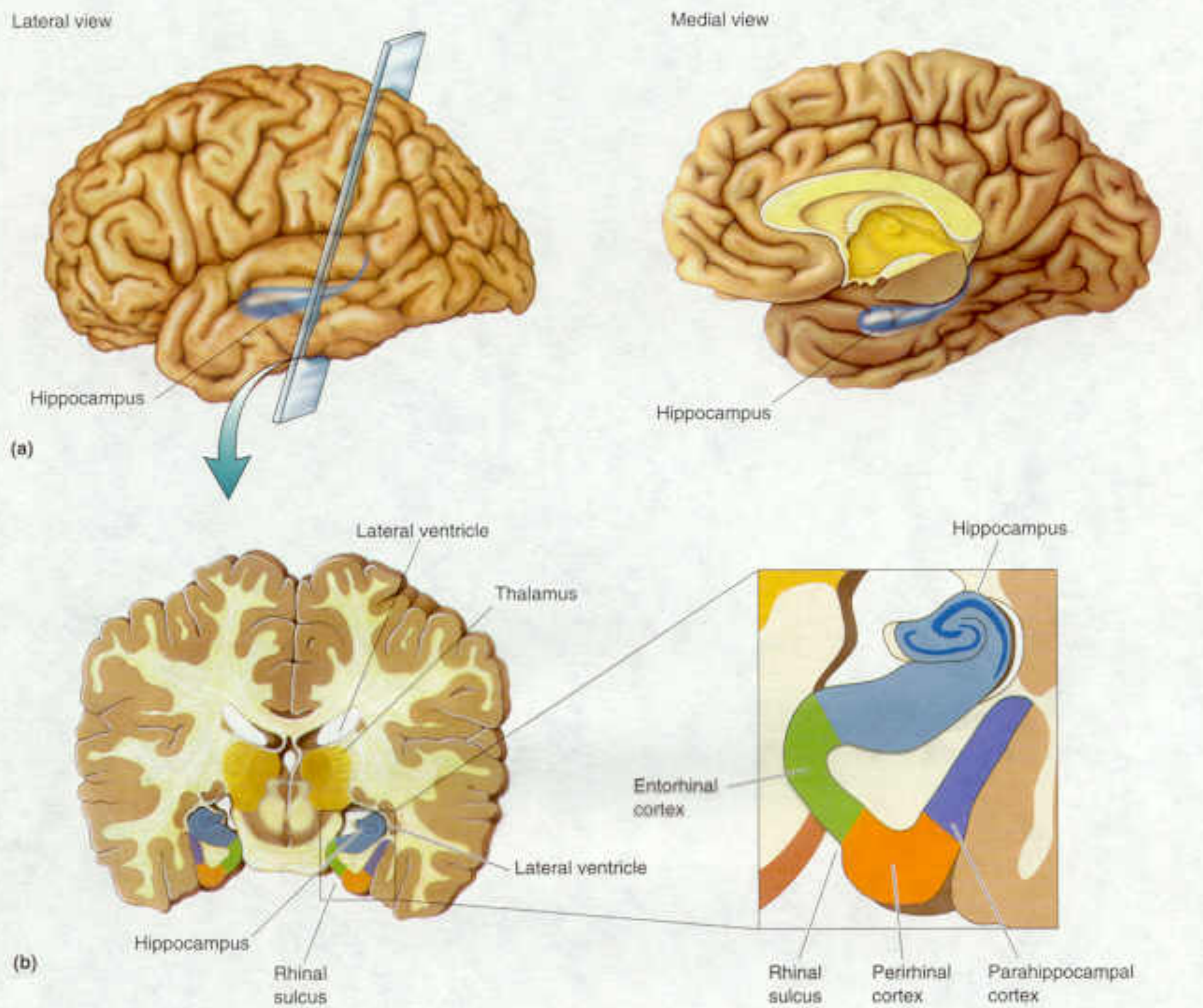
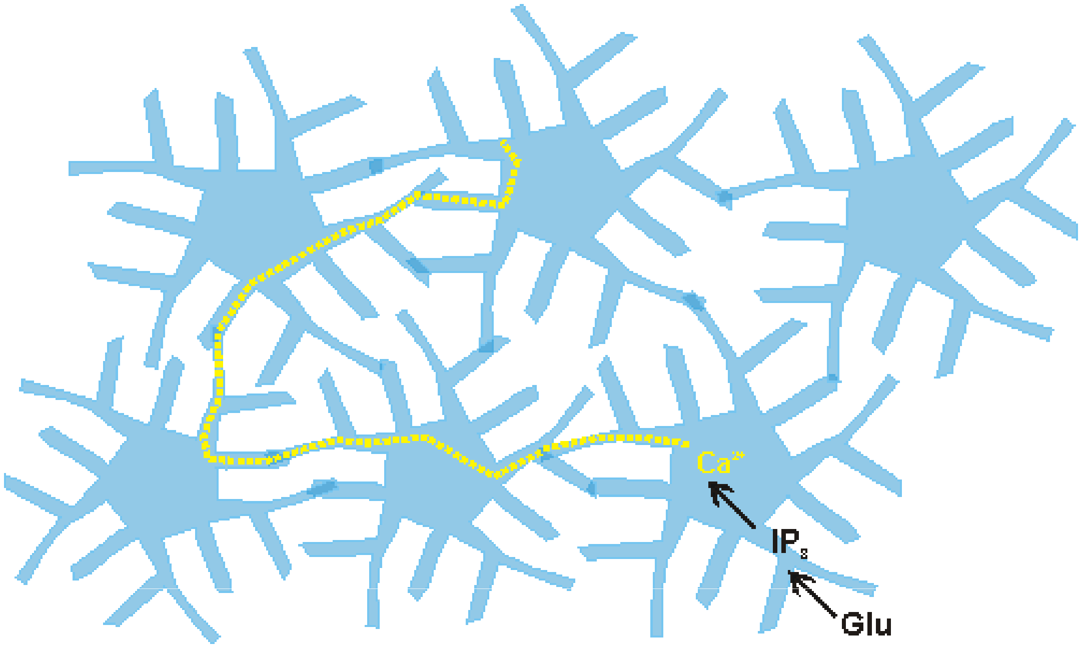
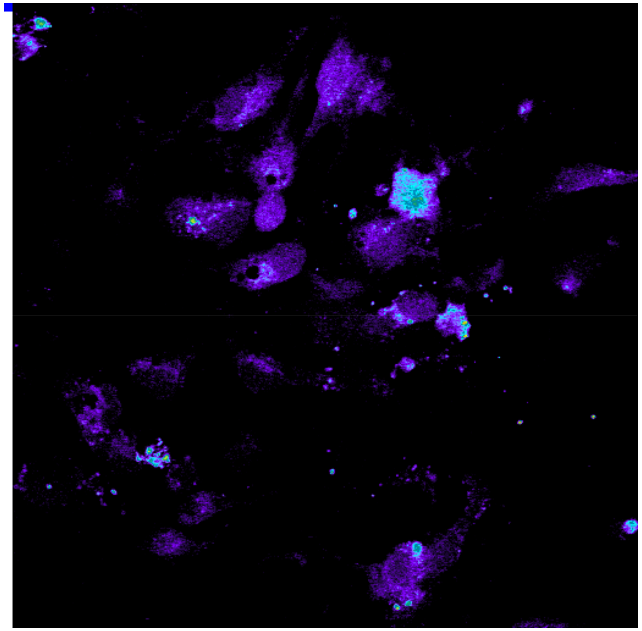


Figure 19.7
Structures in the medial temporal lobe. (a) Lateral and medial views show the location of the hippocampus in the temporal lobe. **(b)** The brain is sectioned coronally to show the hippocampus and cortex of the medial temporal lobe.

Astrocytes and calcium





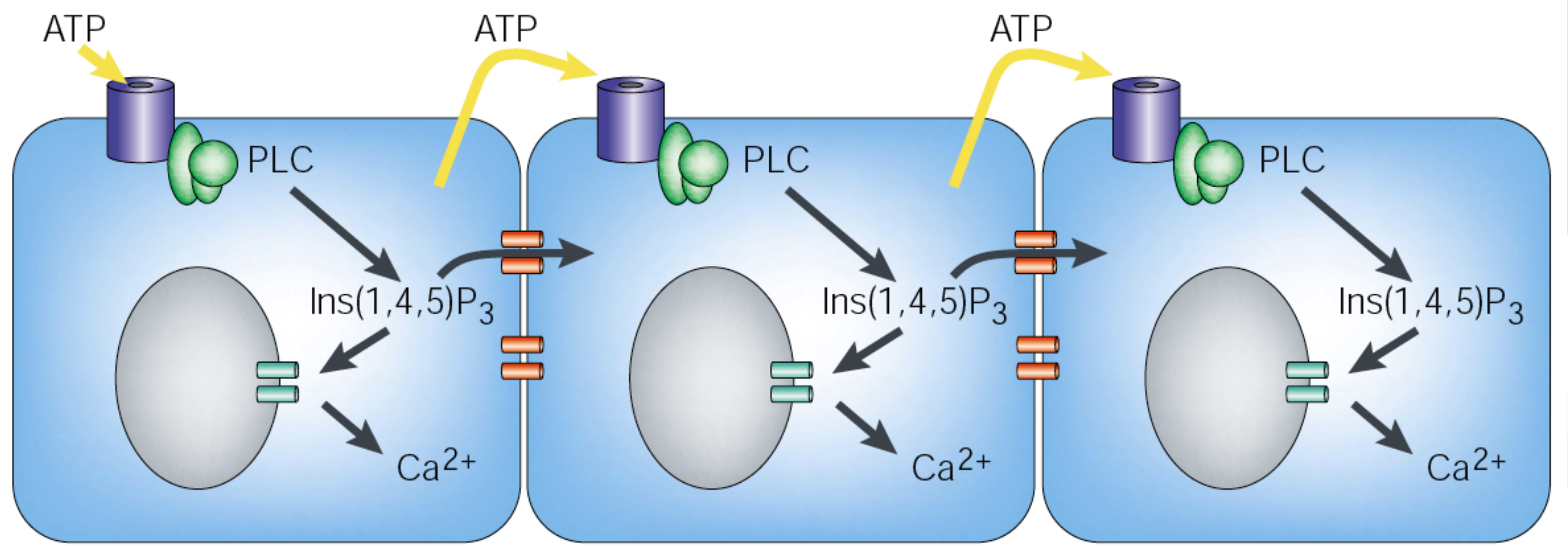
- Calcium waves propagate through the syncytium GAP JUNCTIONS, a non-synaptic means of communication within the brain

- Waves can be induced by mechanical stimulation and by glutamate

- Influx of calcium leads to calcium-sensitive release and uptake of ions and neuromodulators

Ca^{2+} Waves

(Cornell-Bell et al., M. Sanderson, A. Charles)

