University of Pisa

Neural and Neuron-Astrocyte Modeling

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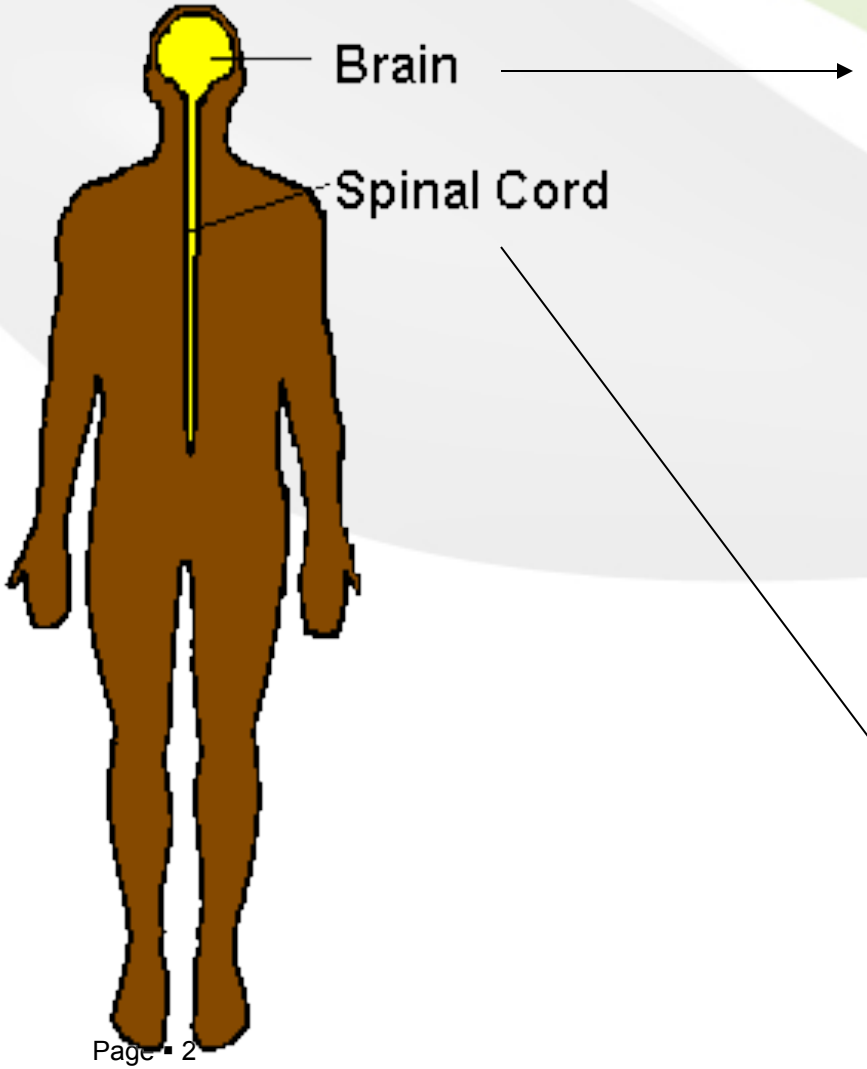
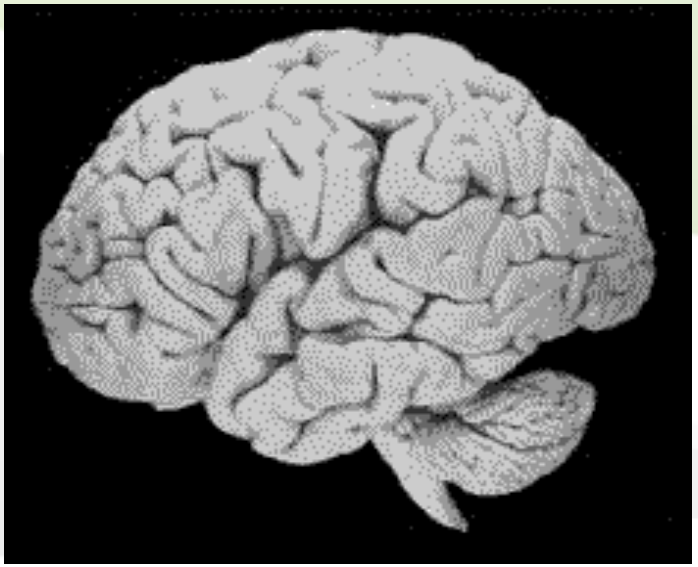
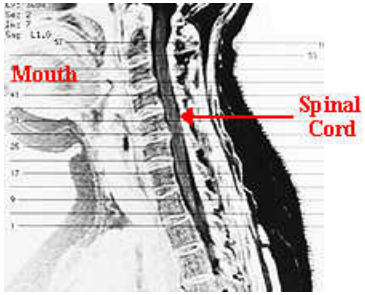
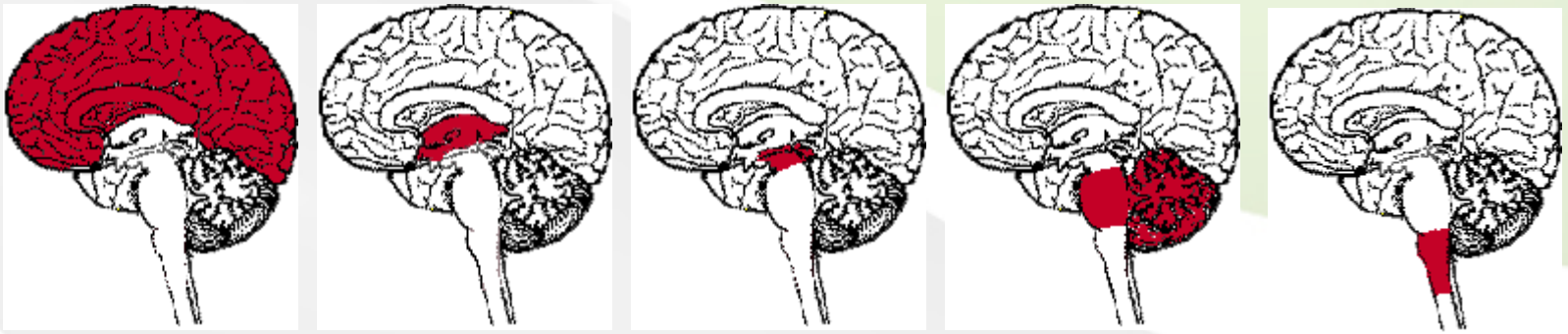
Central Nervous System (CNS)



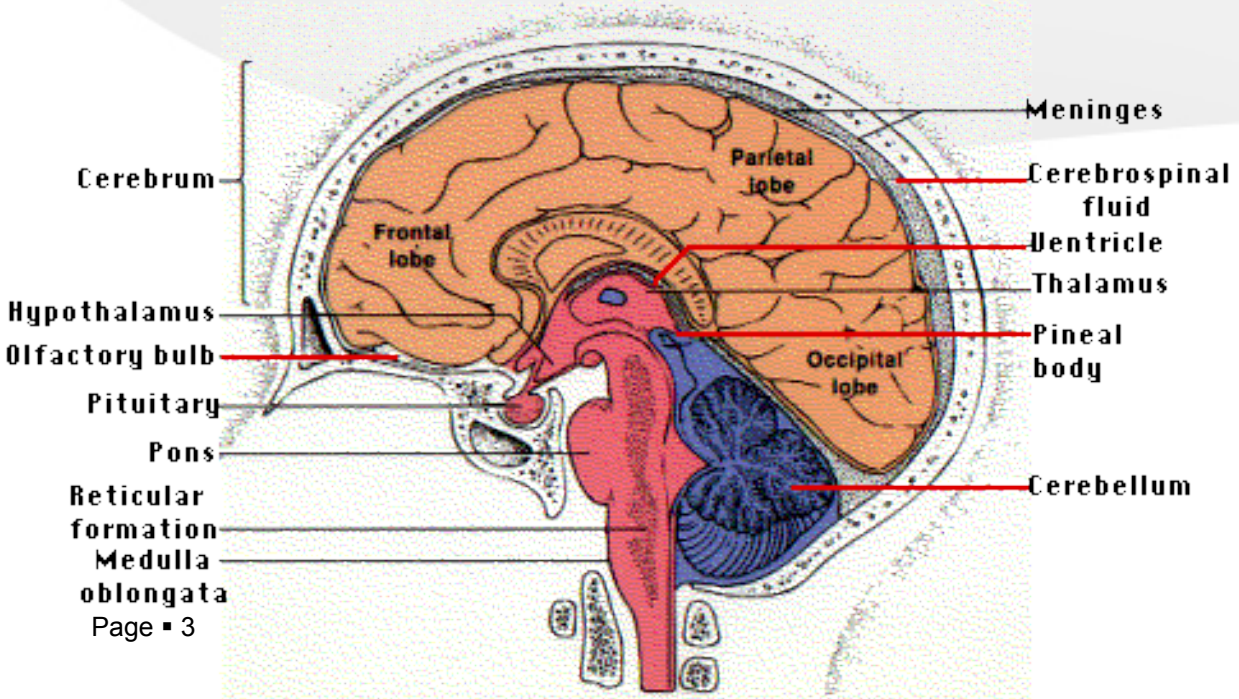




Encephalon: Anatomical division

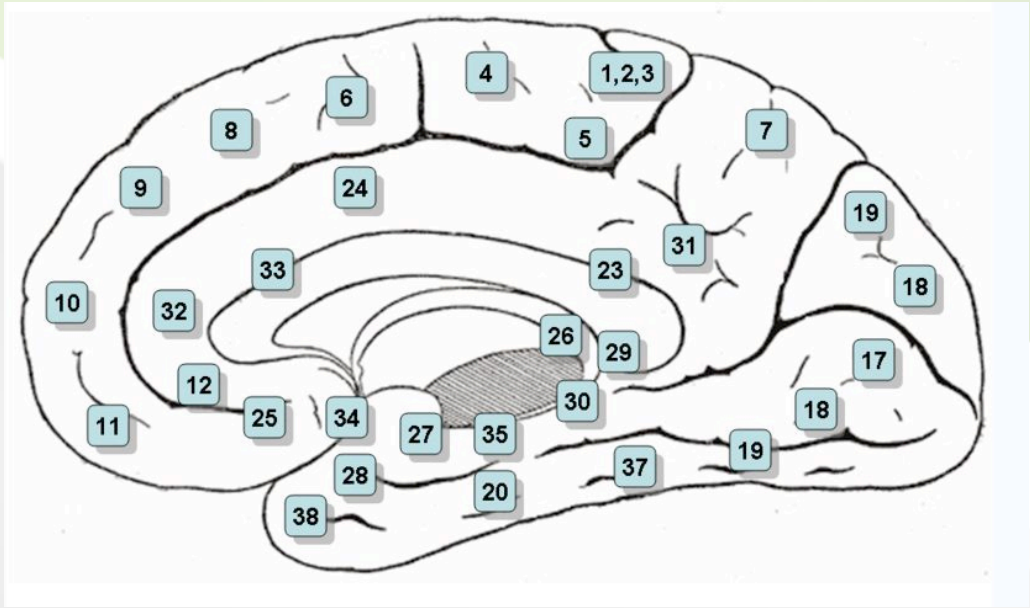


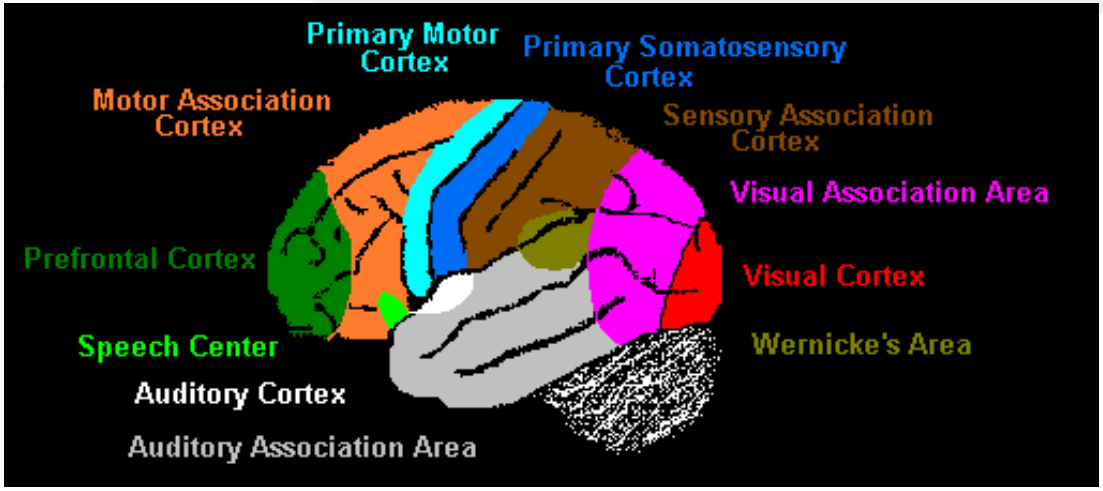
Telencephalon Diencephalon Mesencephalon Metencephalon Mielencephalon



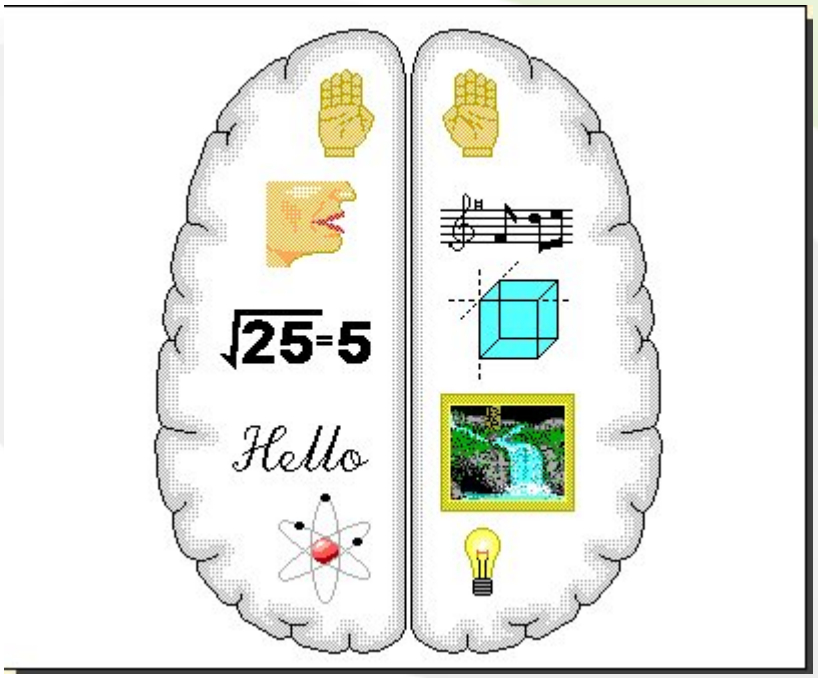
The Cerebral Cortex: Functional Division

Brodmann Areas

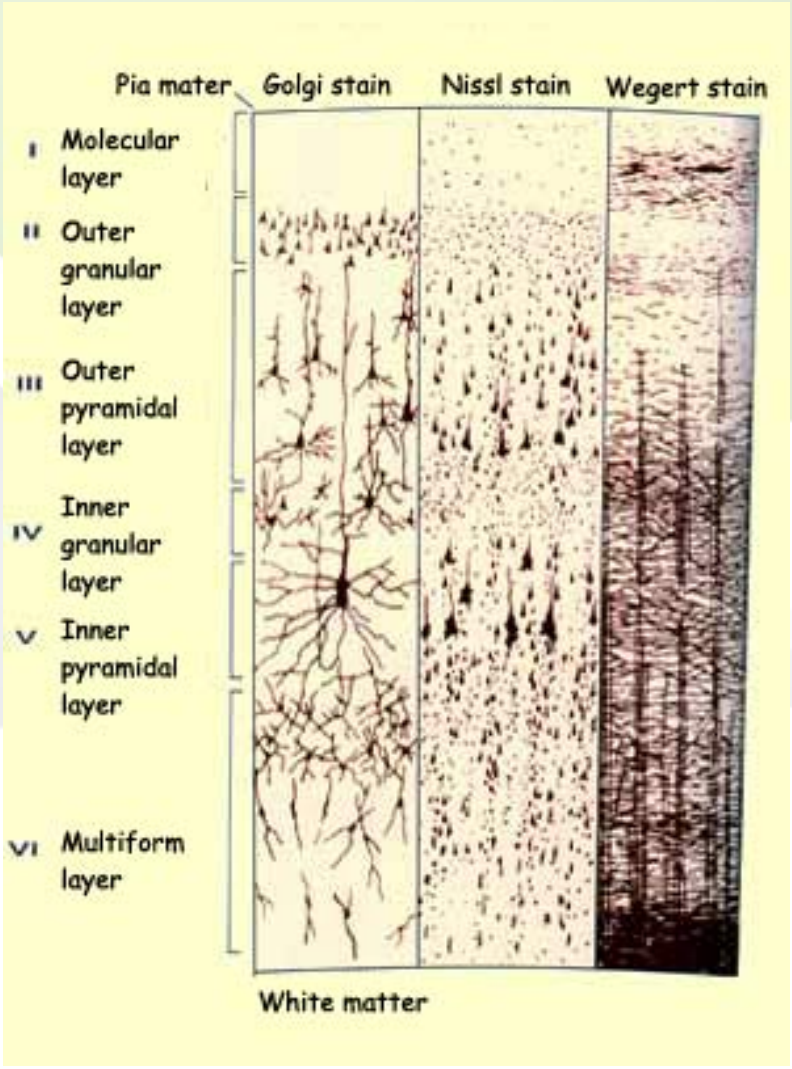




The Cerebral Cortex (1)

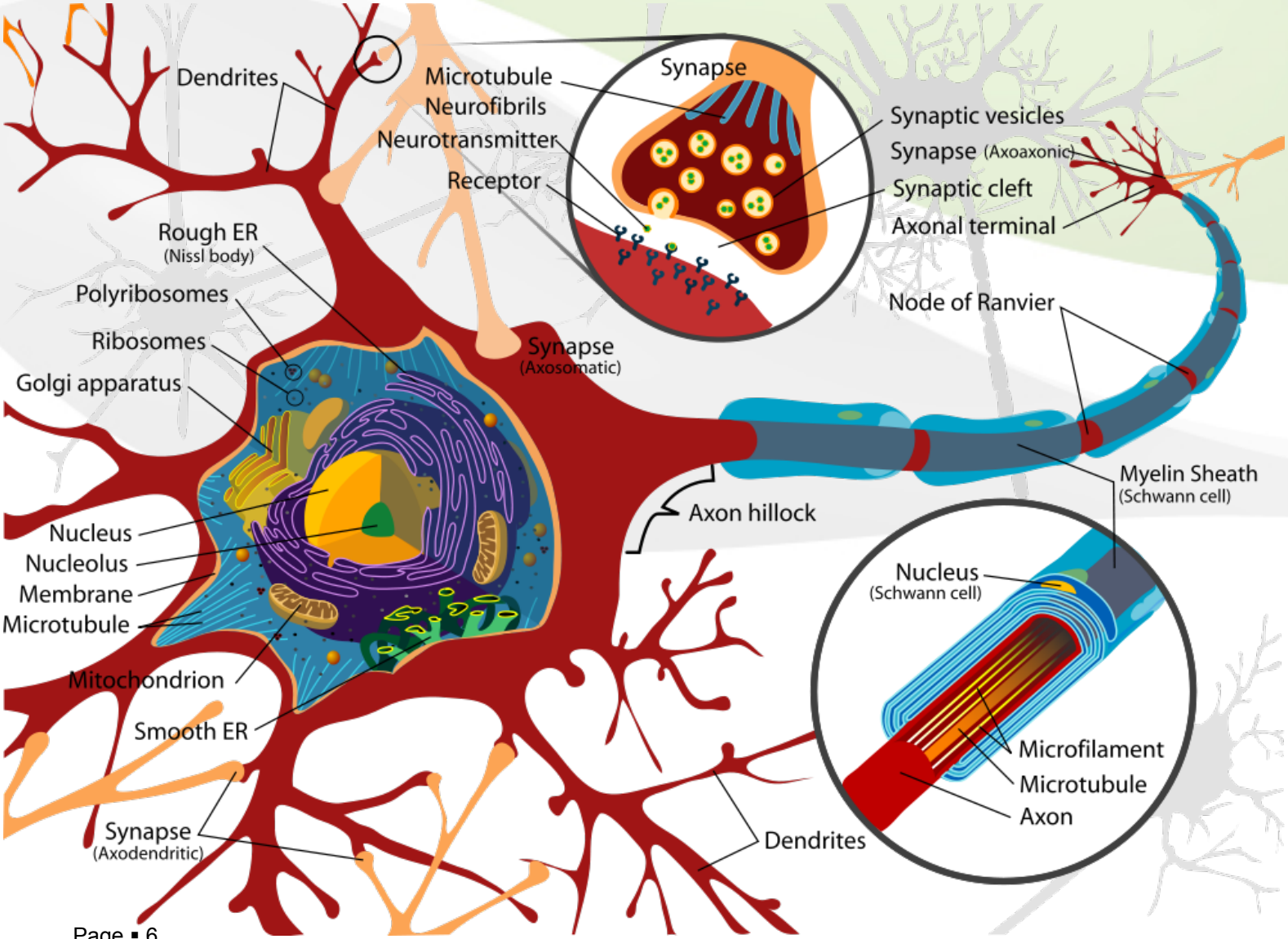


The cerebral cortex is responsible of many cognitive functions such as language, memory, emotional processing, etc.



Six layers of neurons

Modelling Neural Dynamics



Levels of Modeling

Brain as a whole

Specific brain systems (visual system,…)

Large scale neural networks

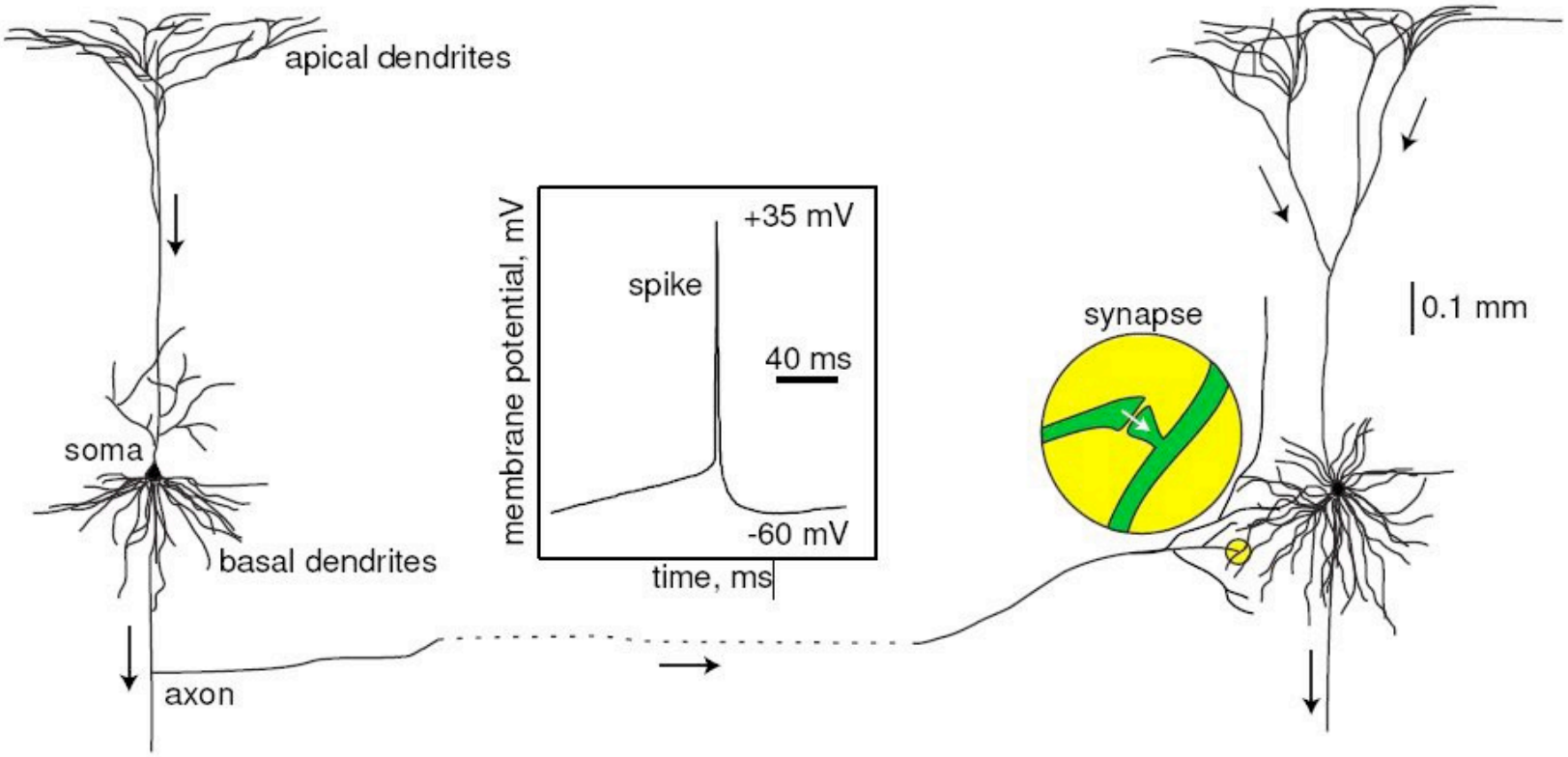
Small neural networks

Neurons

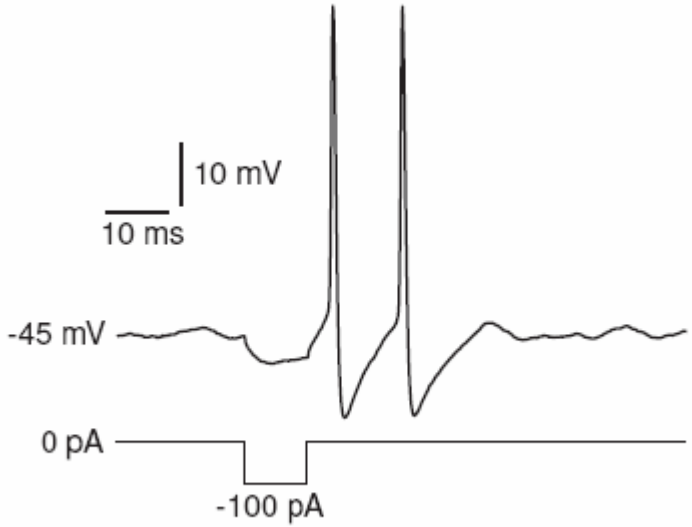
Ion channels and synapses

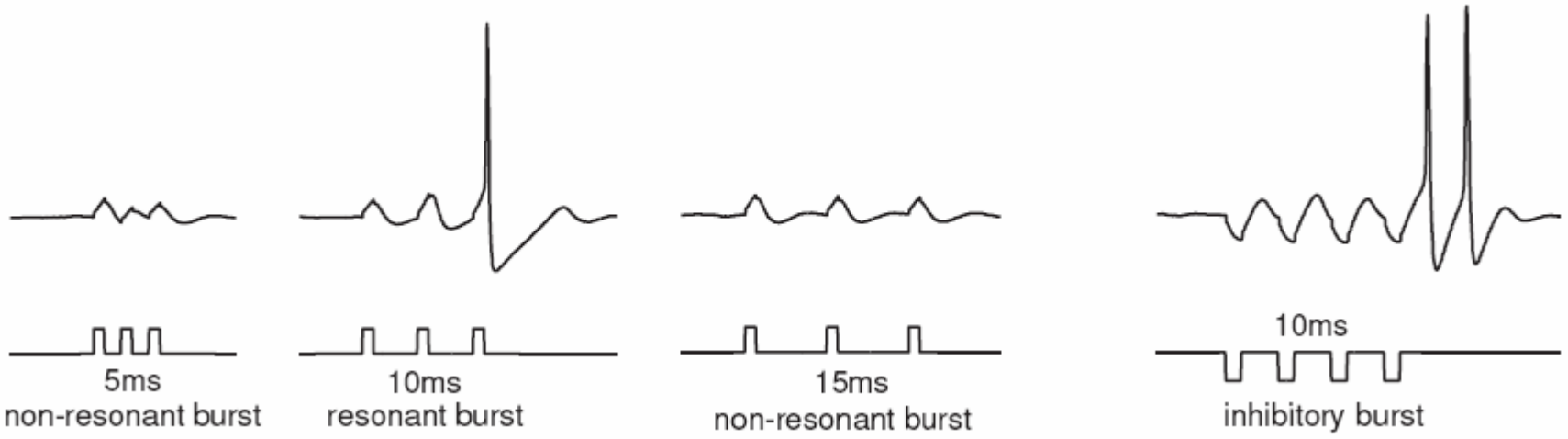
Molecular processes

Neural Spiking

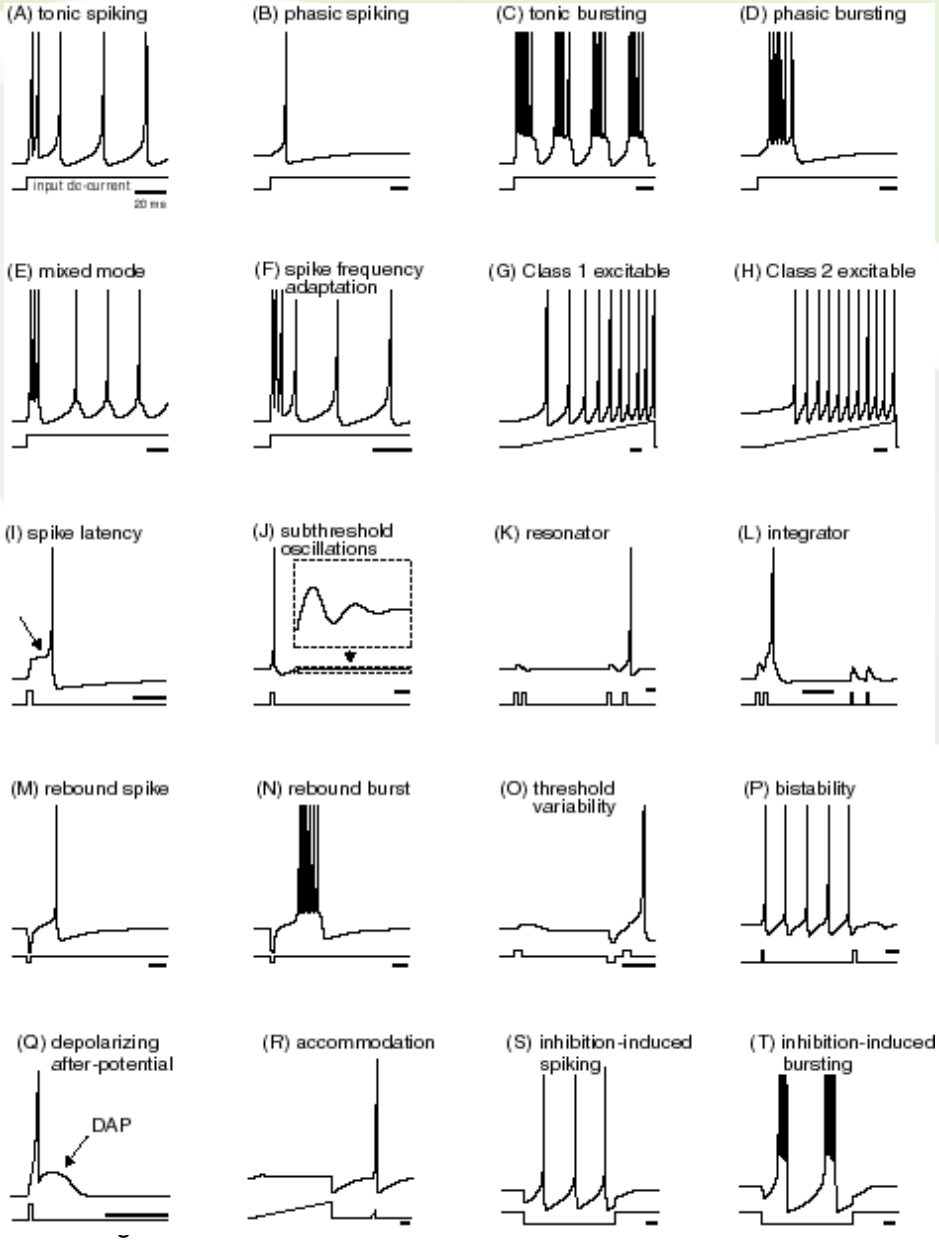


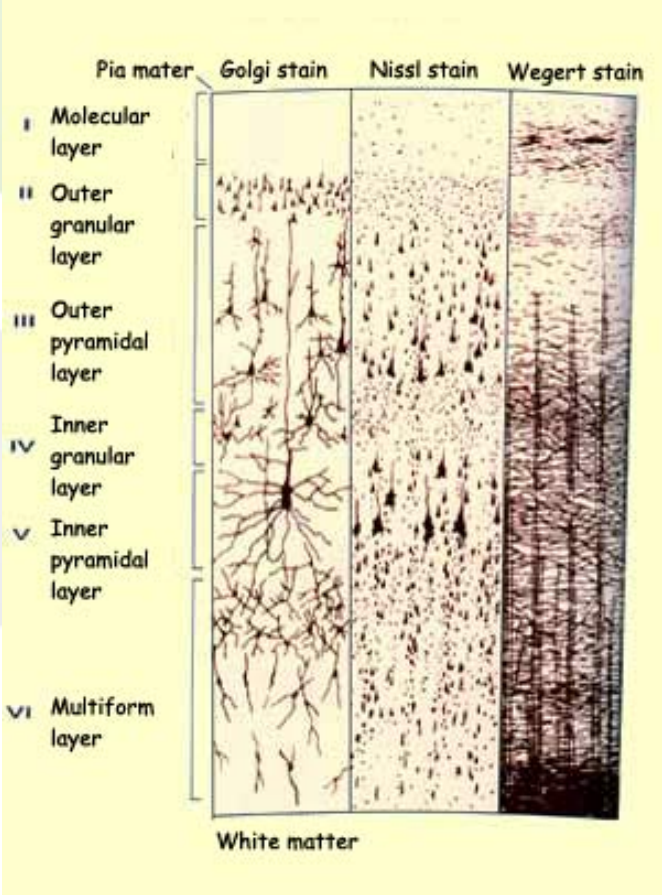
Neural Spiking





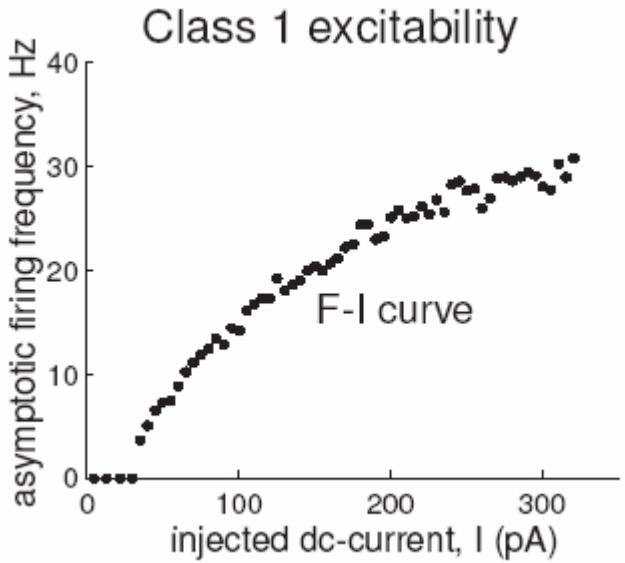
Particular Neural Dynamics



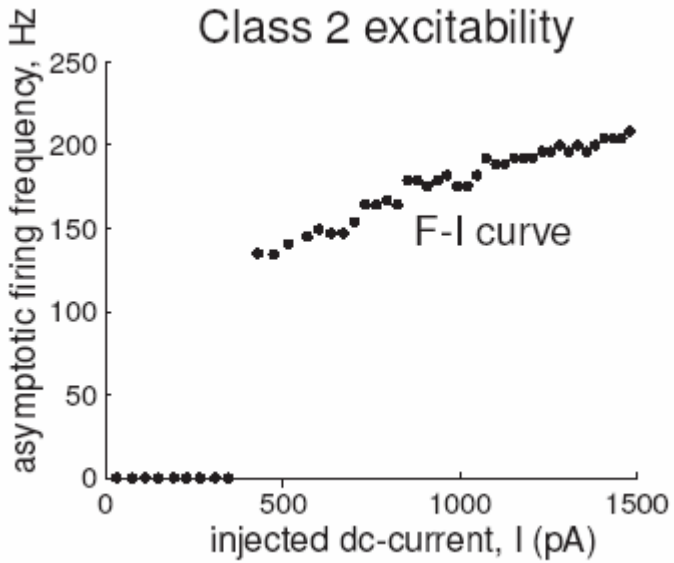


Hodgking classification of neural excitability

- CLASS 1 NEURAL EXCITABILITY. Action potentials can be generated with arbitrarily low frequency, depending on the strength of the applied current.
- CLASS 2 NEURAL EXCITABILITY. Action potentials are generated in a certain frequency band that is relatively insensitive to changes in the strength of the applied current.
- CLASS 3 NEURAL EXCITABILITY. A single action potential is generated in response to a pulse of current. Repetitive (tonic) spiking can be generated only for extremely strong injected currents or not at all.



