Pierre Magistretti, MD, PhD

Food for thought : a neuroenergetic perspective on brain function

The Brain Forum
Jeddah, December 3, 2013

The brain has considerable energetic requirements

- 2% of body mass

yet

- 15% of cardiac output
- 25% of whole body glucose utilization
- 20% of oxygen consumption

ON THE REGULATION OF THE BLOOD-SUPPLY OF THE BRAIN. By C. S. ROY, M.D., F.R.S., *Professor of Pathology, University of Cambridge*, AND C. S. SHERRINGTON, M.B., M.A., *Fellow of Gonville and Caius College. Lecturer on Physiology in the School of St Thomas's Hospital, London.* Plates II., III. and IV.

From the Cambridge Pathological Laboratory.

« We conclude then that the chemical products of cerebral metabolism contained in the lymph which bathes the walls of the arterioles of the brain can cause variations of the calibre of the cerebral vessels: that in this re-action *the brain possesses an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations of functional activity.* »

In: Journal of Physiology (London) 11:85-108 (1890)

*** High relative metabolic cost**

*** Highly regulated in space and time in register with synaptic activity**

------> Functional brain imaging

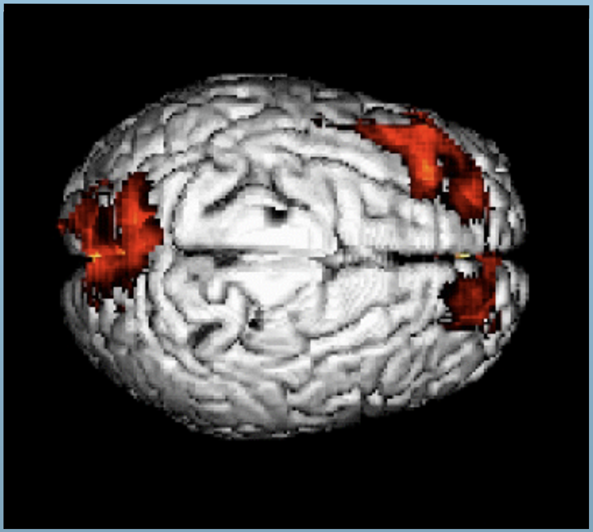
Techniques for functional brain imaging

Positron Emission Tomography (*PET*):

^{18}F-deoxyglucose
$^{15}O_2$
$H_2{}^{15}O_2$

Functional MRI (fMRI):