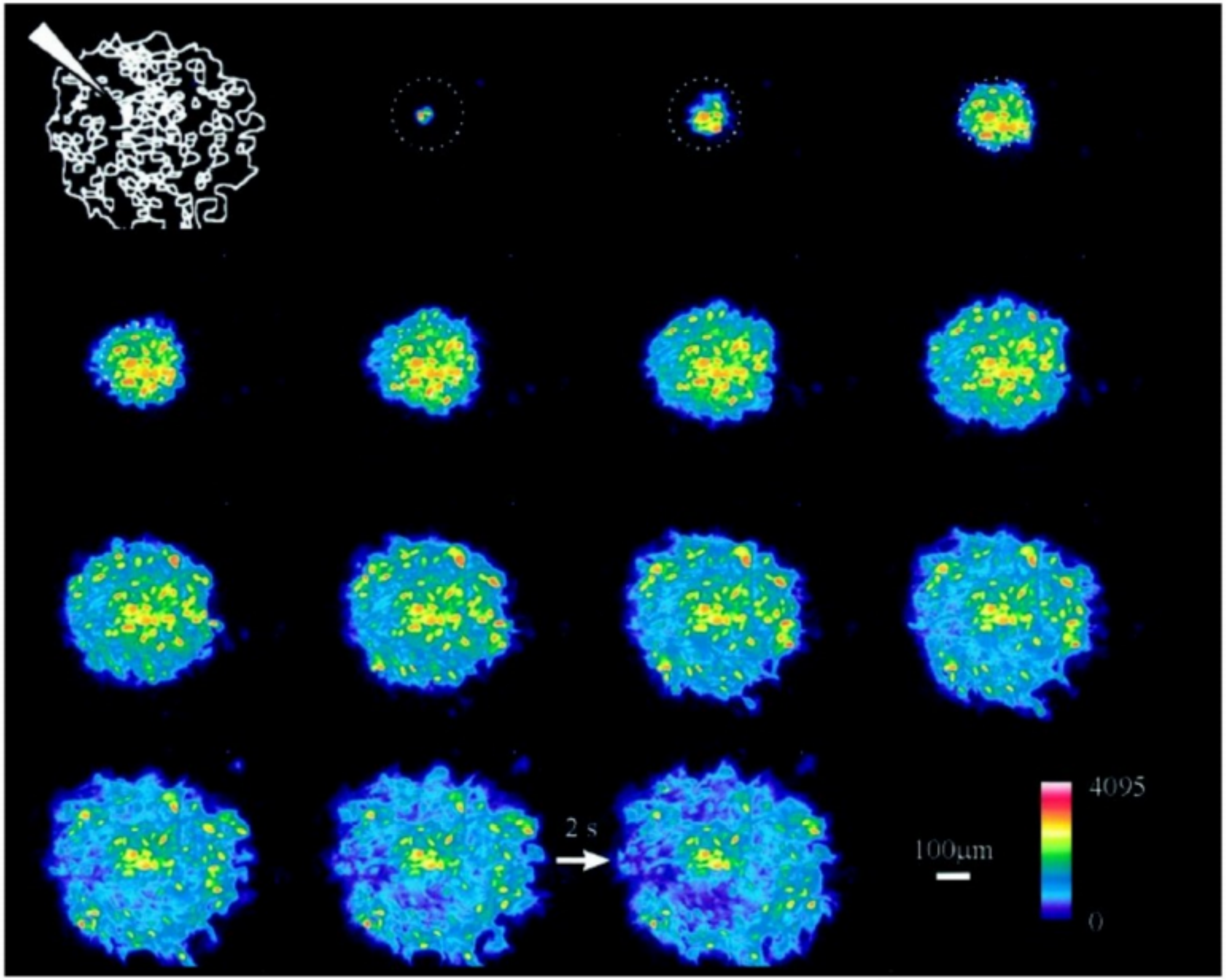


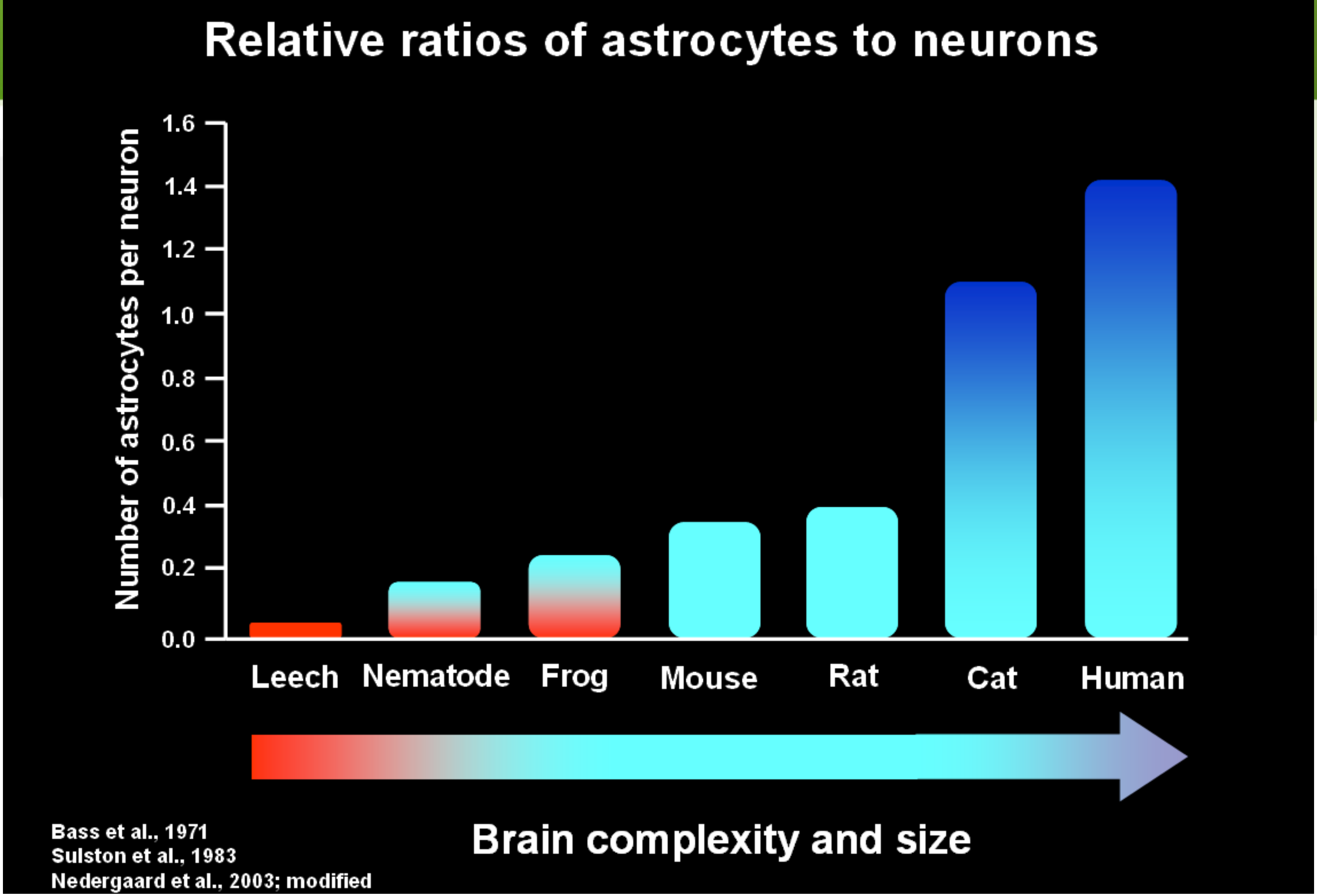
Speed: ~20μm/s

Range: a few hundred μm

Time scale: seconds to minutes

Ca^{2+} waves have been observed in the hippocampus



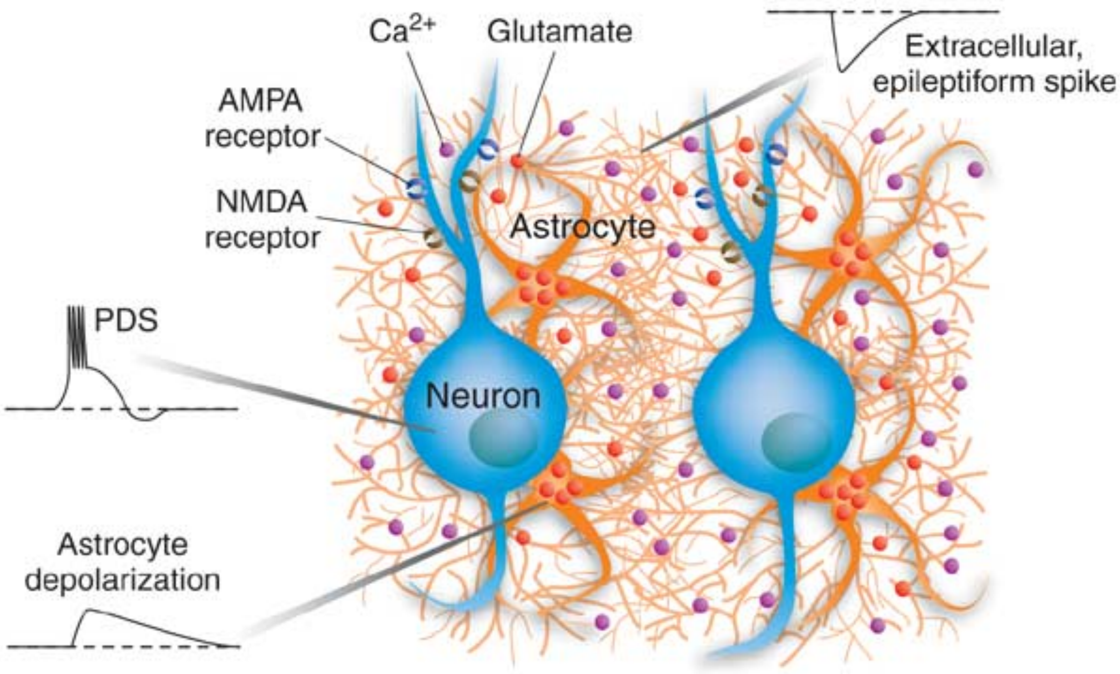


A single astrocyte can cover 20 000 – 100 000 synapses in rodents...
and possibly up to 2 million in primates and humans.

Astrocytes and Epileptic Seizures

Tian et al.:*An astrocytic basis of epilepsy* (Nature Medicine, 11 (2005))

Epileptic discharges through local paroxysmal depolarization shift (PDS) driving groups pf neurons into synchronous bursting activity.



-- Ca2+ increased in Astrocyte

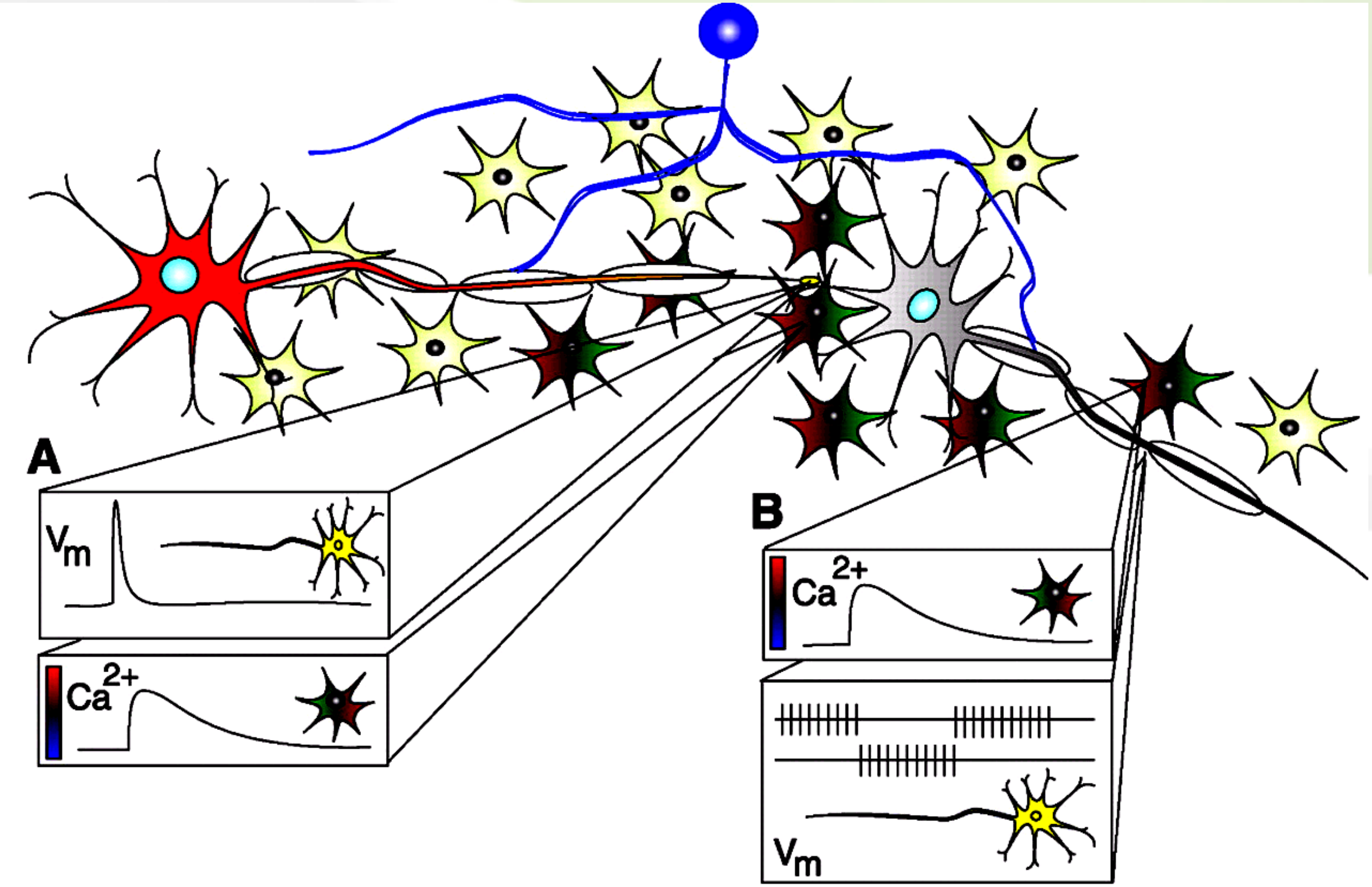
– PDS - like epileptiform responses in neighboring neurons

– PDS in nearby neurons in in-vitro epilepsy models with blocked synaptic transmission