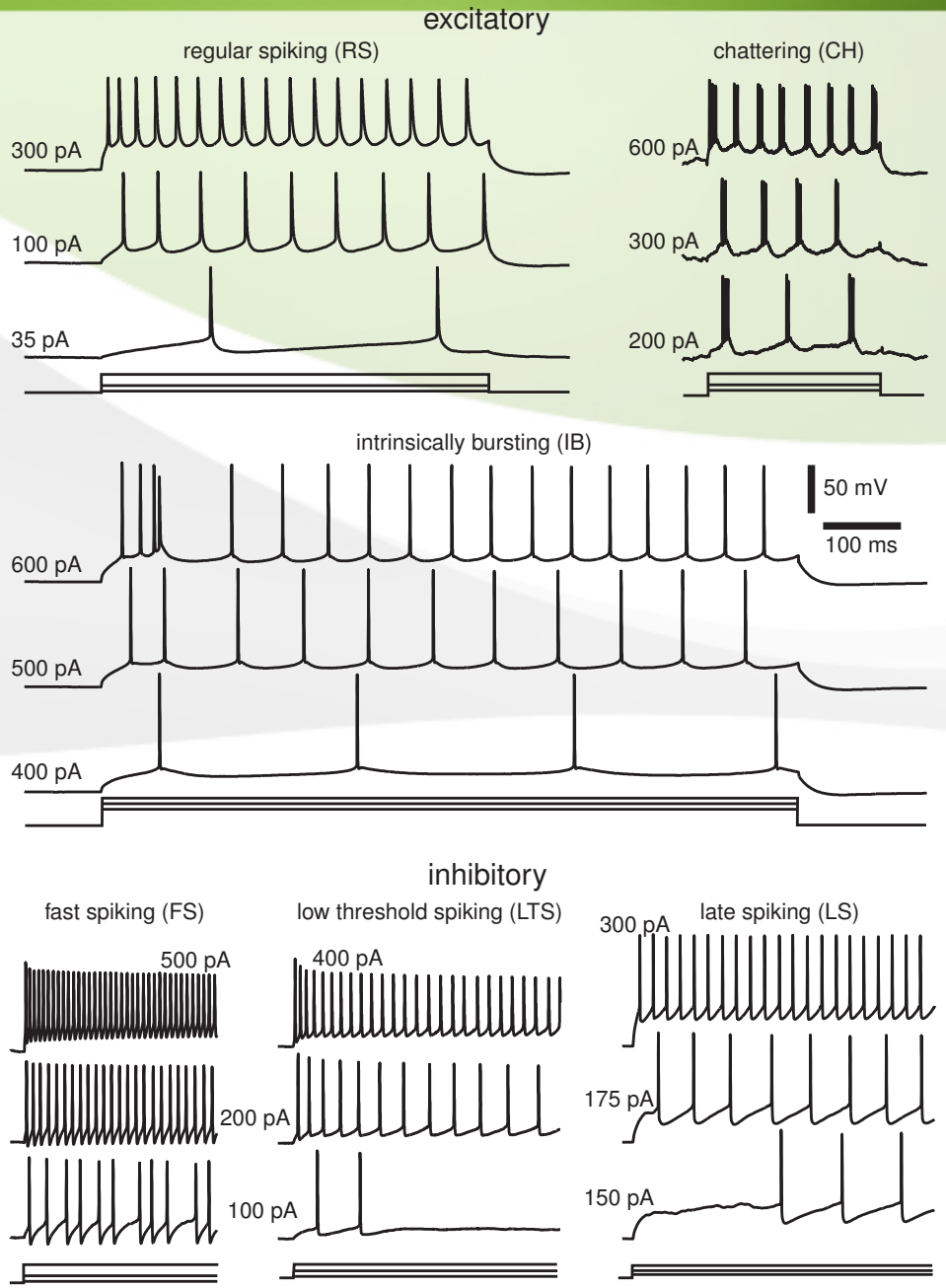
e.g. in cortical pyramidal neurons



e.g. brainstem mesV

Particular Neural Dynamics in the Neocortex

Six most fundamental classes of firing patterns of neocortical neurons in response to pulses of depolarizing dc-current. RS and IB are in vitro recordings of pyramidal neurons of layer 5 of primary visual cortex of a rat, CH was recorded in vivo in cat's visual cortex. FS was recorded in vitro in rat's primary visual cortex, LTS was recorded in vitro in layer 4 or 6 of rat's barrel cortex. LS was recorded in layer 1 of rat's visual cortex.



Biologically-Inspired Single-Neuron Simulation

Benefits

- Can reproduce activity of single neurons
- Can be used to model detailed changes (external currents or the effect of drugs)

Disadvantages

- Needs neuron morphology (dendritic layout)
- Needs information about ion channels, synapse position, neurotransmitter type
- Is slow to calculate for large numbers of neurons

=> Need for simplified neuron models

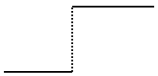
Modelling Neural Dynamics

The McCulloch-Pitts neuron (1943)

$$h = \sum_i x_i^{\text{in}}$$

Summation of input (no synaptic weights!)

$$x^{\text{out}} = \begin{cases} 1 & \text{if } h > \Theta \\ 0 & \text{otherwise} \end{cases}$$



Step-wise activation function

-> Birth of artificial neural network (ANN) research

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 5, 1943

A LOGICAL CALCULUS OF THE IDEAS IMMANENT IN NERVOUS ACTIVITY

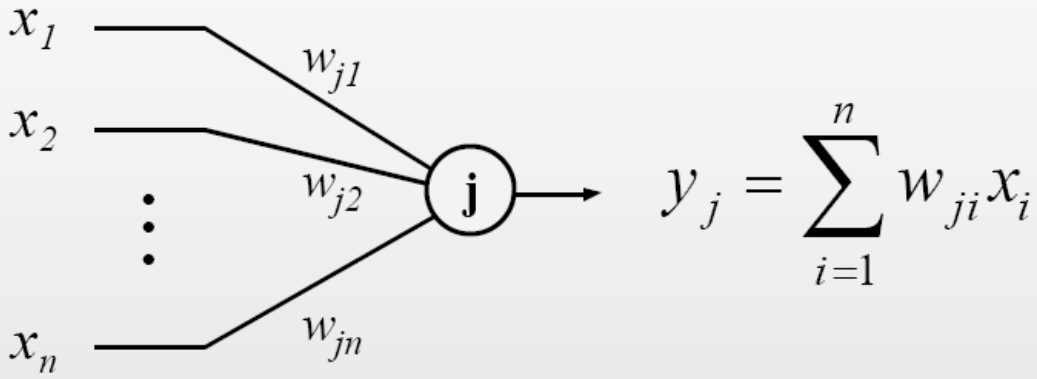
WARREN S. MCCULLOCH AND WALTER PITTS

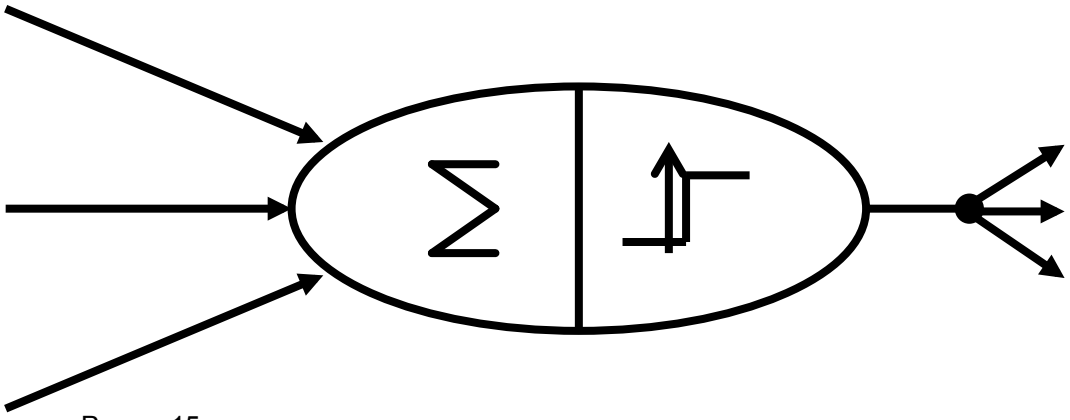
FROM THE UNIVERSITY OF ILLINOIS, COLLEGE OF MEDICINE,
DEPARTMENT OF PSYCHIATRY AT THE ILLINOIS NEUROPSYCHIATRIC INS
AND THE UNIVERSITY OF CHICAGO

Because of the "all-or-none" character of nervous activity, r
events and the relations among them can be treated by means of p
sitional logic. It is found that the behavior of every net can be desc
in these terms, with the addition of more complicated logical mean
nets containing circles; and that for any logical expression satis

Modelling Neural Dynamics

The first artificial neuron



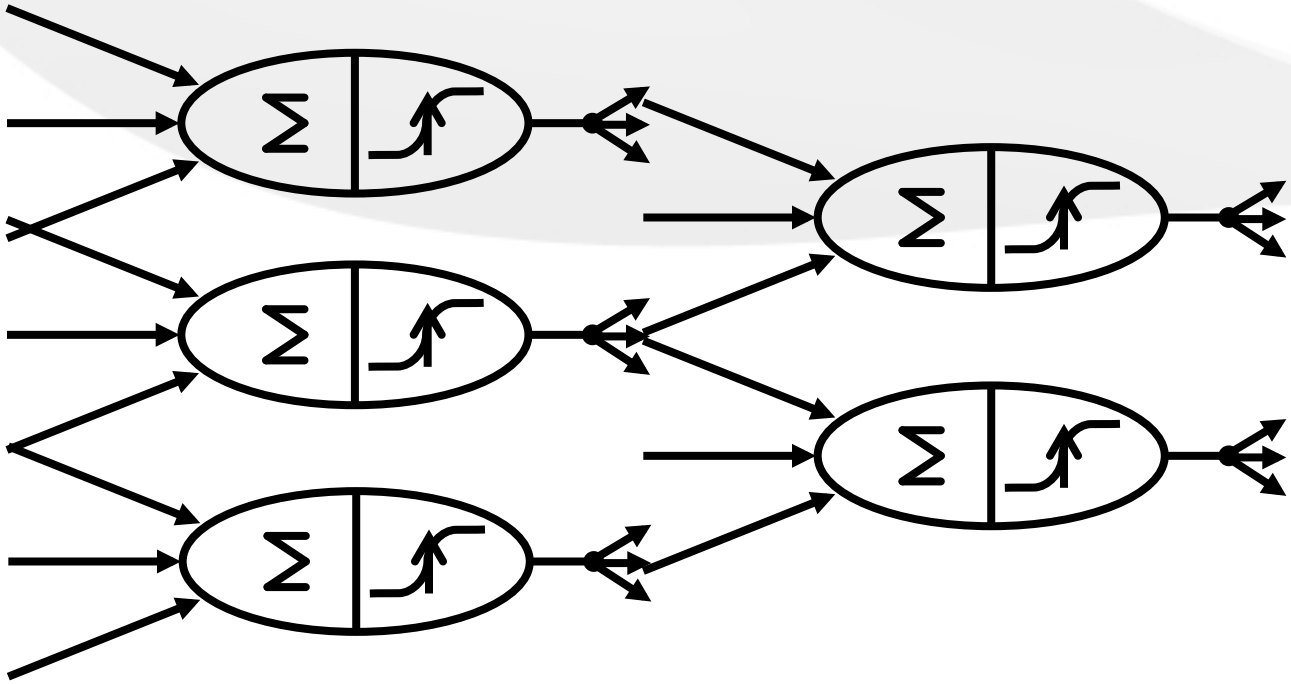


$$y_j = \begin{cases} 1, if \sum_{i=1}^{n} w_{ji} x_i \geq \theta \\ 0, if \sum_{i=1}^{n} w_{ji} x_i < \theta \end{cases}$$

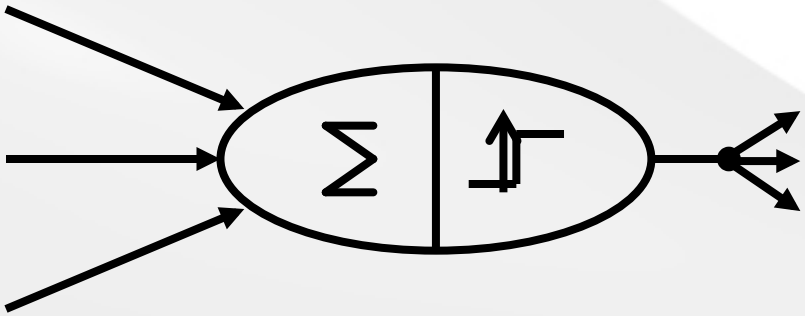
Modelling Neural Dynamics

$$y_j = f\left(\sum_{i=1}^{n} w_{ji} x_i\right)$$

Multilayered Perception is **a universal approximator**

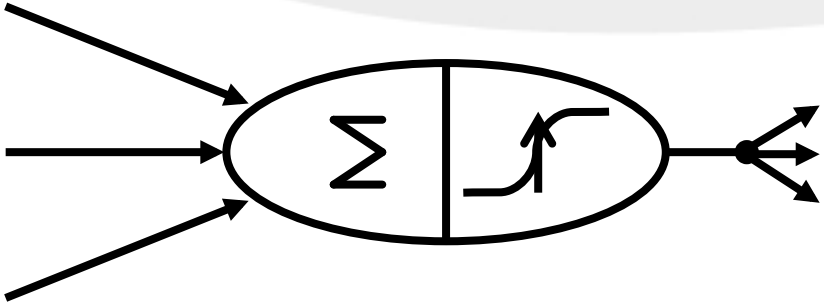


Modelling Neural Dynamics



$$y = \begin{cases} 1 & \text{spike occurrence} \\ 0 & \text{spike absence} \end{cases}$$

From neurophysiology point of view, *y* is **existence of an output spike**



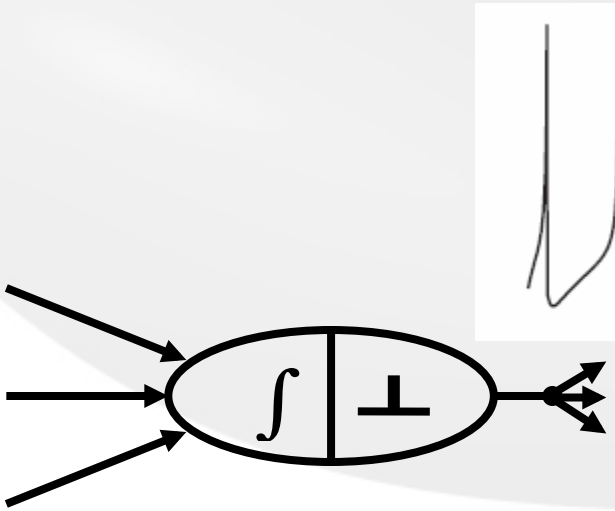
$$y = \frac{\textit{Number of spikes}}{\textit{Time frame}}$$

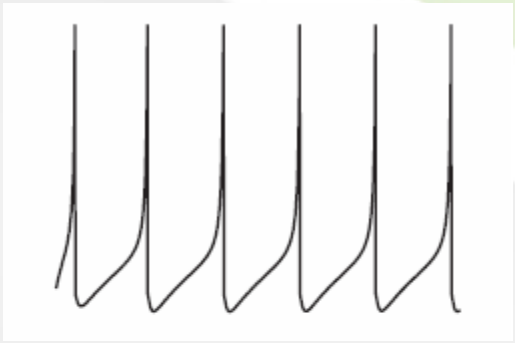
From neurophysiology point of view, *y* is **firing rate**

Spike timing is **not considered** at all!

Modelling Neural Dynamics

Spiking neuron model





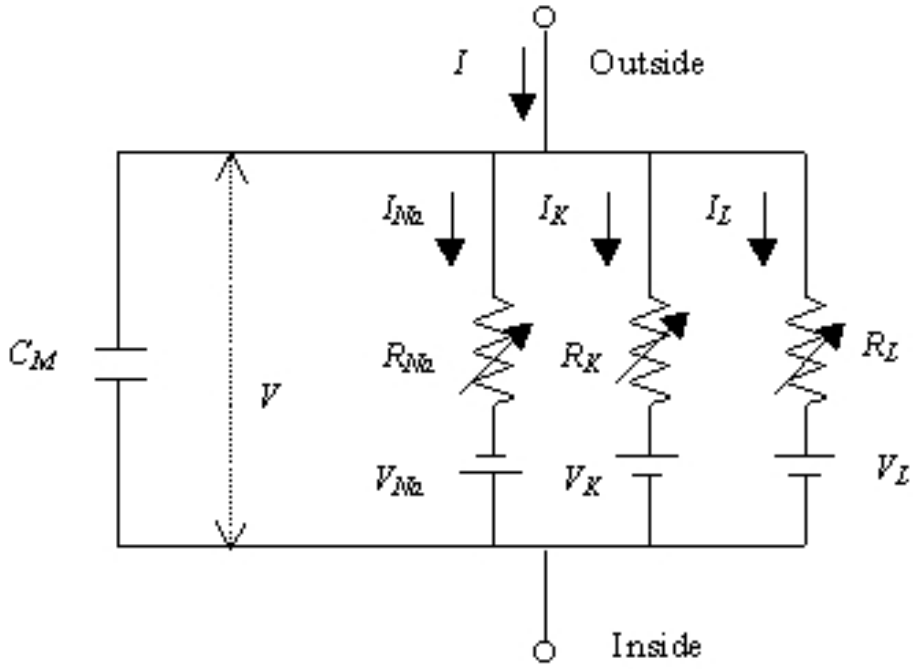
Spiking neural networks are
- biologically **more plausible**,
- computationally **more powerful**,
- considerably **faster**

than networks of the second generation

Modelling Neural Dynamics

Hodgkin-Huxley (first biologically-plausible neural model - 1952)

$$
\begin{aligned}
C\dot{V} &= I - \overbrace{\bar{g}_{\mathrm{K}} n^4 (V - E_{\mathrm{K}})}^{I_{\mathrm{K}}} - \overbrace{\bar{g}_{\mathrm{Na}} m^3 h (V - E_{\mathrm{Na}})}^{I_{\mathrm{Na}}} - \overbrace{g_{\mathrm{L}} (V - E_{\mathrm{L}})}^{I_{\mathrm{L}}} \\
\dot{n} &= \alpha_n(V)(1-n) - \beta_n(V) n \\
\dot{m} &= \alpha_m(V)(1-m) - \beta_m(V) m \\
\dot{h} &= \alpha_h(V)(1-h) - \beta_h(V) h \ ,
\end{aligned}
$$



Hodgkin-Huxley model

$$\frac{dv}{dt} = \frac{I_{external} - (I_K + I_{Na} + I_{leak})}{C}$$

$$I_K = g_K n^4 (v - V_K)$$
$$I_{Na} = g_{Na} m^3 h (v - V_{Na})$$
$$I_{leak} = g_{leak} (v - V_{leak})$$

$$\frac{dm}{dt} = \alpha_m(v)(1-m) - \beta_m(v)m$$
$$\frac{dn}{dt} = \alpha_n(v)(1-n) - \beta_n(v)n$$
$$\frac{dh}{dt} = \alpha_h(v)(1-h) - \beta_h(v)h$$

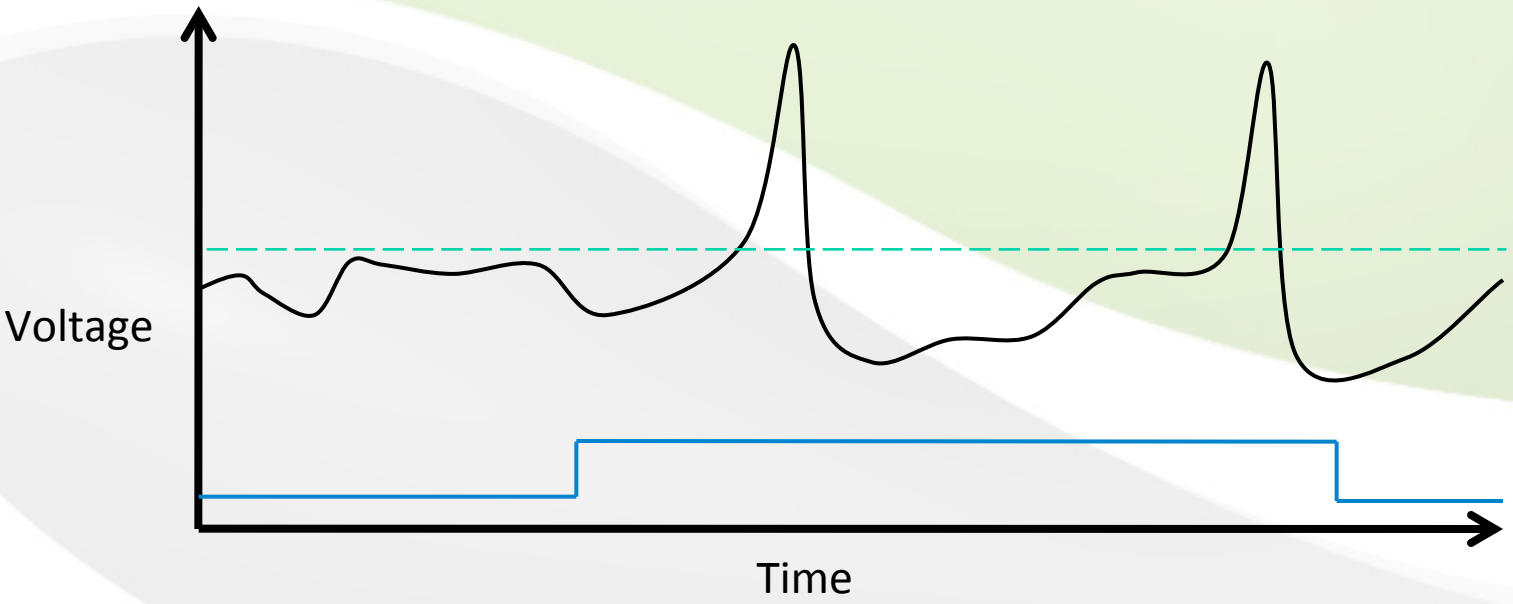
$$\alpha_m(v) = 0.1(v+25)/(e^{(v+25)/10} - 1)$$
$$\alpha_n(v) = 0.01(v+10)/(e^{(v+10)/10} - 1)$$
$$\alpha_h(v) = 0.07e^{v/20}$$

$$\beta_m(v) = 4e^{v/18}$$
$$\beta_n(v) = 0.125e^{v/80}$$
$$\beta_h(v) = 1/(e^{(v+30)/10} + 1)$$

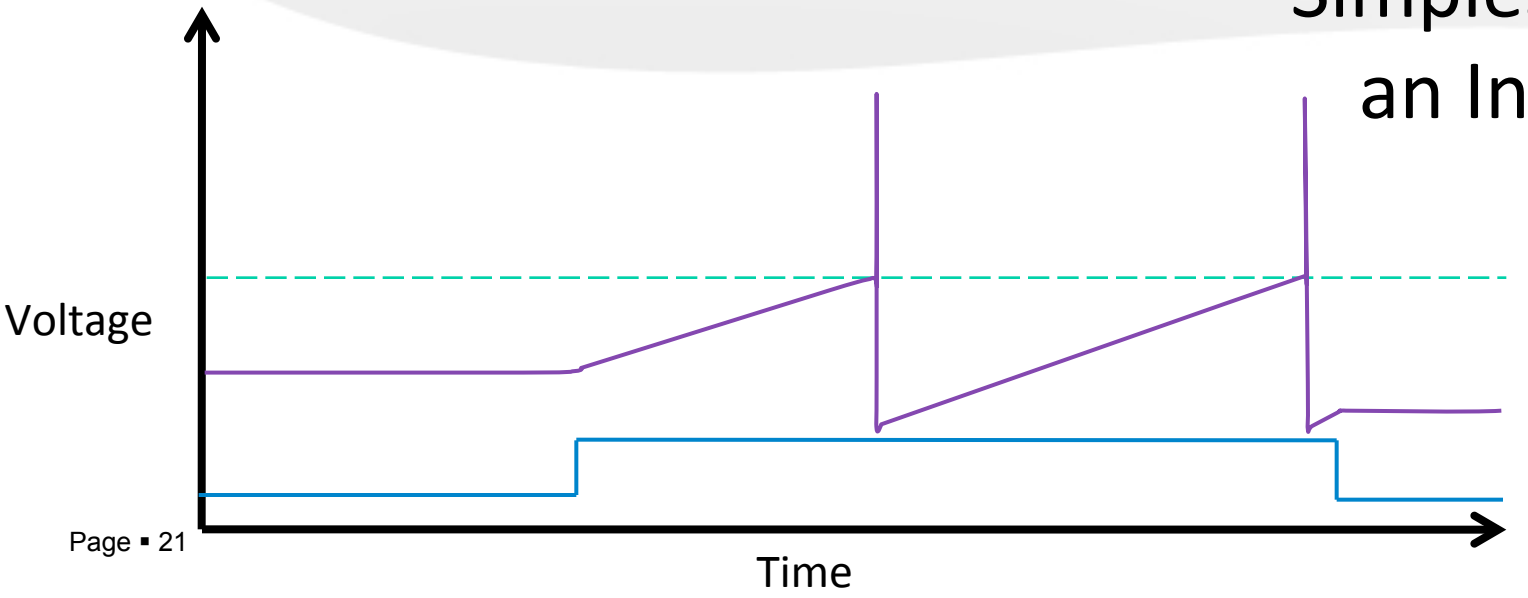
Sign is wrong in the paper from 1952!

K conductance:	g_K	= 36
Na conductance:	g_{Na}	= 120
Leak conductance:	g_{leak}	= 0.3
Membrane Capacitance:	C	= 1
K equlibrium:	V_K	= 12
Na equlibrium:	V_{Na}	= -115
Leak equlibrium:	V_{leak}	= -10.6
Initial and Rest potential	v_0	= 0
Initial channel activations	m_0, n_0, h_0	= 0

What does a neuron do?



Simplest idea – an Integrator



A neuron as an Integrator

Input current: I
Membrane Capacitance: C

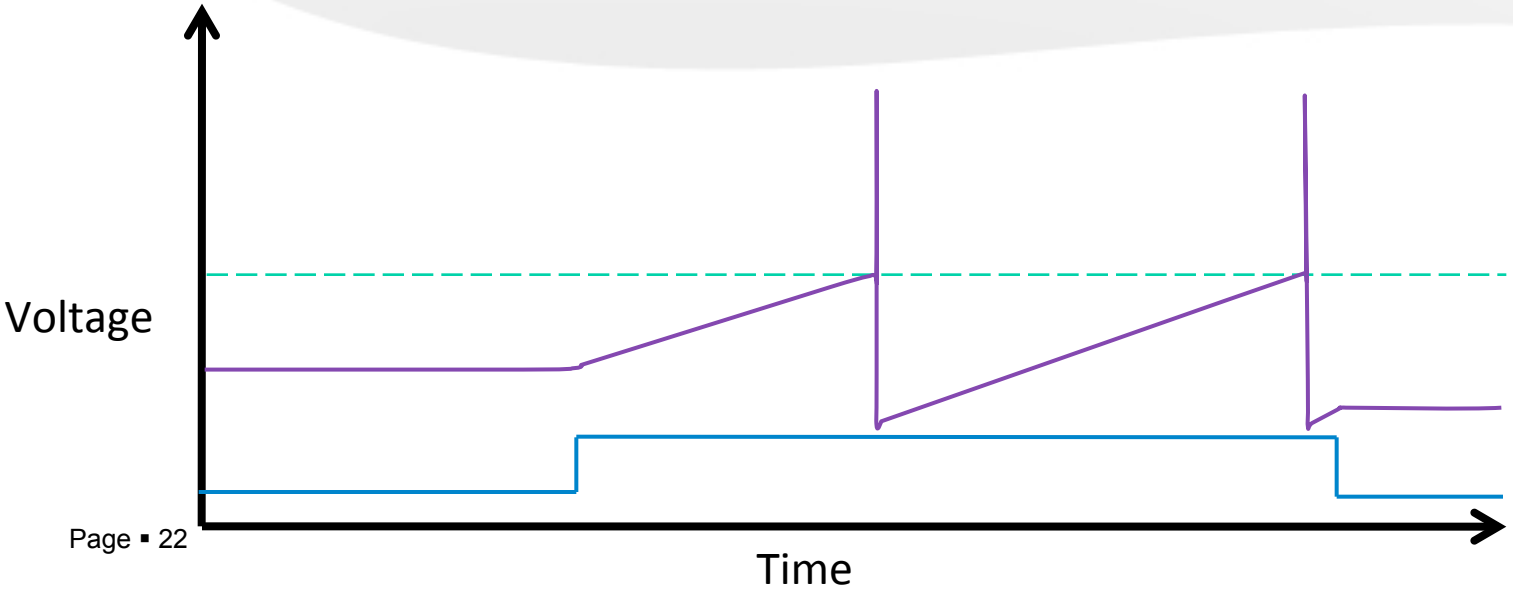
Spike threshold: V_{thresh}
Reset voltage: V_{reset}

Membrane Voltage: $\frac{dv}{dt} = \frac{I}{C}$

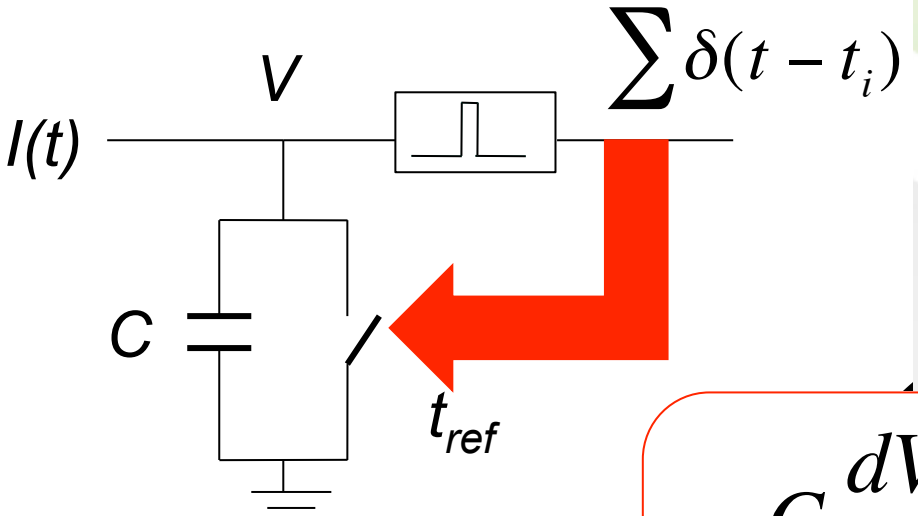
$if\ v > V_{thresh}$
$\rightarrow v = V_{reset}$

- Firing rate is unlimited
- Integration is "perfect"

→ Neuron response is linear



A neuron as an Integrator



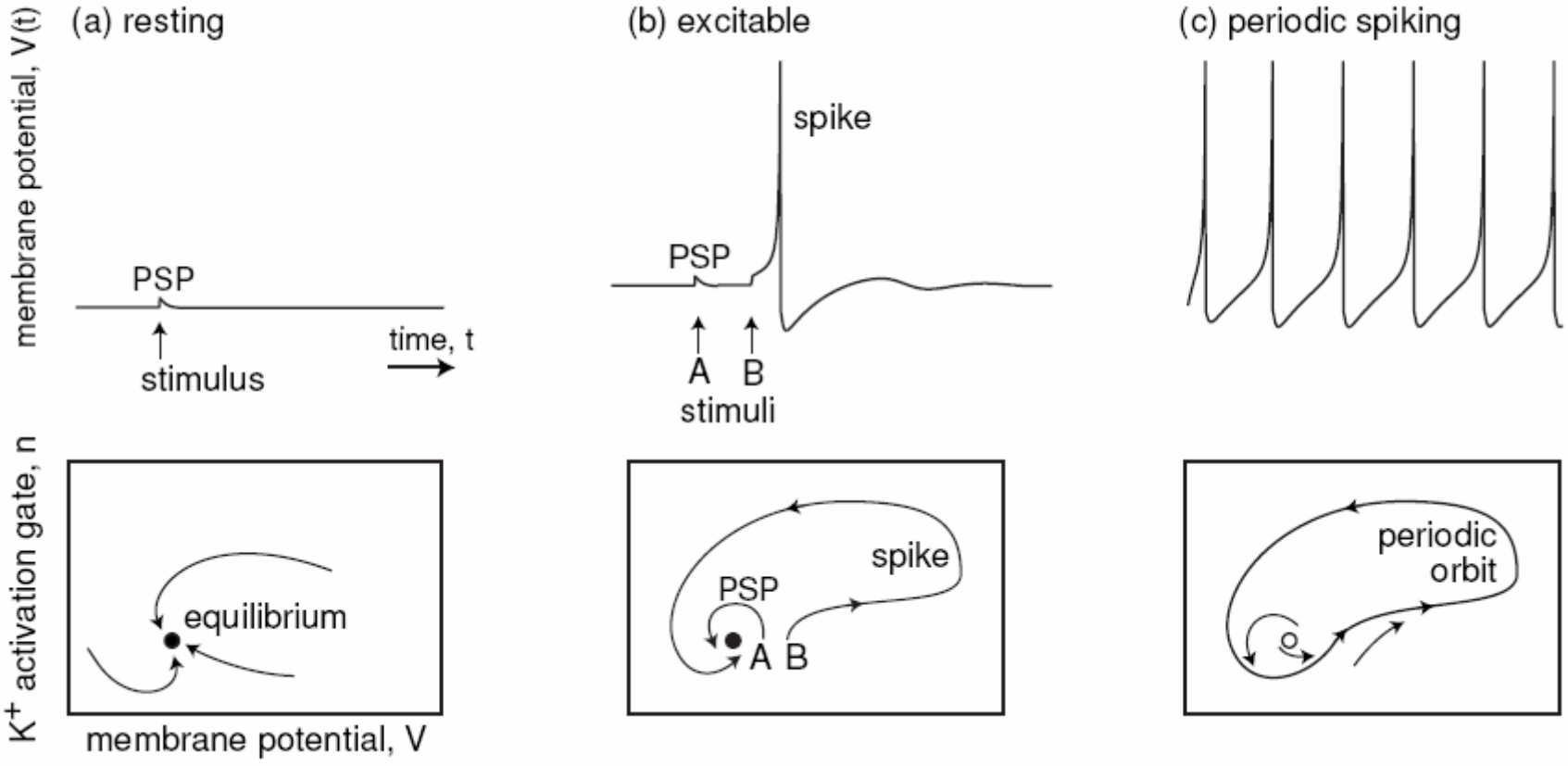
$$C\frac{dV(t)}{dt} = I(t) \qquad \textit{linear}$$

$$V(t) = V_{Thr} \Rightarrow \textit{Fire+reset threshold}$$

$$\int_{t_i}^{t_{i+1}} I(t)dt = CV_{th}$$

Neural Modeling and Dynamics

Neurons as dynamical systems: phase space



- Neurons are dynamical systems.
- Resting state of neurons corresponds to a stable equilibrium, tonic spiking state corresponds to a limit cycle attractor.
- Neurons are excitable because the equilibrium is near a bifurcation.