change in the ratio of oxy-/deoxy hemoglobin



They detect signals related to energy consumption and production,

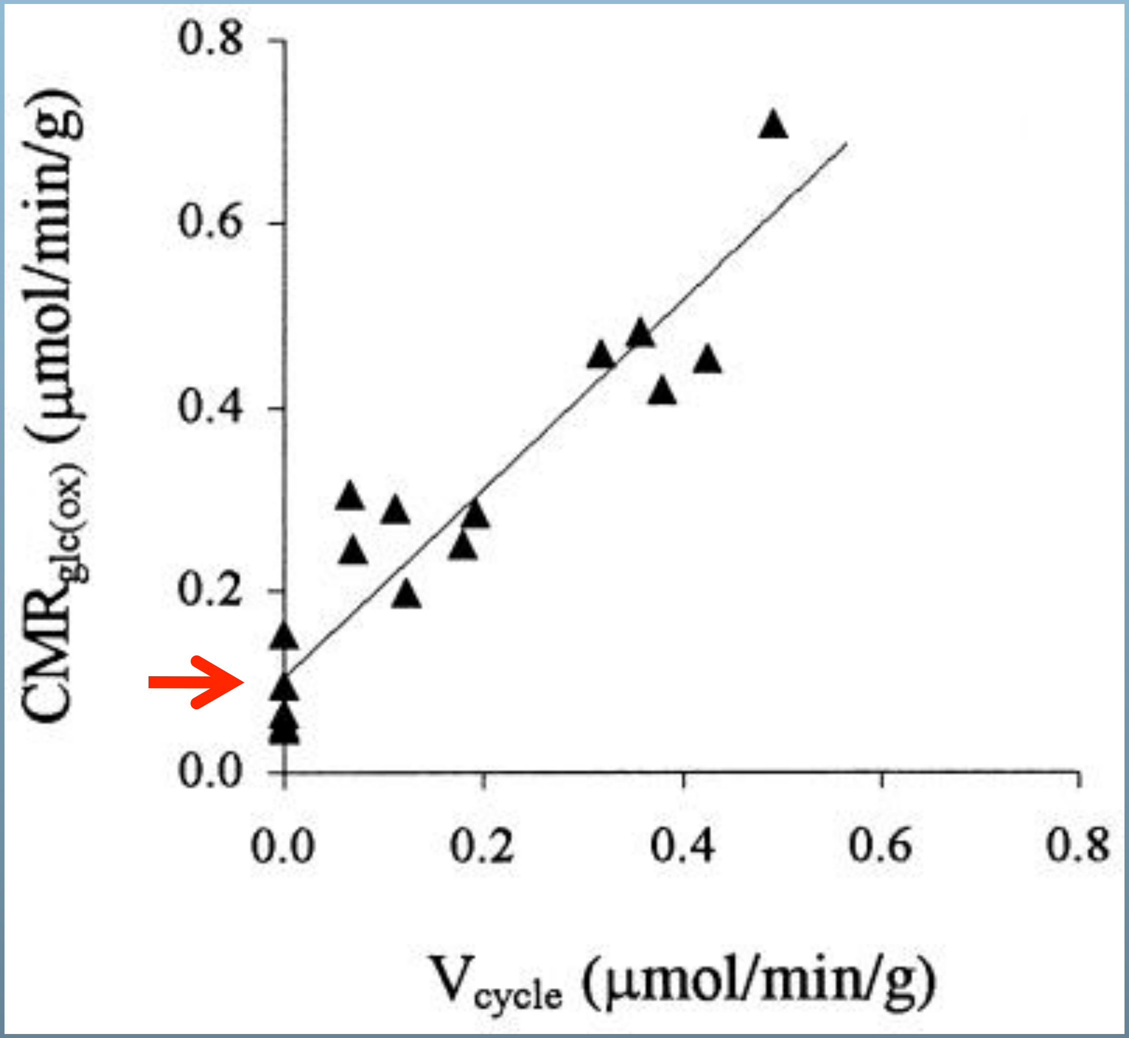
neuroenergetics

Neuroenergetics

- **What costs energy ?**

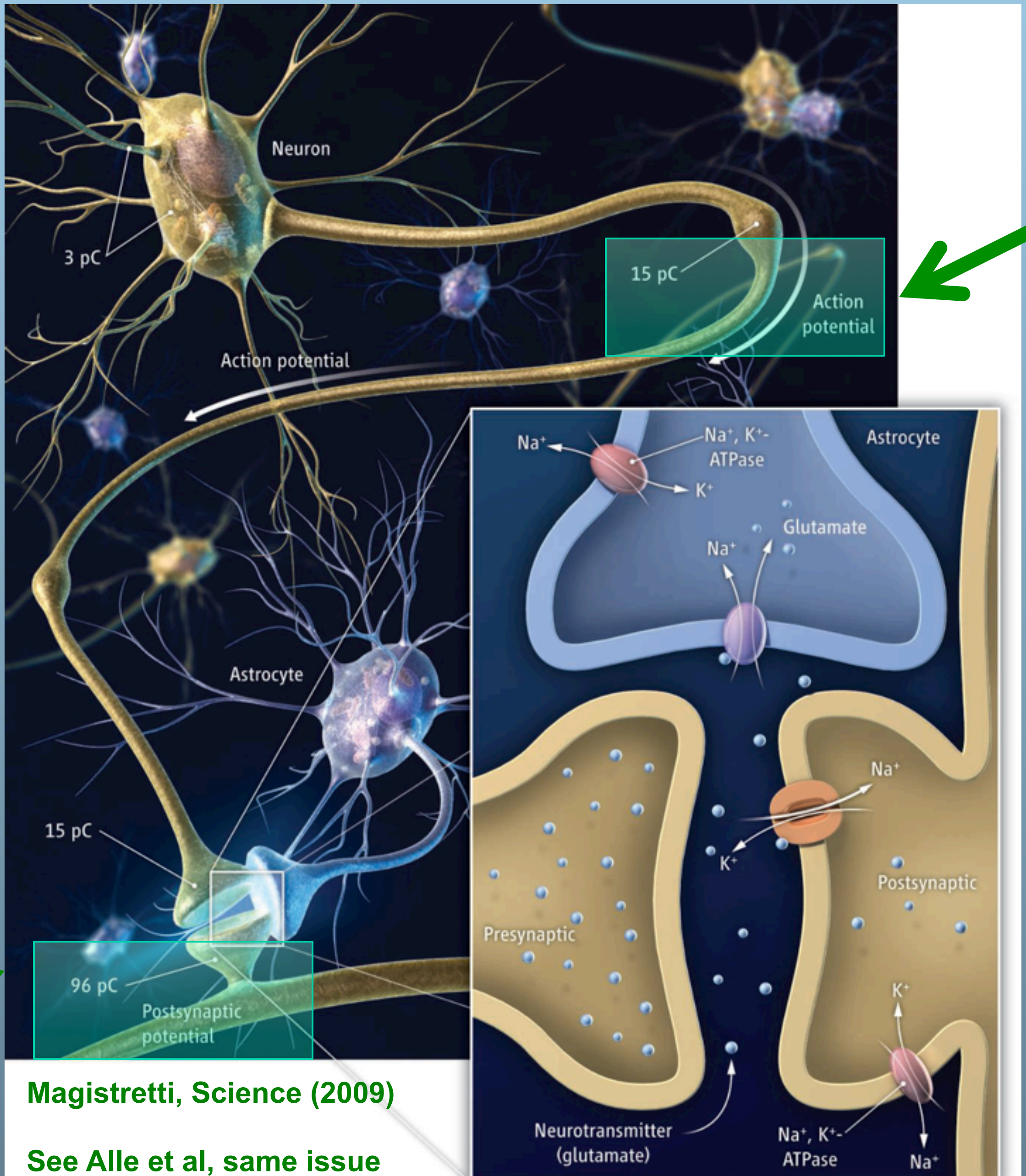
- **How is energy delivered and produced ?**