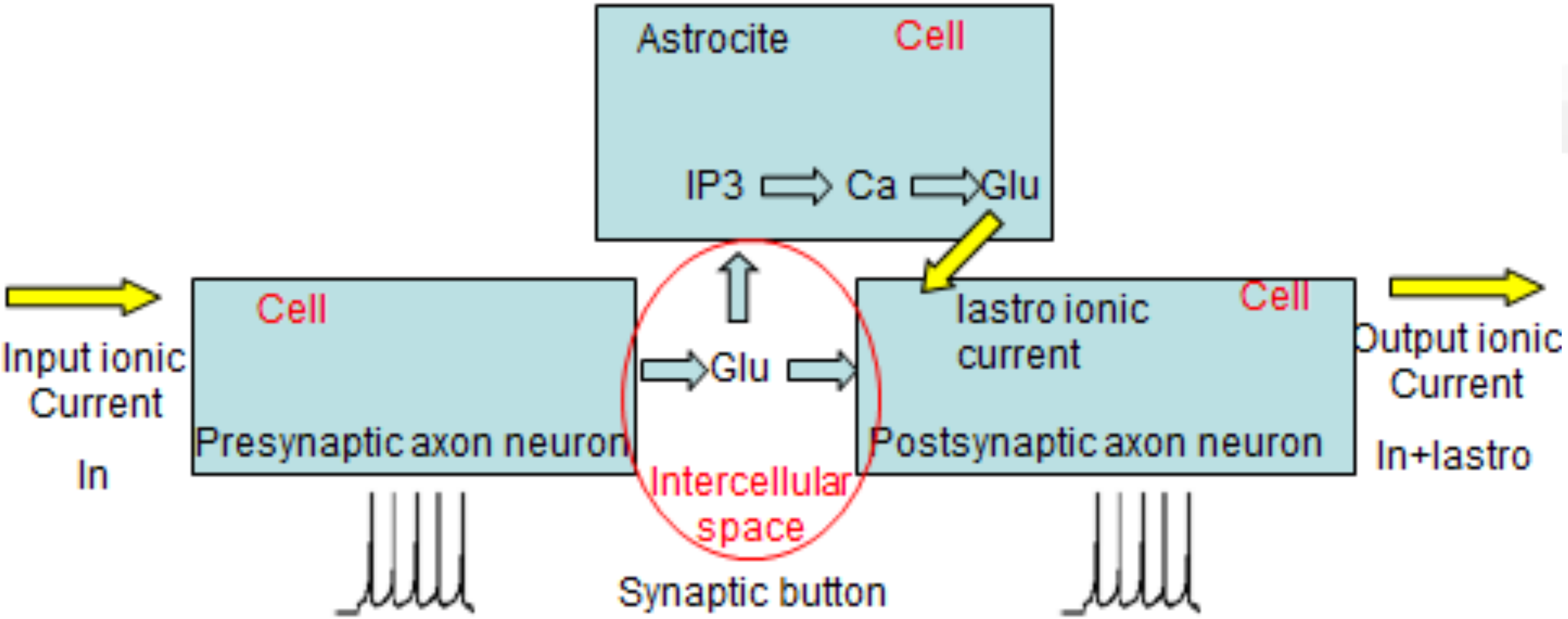
– Anti-epileptics reduced Ca2+ signal in astrocyte

Astrocytes and Calcium Waves

intra-inter-cellular communications



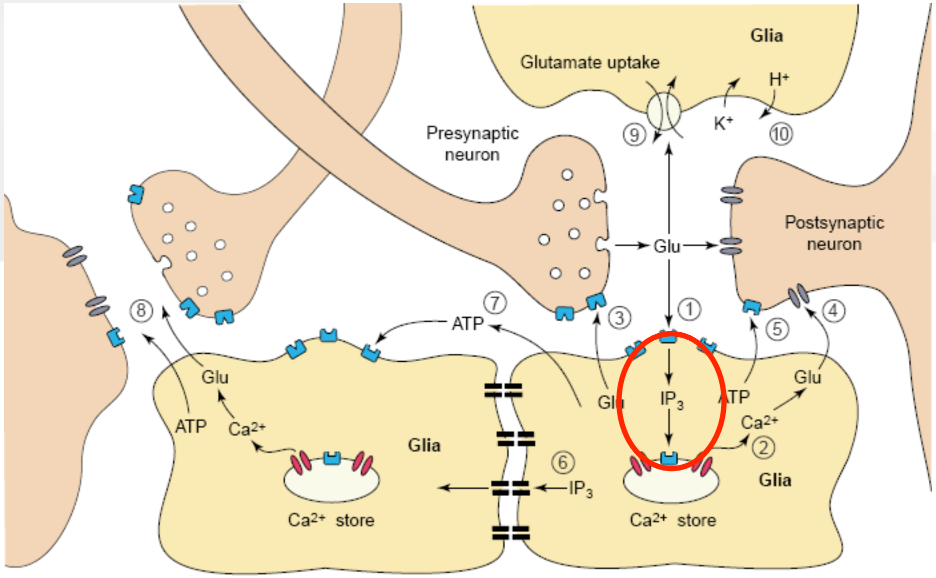
Biological Model of tripartite synapse



The intracellular IP3 production can be modelled by:

$$\frac{d[IP_3]}{dt} = \frac{1}{\tau_{IP_3}}([IP_3]^* - [IP_3]) + r_{IP_3}\Theta(v - 50\,mV)$$

where [IP3]* is the equilibrium concentration. τ is the IP3 degradation time constant and *r* is the production rate of IP3 in response to an action potential



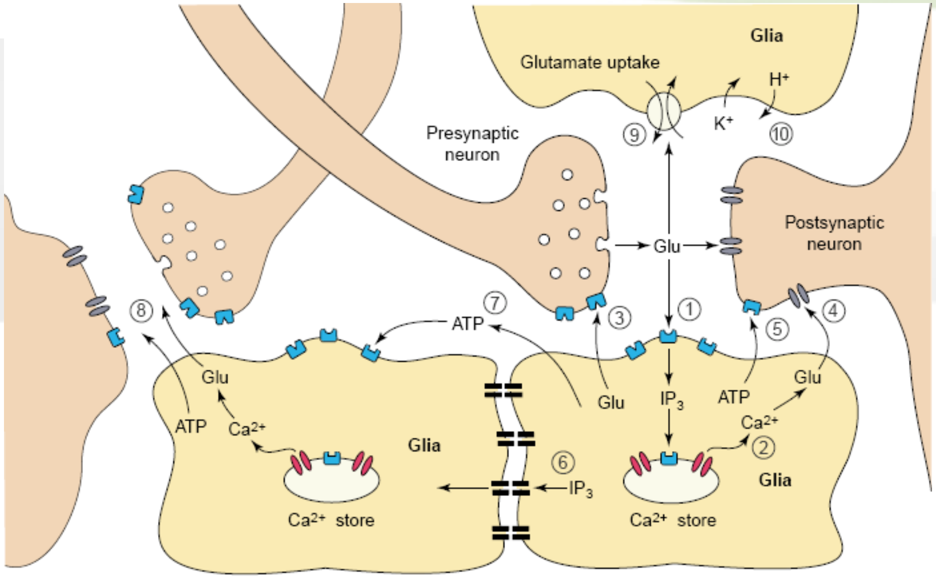
Wang S.S.H., Alousi A.A. and Thompson S.H. The life time of inositol 1,4,5-triphosphate in single cells. J. Gen. Physiol., 105:149-171, 1995

Modelling astrocyte-astrocyte interactions

The flux of IP3 can be modelled by:

$$J_G = \sum_{<j>} \kappa \left([IP_3]_j - [IP_3]_i \right)$$

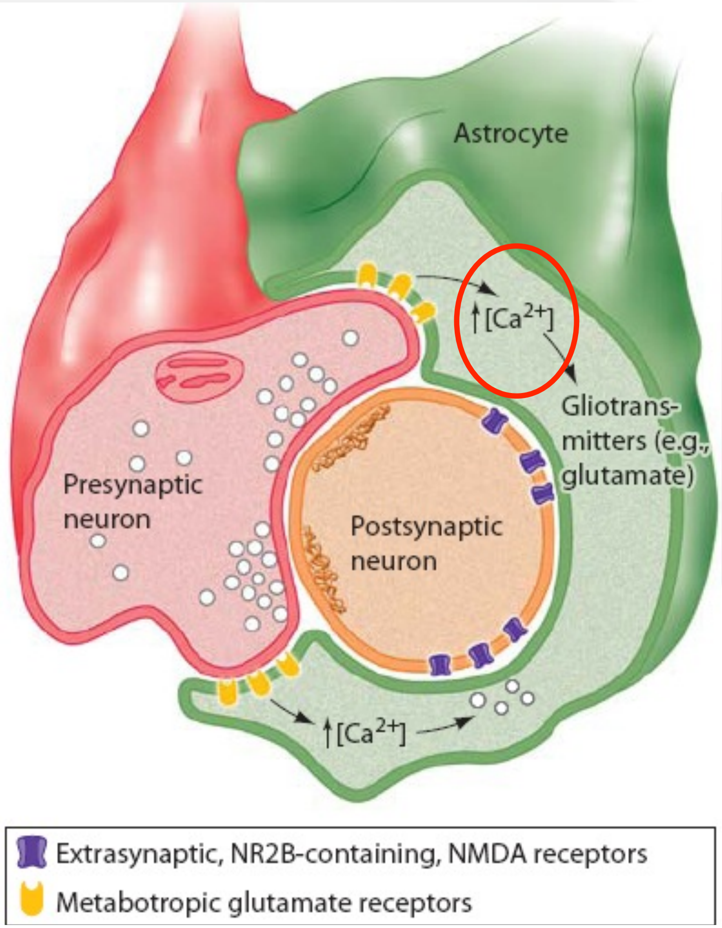
Where *i* indicate the *ith* astrocyte, *k* is the diffusion coupling coefficient through the gap-junction and *<j>* is the contribution of the neighbouring astrocytes



Robb-Gaspers L.D. and Thomas A.P. Coordination of calcium signaling by intercellular propagation of calcium waves in the intact liver. J. Biol. Chem., 270, 8102-8107, 1995.

Ullah G., Jung P. and Cornell-Bell A.H. Anti-phase calcium oscillations in astrocytes via initosl (1, 4, 5)-triphosphate regeneration. Cell Calcium, 39, 197-208, 2006

The Li-Rinzel model of Astrocyte



$$\frac{d[Ca^{2+}]}{dt} = -J_{channel}(q) - J_{pump} - J_{leak}$$

$$\frac{dq}{dt} = \alpha_q(1-q) - \beta_q q$$

$$J_{channel} = c_1 v_1 m_\infty^3 n_\infty^3 q^3 \left([Ca^{2+}] - [Ca^{2+}]_{ER}\right)$$

$$J_{pump} = \frac{v_3[Ca^{2+}]^2}{k_3^2 + [Ca^{2+}]^2}$$

$$J_{leak} = c_1 v_2 \left([Ca^{2+}] - [Ca^{2+}]_{ER}\right)$$

$$m_\infty = \frac{[IP_3]}{[IP_3] + d_1}$$

$$n_\infty = \frac{[Ca^{2+}]}{[Ca^{2+}] + d_5}$$

$$\alpha_q = a_2 d_2 \frac{[IP_3] + d_1}{[IP_3] + d_3}$$

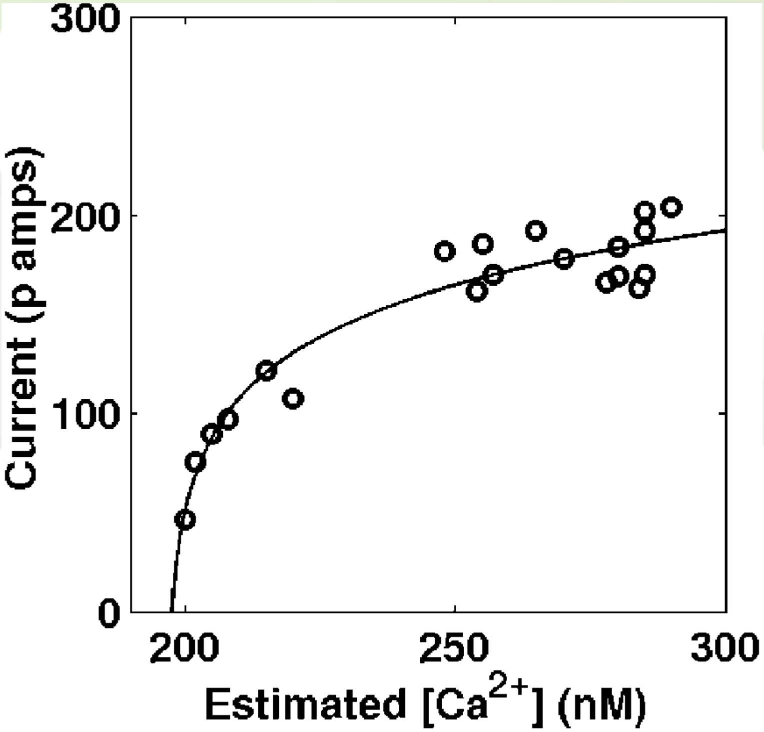
$$\beta_q = a_2[Ca^{2+}]$$

Experimental model for astrocyte-neuron interaction

Experimental data can be useful to model the correlation of the Ca^{2+} concentration into the astrocyte environment with the weak additional synaptic currents coming from the neighbouring astrocytes