Neural Excitability

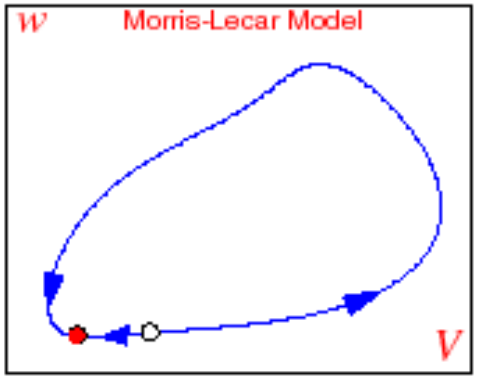
Excitability is the **most fundamental** property of **neurons** allowing **communication via action potentials or spikes.**

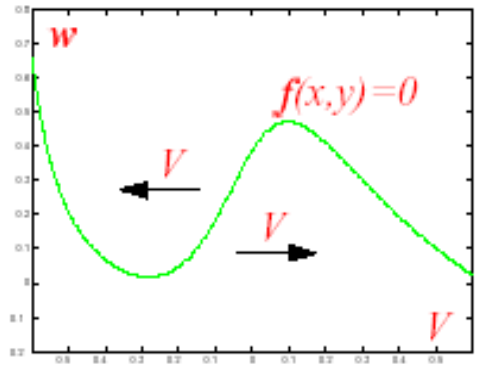
From **mathematical point of view** a system is **excitable** when small **perturbations** near a rest state can cause large **excursions** for the solution before it returns to the rest.

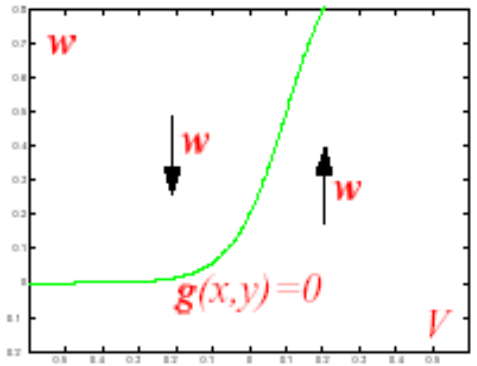
Systems are excitable because they are ***near bifurcations*** from **rest to oscillatory** dynamics.

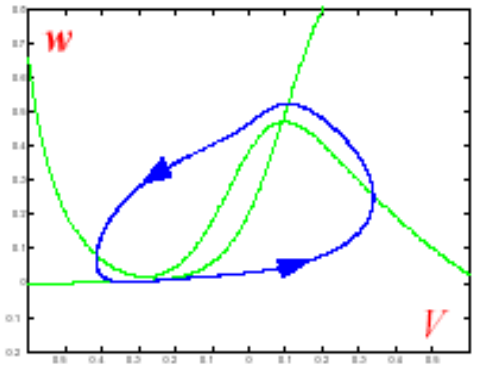
The **type of bifurcation** determines **excitable properties** and hence **neuro-computational** features of the brain cells. Revealing these features is the most important goal of **mathematical neuroscience.**

The neuron produse spikes periodically when there is a **large amplitude limit cycle attractor,** which may **coexist** with the **quiescent state**.









Most of the bifurcations discussed here can be illustrated using a two-dimensional (planar) system of the form

$$\mu \cdot x' = f(x, y)$$
$$y' = g(x, y)$$

Much insight into the behavior of such systems can be gained by considering their nullclines.

the sets determined by the conditions f(x, y) = 0 or g(x, y) = 0.

When $0 < \mu \ll 1$ nullclines are called fast and slow, respectively. Since the language of nullclines is universal in many areas of applied mathematics

Bursters

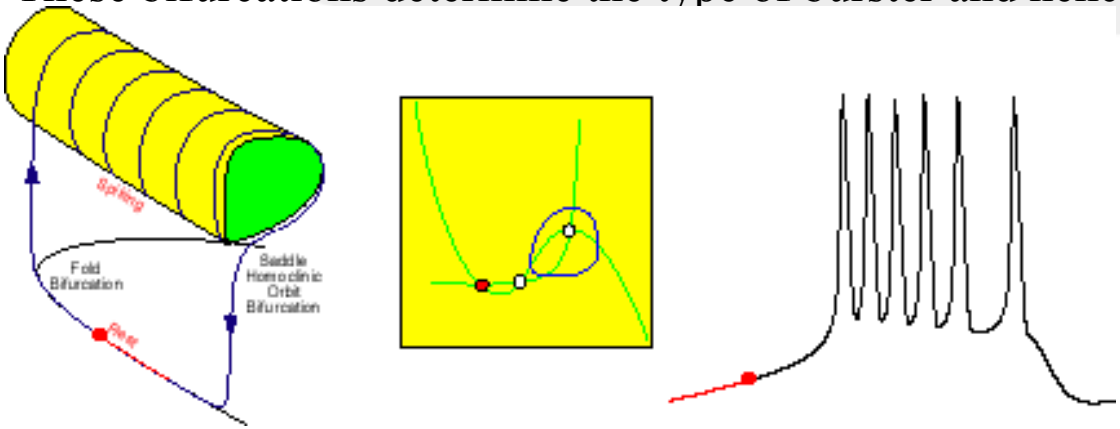
When neuron activity **alternates** between a **quiescent state** and **repetitive spiking**, the neuron activity is said to be **bursting**. It is usually caused by a slow voltage- or calcium-dependent process that can modulate fast spiking activity.

There are **two important bifurcations** associated with bursting:

Bifurcation of a quiescent state that leads to repetitive spiking.

Bifurcation of a spiking attractor that leads to quiescence.

These bifurcations determine the type of burster and hence its neuro-computational features.



Modelling Neural Dynamics

Usually they are express in form of

ODEs (Ordinary Differential Equations)

INTEGRATE-AND-FIRE

$v' = I + a - bv$ if $v \geq v_{thresold}$ then $v \leftarrow c$

I → Input Current

v → Membrane Potential

c → Reset Value

FLOPS 5 for 1 ms

Bio mean	Ton sp	Ph sp	Ton bur	Ph bur	Mix md	frq ad	Sp lat	Sub osc	Res	Integ	Reb sp	Reb bur	Th var	Bist	DAP	Acc	Inib sp	Inib bur	chaos
-	+	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-

IF WITH ADAPTATION

$$v' = I + a - bv + g(d - v)$$
$$g' = (e\delta(t) - g)/\tau$$

g → Conductance

δ → Dirac

FLOPS 10 for 1 ms

Bio mean	Ton sp	Ph sp	Ton bur	Ph bur	Mix md	frq ad	Sp lat	Sub osc	Res	Integ	Reb sp	Reb bur	Th var	Bist	DAP	Acc	Inib sp	Inib bur	chaos
-	+	-	-	-	-	+	-	-	-	+	-	-	-	-	+	-	-	-	-

Modelling Neural Dynamics

QUADRATIC IF (Ermentrout-Koppel)

$$v' = I + a(v - v_{rest})(v - v_{thresold}) \quad se \quad v = v_{peak} \quad allora \quad v \leftarrow c$$

v_{rest} → Threshold

$v_{thresold}$ → V Threshold

FLOPS 7 for 1 ms

Bio mean	Ton sp	Ph sp	Ton bur	Ph bur	Mix md	frq ad	Sp lat	Sub osc	Res	Integ	Reb sp	Reb bur	Th var	Bist	DAP	Acc	Inib sp	Inib bur	chaos
-	+	-	-	-	-	-	+	-	-	+	-	-	+	+	-	-	-	-	-

RESONATE-AND-FIRE

$$z' = I + (b + i\omega)z \quad se \quad \mathrm{Im} z \geq a_{thresold} \quad allora \quad z \leftarrow z_0(z)$$

z → Membrane Potential

$z_0(z)$ → Reset Value

FLOPS 10 for 1 ms

Bio mean	Ton sp	Ph sp	Ton bur	Ph bur	Mix md	frq ad	Sp lat	Sub osc	Res	Integ	Reb sp	Reb bur	Th var	Bist	DAP	Acc	Inib sp	Inib bur	chaos
-	+	+	-	-	-	-	-	+	+	+	+	-	-	+	+	+	-	-	+

IF OR BURST

$$v' = I + a - bv + gH(v - v_h)h(v_T - v) \quad se \quad v = v_{thresold} \quad allora \quad v \leftarrow c$$

$$h' = \begin{cases} -h/\tau^- & se \quad v > v_h \\ (1-h)/\tau^+ & se \quad v < v_h \end{cases}$$

H → Heaviside Function

h → T-current function

FLOPS 13 for 1 ms

Bio mean	Ton sp	Ph sp	Ton bur	Ph bur	Mix md	frq ad	Sp lat	Sub osc	Res	Integ	Reb sp	Reb bur	Th var	Bist	DAP	Acc	Inib sp	Inib bur	chaos
-	+	+	?	+	-	-	-	-	-	+	+	+	-	+	+	-	-	-	?

FITZHUGH-NAGUMO

$$v' = a + bv + cv^2 + dv^3 - u$$

$$u' = \varepsilon(ev - u)$$

u → Recovery variable

FLOPS 72 for 1 ms

Bio mean	Ton sp	Ph sp	Ton bur	Ph bur	Mix md	frq ad	Sp lat	Sub osc	Res	Integ	Reb sp	Reb bur	Th var	Bist	DAP	Acc	Inib sp	Inib bur	chaos
-	+	+	-	?	-	-	+	+	+	-	+	-	+	+	-	+	+	-	-

Modelling Neural Dynamics

HINDMARSH-ROSE

$$v' = u - F(v) + I - w$$
$$u' = G(v) - u$$
$$w' = (H(v) - w)/\tau$$

FLOPS 120 for 1 ms

Bio mean	Ton sp	Ph sp	Ton bur	Ph bur	Mix md	frq ad	Sp lat	Sub osc	Res	Integ	Reb sp	Reb bur	Th var	Bist	DAP	Acc	Inib sp	Inib bur	chaos
-	+	+	+	?	?	+	+	+	+	+	+	+	+	+	+	+	+	?	+

MODELLO POLINOMIALE (Wilson)

$$C\,v' = -m_\infty(v-0.5) - 26\,u(v+0.95) - g_T T(v-1.2) - g_H H(v+0.95) + I$$
$$u' = \frac{1}{\tau_u}(-u + u_\infty(v))$$
$$T' = \frac{1}{14}(-T + T_\infty(v))$$
$$H' = \frac{1}{45}(-H + 3T)$$

FLOPS 180 for 1 ms

Bio mean	Ton sp	Ph sp	Ton bur	Ph bur	Mix md	frq ad	Sp lat	Sub osc	Res	Integ	Reb sp	Reb bur	Th var	Bist	DAP	Acc	Inib sp	Inib bur	chaos
-	+	+	+	?	?	+	+	+	+	+	+	+	+	?	+	+	?	?	?

MORRIS-LECAR

$$C\,v' = -g_L(v-v_L) - g_{Ca} m_\infty(v-v_{Ca}) - g_K n(v-v_K) + I$$
$$n' = \frac{n_\infty - n}{\tau_n}$$

HODGKIN-HUXLEY

$$C\,v' = -g_K n^4(v-v_K) - g_{Na} m^3 h(v-v_{Na}) - g_l(v-v_l) + I$$
$$m' = \alpha_m(1-m) - \beta_m m$$
$$n' = \alpha_n(1-n) - \beta_n n$$
$$h' = \alpha_h(1-h) - \beta_h h$$

FLOPS 600 for 1 ms

Bio mean	Ton sp	Ph sp	Ton bur	Ph bur	Mix md	frq ad	Sp lat	Sub osc	Res	Integ	Reb sp	Reb bur	Th var	Bist	DAP	Acc	Inib sp	Inib bur	chaos
+	+	+	-	?	-	-	+	+	+	+	+	?	+	+	-	+	+	-	-

FLOPS 1200 for 1 ms

Bio mean	Ton sp	Ph sp	Ton bur	Ph bur	Mix md	frq ad	Sp lat	Sub osc	Res	Integ	Reb sp	Reb bur	Th var	Bist	DAP	Acc	Inib sp	Inib bur	chaos
+	+	+	+	?	?	+	+	+	+	+	+	+	+	+	+	+	+	?	+

Modelling Neural Dynamics

IZHIKEVICH

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

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

If $v \geq +30\ mV$, Then $\begin{cases} v \leftarrow c \\ u \leftarrow u + d. \end{cases}$

v → Membrane Potential

u → Recovery

FLOPS — 13 for 1 ms

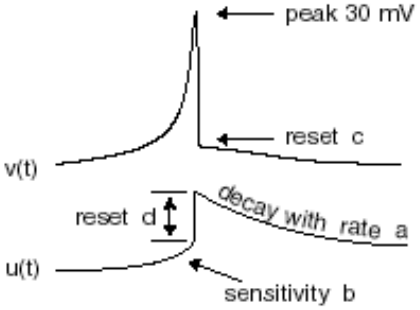
Bio mean	Ton sp	Ph sp	Ton bur	Ph bur	Mix md	frq ad	Sp lat	Sub osc	Res	Integ	Reb sp	Reb bur	Th var	Bist	DAP	Acc	Inib sp	Inib bur	chaos
-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

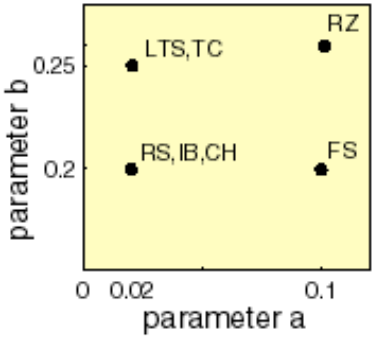
Izhikevich Model

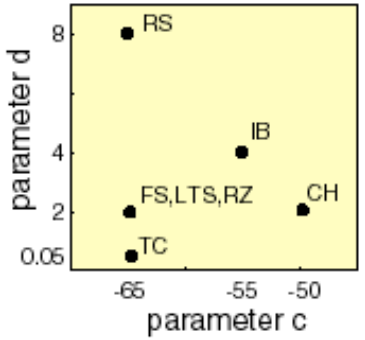
$v' = 0.04v^2 + 5v + 140 - u + I$

$u' = a(bv - u)$

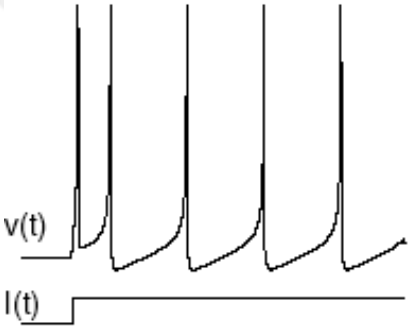
if $v = 30$ mV,
then $v \leftarrow c$, $u \leftarrow u + d$



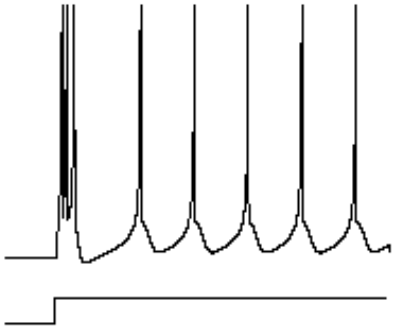




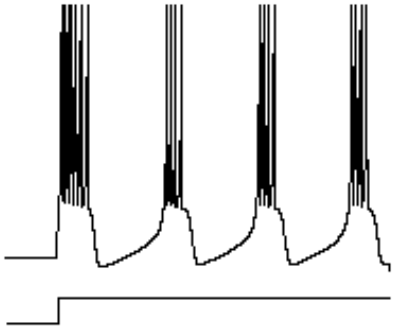
regular spiking (RS)



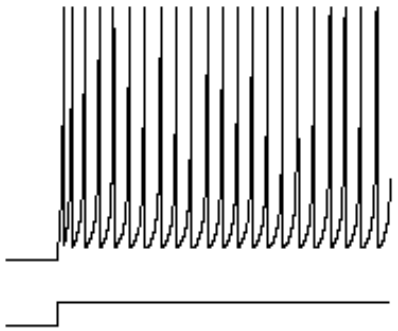
intrinsically bursting (IB)



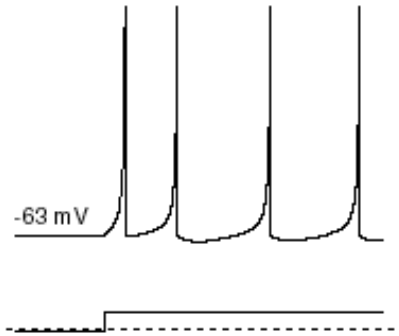
chattering (CH)



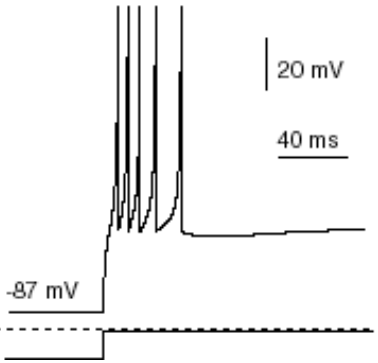
fast spiking (FS)



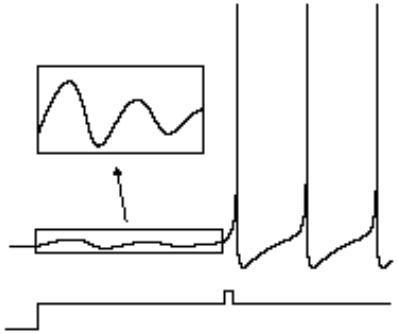
thalamo-cortical (TC)



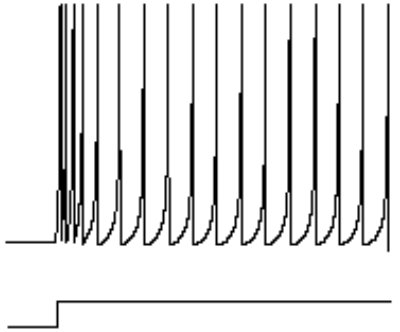
thalamo-cortical (TC)

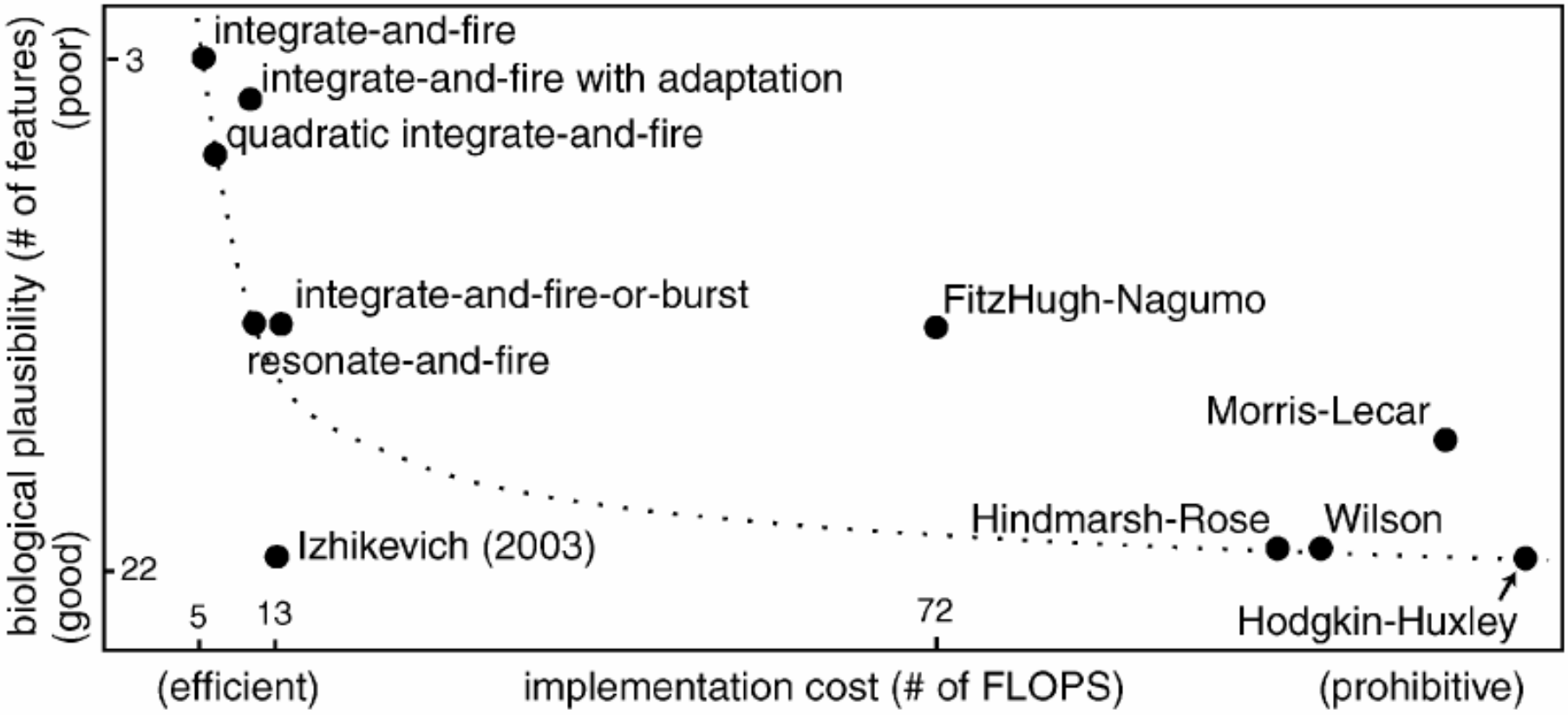


resonator (RZ)



low-threshold spiking (LTS)




integrate-and-fire
integrate-and-fire with adaptation
quadratic integrate-and-fire
integrate-and-fire-or-burst
resonate-and-fire
FitzHugh-Nagumo
Morris-Lecar
Hindmarsh-Rose
Wilson
Izhikevich (2003)
Hodgkin-Huxley
biological plausibility (# of features)
(poor)
(good)
3
22
5
13
72
(efficient)
implementation cost (# of FLOPS)
(prohibitive)

The Neural Code

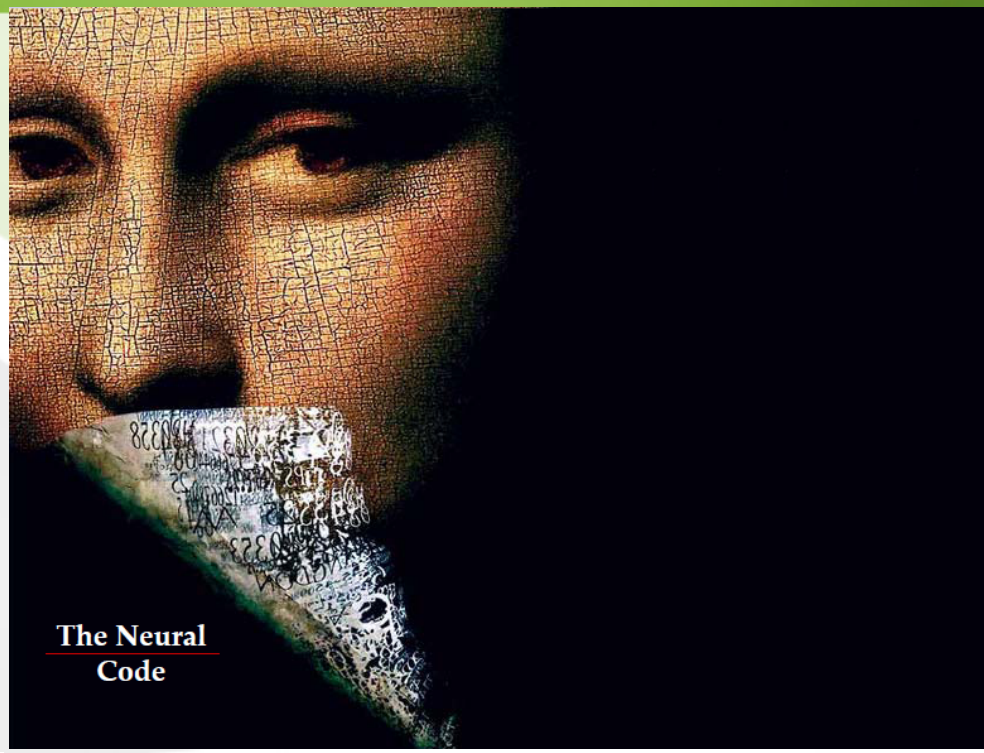
Spike trains

Where is the Information?

Frequency?

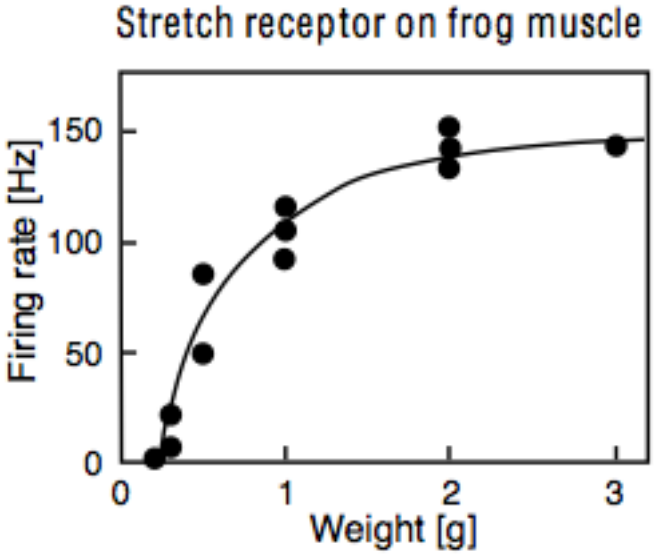
Spikes?

Inter/Intra spike interval?



The firing rate hypothesis

Stimulus features are encoded through the neural firing rate (response curves).

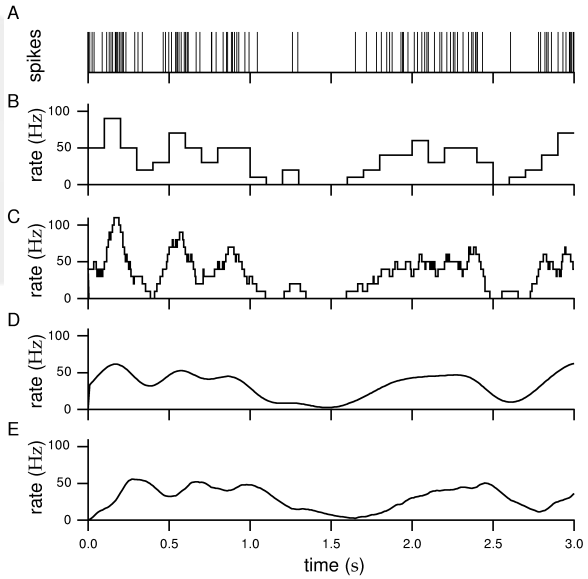


Edgar Adrian
The Nobel Prize in Physiology or Medicine 1932

Time-dependent firing rate counts number of spikes in a short time interval (averaged over trials): $r(t) = \frac{1}{\Delta t} \int_t^{t+\Delta t} \rho(\tau) d\tau$.

For any t > 0, each interval contains 0,1 spike. Then, r(t) averaged over trials is the probability of any trial firing at time t.

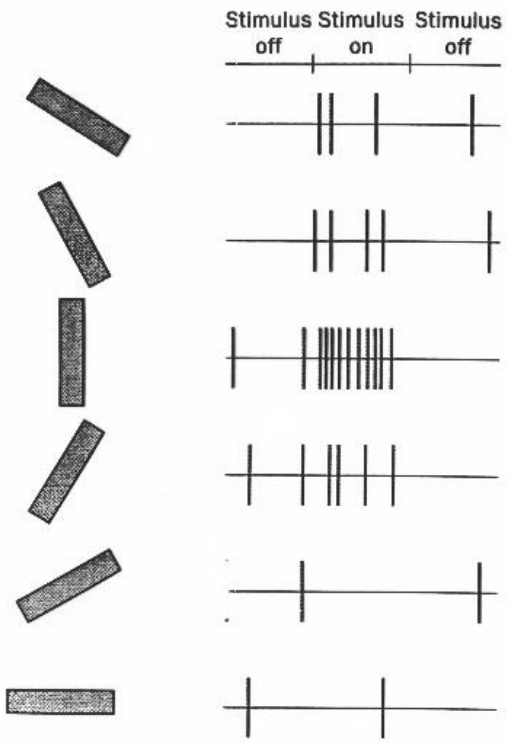
B: 100 ms bins

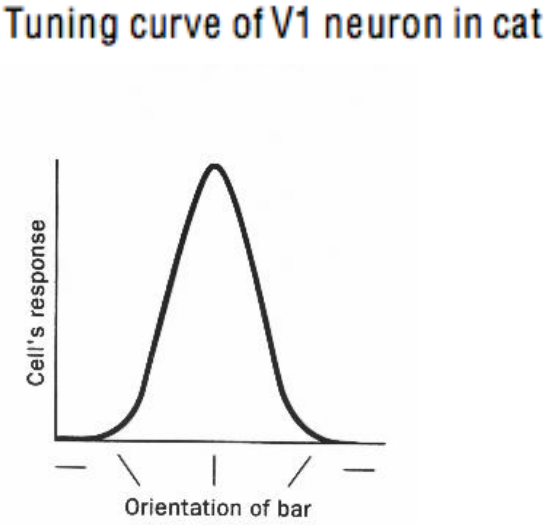


The firing rate hypothesis

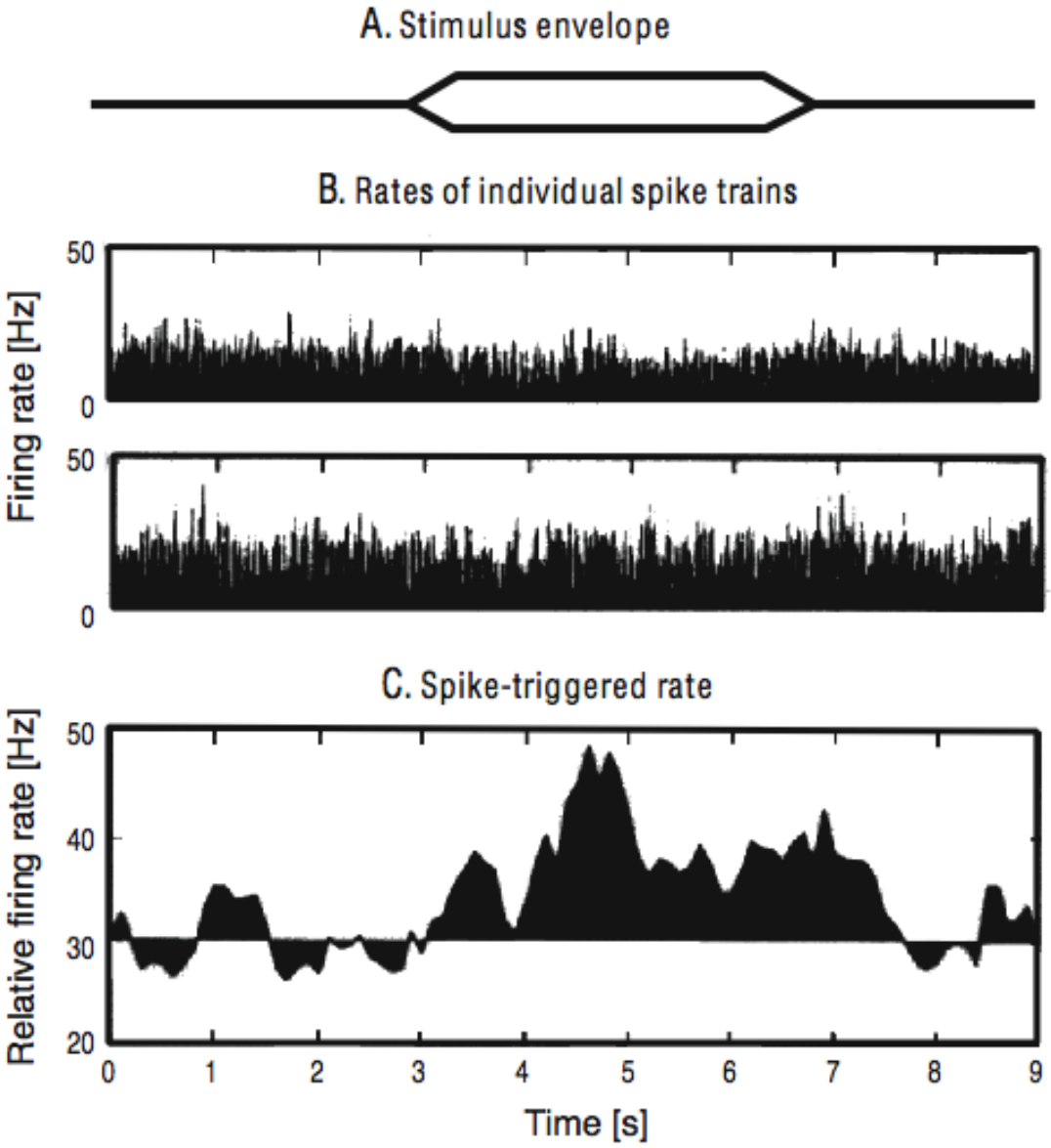
Receptive field: area in the outside/physical world for which a neuron is responsive.