Linear relationship between glutamatergic neurotransmission and glucose utilization (in vivo MRS)



Sibson et al, 1998

Energetic cost of signaling in neurons



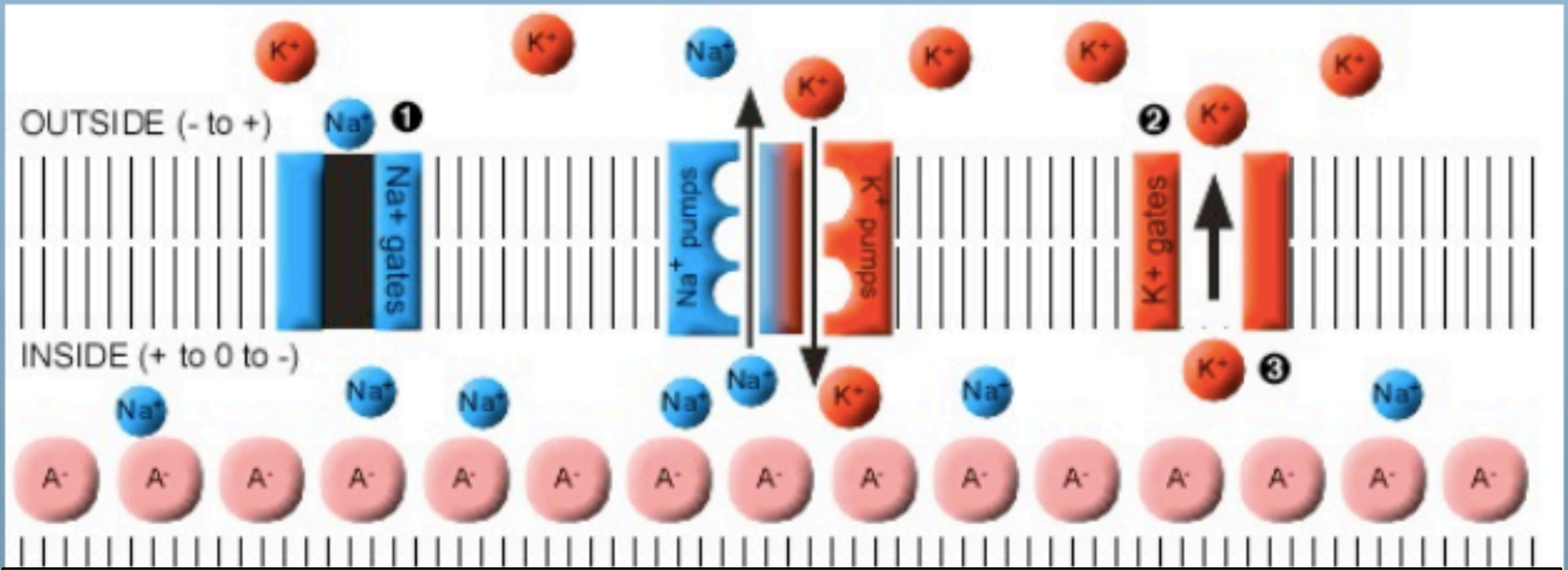
AP ≈ 20%

EPSP ≈ 80%

Magistretti, Science (2009)