$$I_{astro} = 2.11\Theta(\ln y)\ln y$$

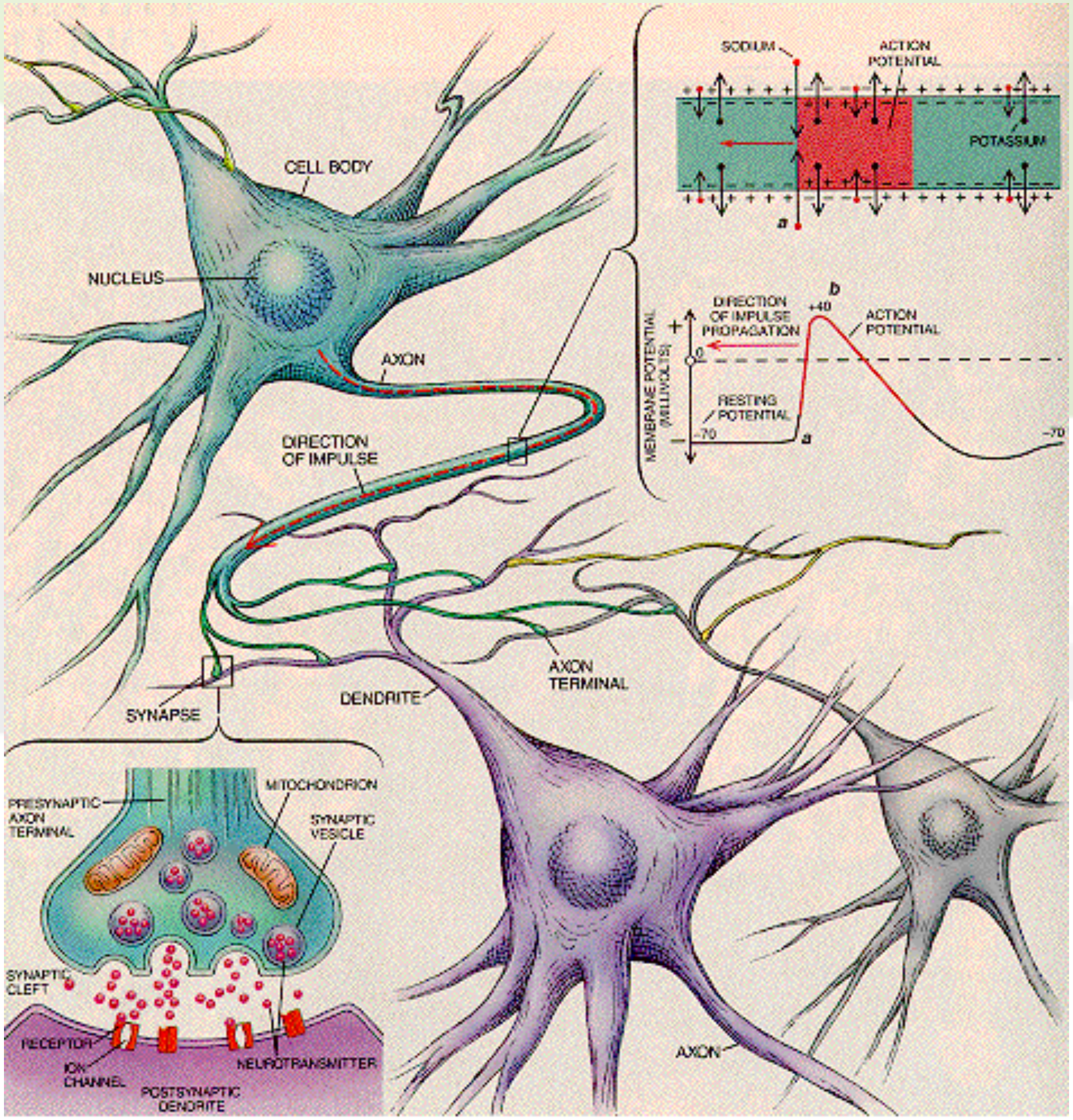
$$y = \frac{[Ca^{2+}]}{nM} - 196.69$$



Nadkarni S. and Jung P., Spontaneous oscillations of dressed neurons: a new mechanism for epilepsy? Phys. Rev. Lett. 91, 268101(4), 2003

NEURO-ASTROCYTE MODELS

Neuro-Astrocyte using Hodgkin Huxley

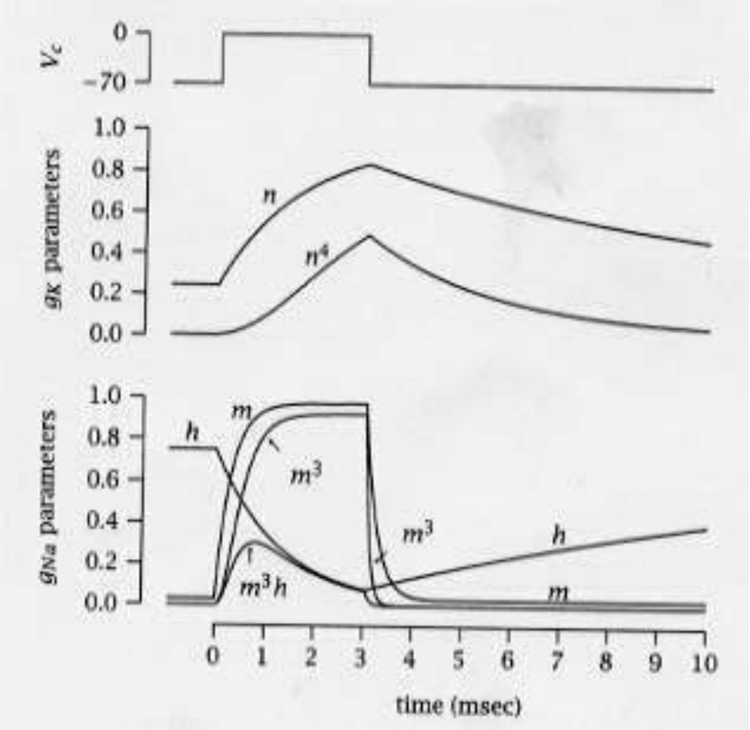


$$C_m \frac{dv}{dt} = -g_K n^4 (v - v_K) - g_{Na} m^3 h (v - v_{Na}) - g_l (v - v_l) + I_{ext} + \boxed{I_{astro}}$$

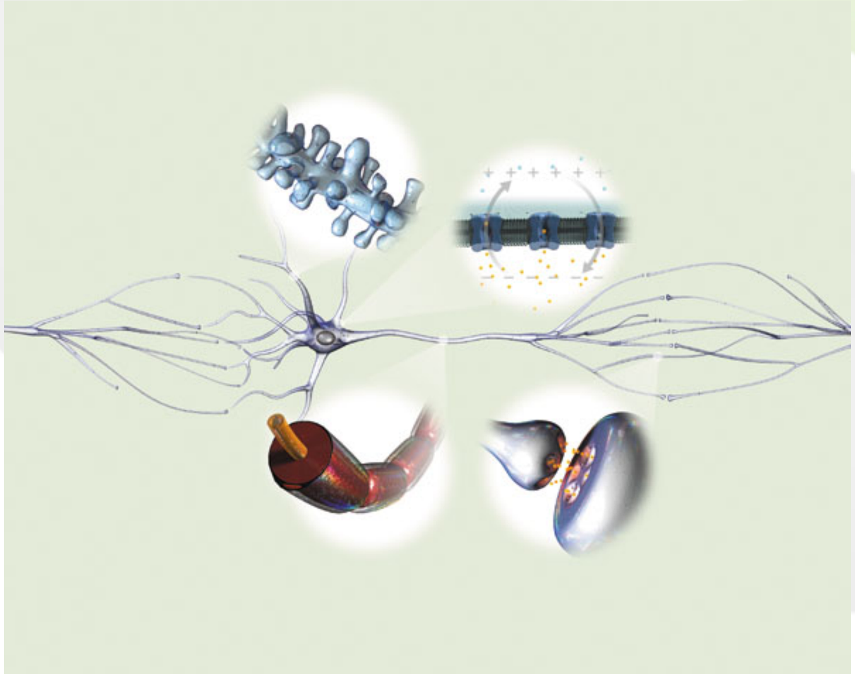
$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m$$

$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n$$

$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h$$



A modified Izhikevich neuronal model

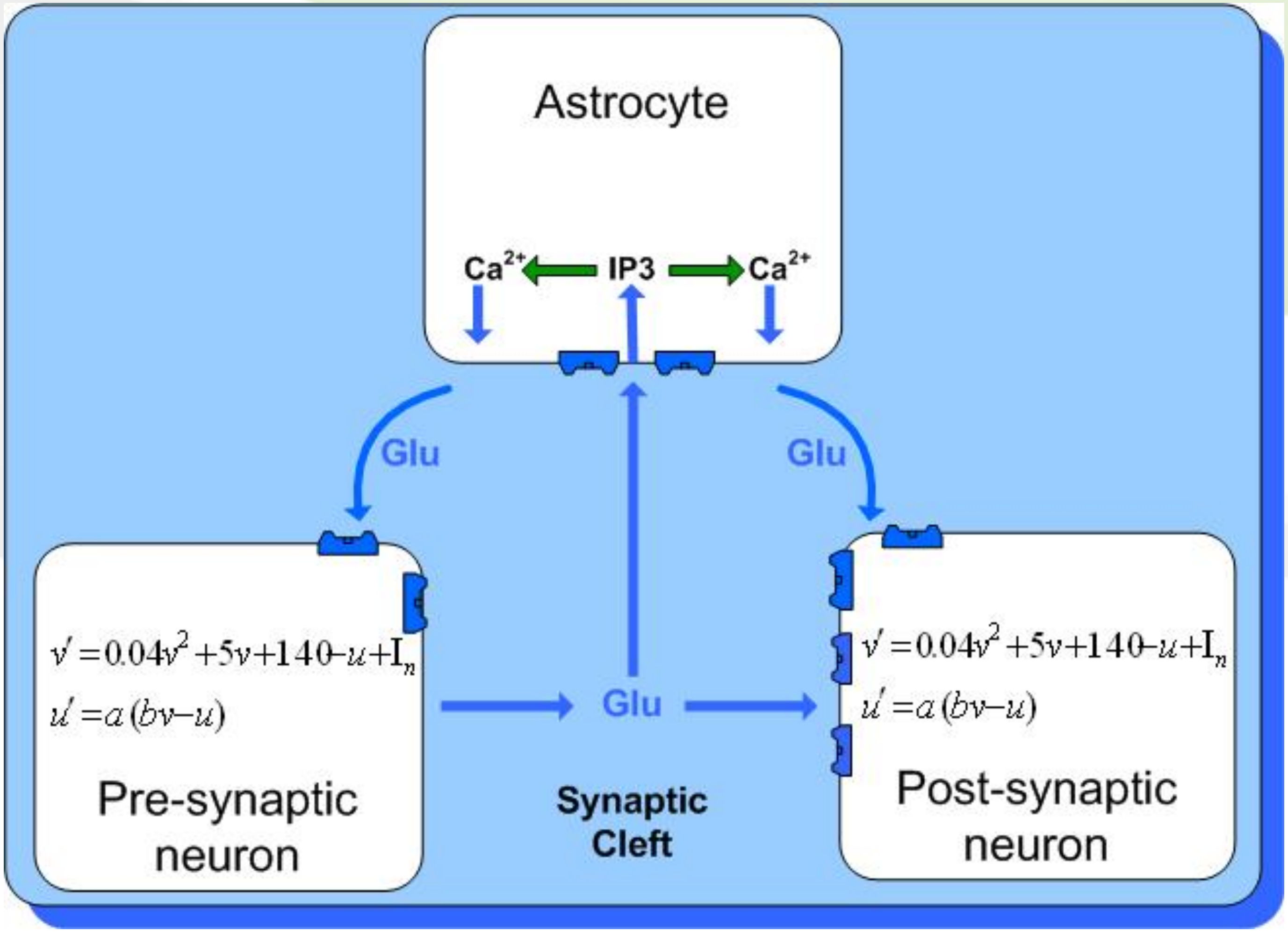


$$\text{if} \quad v \geq +30\, mV, \quad \text{then} \quad \begin{cases} v \leftarrow c \\ u \leftarrow u + d \end{cases}$$