Feature preference





The correlation code hypothesis



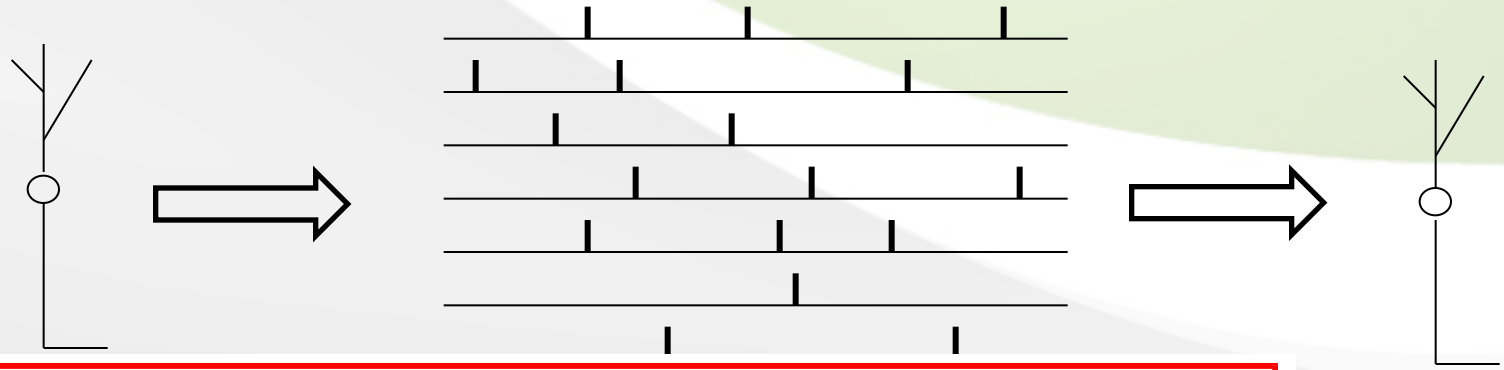
Stimulus features are encoded by neurons firing around the same time

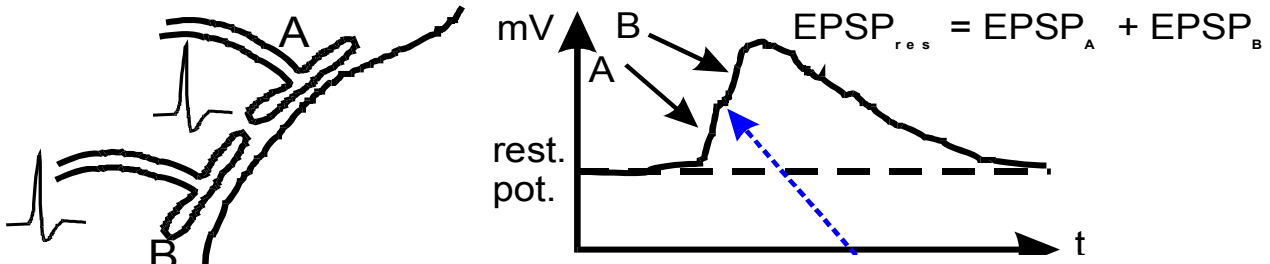
From DeCharms and Merzenich 1996

The Neural Code

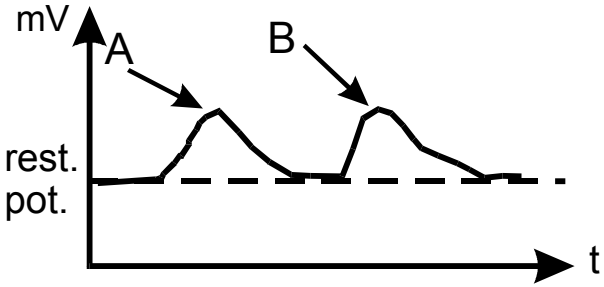
Neurons communicate via **exact spike timing**

Firing rate alone **does not carry** all the relevant **information**





If the difference in arrival times is too large, temporal summation does not occur anymore !



The Neural Code

Edelman (Nobel laureate in Medicine) proposed the **theory of neuronal group selection (TNGS)**, also known as Neural Darwinism,

Edelman stated that DNA does not contain all information needed to code all brain connections.
DNA provides basic species-related information exclusively.

Living and dead cells are regulated by stochastic rules, therefore each brain is different from each other.

Indeed, in the human brain there are 10^{11} neurons, with 10^{15} synapses.
DNA has 109 pairs of nucleotides

The Neural Code

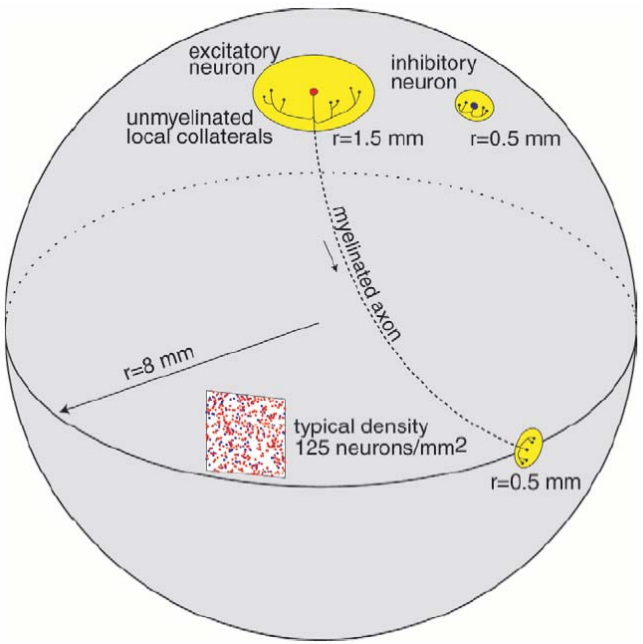
Neural Groups are characterized by:

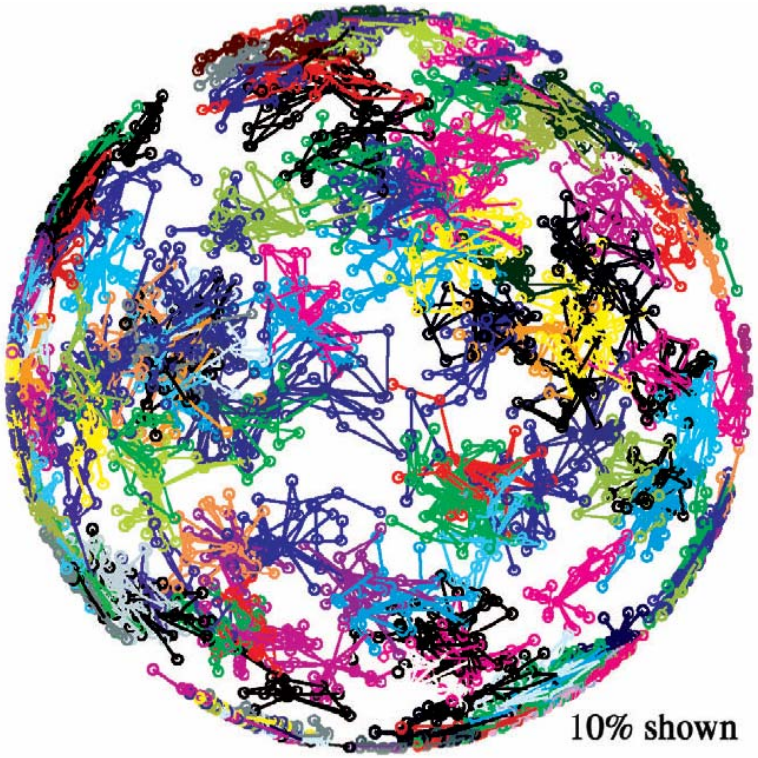
- Biological Selection (DNA)
- Experiential Selection
- **Reentry**

Neural Groups should be considered as the basic processing unit of the brain

How to model Neural Groups in a Spiking Neural Network?

Time must be taken into account





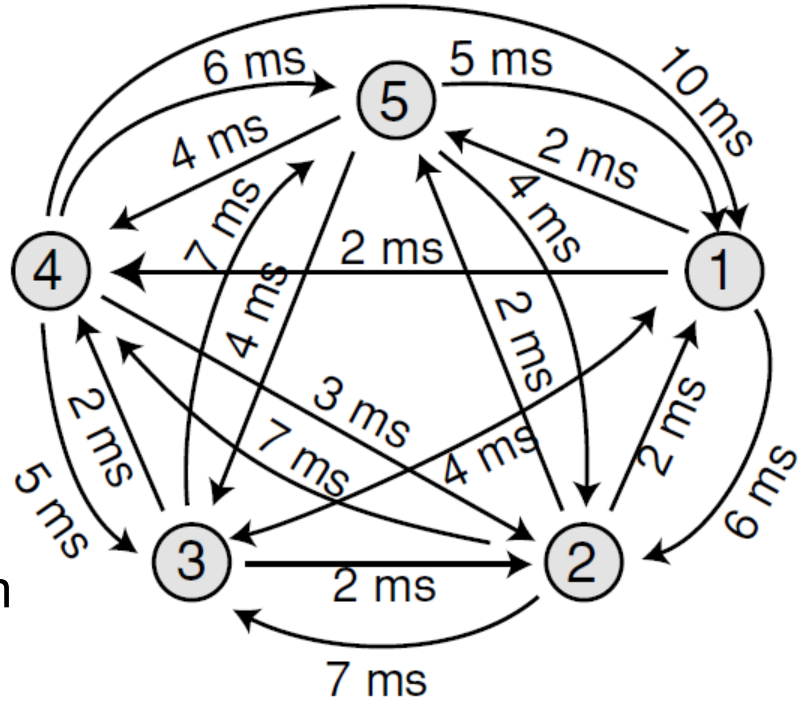
Spiking neural network

The network consists of cortical spiking neurons with axonal conduction delays and spike timing-dependent plasticity (STDP).

The network is sparse with 0.1 probability of connection between any two neurons.

Neurons are connected to each other randomly

Synaptic connections among neurons have fixed conduction delays, which are random integers between 1 ms and 20 ms.

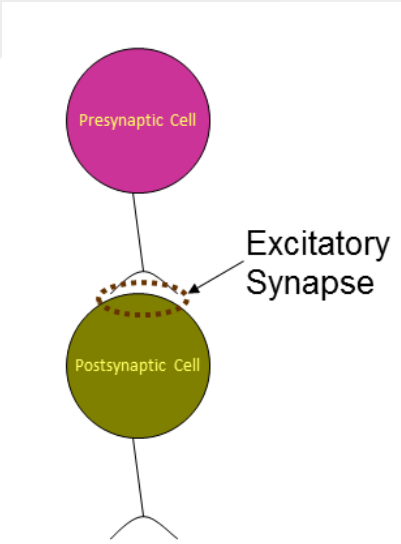


STDP rule (spike-timing-dependent plasticity)

Initially, all synaptic connections have equal weights.

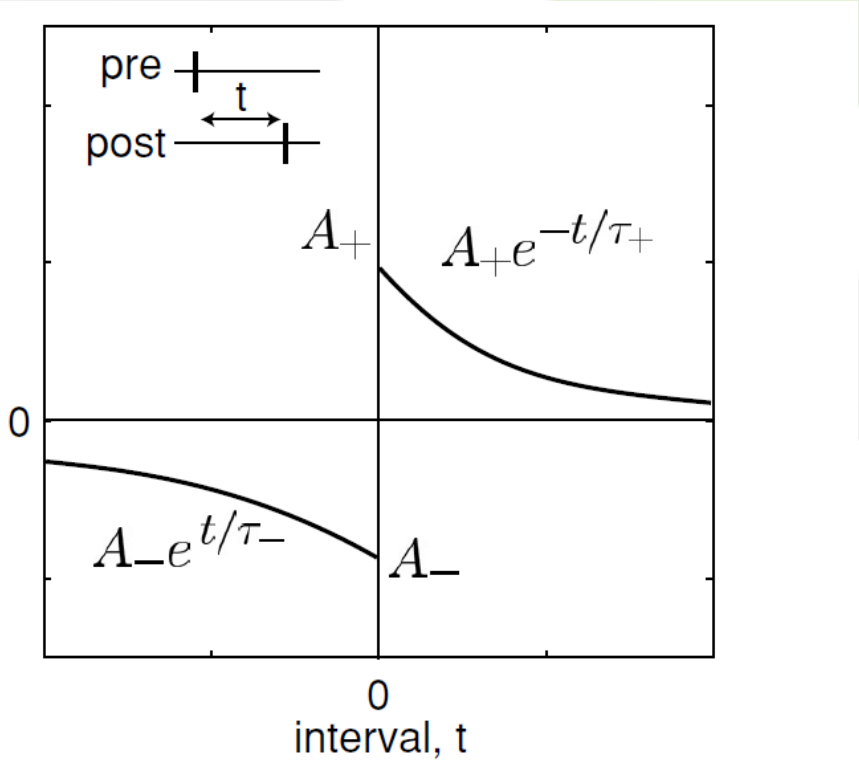
The magnitude of change of synaptic weight

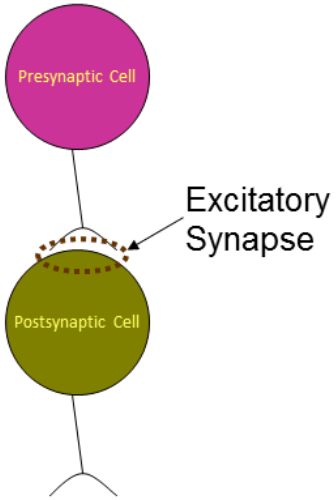
depends on the timing of spikes.



STDP rule (spike-timing-dependent plasticity)

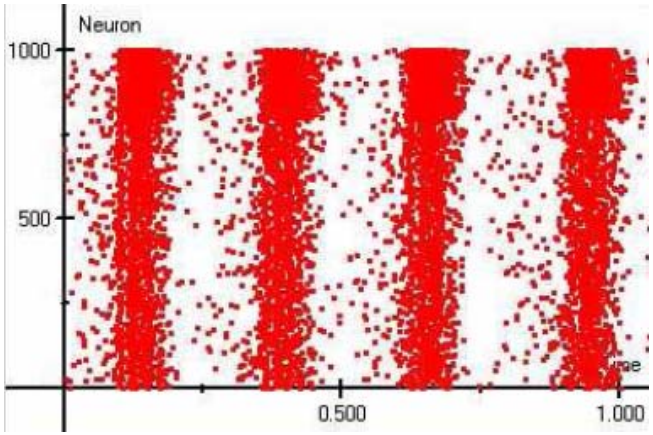
If the presynaptic spike arrives at the postsynaptic neuron before the postsynaptic neuron fires—for example, it causes the firing—the synapse is potentiated.

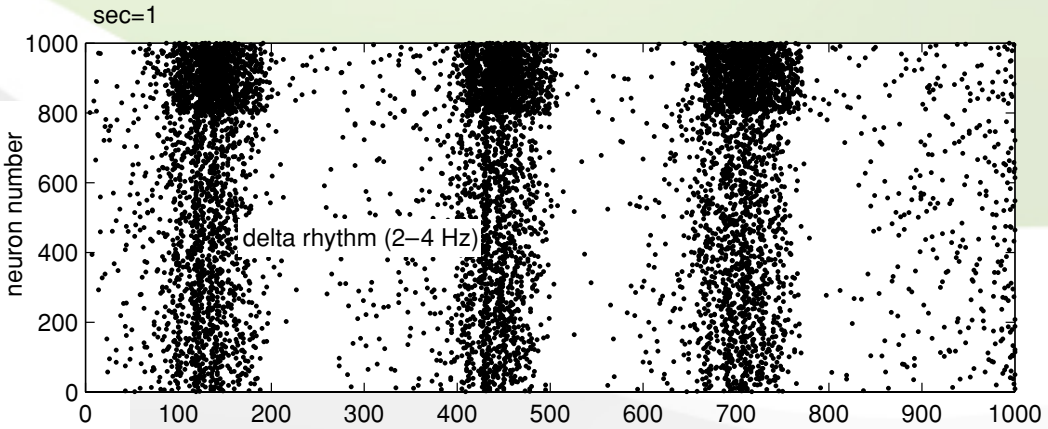


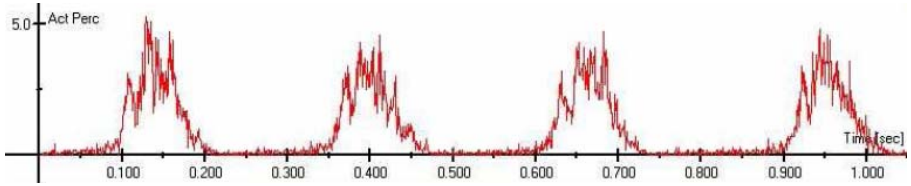


If the presynaptic spike arrives at the postsynaptic neuron after it fired, that is, it brings the news late, the synapse is depressed.

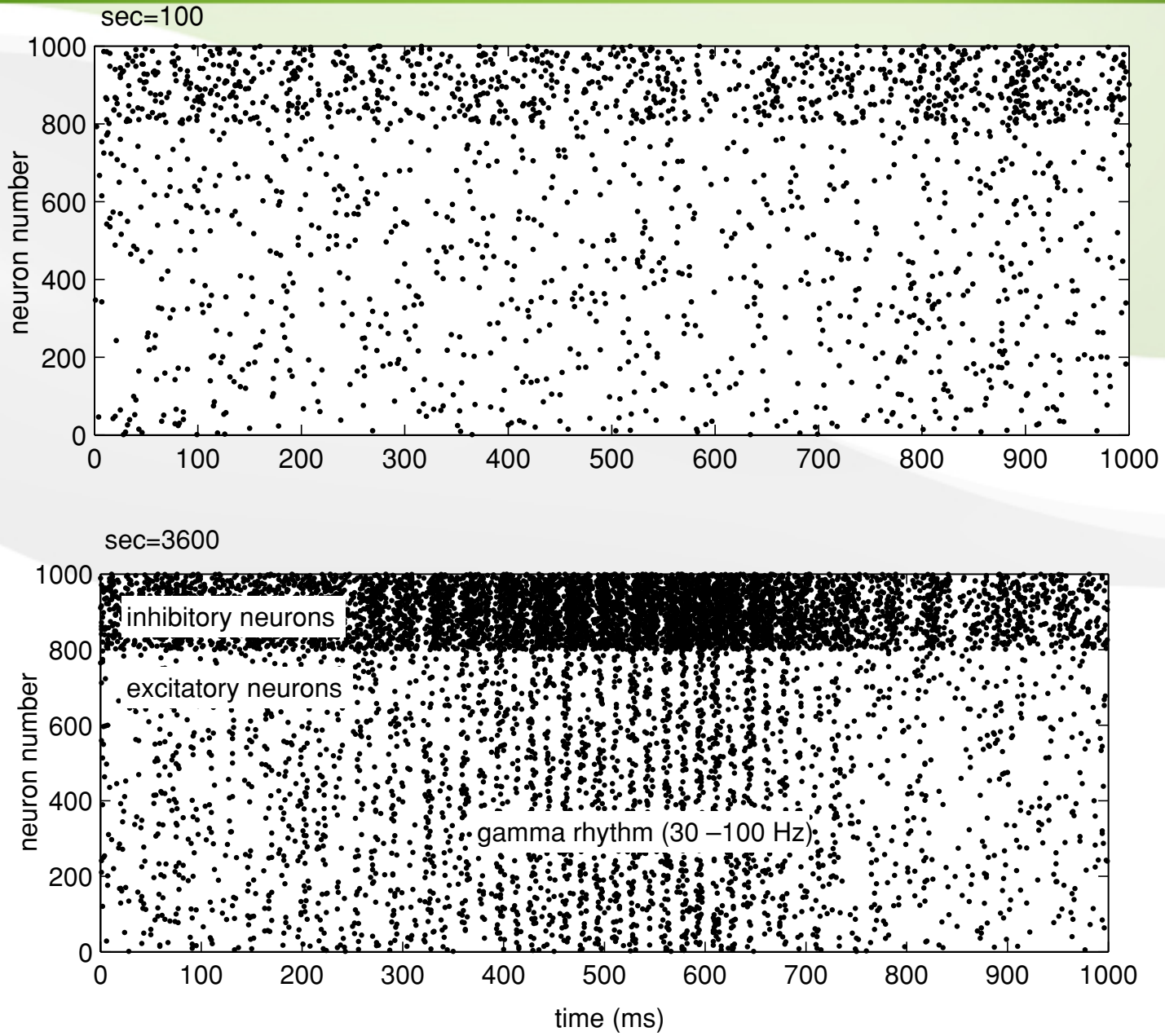
First Seconds of Simulation





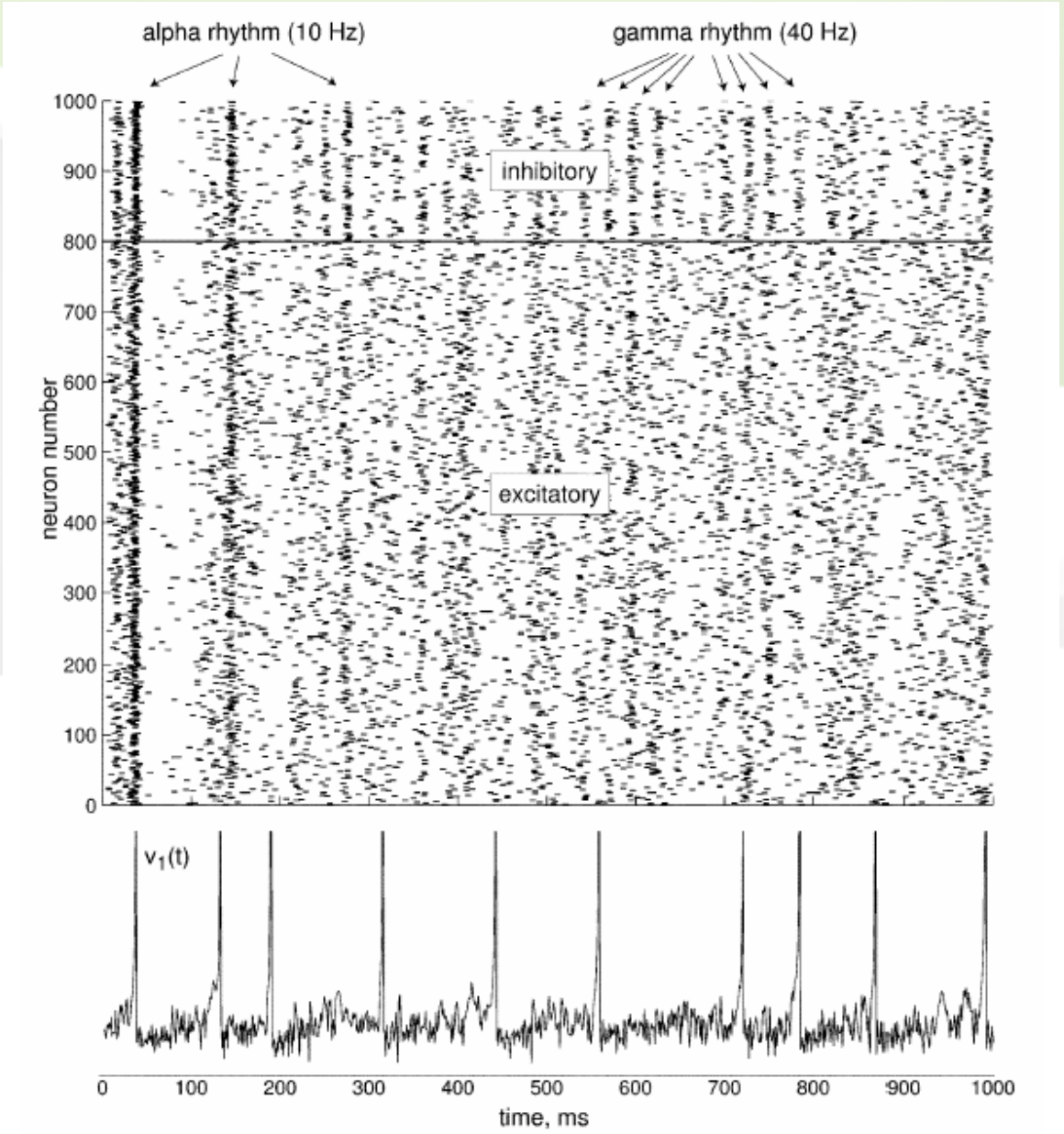


delta waves (<4 Hz)

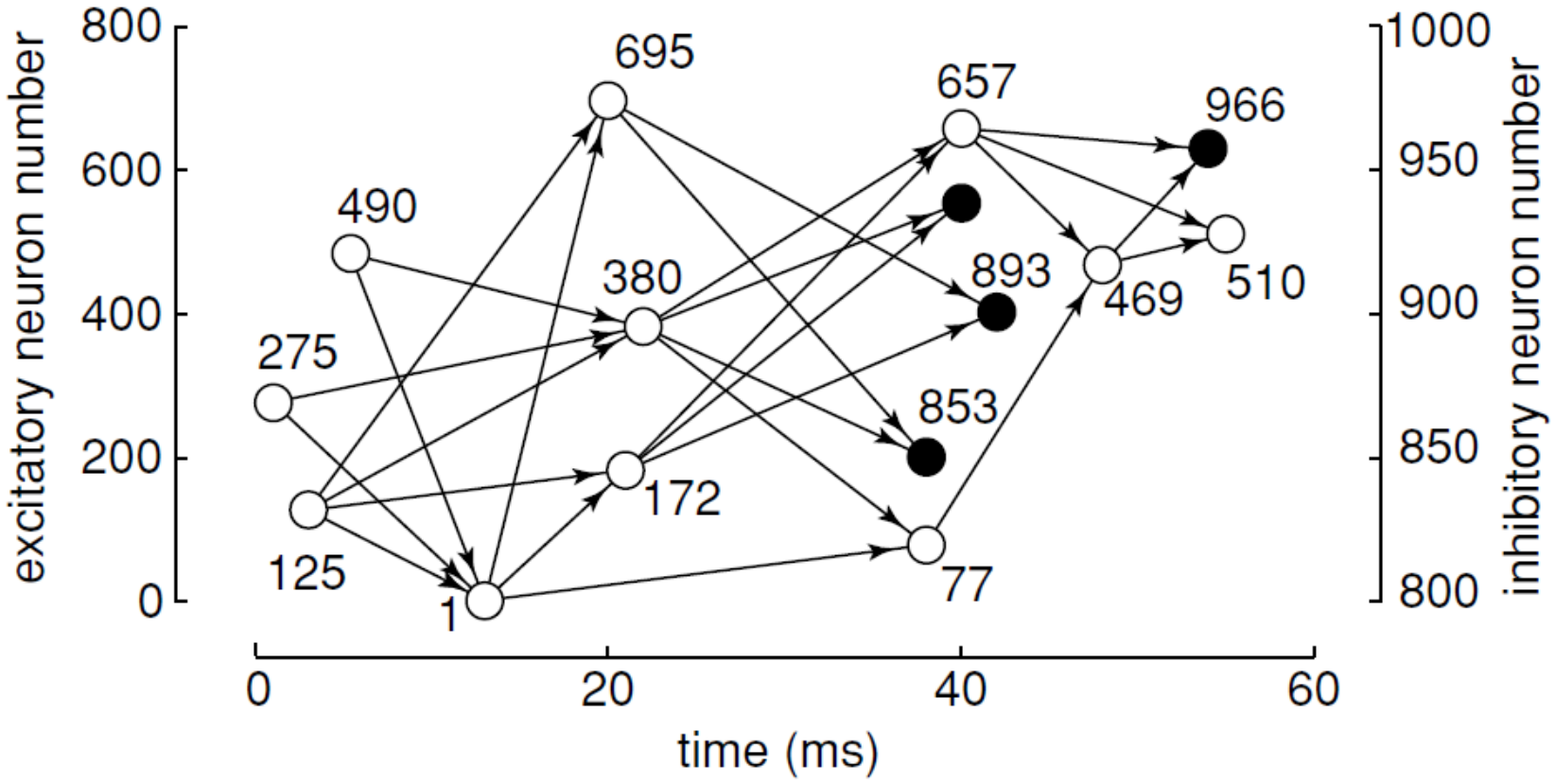

sec=100
neuron number
0
200
400
600
800
1000
0
100
200
300
400
500
600
700
800
900
1000
sec=3600
inhibitory neurons
excitatory neurons
gamma rhythm (30 –100 Hz)
time (ms)

Spiking neural network

First Minutes of Simulation



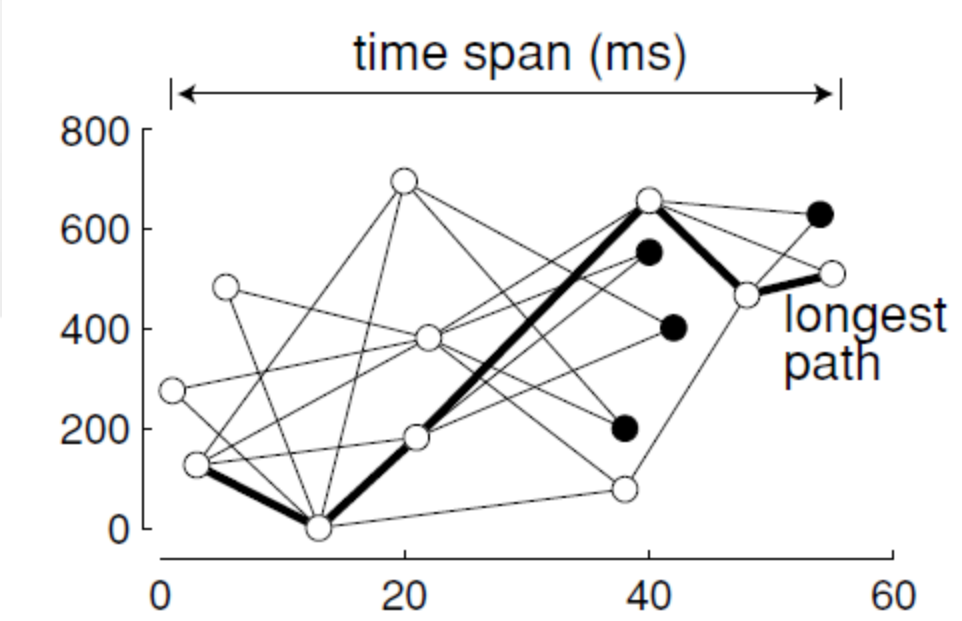
Polychronous Neural Group (PNG)



Characteristics of polychronous groups

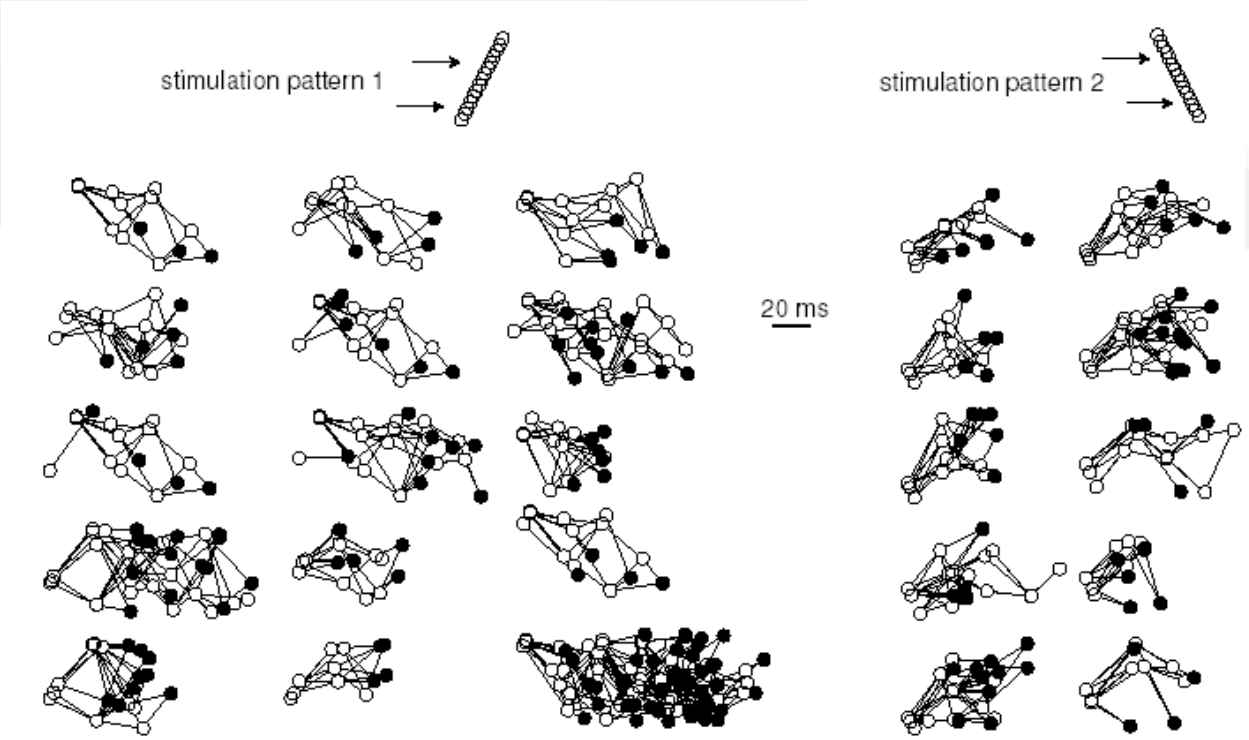
The groups have different

- Sizes
- Lengths
- Time spans

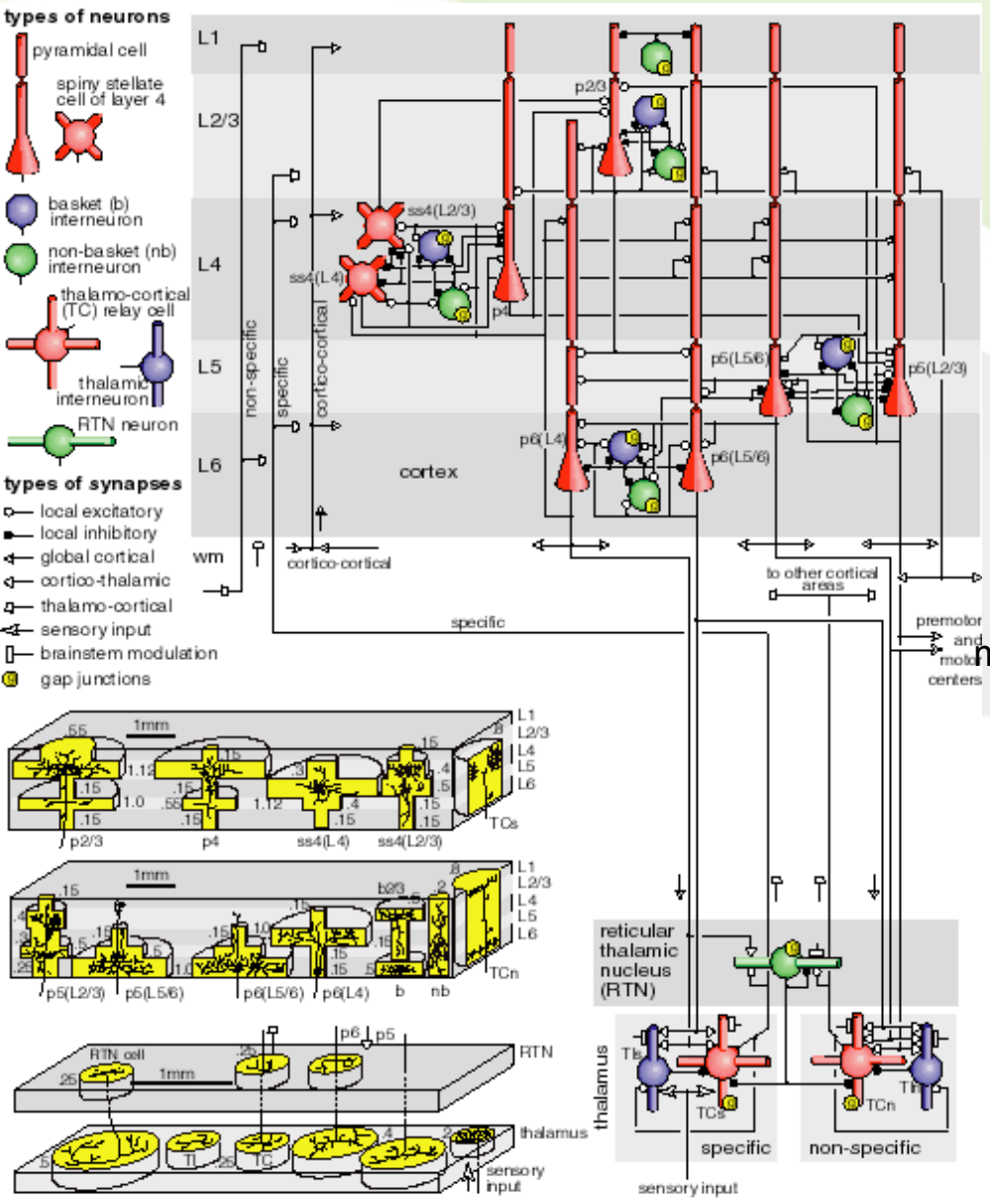


Representations of Memories and Experience

Persistent stimulation of the network with two **spatio-temporal patterns** result in emergence of polychronous groups that represent the patterns. the **groups activate whenever the patterns are present**.