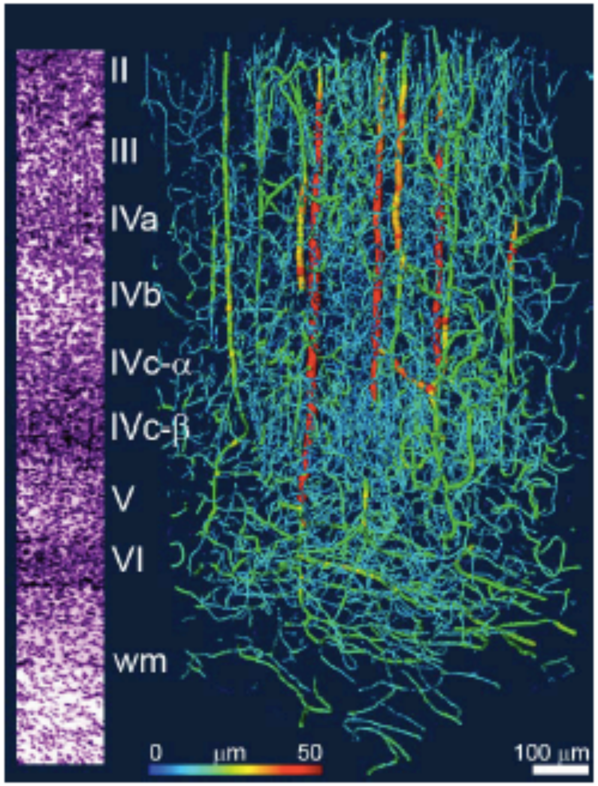
See Alle et al, same issue

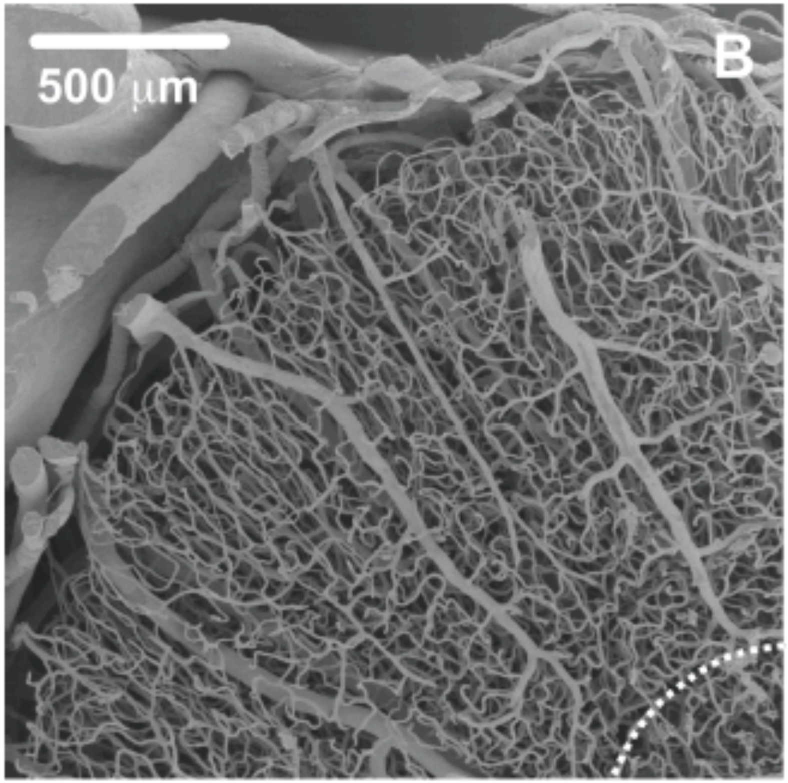
he energy is used to restore the distribution of charge "recharge the batteries "