$$v' = 0.04\, v^2 + 5\, v + 140 - u + \mathrm{I} + \mathrm{I}_{astro}$$

$$u' = a\, (bv - u)$$

Dressed Neuron

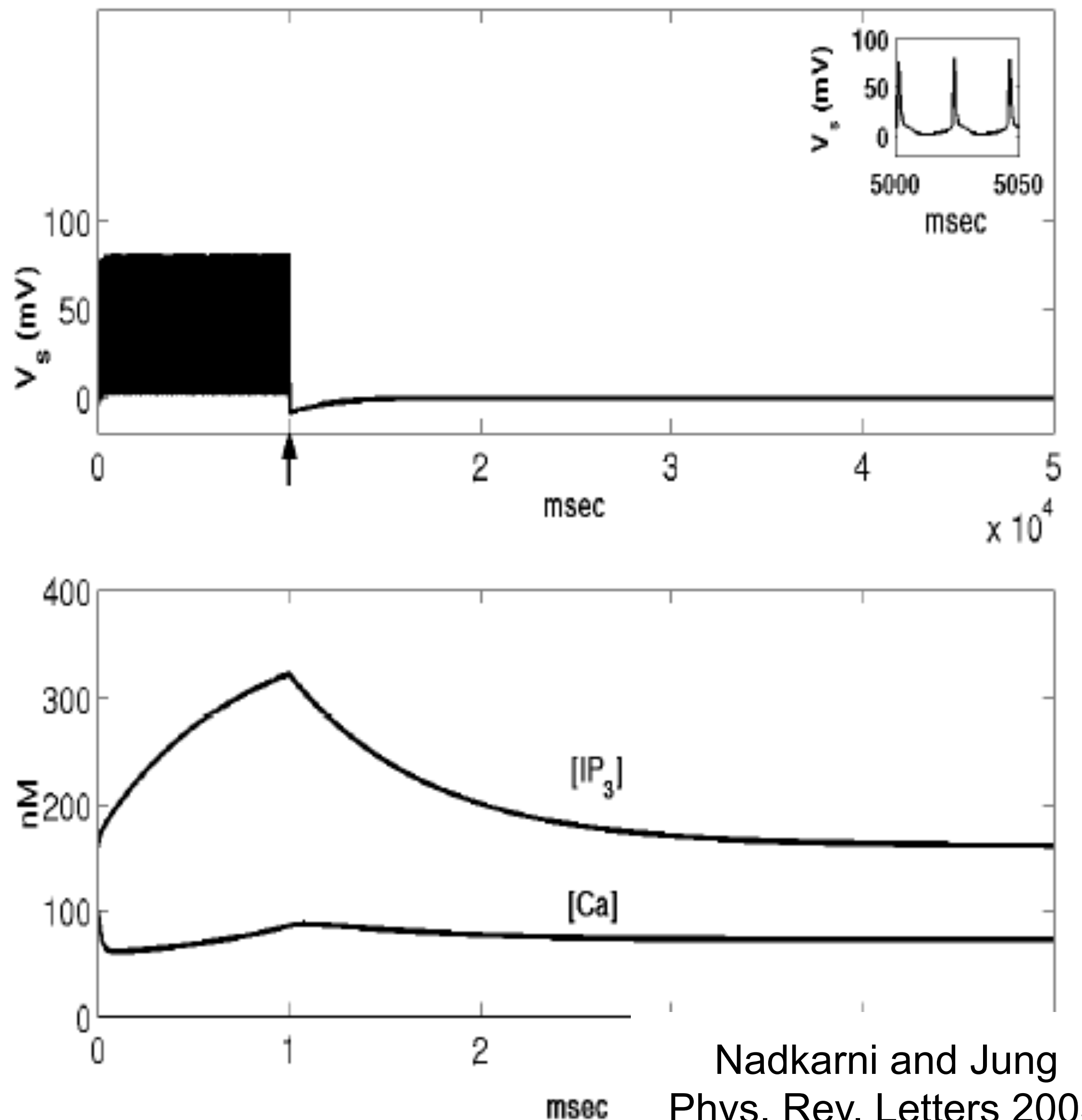


Neural Firing

$[IP3]$ increases

$[Ca^{2+}]$ quite stationary

$I_{astro}=0$

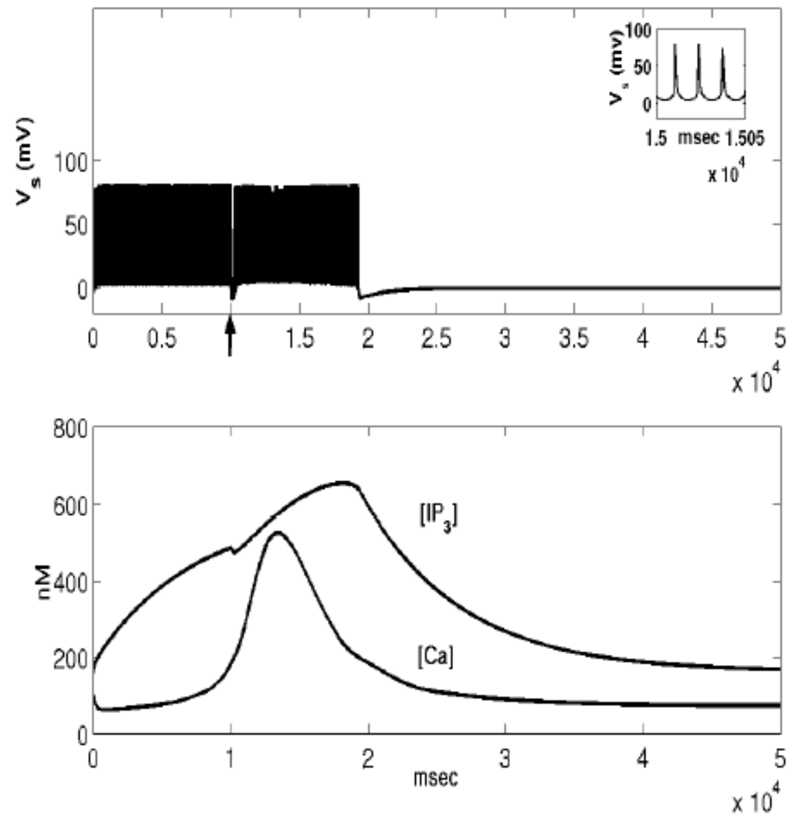


Nadkarni and Jung
Phys. Rev. Letters 2003

10 sec exogenous
Current to neuron

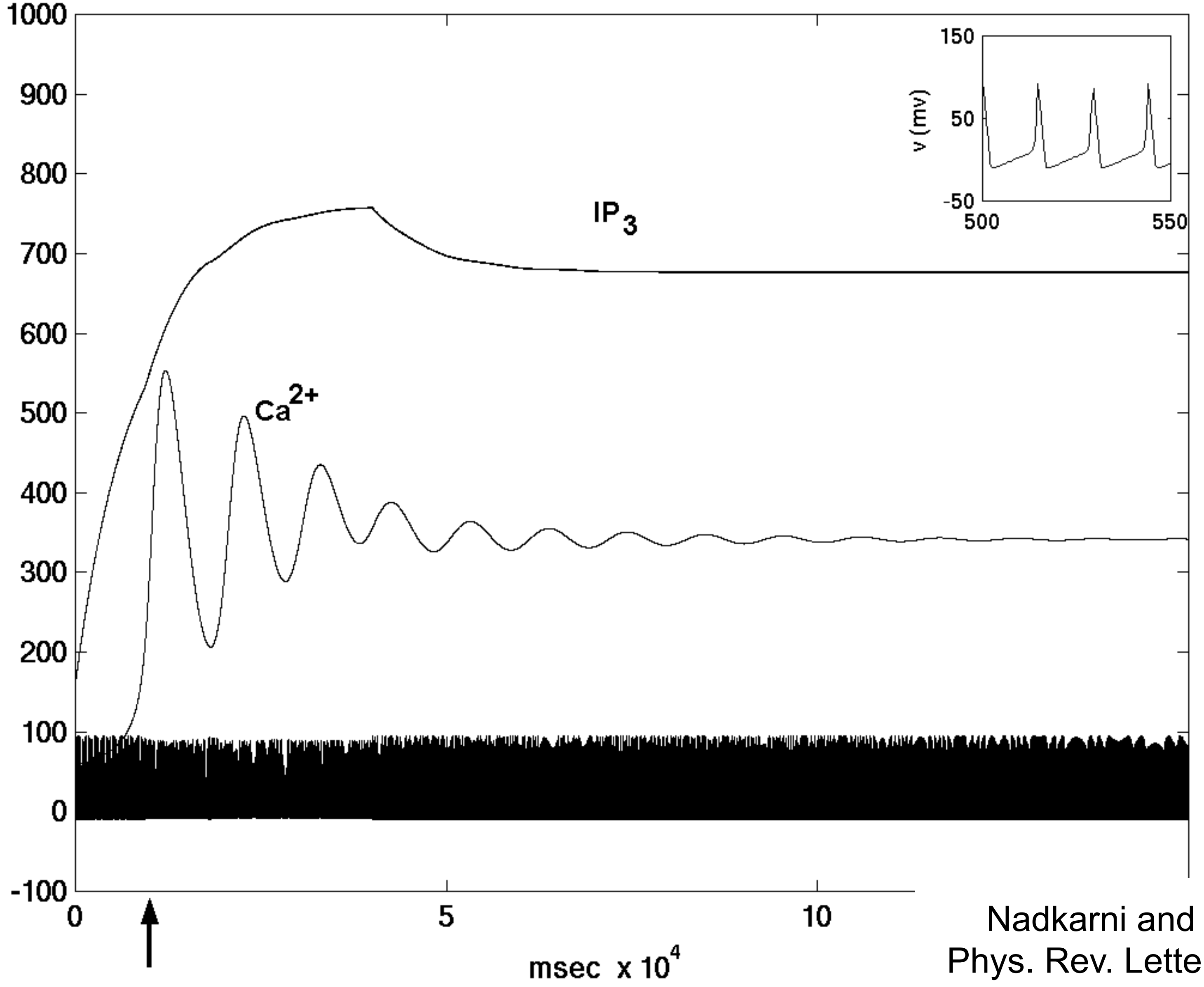
$[IP_3]$ increases

Ca^{2+} oscillations start



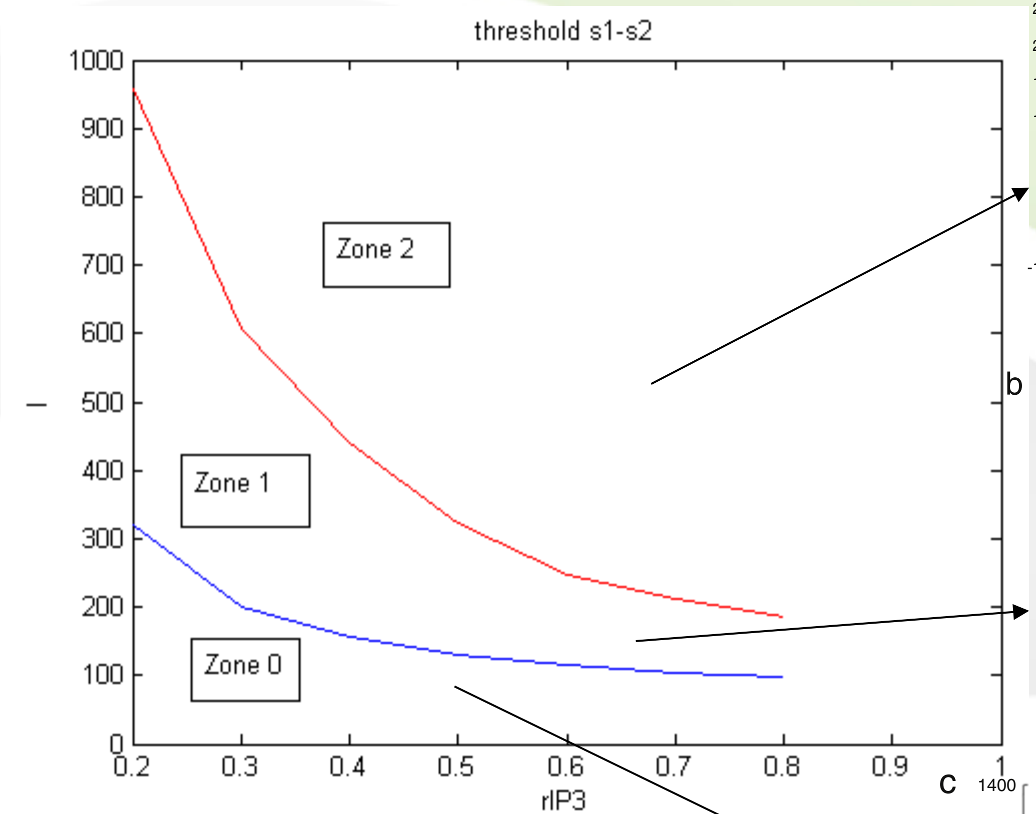
Astrocyte feedback self-sustains Neural activity!