Simulation of Large-Scale Brain Models



In 2005 Izhikevich finished simulation of a model that has the size of the human brain. The model has 100,000,000,000 neurons (hundred billion or 10^11) and almost 1,000,000,000,000,000 (one quadrillion or 10^15) synapses.

It represents 300x300 mm^2 of mammalian thalamo-cortical surface, specific, non-specific, and reticular thalamic nuclei, and spiking neurons with firing properties corresponding to those recorded in the mammalian brain.

The model exhibited alpha and gamma rhythms, moving clusters of neurons in up- and down-states, and other interesting phenomena

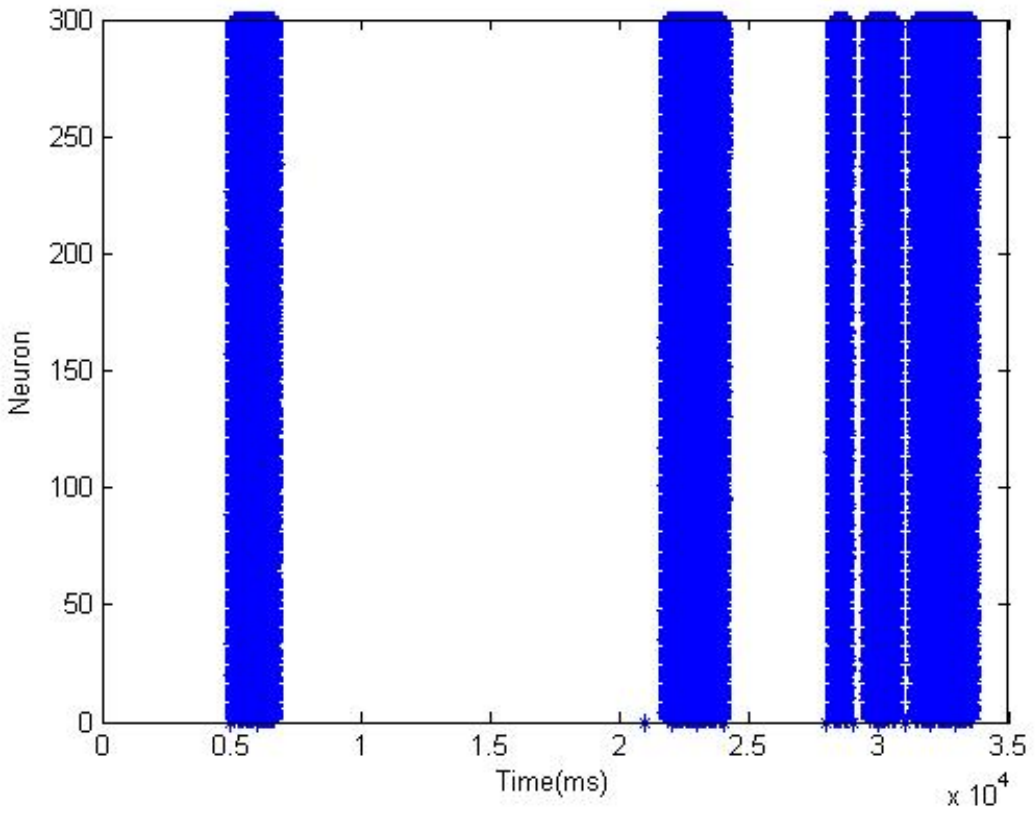
One second of simulation took 50 days on a beowulf cluster of 27 processors (3GHz each).

A stochastich version of Izhichevich Model

$$\frac{dv}{dt} = 0.04v^2 + 5v + 140 - u + \epsilon(\mu, \sigma)$$

$$\frac{du}{dt} = a(bv - u)$$

If v>=30
then {c -> v, u -> u+d

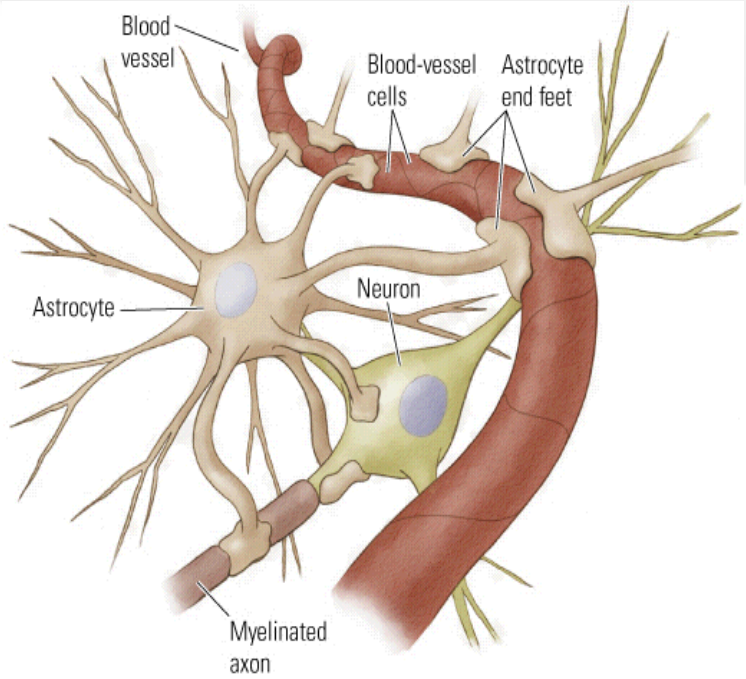


Persistent Bursting Activity!

Cells in the Central Nervous Systems

Neuron

Electrical Activity



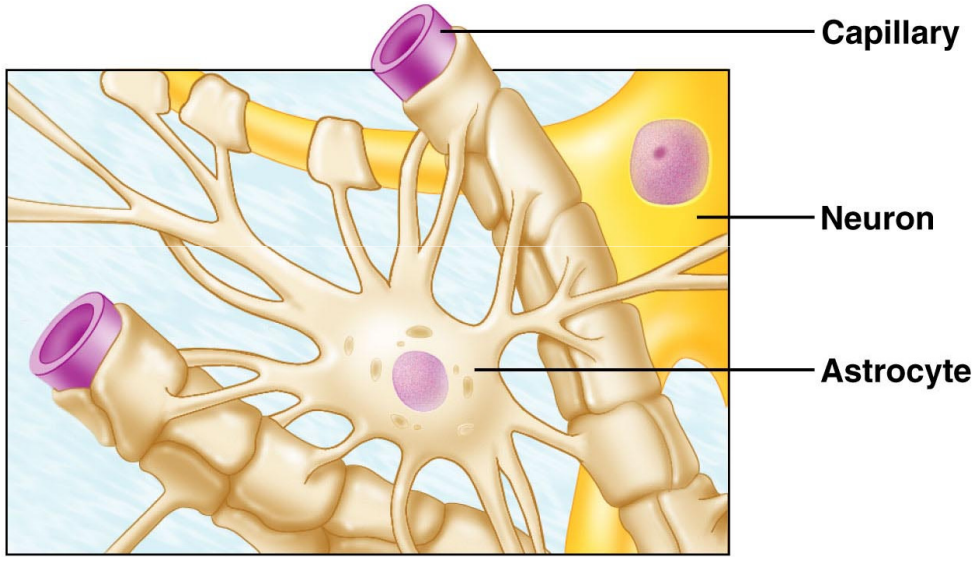
Glia

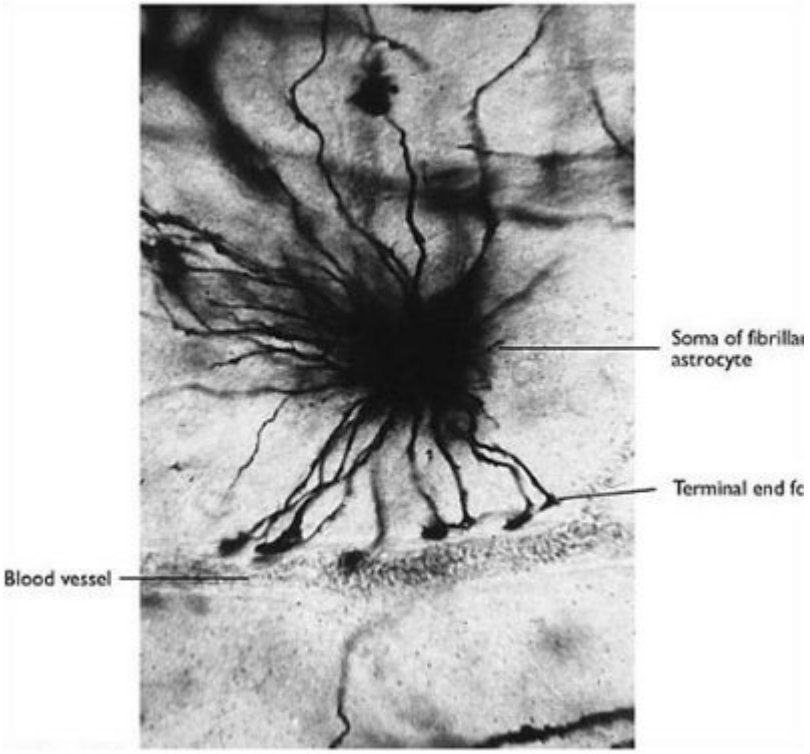
Biochemical Activity

- 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.

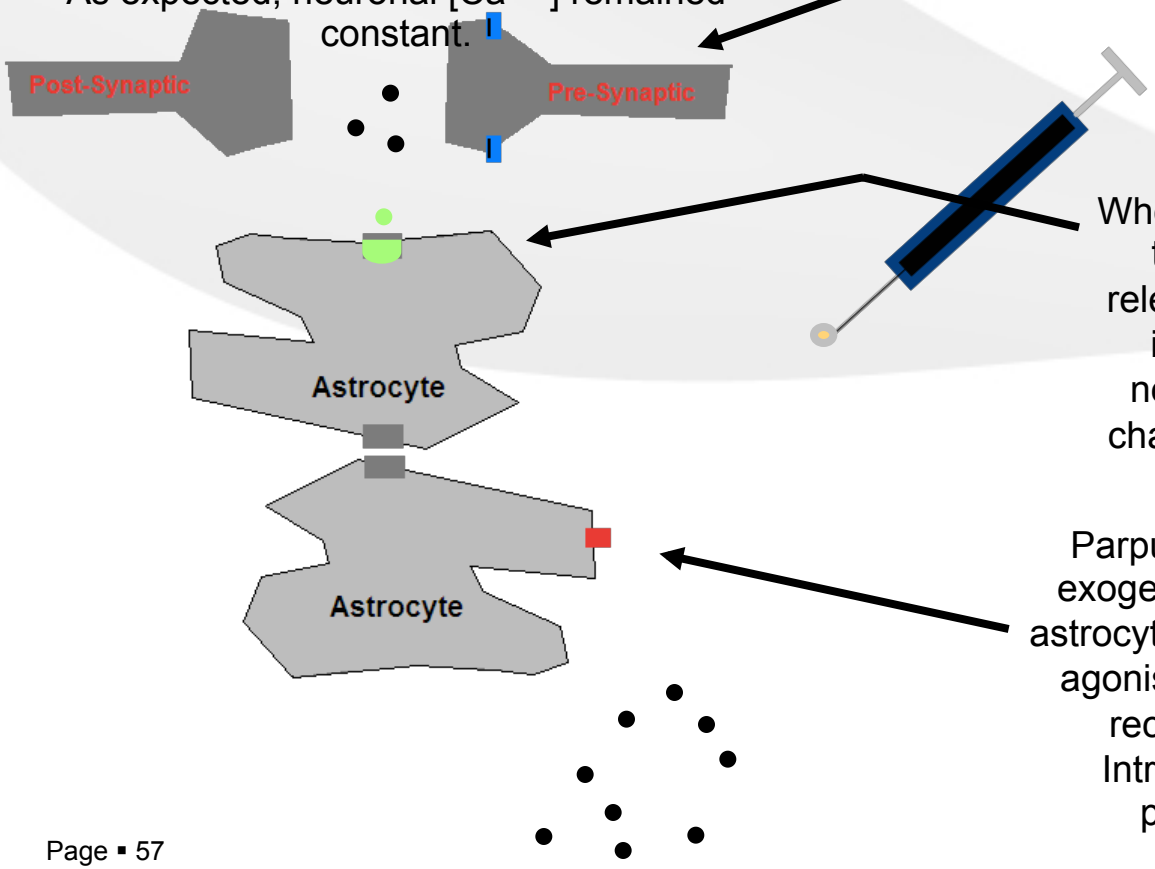
Glia cells exist only for metabolic support

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.

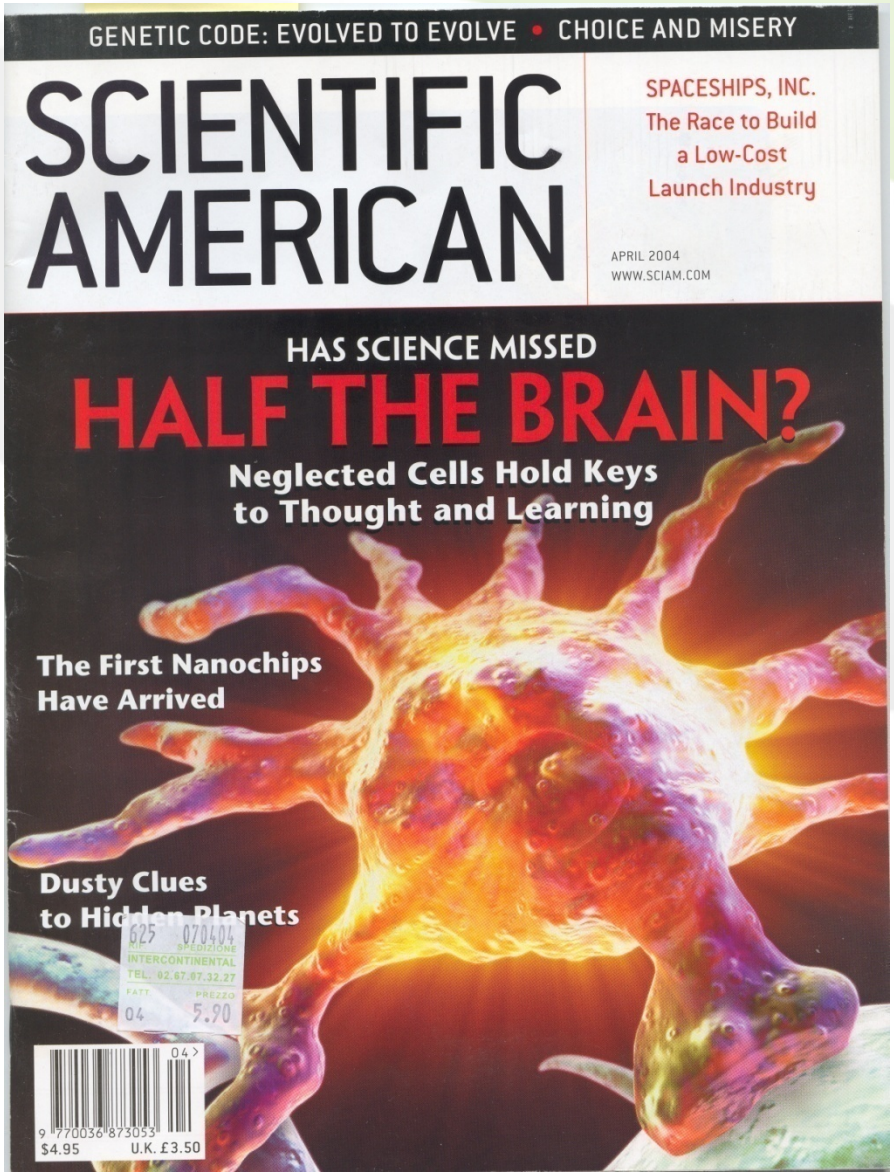
Parpura et al. introduced Bradykinin, an exogenous neuro-ligand, into the neuron-astrocyte co-culture. This glutamate receptor agonist bound to metabotropic glutamate receptor sites on a distal Astrocyte. Intracellular [Ca++] rises, eventually propagating into a global wave.

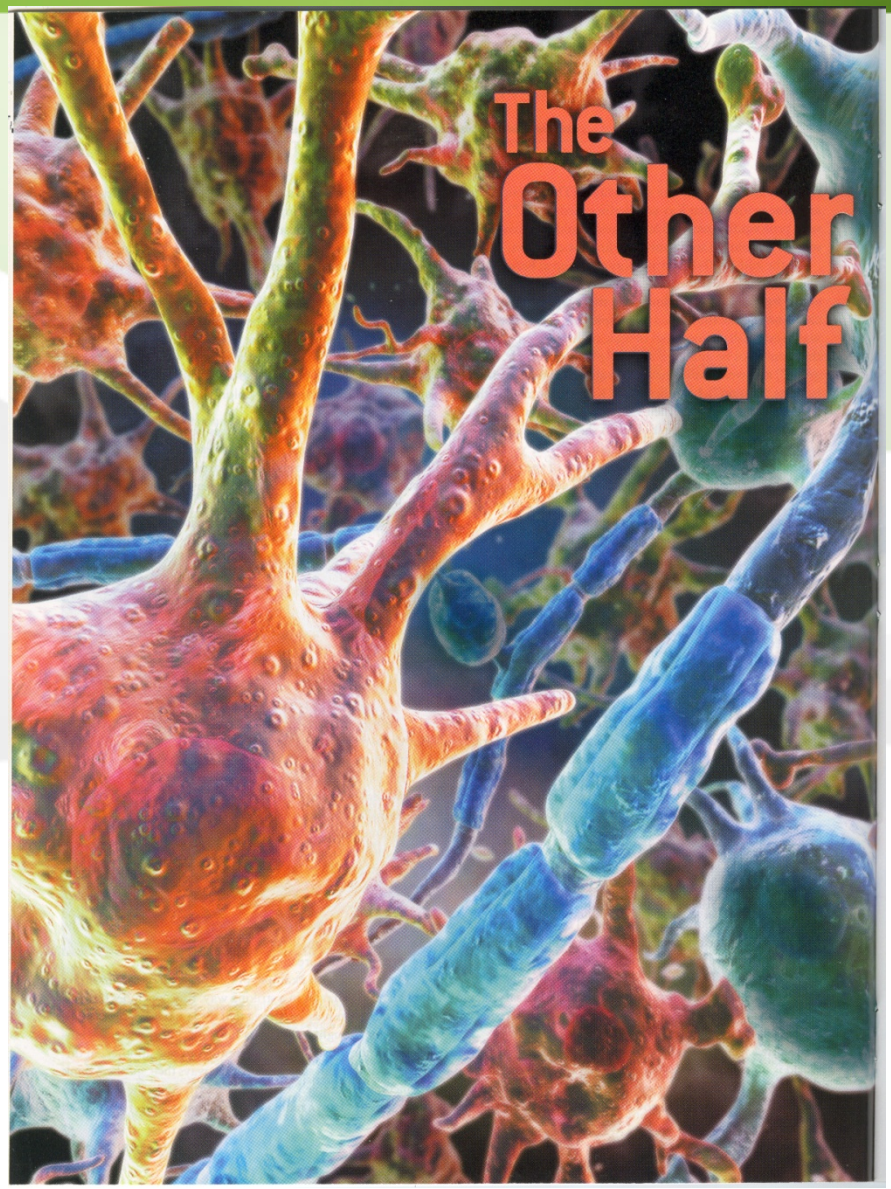
Before 1990: ***Structural support for neurons***

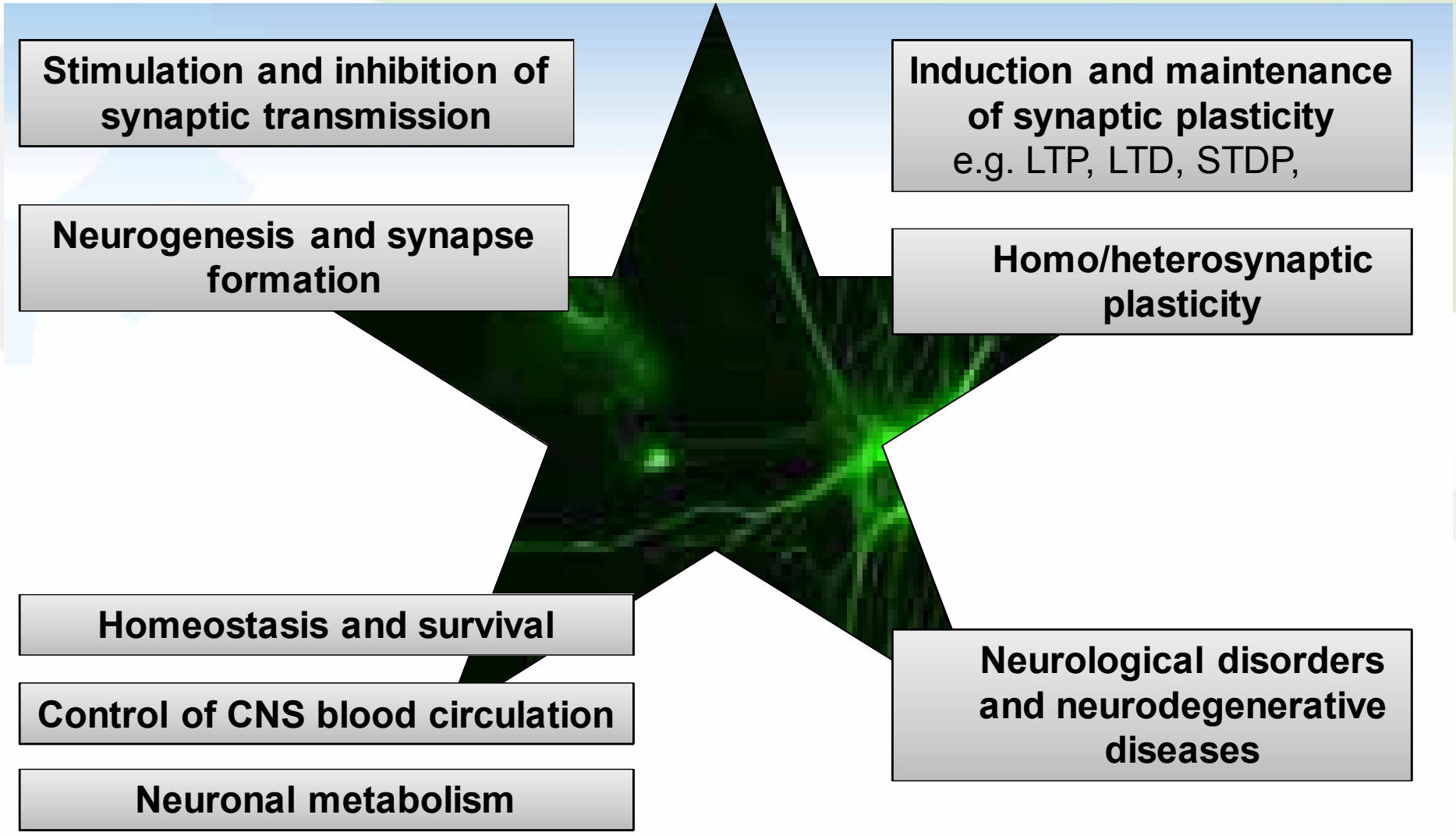
1990-2000: ***"housekeeping" cells with active support roles***

- 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).

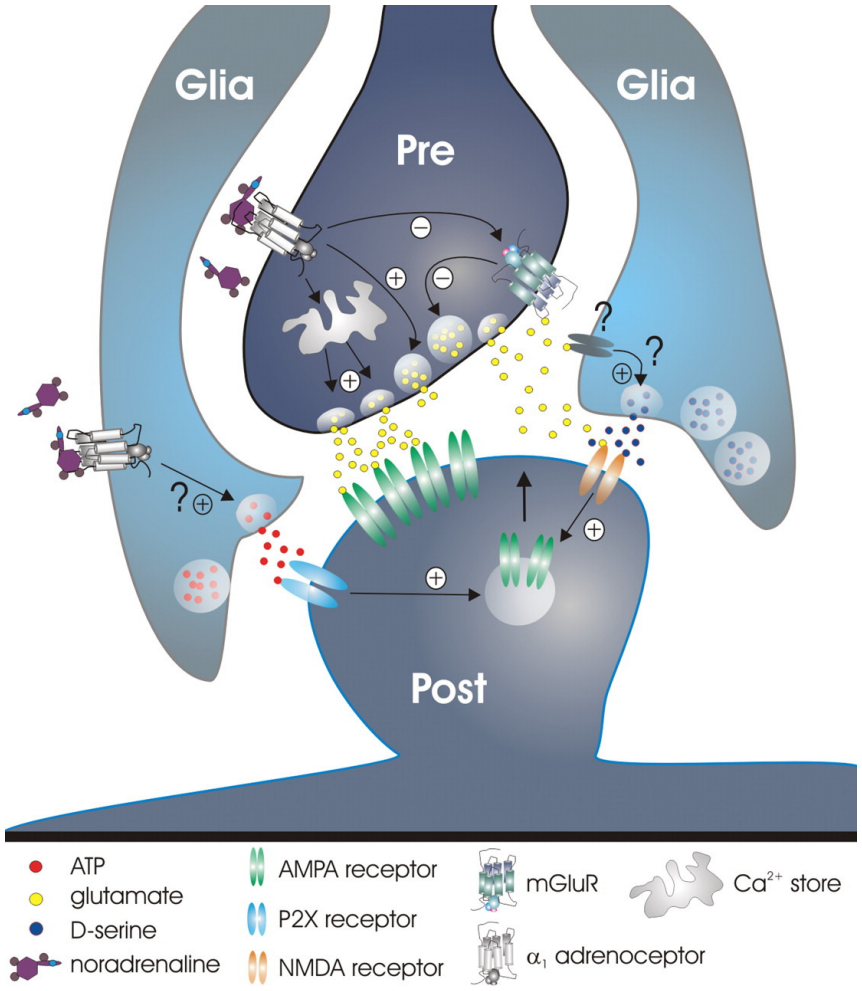
Then…the other half of the brain





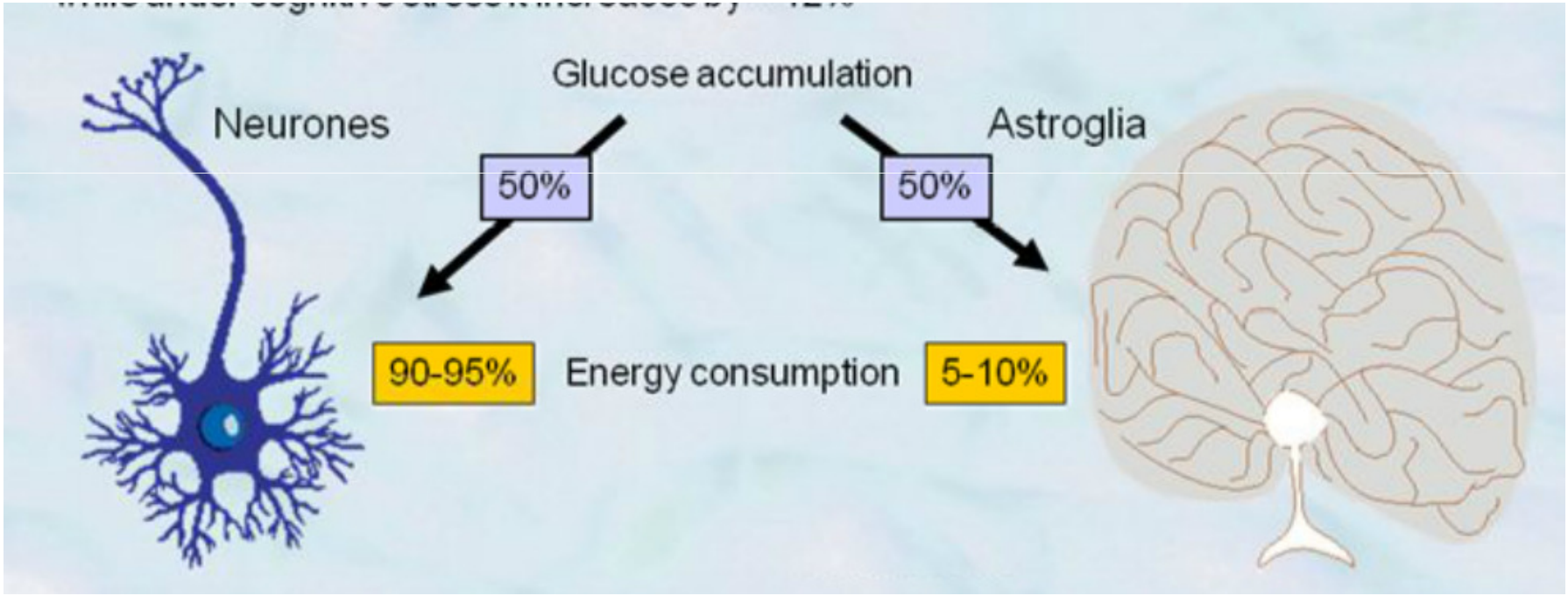

Stimulation and inhibition of synaptic transmission
Induction and maintenance of synaptic plasticity
e.g. LTP, LTD, STDP,
Neurogenesis and synapse formation
Homo/heterosynaptic plasticity
Homeostasis and survival
Control of CNS blood circulation
Neuronal metabolism
Neurological disorders and neurodegenerative diseases

Tripartate synapse



Metabolism

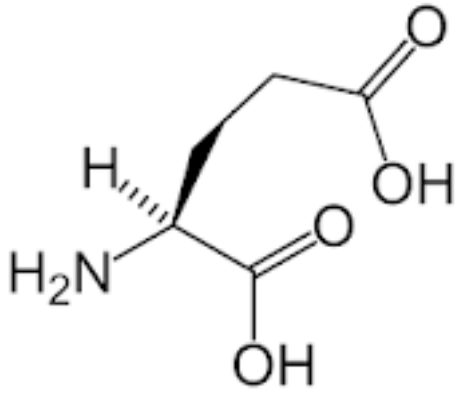
Brain represents approx 2% of total body mass, but consumes 20% of total energy
-decreases by 40% during sleep
-increases by 12% under cognitive stress