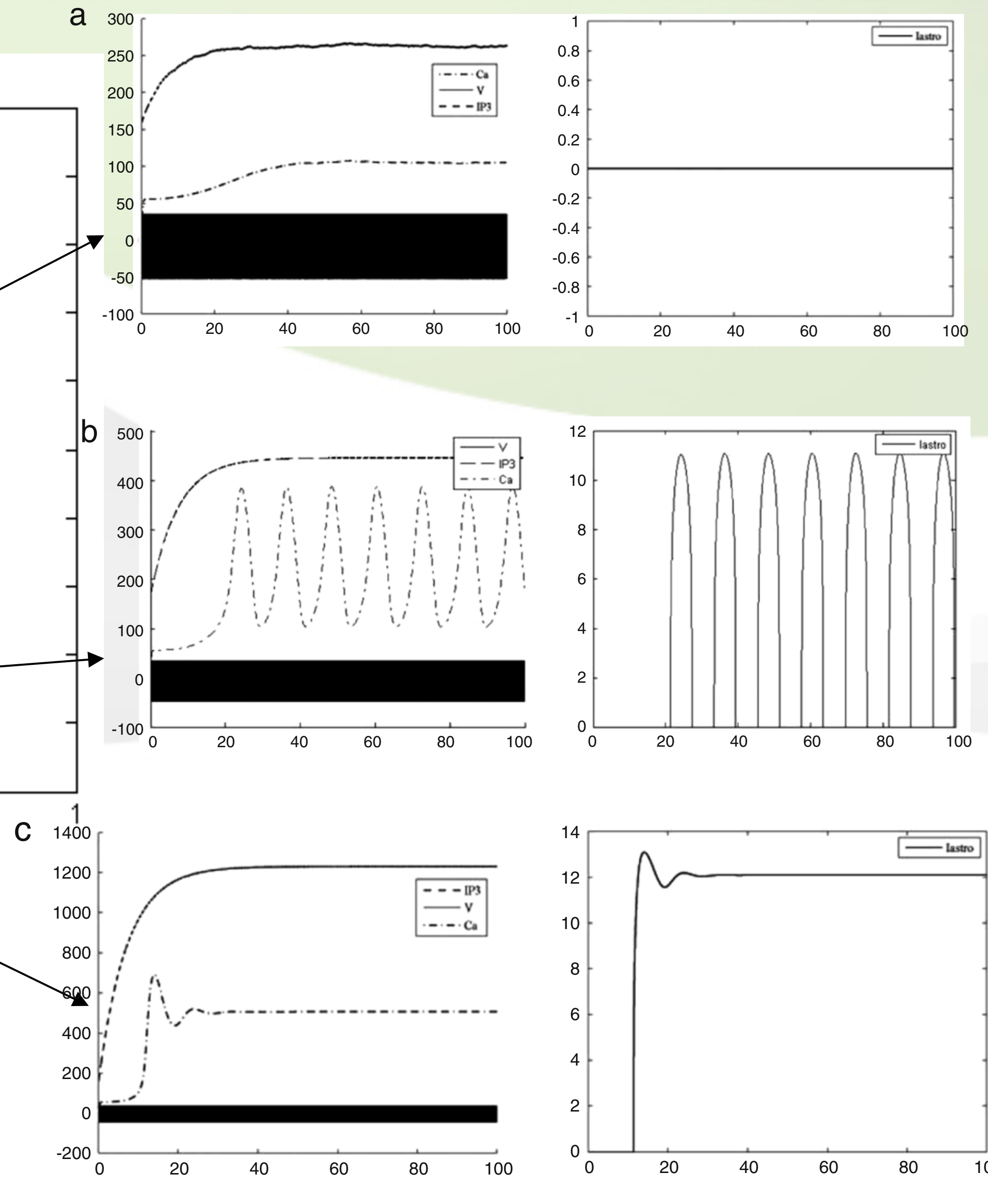
Nadkarni and Jung
Phys. Rev. Letters 2003



Nadkarni and Jung
Phys. Rev. Letters 2003

Neuron-Astrocyte interaction

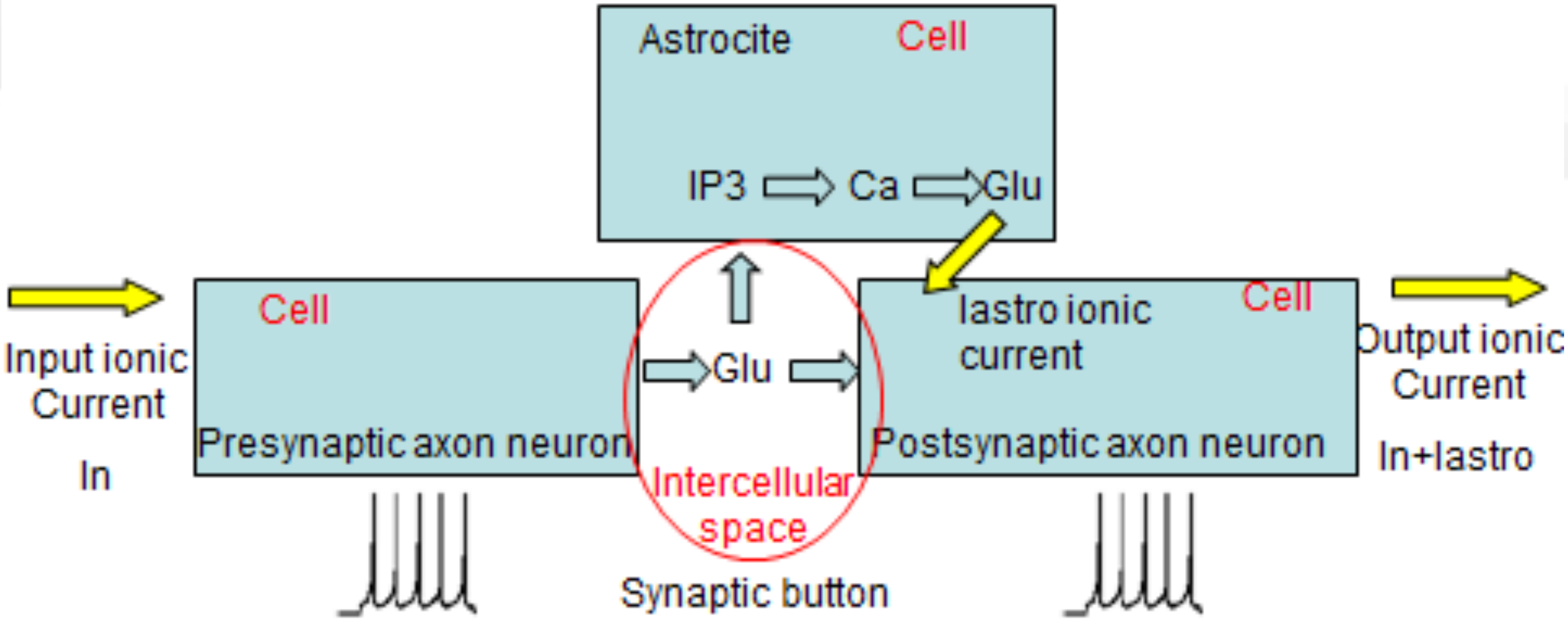




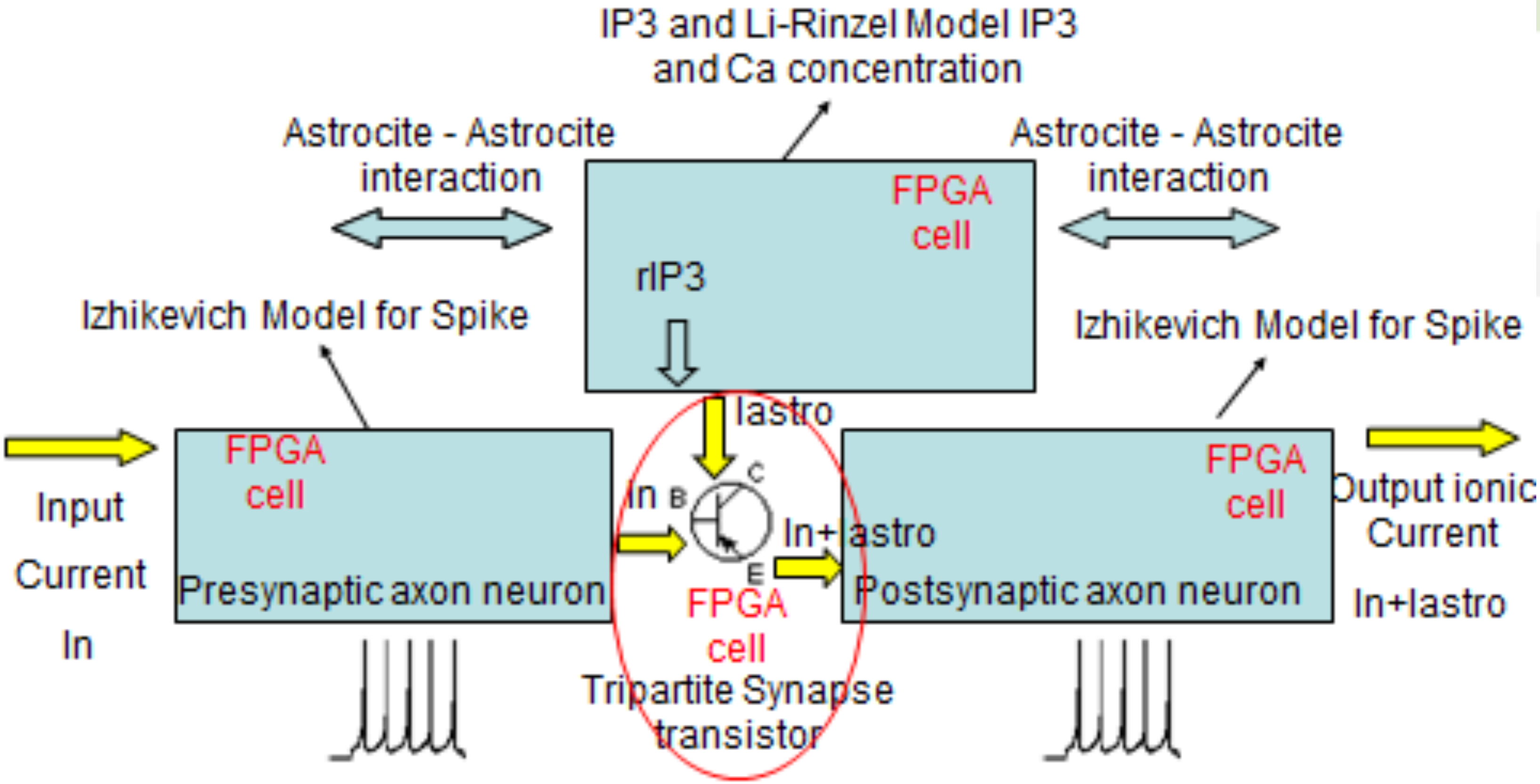
variables $\begin{cases} r_{IP3} \\ I_{neuron} \end{cases}$

Valenza & De Rossi et al.
Neural Networks 2011

Biological Model of tripartite synapse

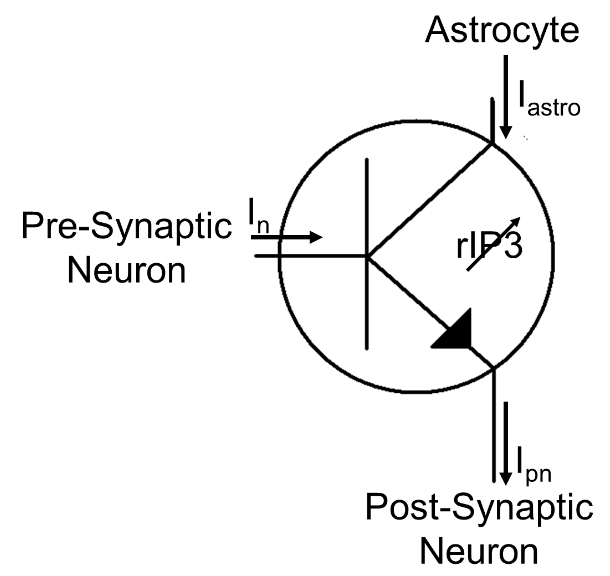


Computational Hardware Model of tripartite synapse



Our model: toward a transistor-based approach

$$I_{astro} = I_{neuron} \cdot h_{fe}$$

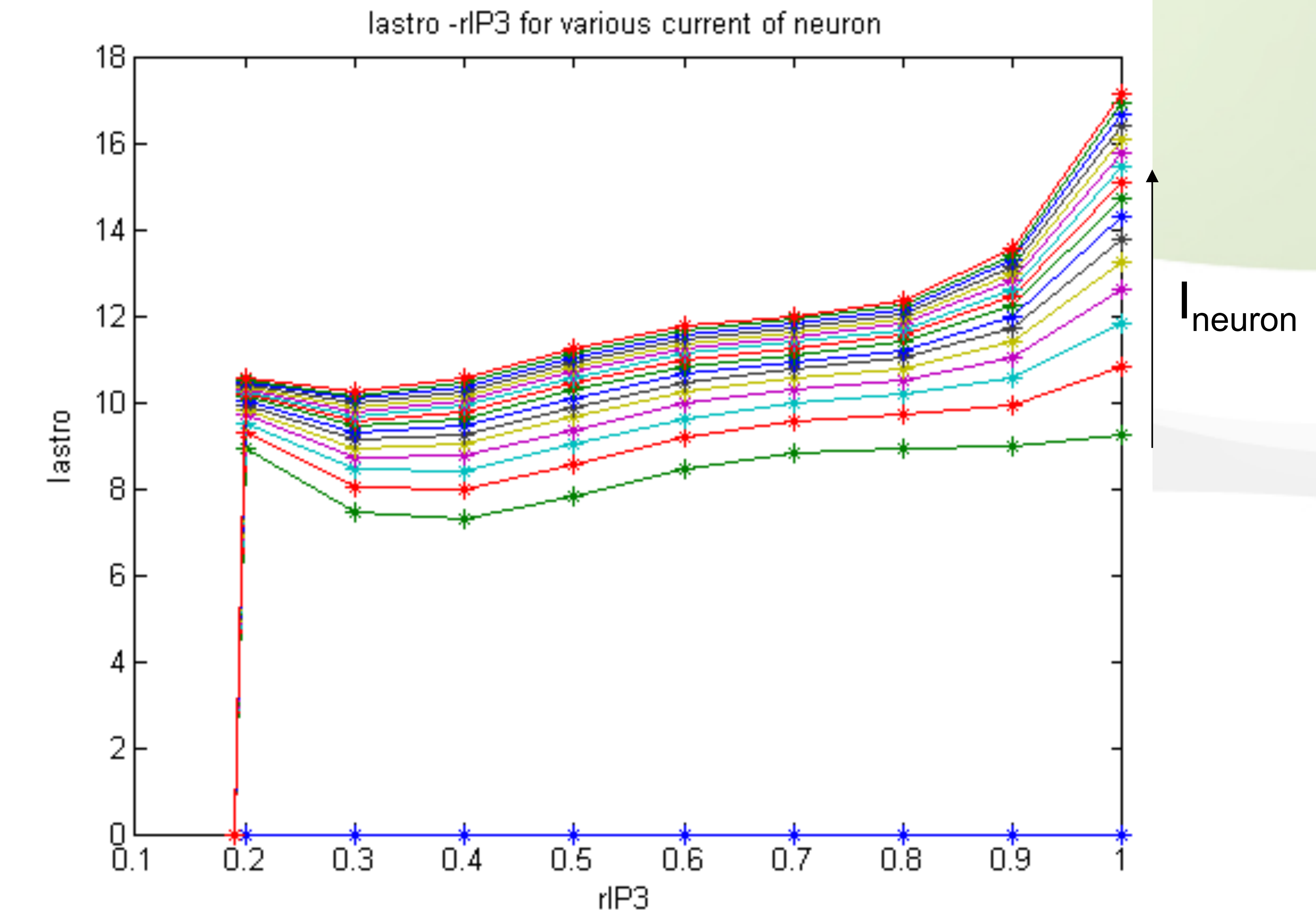


$$h_{fe} = \begin{cases} 0 & if \quad I_n \le s_1(rIP3) \\ \phi(t - d_1(A_1))A_1\left(rIP3, In, s_1\right)\sin\left(h\left(A_1\right)\right) & if \quad s_1(rIP3) < I_n \le s_2(rIP3) \\ \phi(t - d_2(\mathrm{I}_{\mathrm{fin}}))\dfrac{\left[\mathrm{I}_{\mathrm{fin}} + (\mathrm{A}_2 \mathrm{e}^{-\frac{t}{\tau}}\sin(2\pi \mathrm{f}\mathrm{t}))\right]}{\mathrm{I}_{\mathrm{n}}} & if \quad I_n > s_2(rIP3) \end{cases}$$

where s_1 and s_2 are the threshold for the zone 0,1,2

Valenza & De Rossi et al.
Neural Networks 2011

The Neuron-Astrocyte IS a non-linear transistor



The role of Astrocytes:Tripartite Synapses

In summary as input-output model:

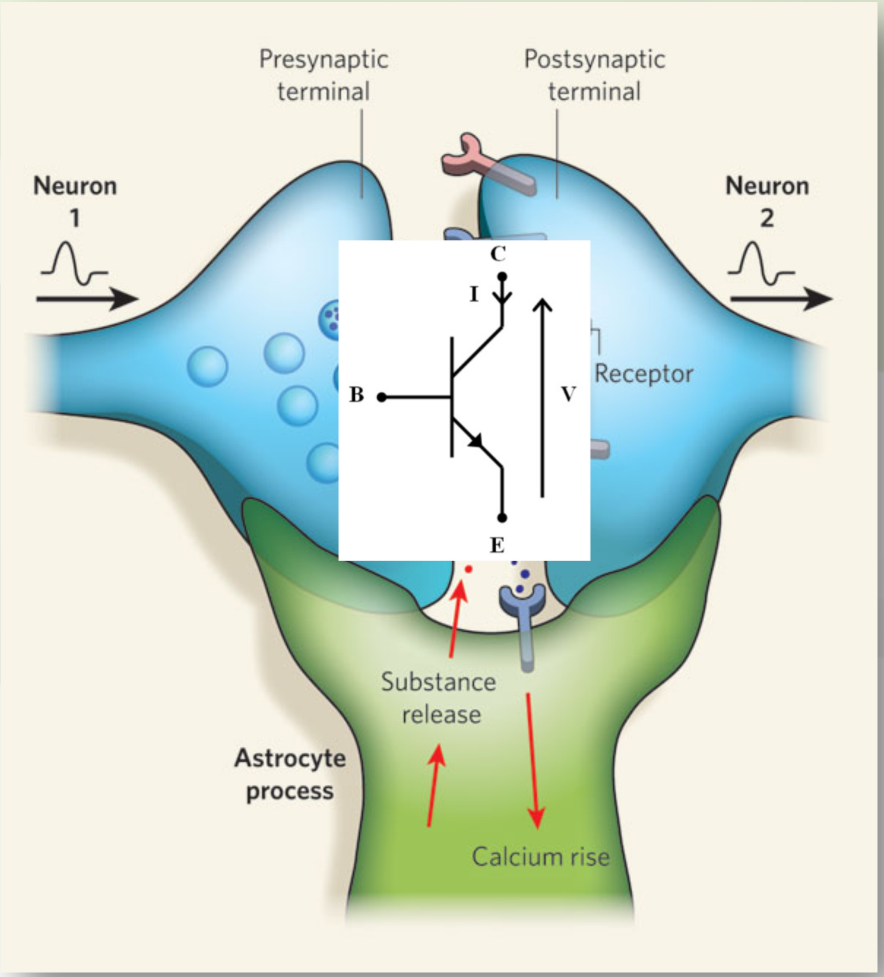
Pre-synaptic Neuron

Neurotransmitters

Inositol 1,4,5-trisphosphate (IP3) rate of production (rIP3)

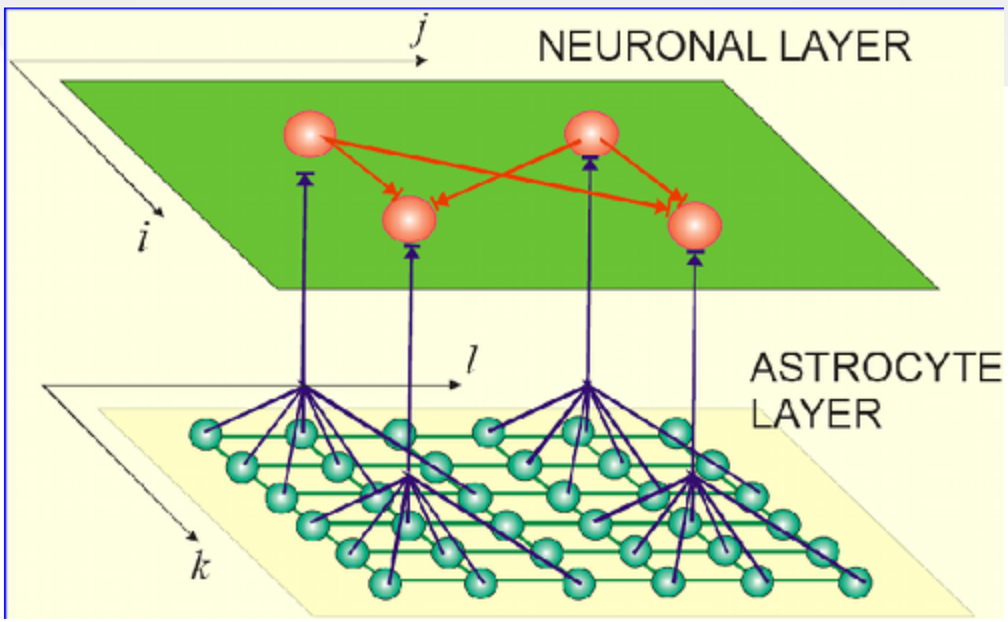
Calcium Oscillation

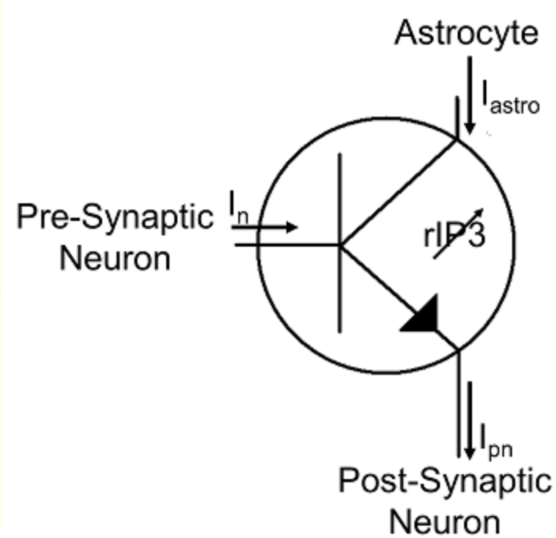
Post-synaptic Neuron



Are SNAN possible?

Develop a novel and efficient computational implementation of a Spiking Neuron-Astrocyte Network (SNAN)



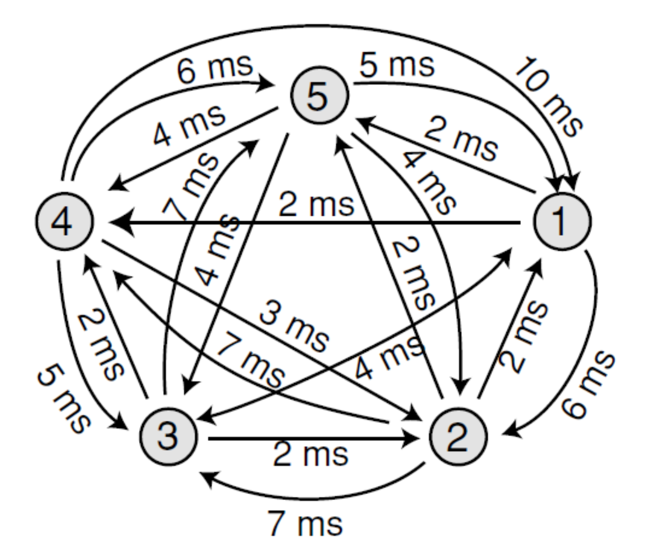


Policronization in SNN

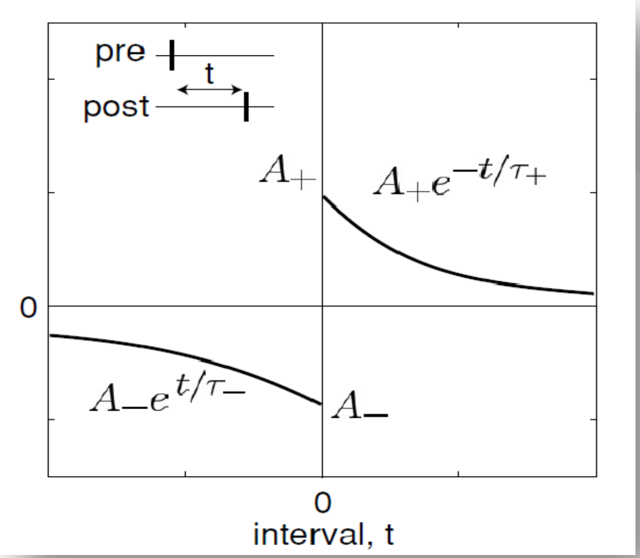
Edelman → Theory of neuronal group selection (TNGS, Neural Darwinism)

Izhikevich Network

Axonal Conduction Delays



Spike-Timing-Dependent Plasticity (STDP)