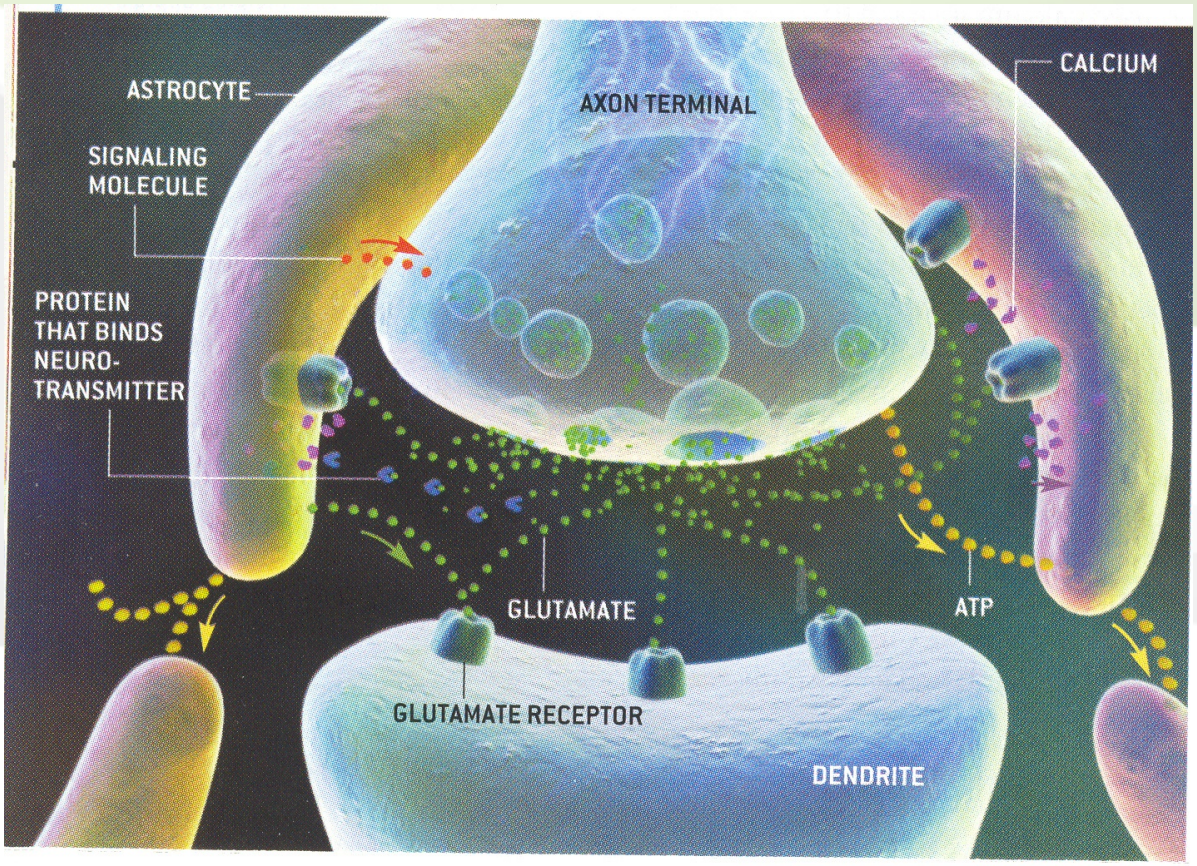


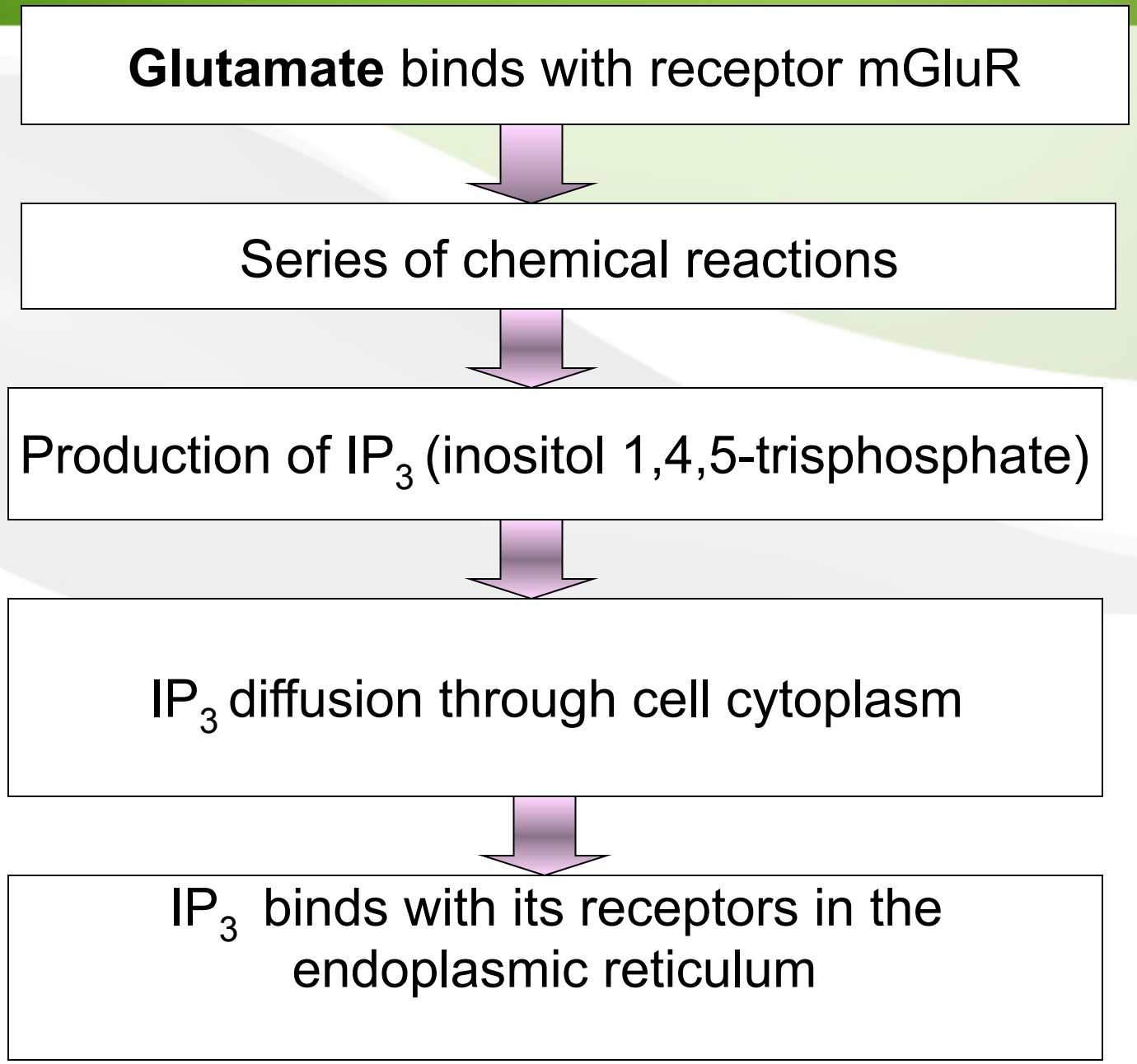
Energy for transmembrane ion gradients

Glutamate

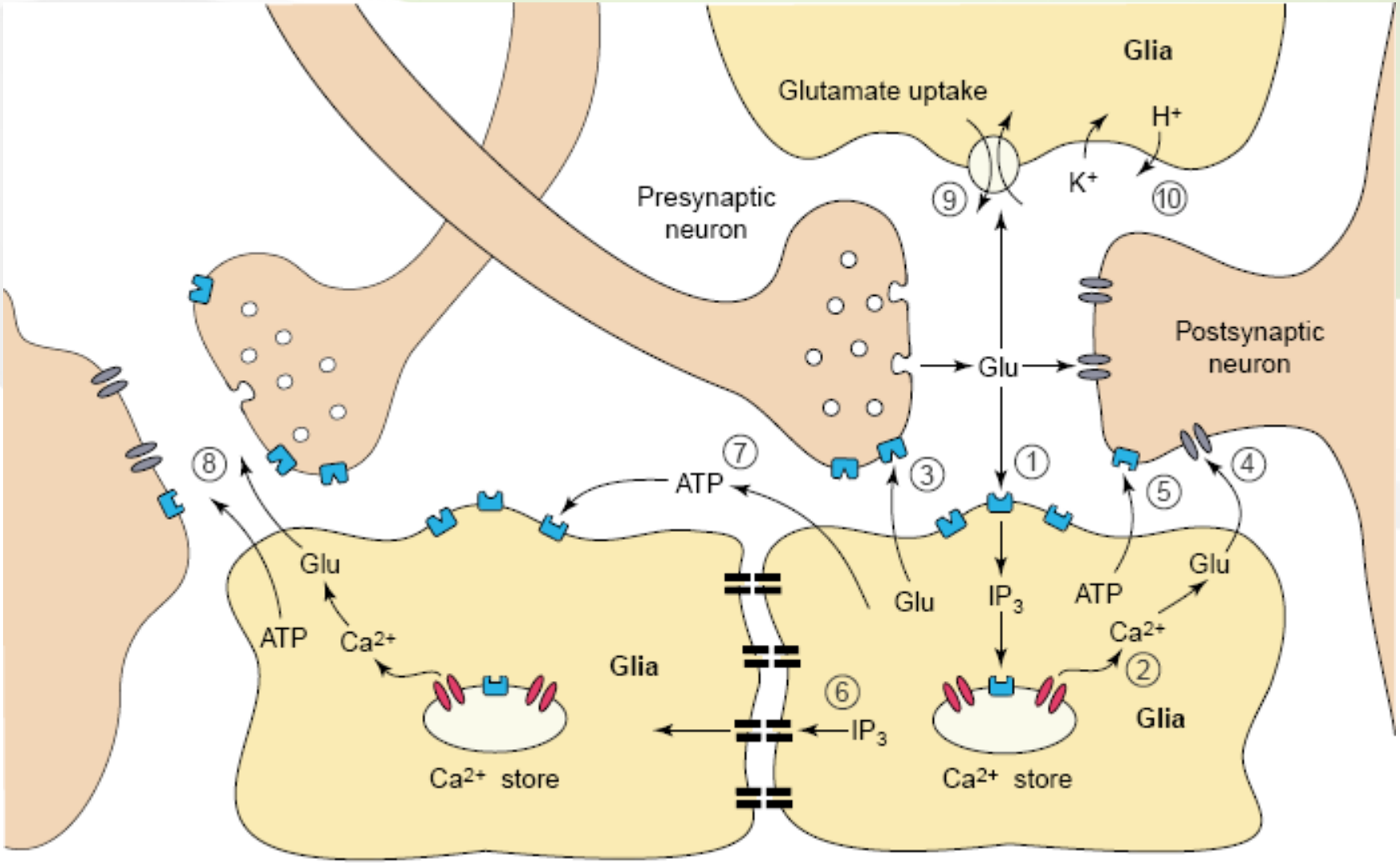
Glutamate (the conjugate base of glutamic acid) is abundant in the human body, but particularly in the nervous system and especially prominent in the human brain.
It is the brain's main excitatory neurotransmitter






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



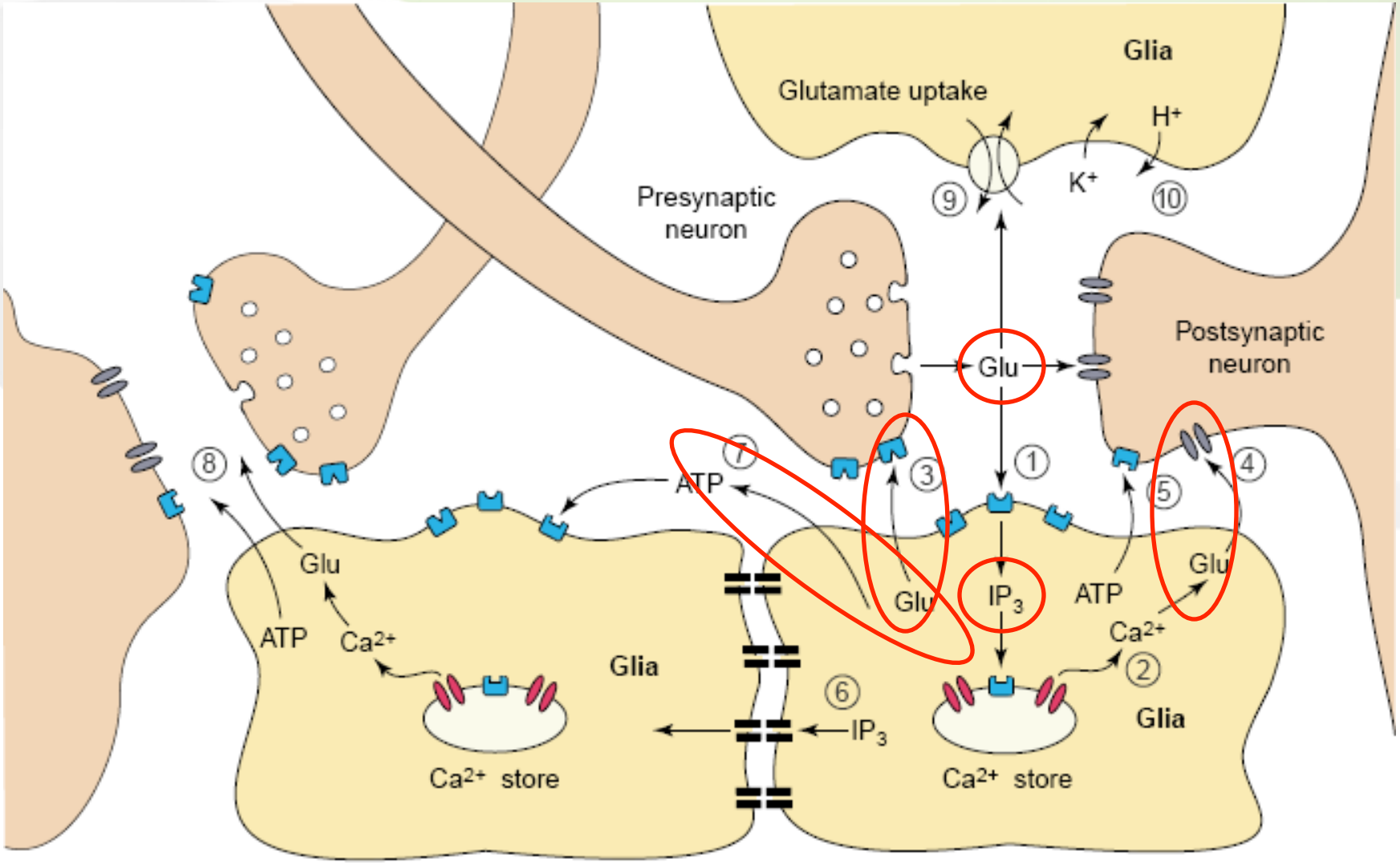
IP_3 receptors release Ca^{2+} in the endoplasmic reticulum

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

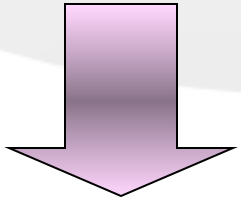
IP_3 receptors are then re-activated and release Ca^{2+} in the cell cytoplasm

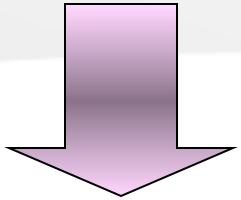
An auto-catalytic process starts

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.

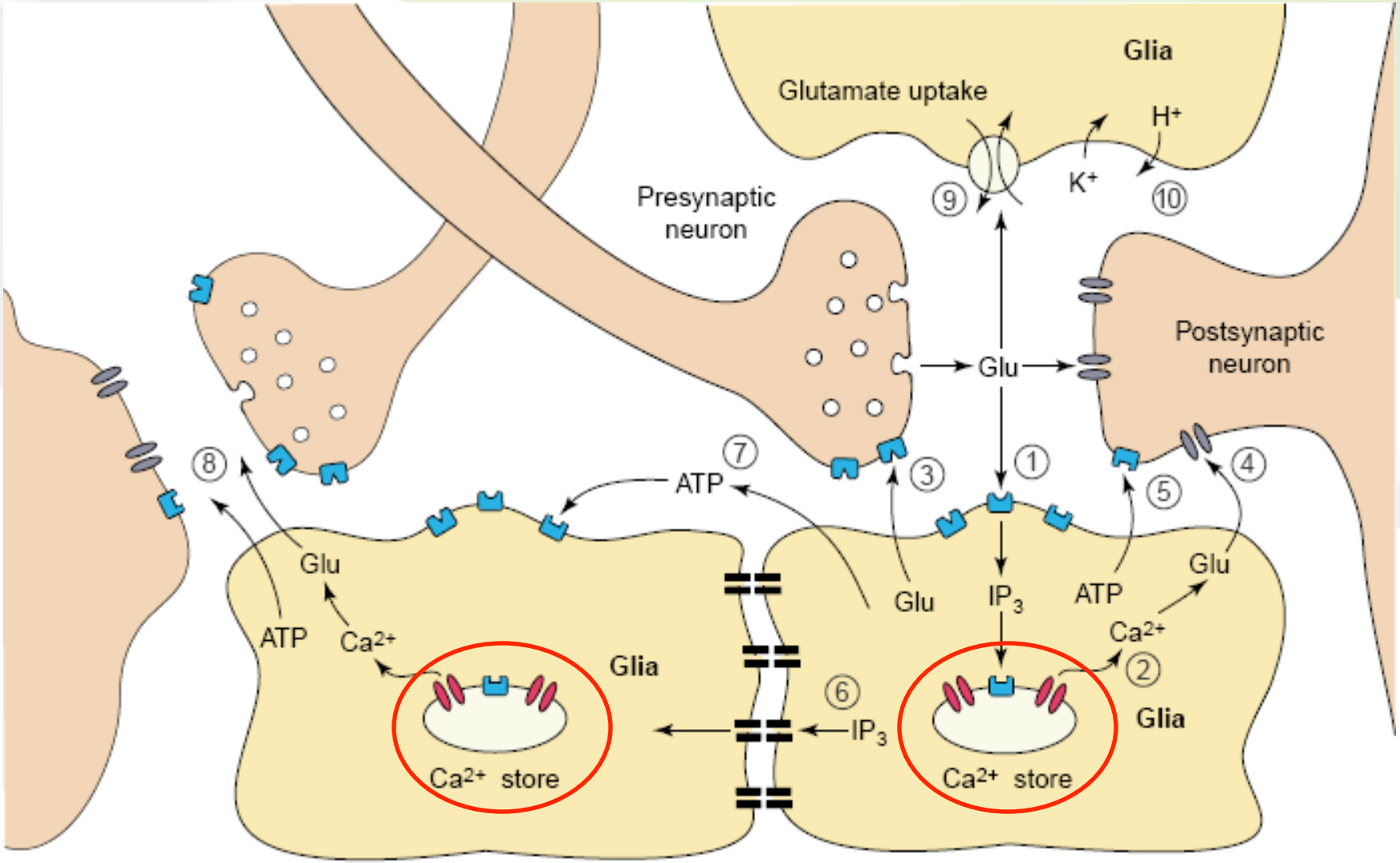




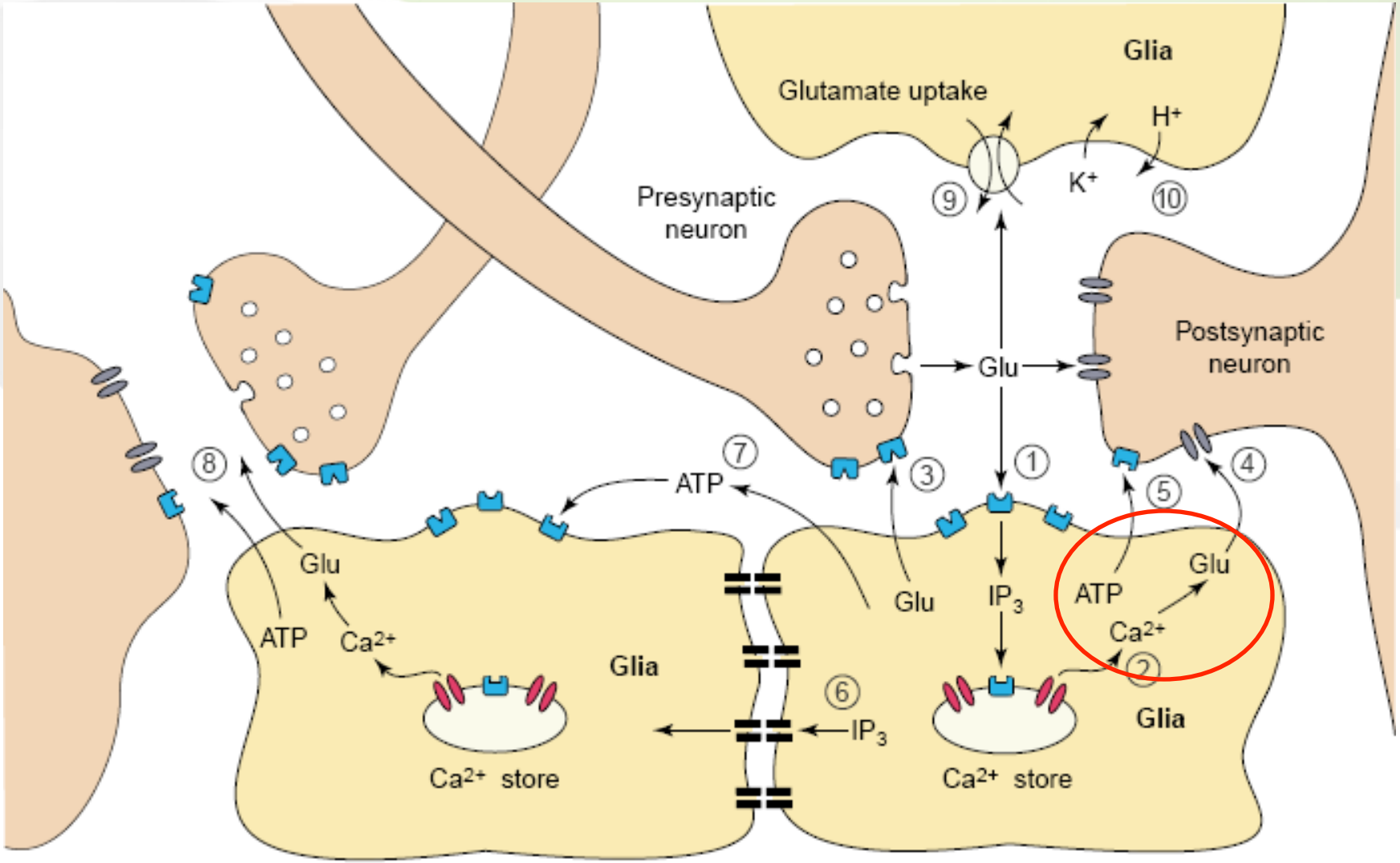
INTERcellular waves

INTRAcellular waves

The tripartite synapse



The tripartite synapse



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

Zonta et al., 2003

↑ Neural Activity

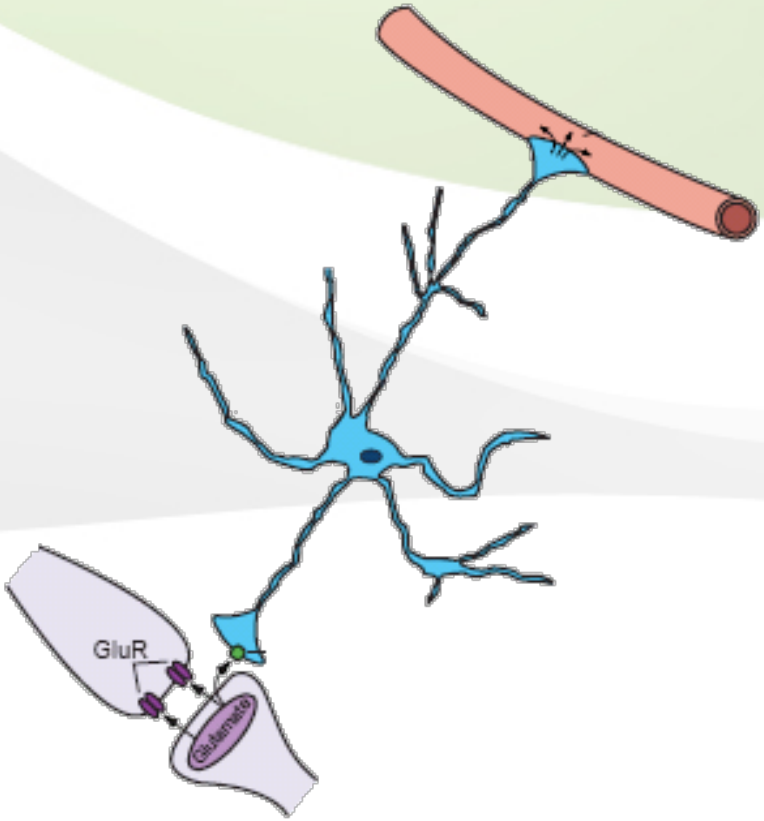
↑ Ca++ propagation throughout astrocytic syncytium

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

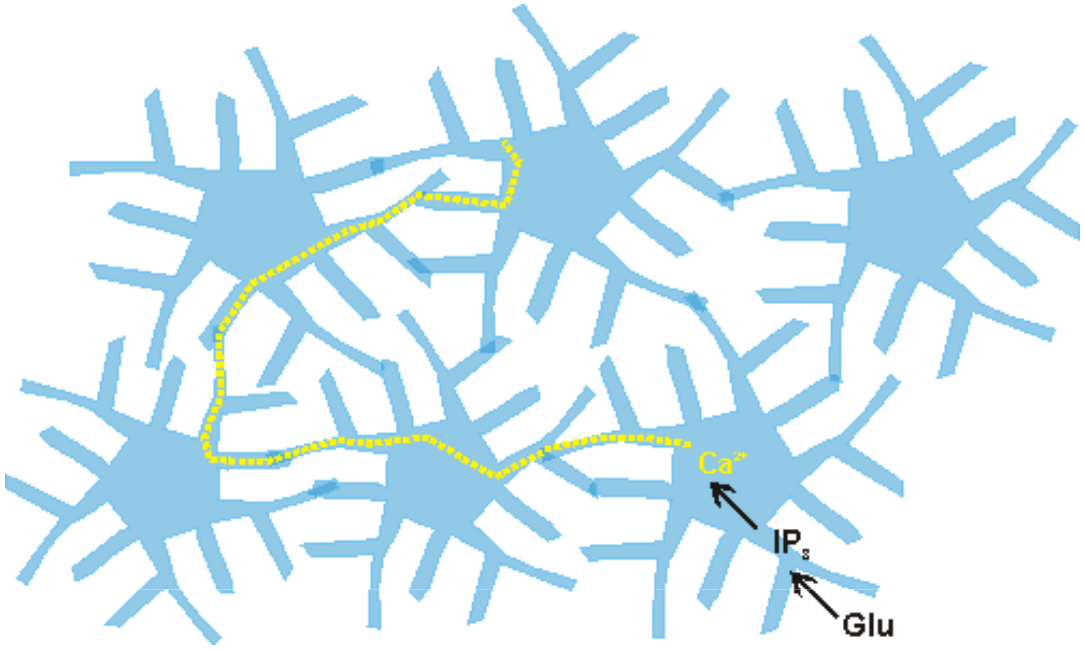
↑ Vesicular release of prostanoids

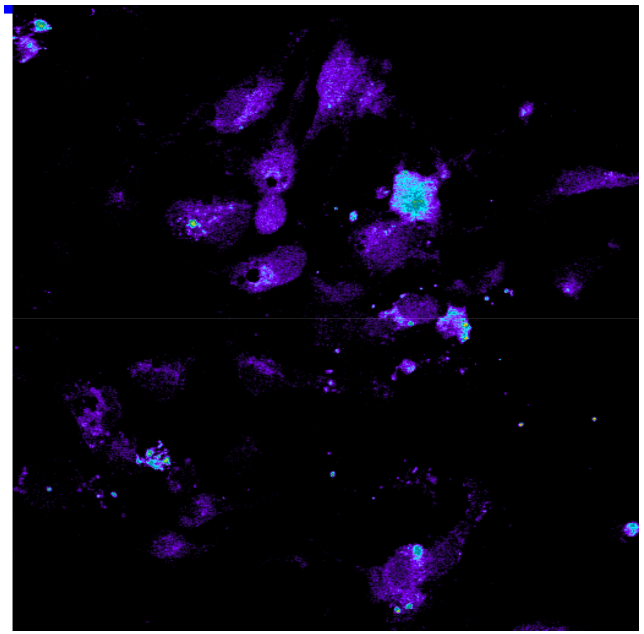
↑ Relaxation of capillary walls; decrease in vascular tone

↑ **Bloodflow**



Astrocytes and calcium

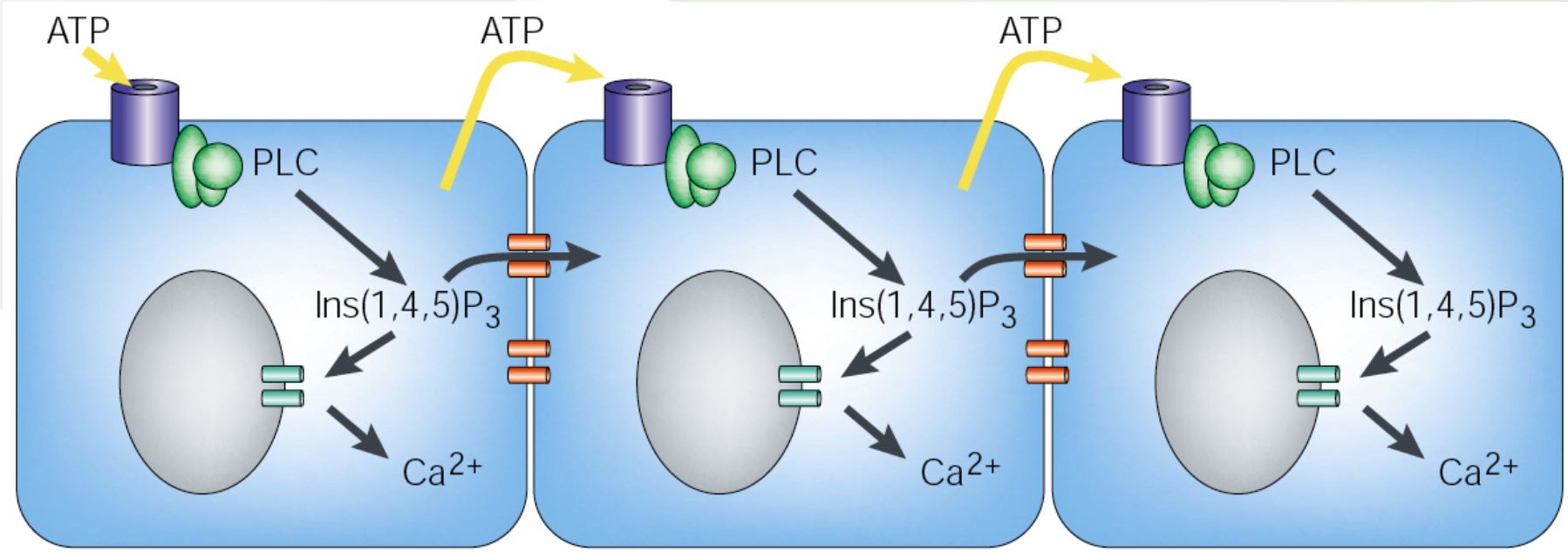




- Calcium waves propagate through the syncytium **GAP JUNCTIONS,** a non-synaptic means of communication within the brain
- Waves can be induced by mechanical stimulation and by glutamate
- Influx of calcium leads to calcium-sensitive release and uptake of ions and neuromodulators

Ca^{2+} Waves

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

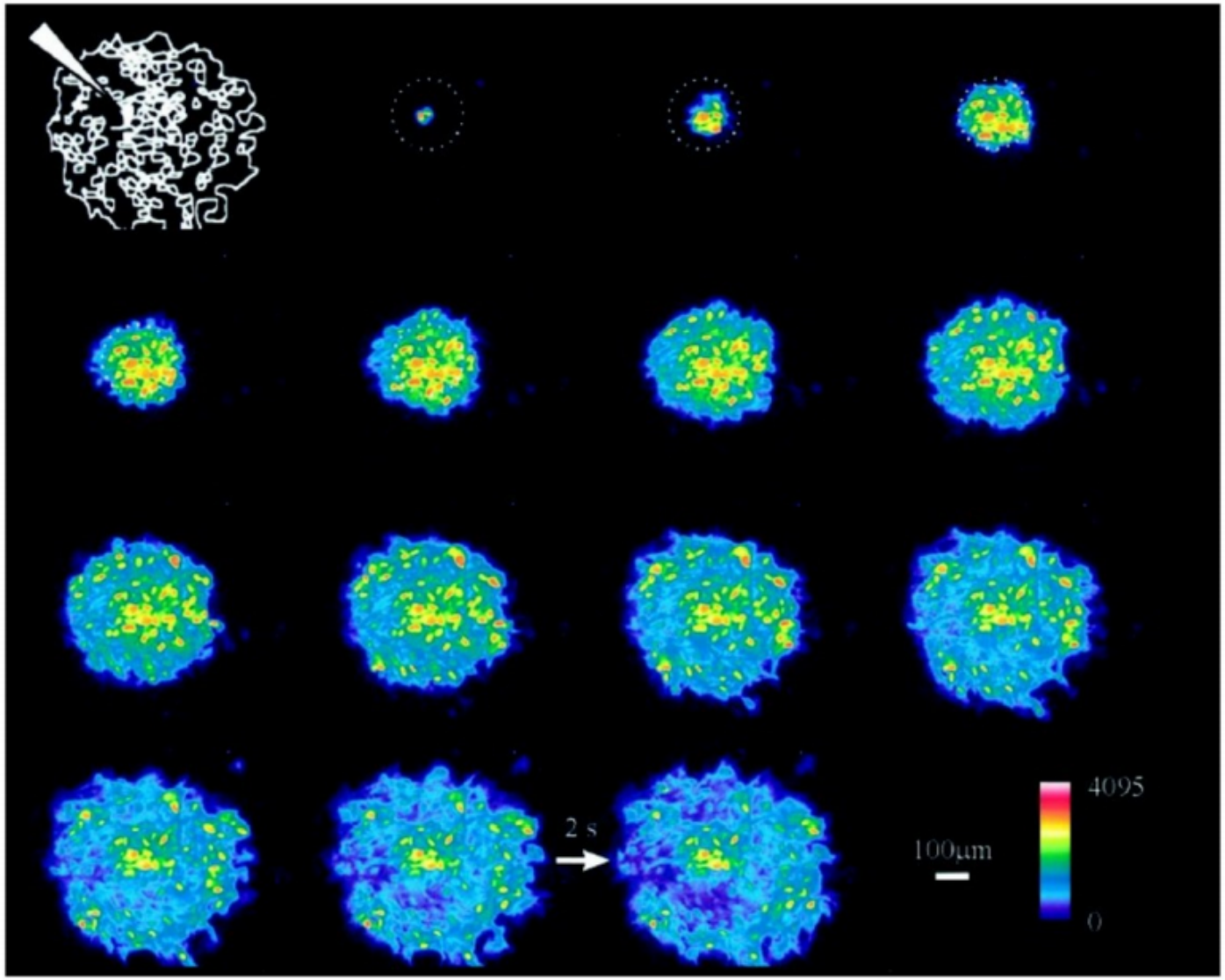


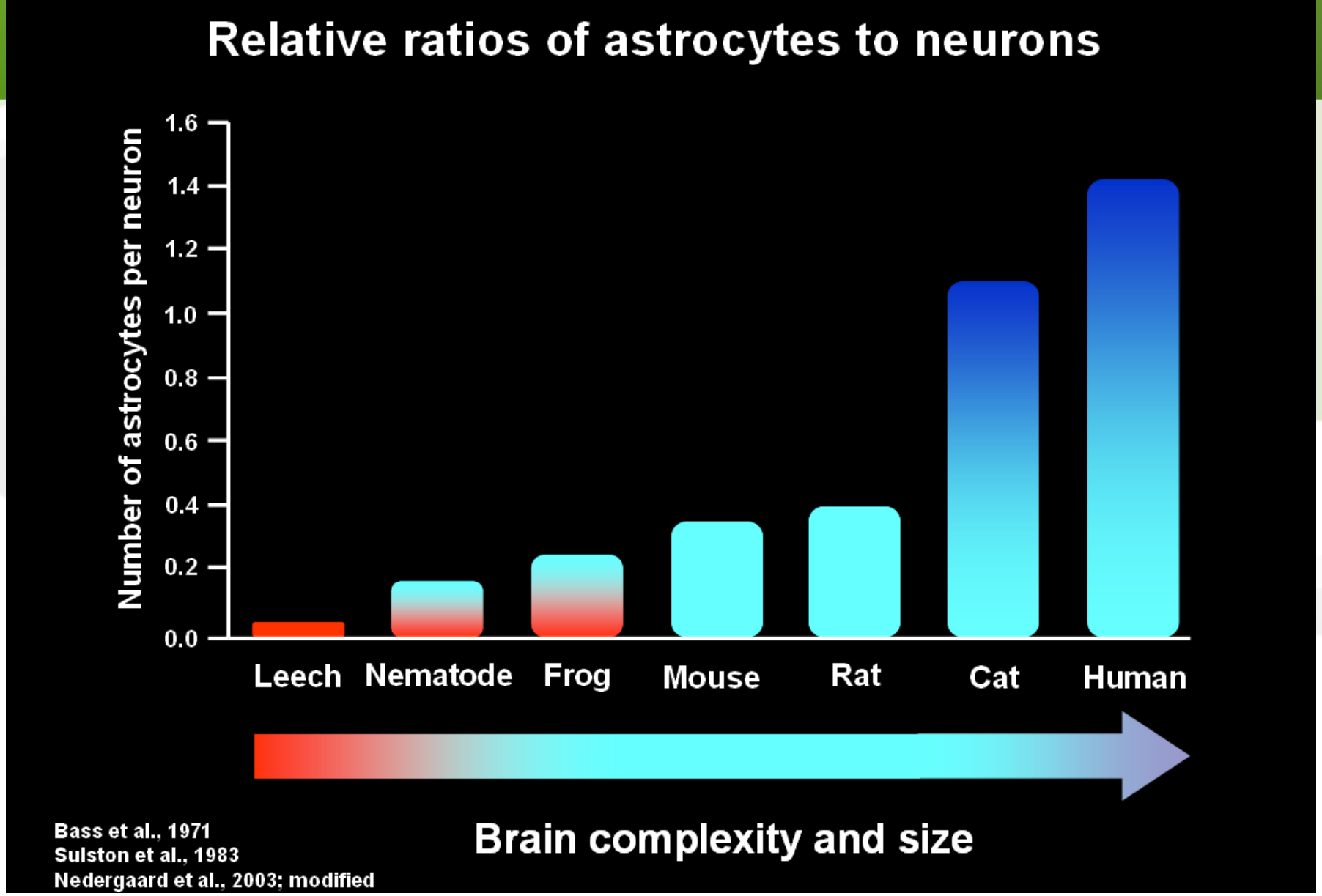
Speed: ~20μm/s

Range: a few hundred μm

Time scale: seconds to minutes

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



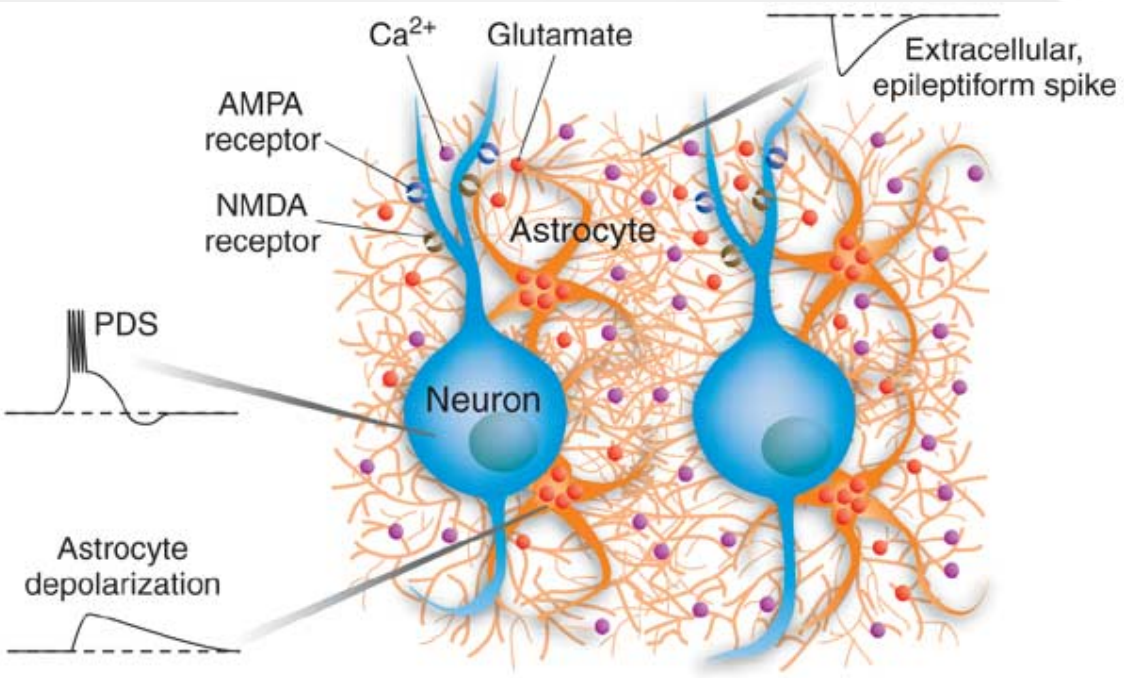


A single astrocyte can cover 20 000 – 100 000 synapses in rodents... and possibly up to 2 million in primates and humans.