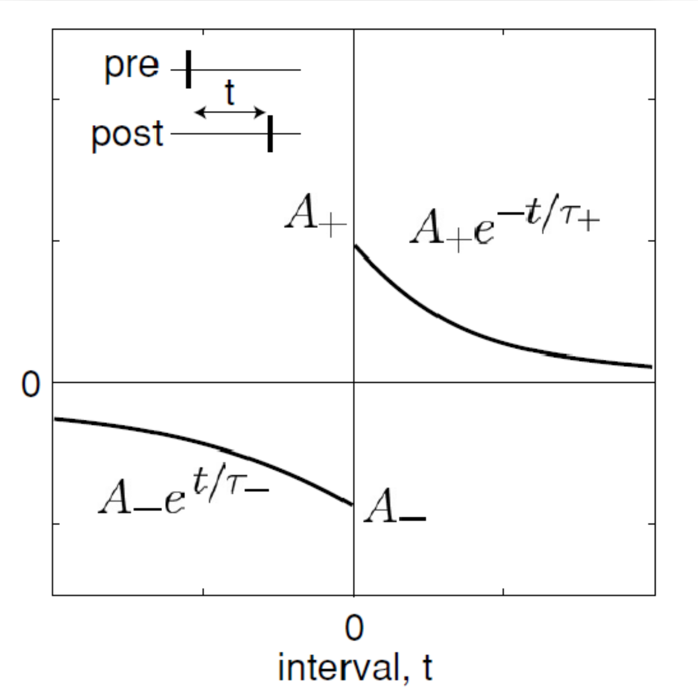


Policronization

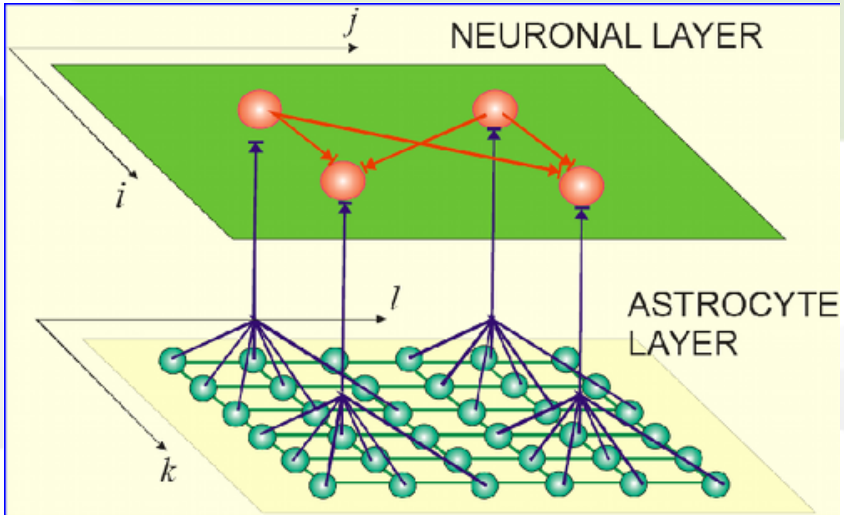
Izhikevich 2006

How to define a SNAN

Two learning rules:



Neural weight are updated according to the Spike-Timing-Dependent Plasticity (STDP).



rIP3 values are updated according to the following rule:

$$r_{IP3}(n+1) = r_{IP3}(n) + 0.05(r_{IP3}(n) - r_{IP3}(n-1))$$

Biologically Inspired Astrocyte-Neuron ratio of 1.5

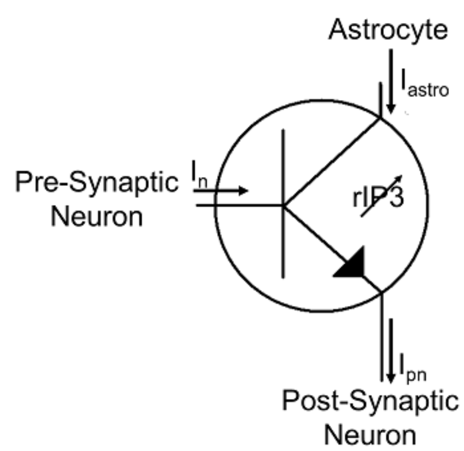
How to define a SNAN: Timing

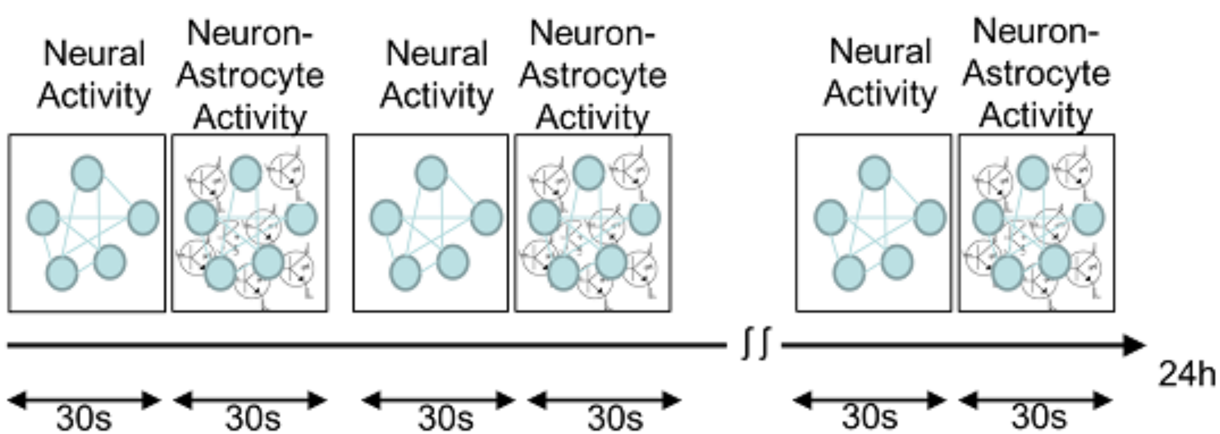
Inizialization of neurons

Neural activity only (30s)

Inizialization of astrocytes

Simultaneous Activity of Neurons and Astrocytes





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Experimental results

24h simulation

Evaluations after

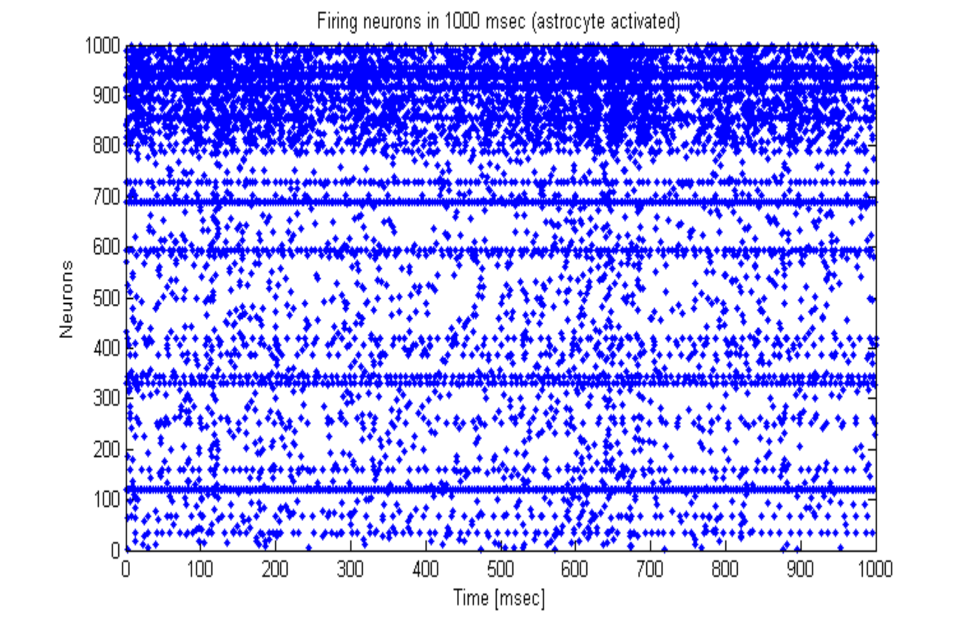
- 3h
- 6h
- 12h
- 18h
- 24h

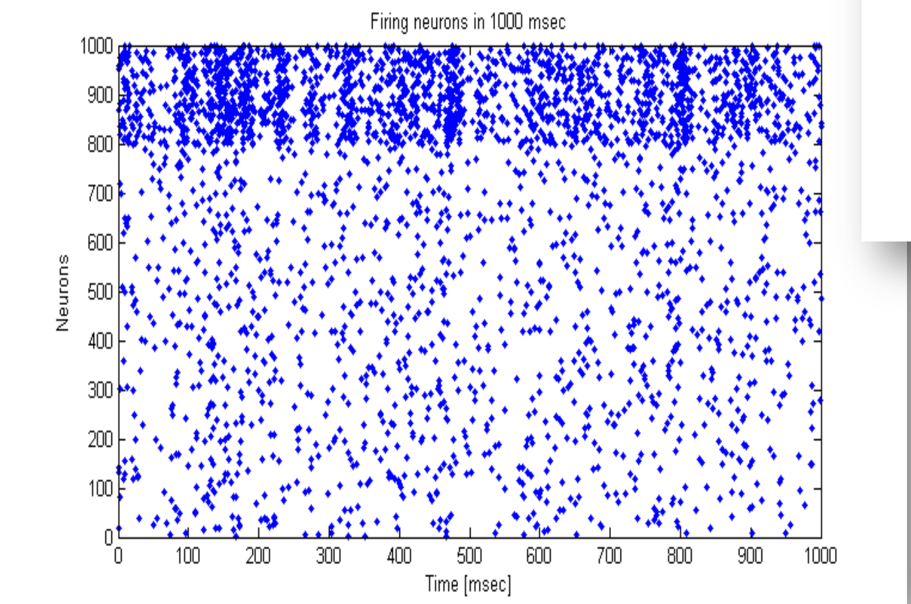
Network dimension

Neurons	*1000*
Astrocytes	*1500*

Experimental Results

SNAN with 1000 Neurons and 1500 Astrocytes

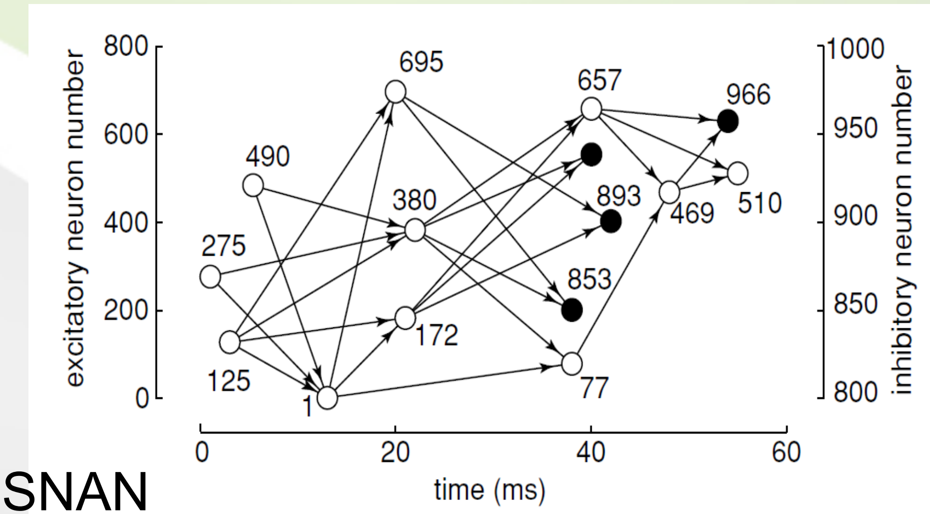


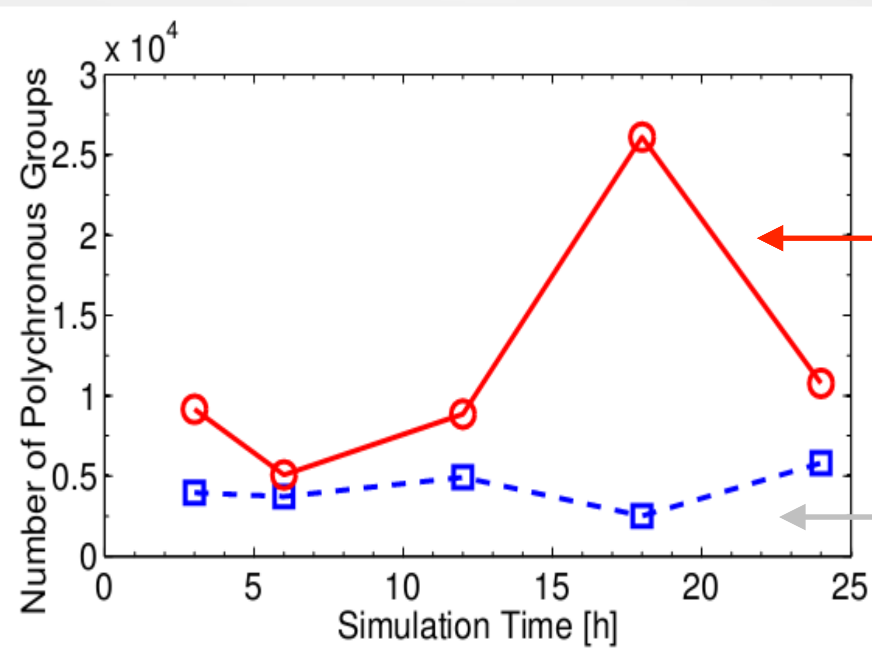


SNN with 1000 neurons

Experimental results

Comparison, in terms of number of polychronous groups, of the network implementations.





SNAN

SNN