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.



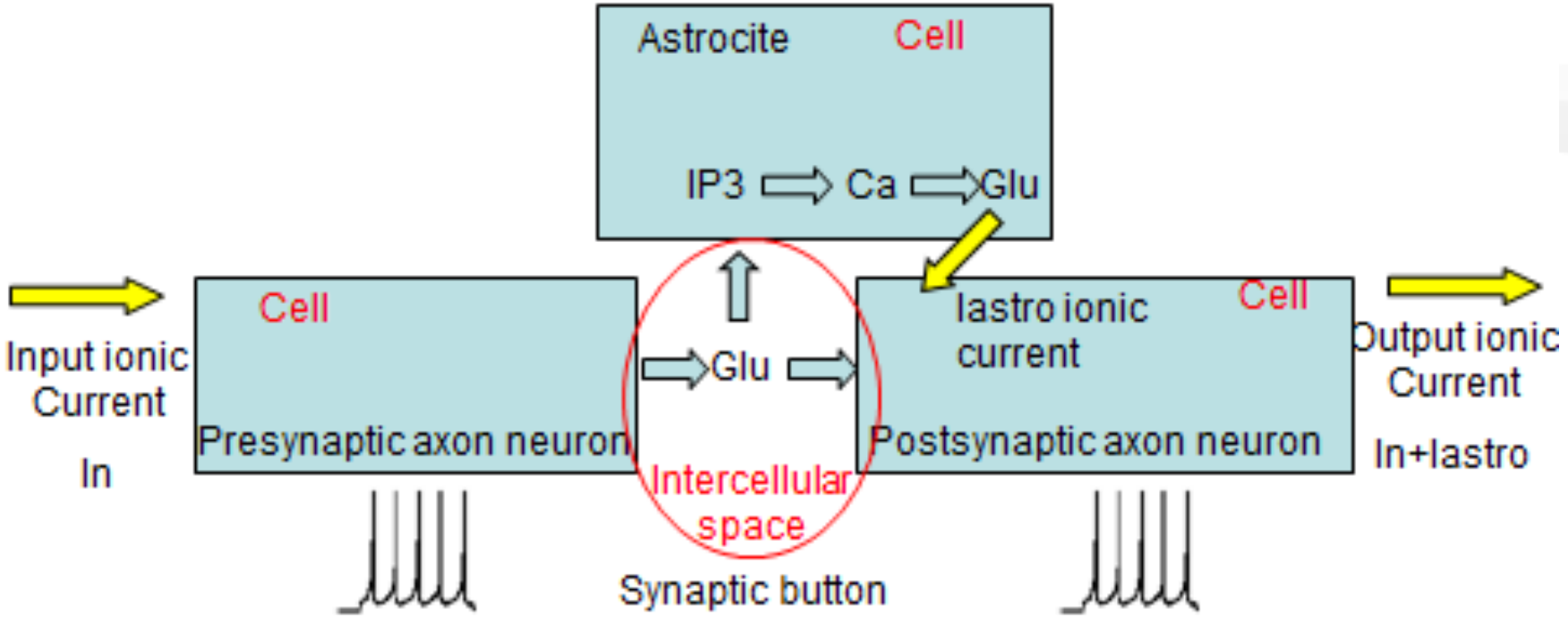
-- Ca2+ increased in Astrocyte

– 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

Biological Model of tripartite synapse

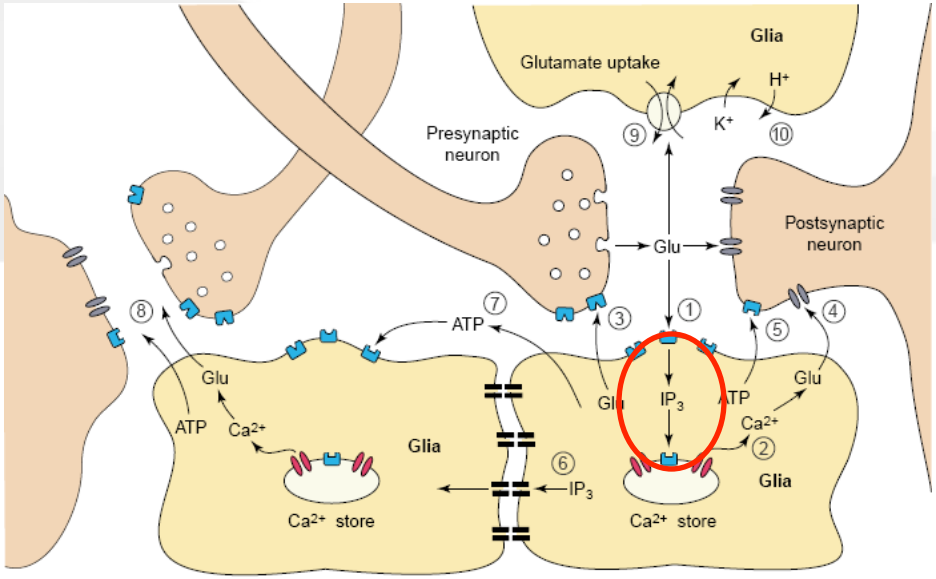


Modelling neuron-astrocyte interactions

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



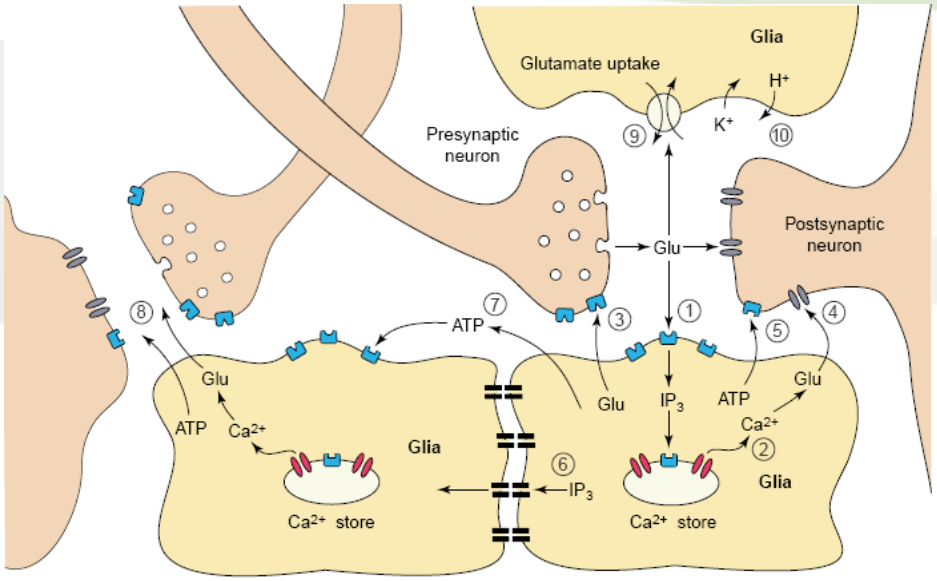
Wang S.S.H., Alousi A.A. and Thompson S.H. The life time of inositol 1,4,5-triphosphate in single cells. J. Gen. Physiol., 105:149-171, 1995

Modelling astrocyte-astrocyte interactions

The flux of IP3 can be modelled by:

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

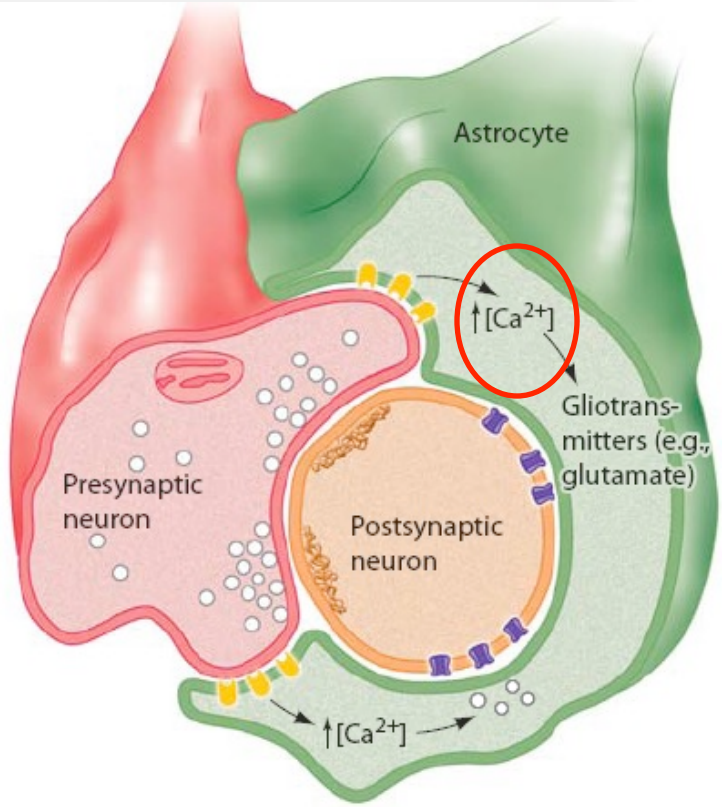
Where *i* indicate the *ith* astrocyte, *k* is the diffusion coupling coefficient through the gap-junction and <*j*> is the contribution of the neighbouring astrocytes



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



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

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

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

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

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

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

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

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

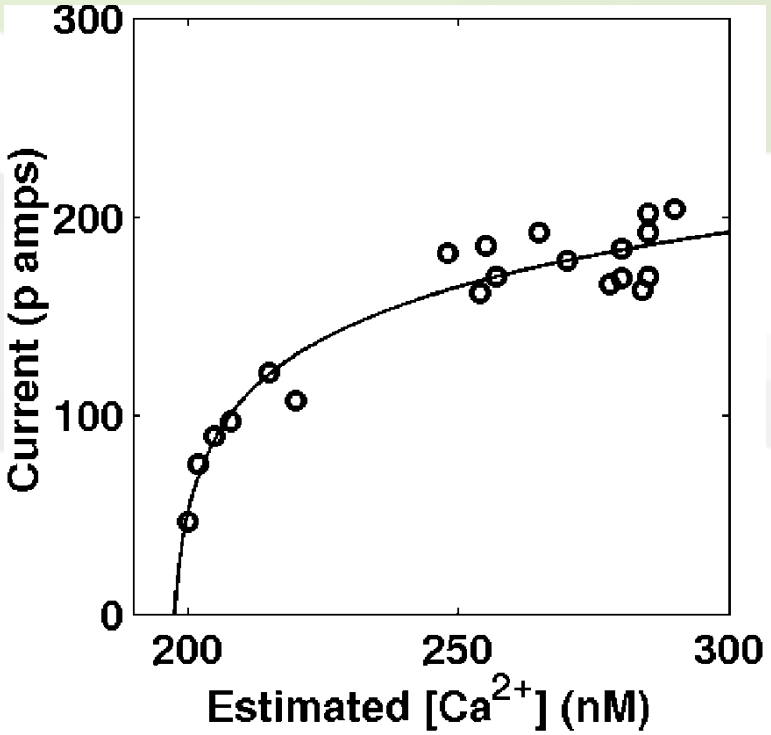
$$\beta_q = a_2 [Ca^{2+}]$$

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

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

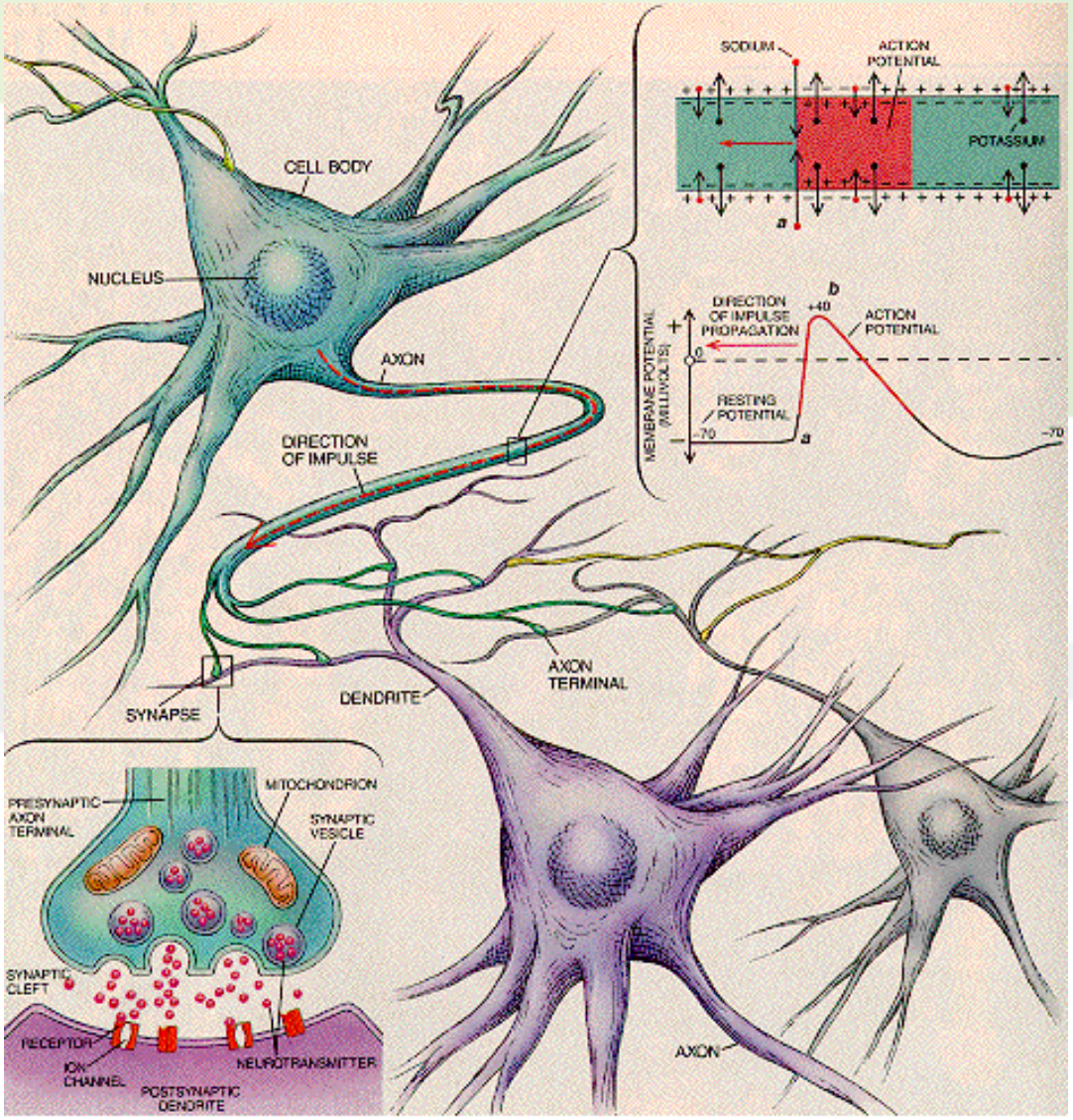
$$y = \frac{[Ca^{2+}]}{nM} - 196.69$$



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

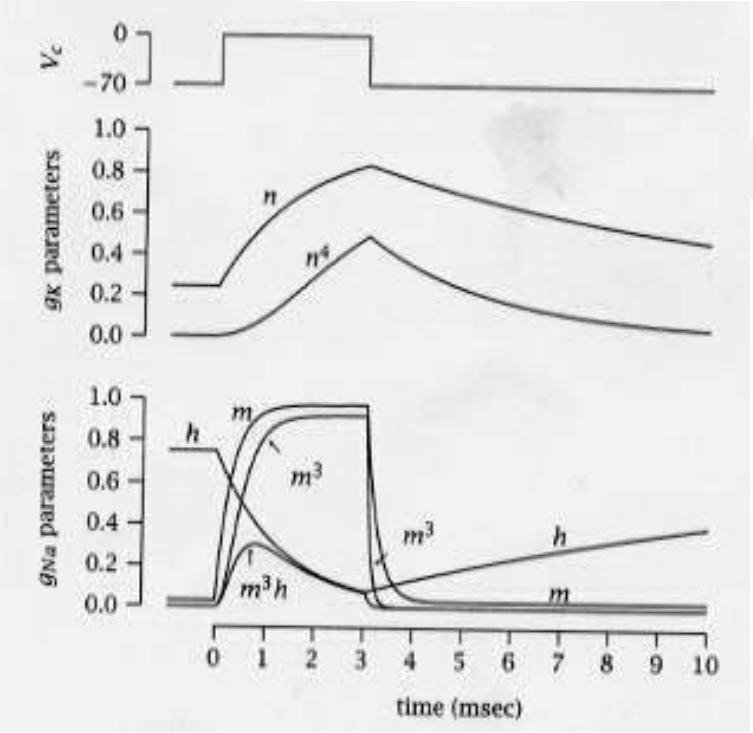


$$C_m \frac{dv}{dt} = -g_K n^4 (v - v_K) - g_{Na} m^3 h (v - v_{Na}) - g_l (v - v_l) + I_{ext} + I_{astro}$$

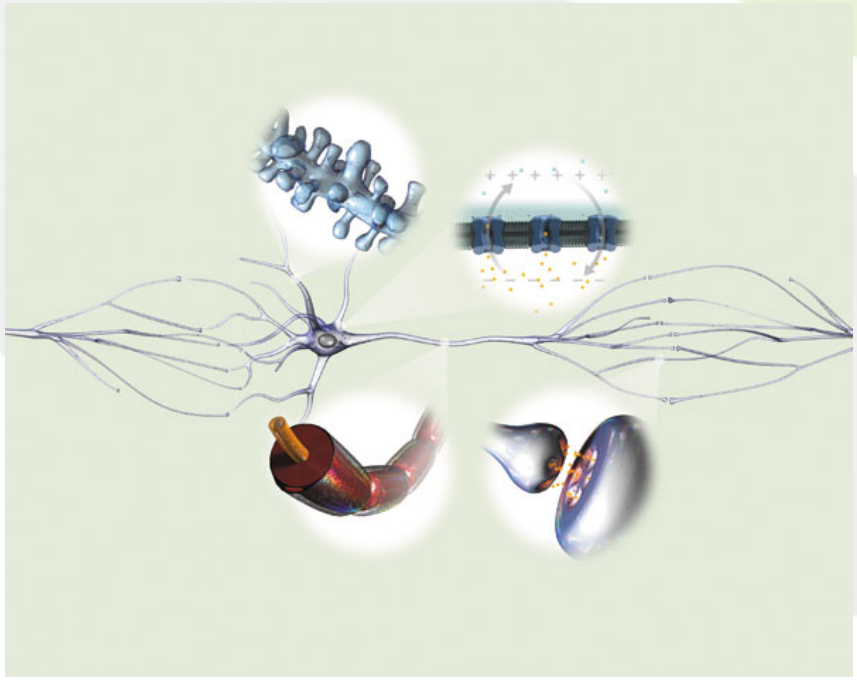
$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m$$

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

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



A modified Izhikevich neuronal model

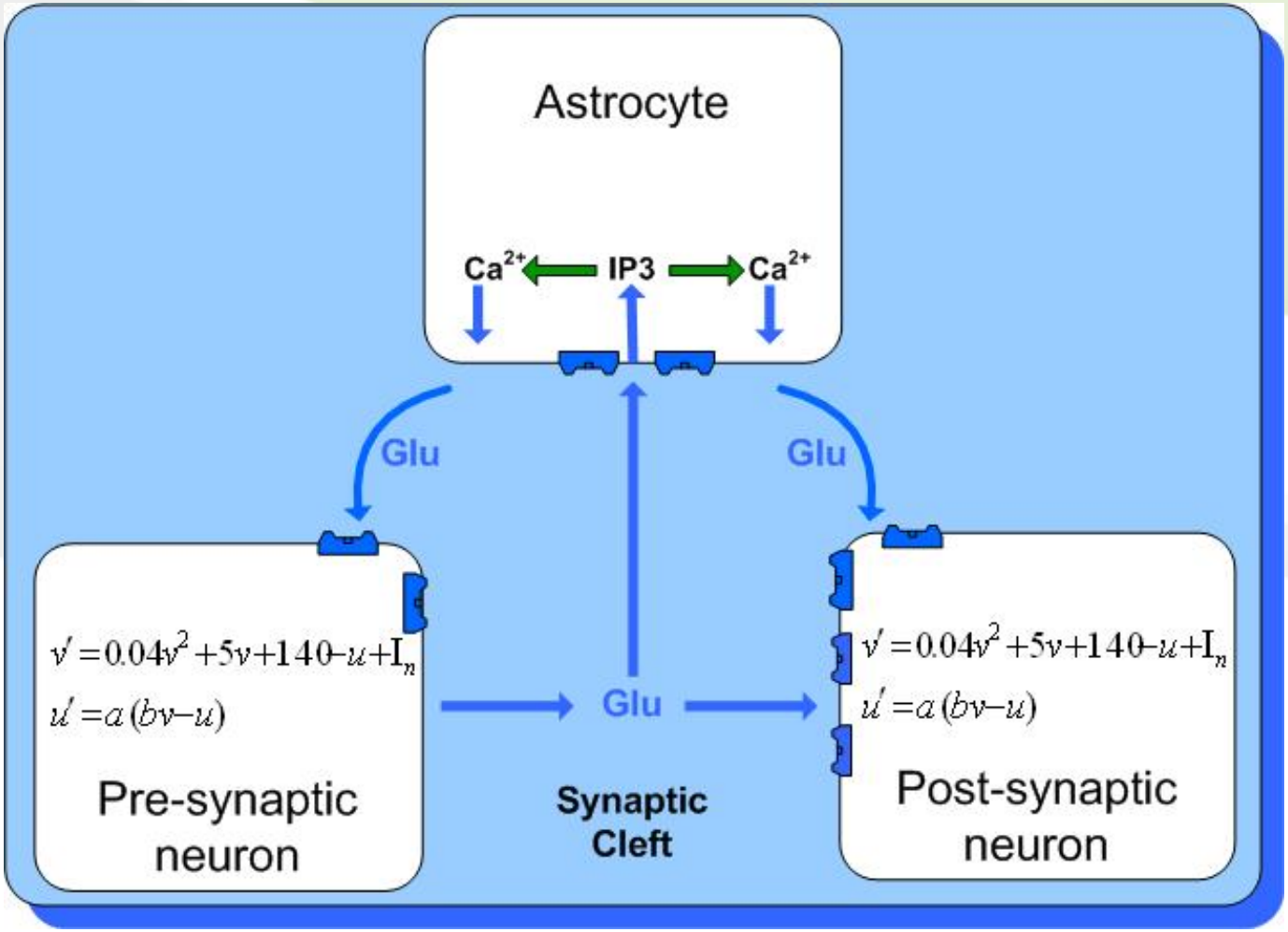


$$if \quad v \geq +30\,mV, \quad then \quad \begin{cases} v \leftarrow c \\ u \leftarrow u + d \end{cases}$$

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

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

Dressed Neuron



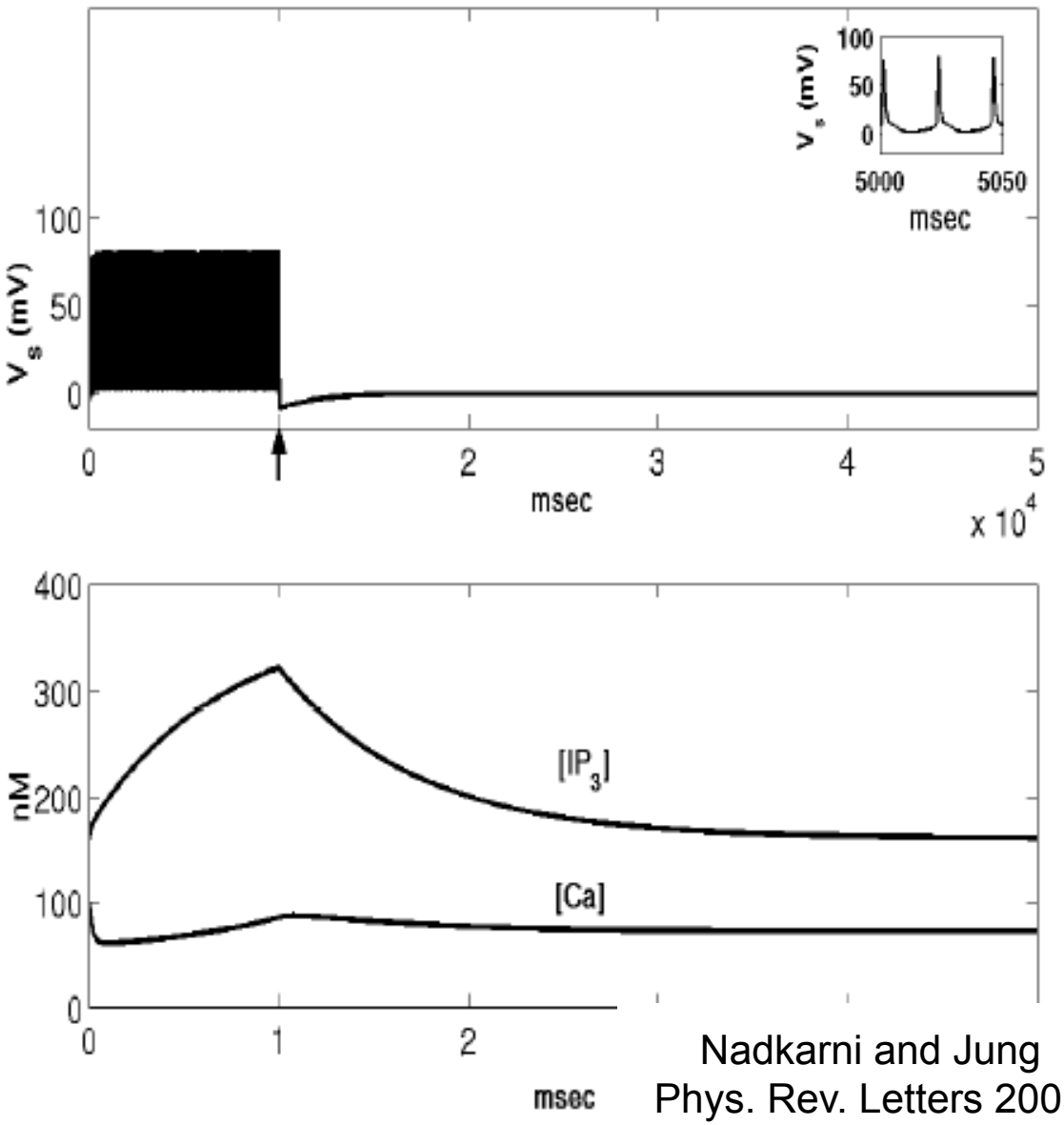
Neural Firing

↓

[IP3] increases

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

$I_{astro}=0$



Nadkarni and Jung
Phys. Rev. Letters 2003

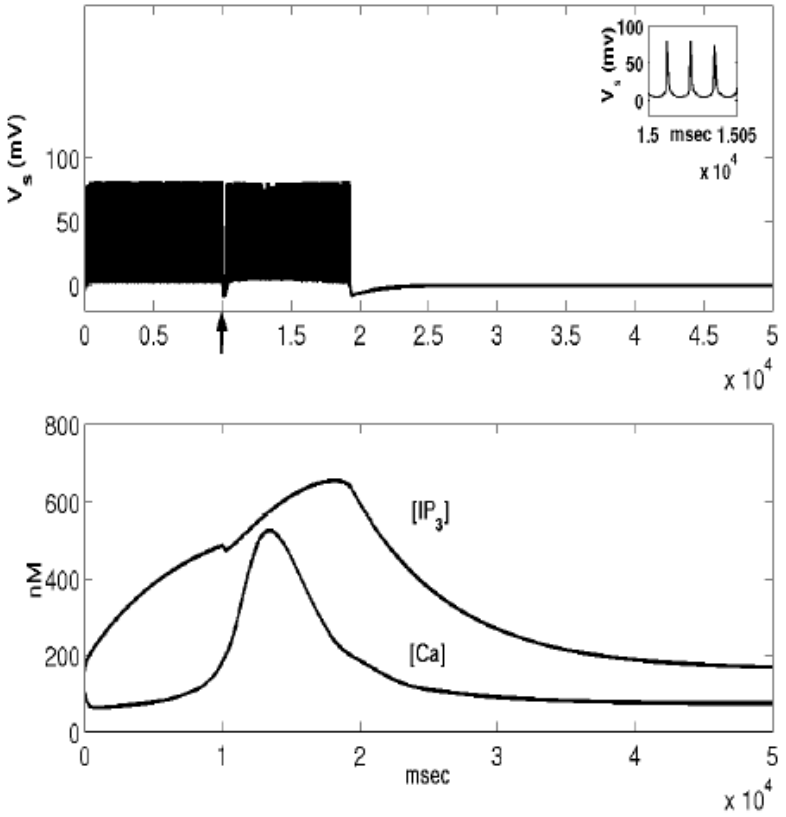
10 sec exogenous
Current to neuron

↓

$[IP_3]$ increases

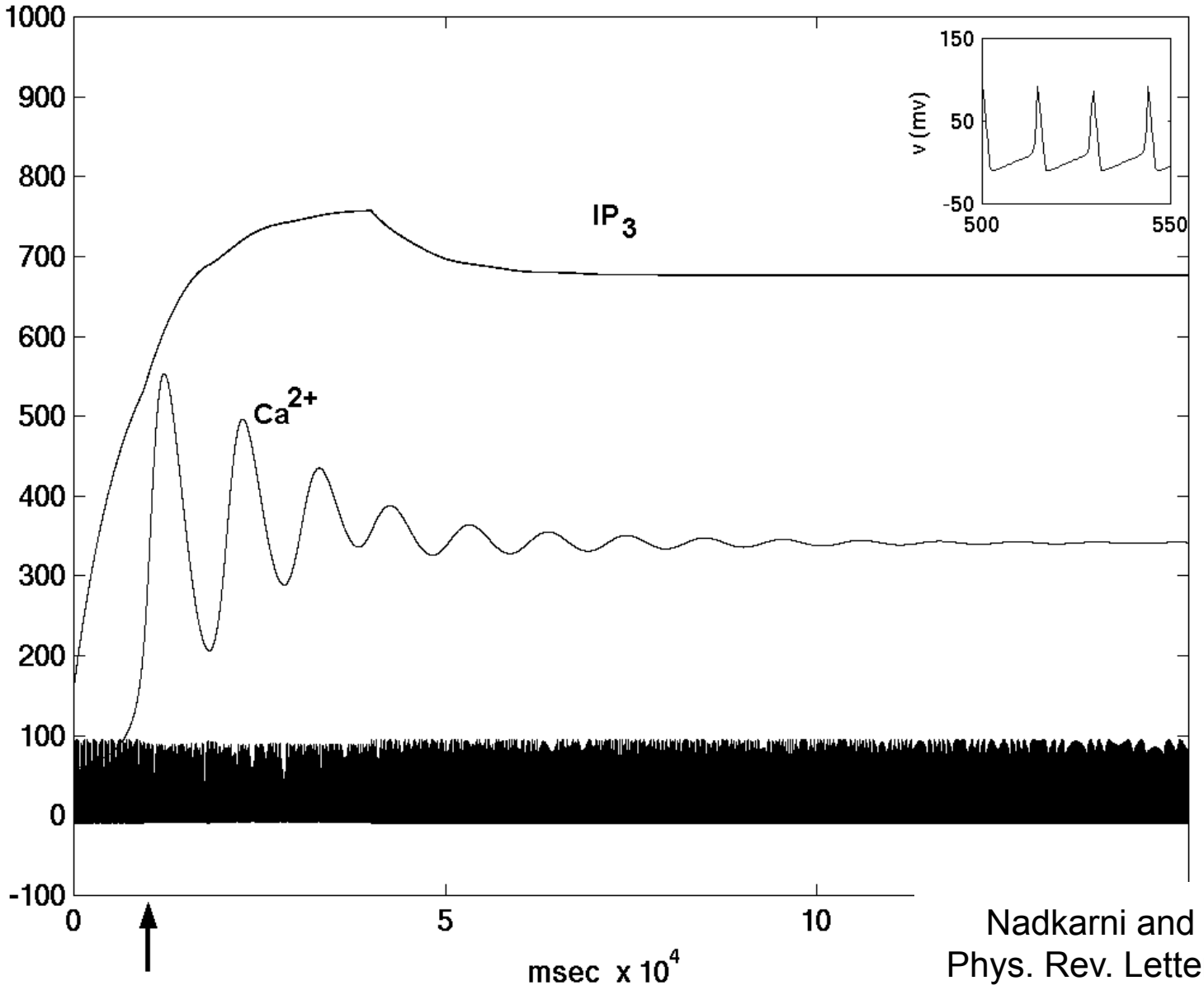
↓

Ca^{2+} oscillations start



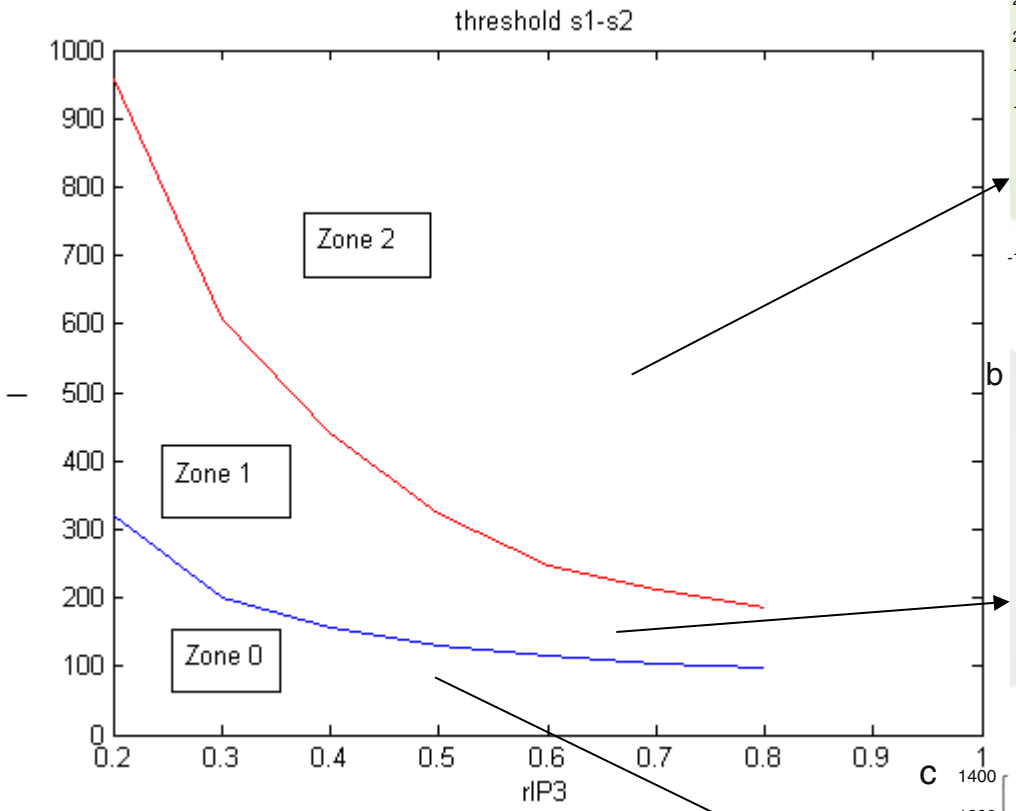
Astrocyte feedback self-sustains Neural activity!

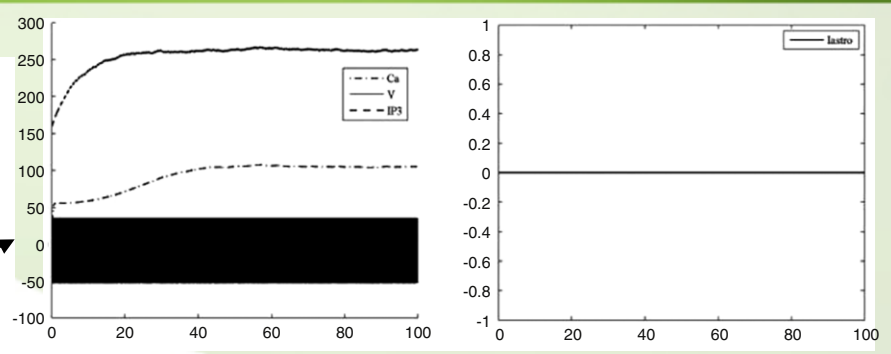
Nadkarni and Jung
Phys. Rev. Letters 2003

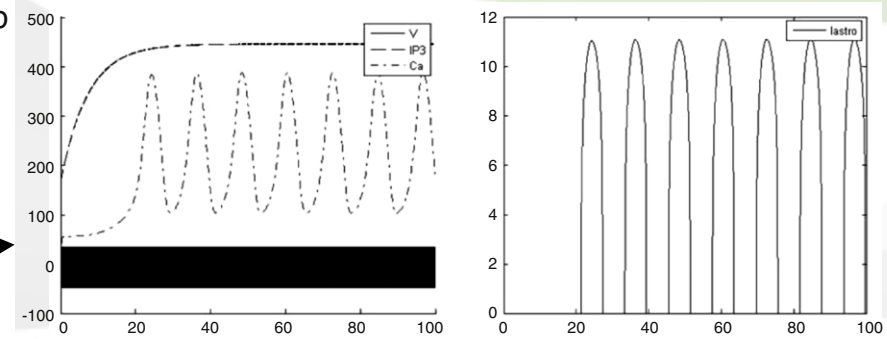


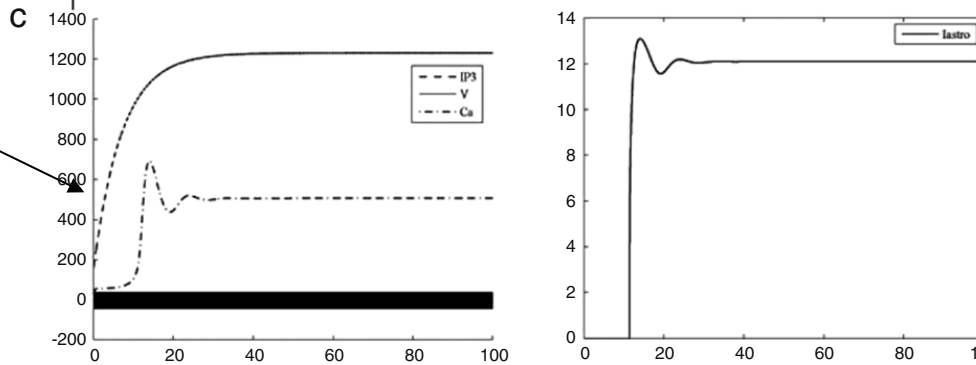
Nadkarni and Jung
Phys. Rev. Letters 2003

Neuron-Astrocyte interaction





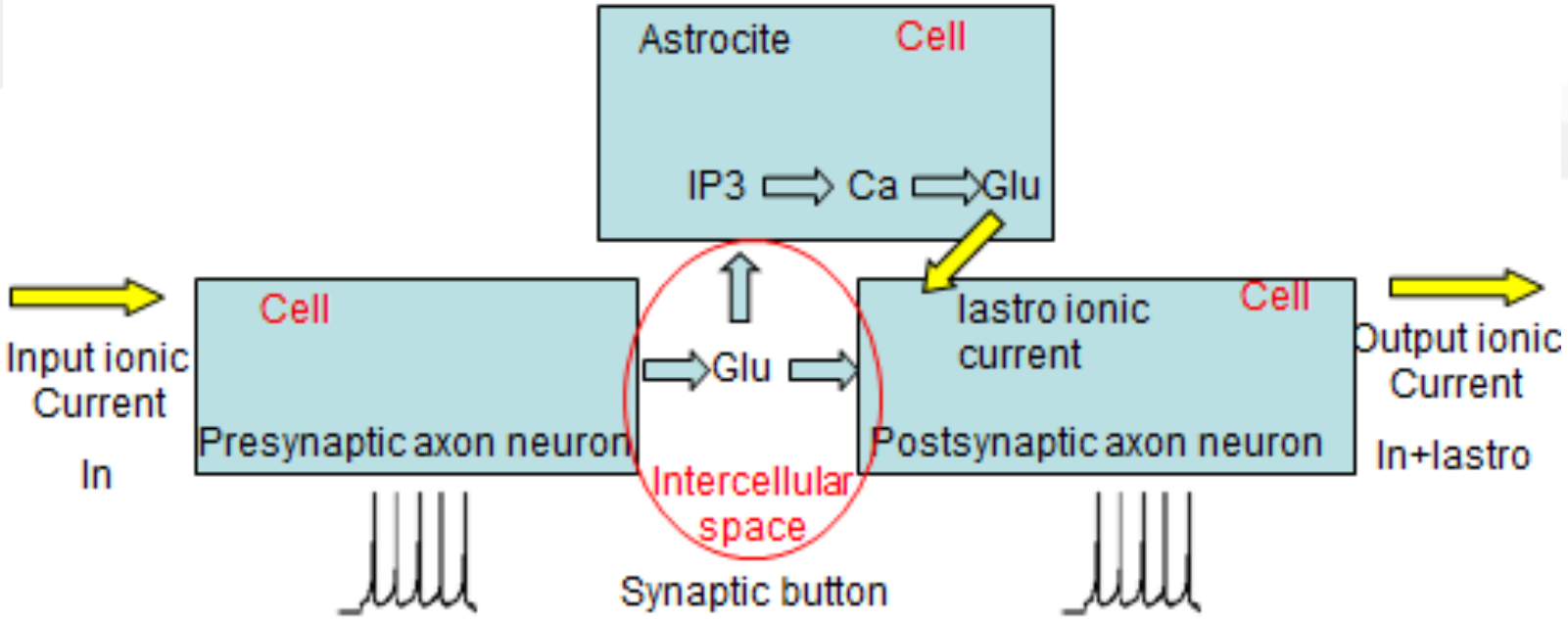




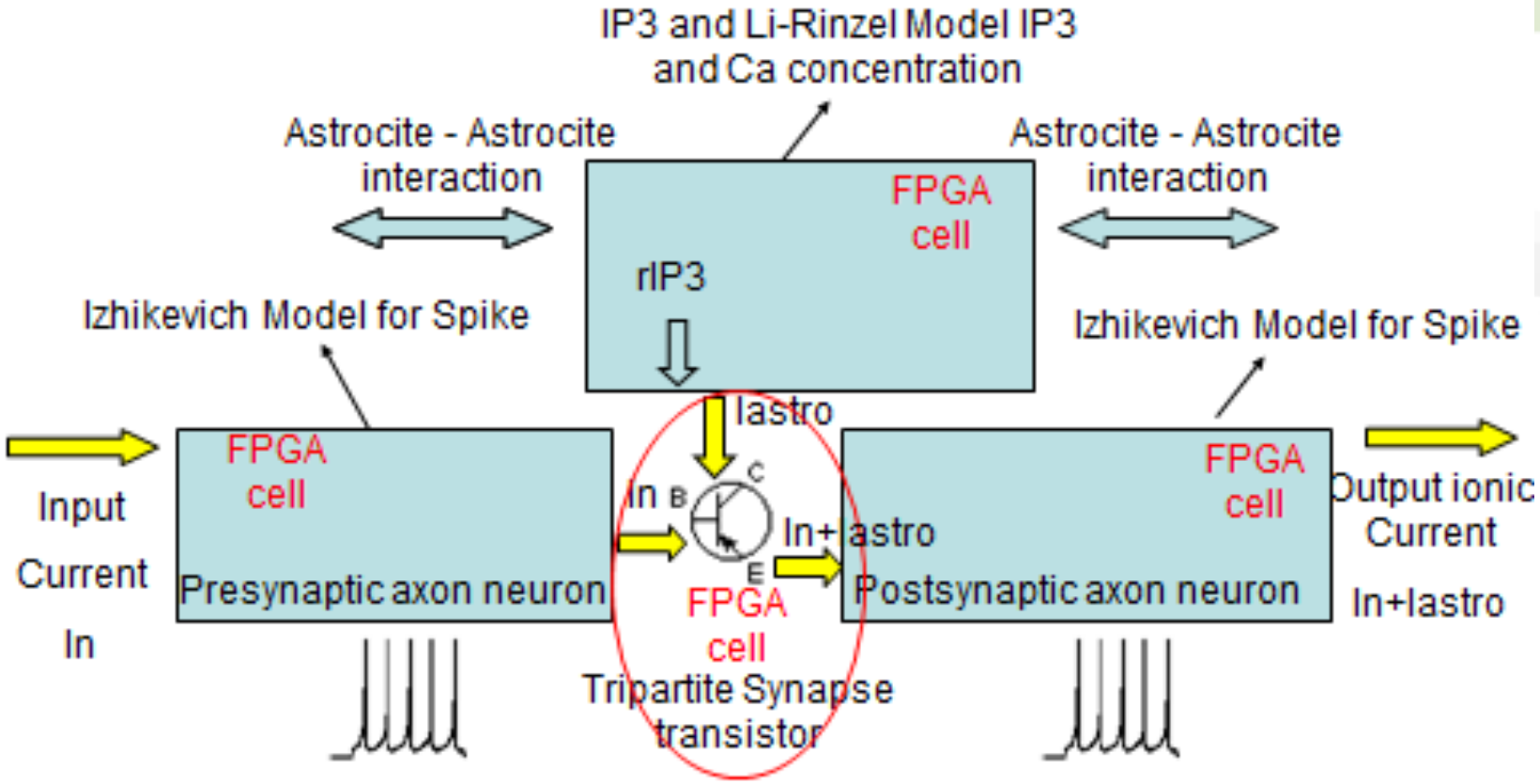
variables $\begin{cases} r_{IP3} \\ I_{neuron} \end{cases}$

Valenza & De Rossi et al.
Neural Networks 2011

Biological Model of tripartite synapse

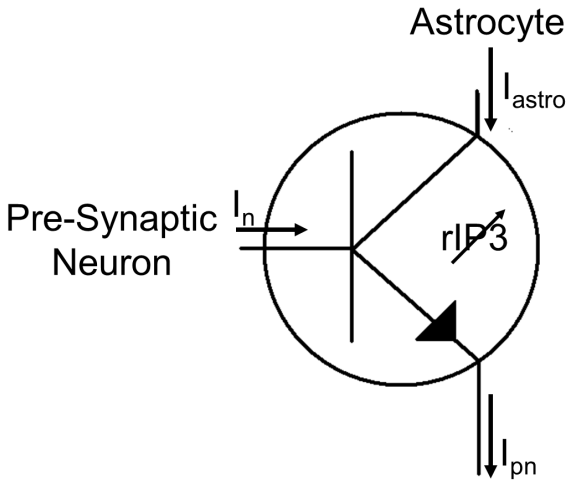


Computational Hardware Model of tripartite synapse



Our model: toward a transistor-based approach

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

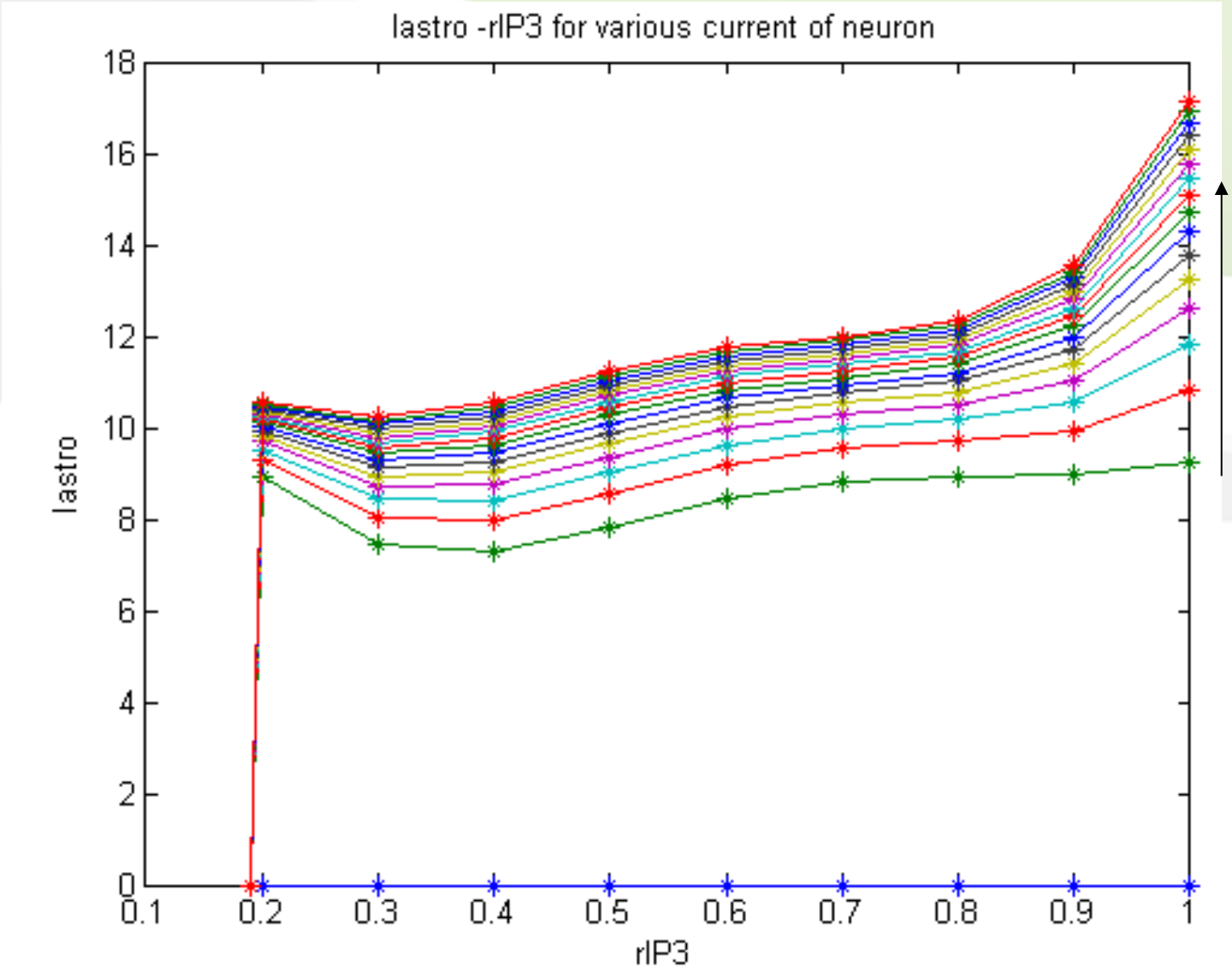


$$h_{fe} = \begin{cases} 0 & if \quad I_n \leq s_1(rIP3) \\ \phi(t - d_1(A_1))A_1(rIP3, In, s_1)\sin(h(A_1)) & if \quad s_1(rIP3) < I_n \leq s_2(rIP3) \\ \phi(t - d_2(\mathrm{I_{fin}}))\dfrac{\left[\mathrm{I_{fin}} + (\mathrm{A_2 e^{-\frac{t}{\tau}} \sin(2\pi ft)})\right]}{\mathrm{I_n}} & if \quad I_n > s_2(rIP3) \end{cases}$$

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

↓

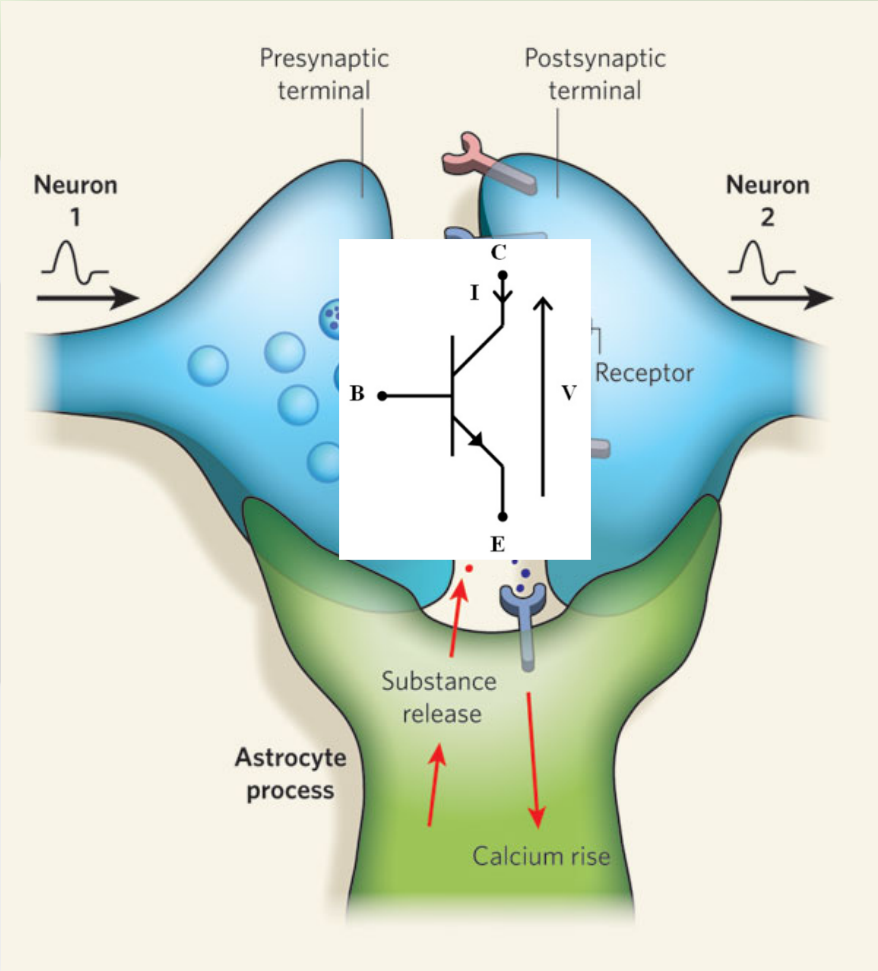
Inositol 1,4,5-trisphosphate (IP3) rate of production (rIP3)

↓

Calcium Oscillation

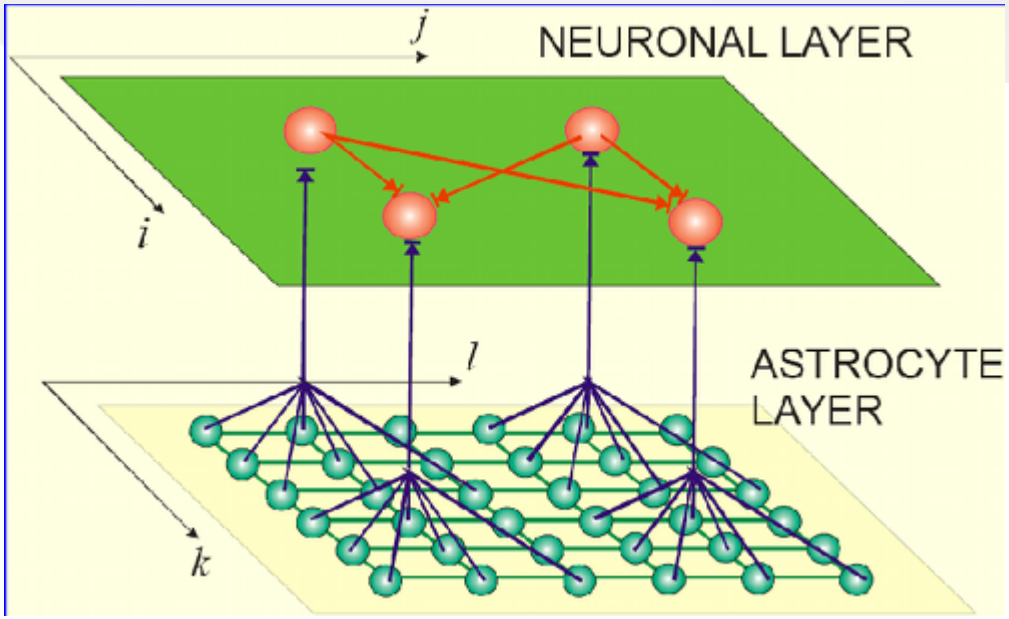
↓

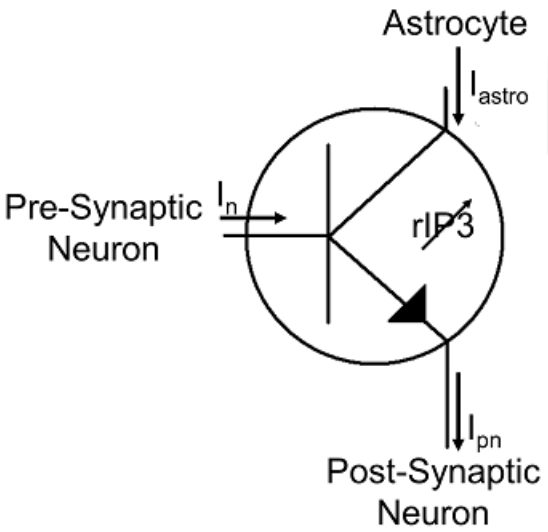
Post-synaptic Neuron



Are SNAN possible?

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



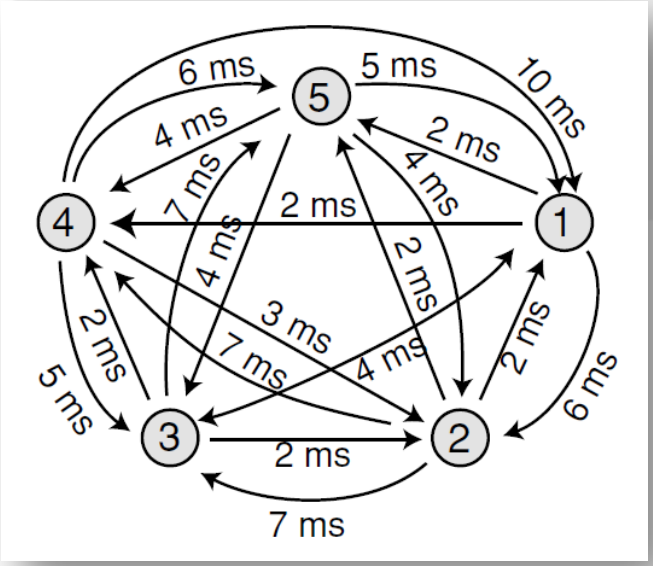


Policronization in SNN

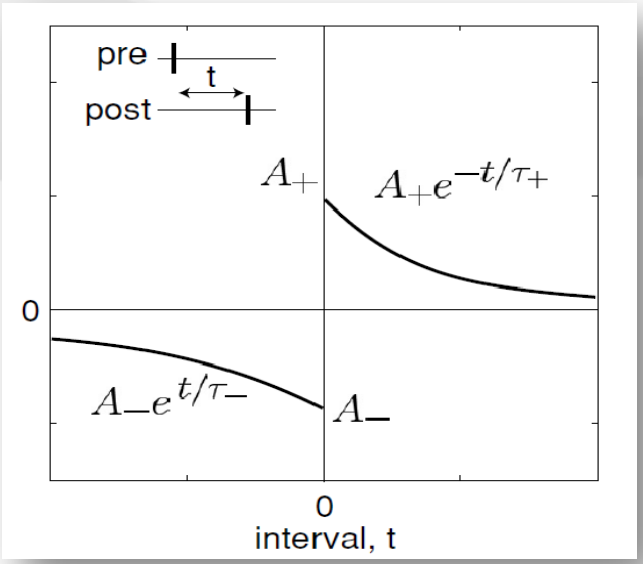
Edelman → Theory of neuronal group selection (TNGS, Neural Darwinism)

Izhikevich Network

Axonal Conduction Delays



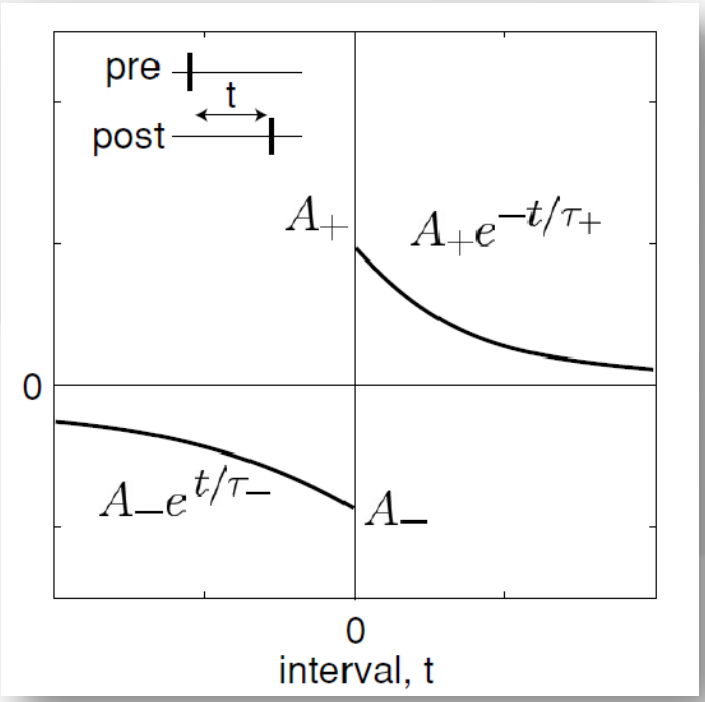
Spike-Timing-Dependent Plasticity (STDP)



Policronization

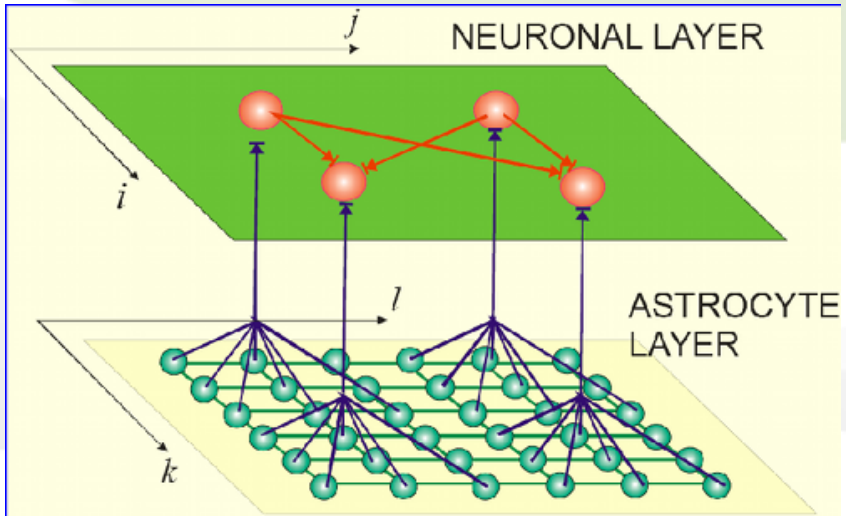
Izhikevich 2006

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

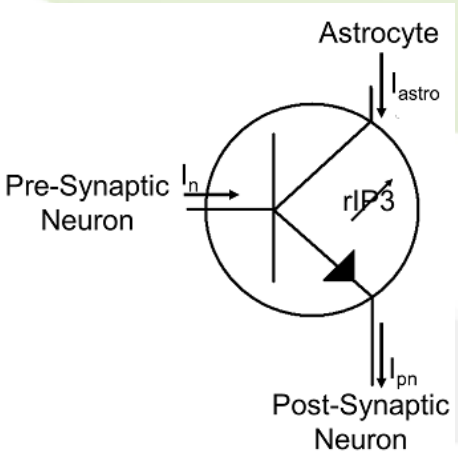
How to define a SNAN: Timing

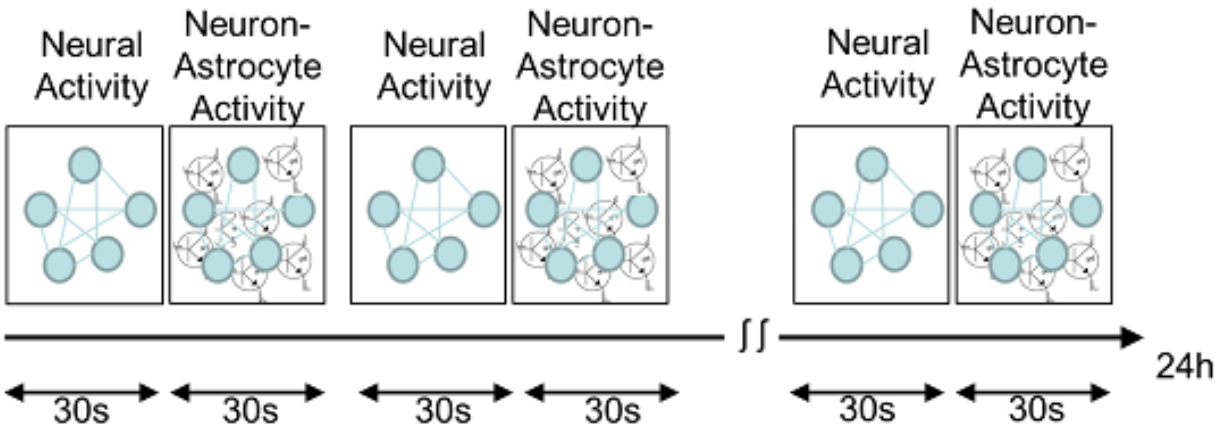
Inizialization of neurons

Neural activity only (30s)

Inizialization of astrocytes

Simultaneous Activity of Neurons and Astrocytes





Experimental results

24h simulation

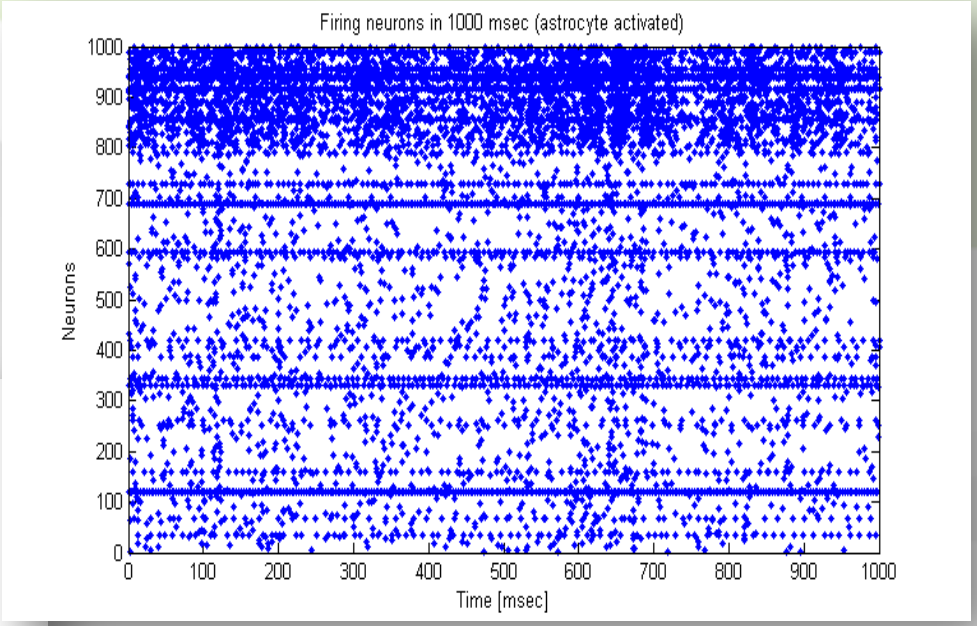
Evaluations after
- 3h
- 6h
- 12h
- 18h
- 24h

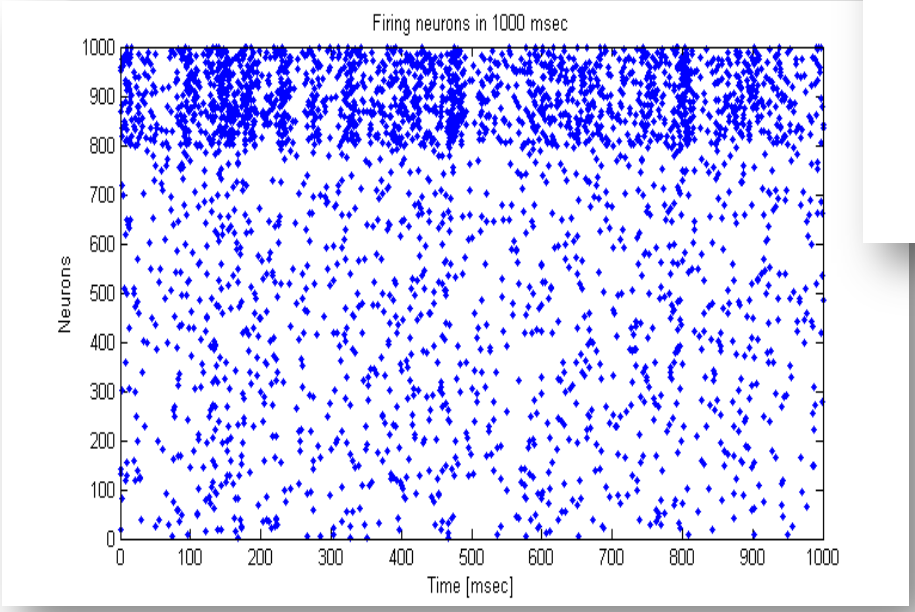
Network dimension

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.