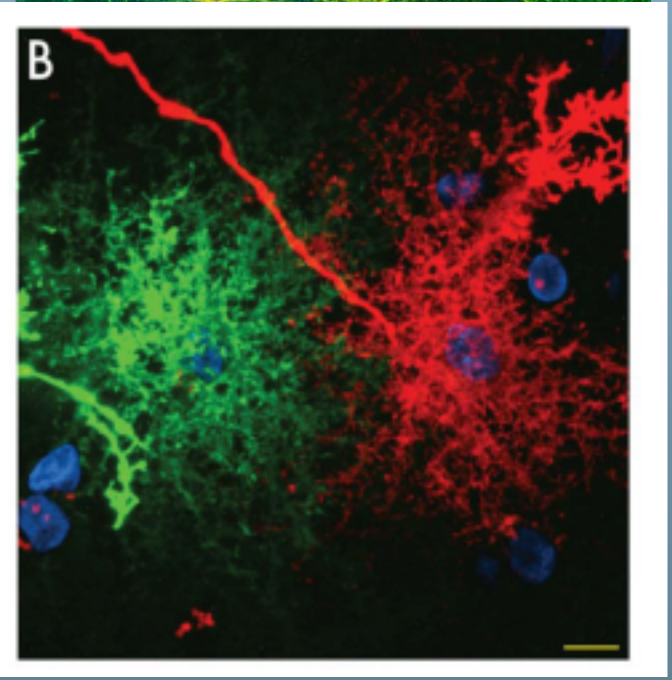
Neuroenergetics

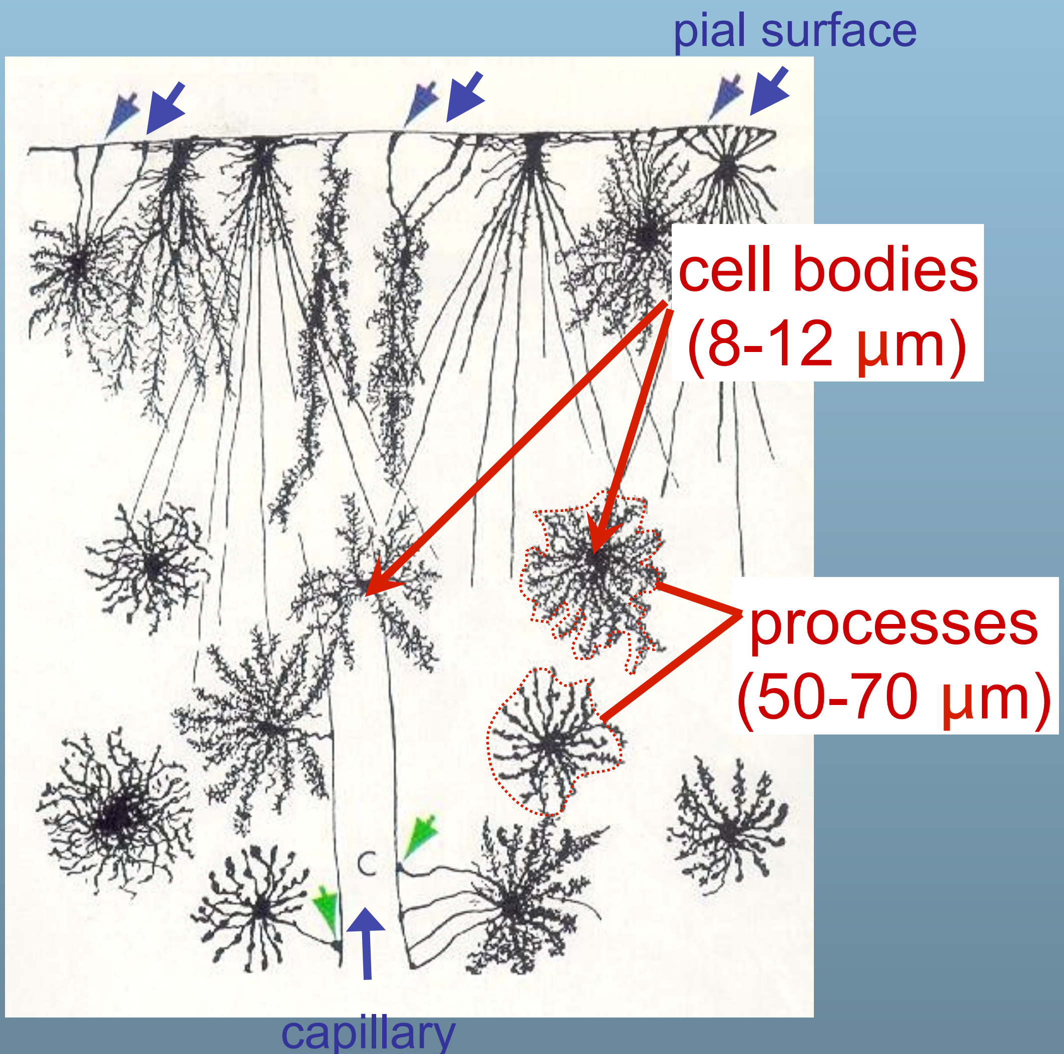
- What costs energy ?
- **How is energy delivered and produced ?**

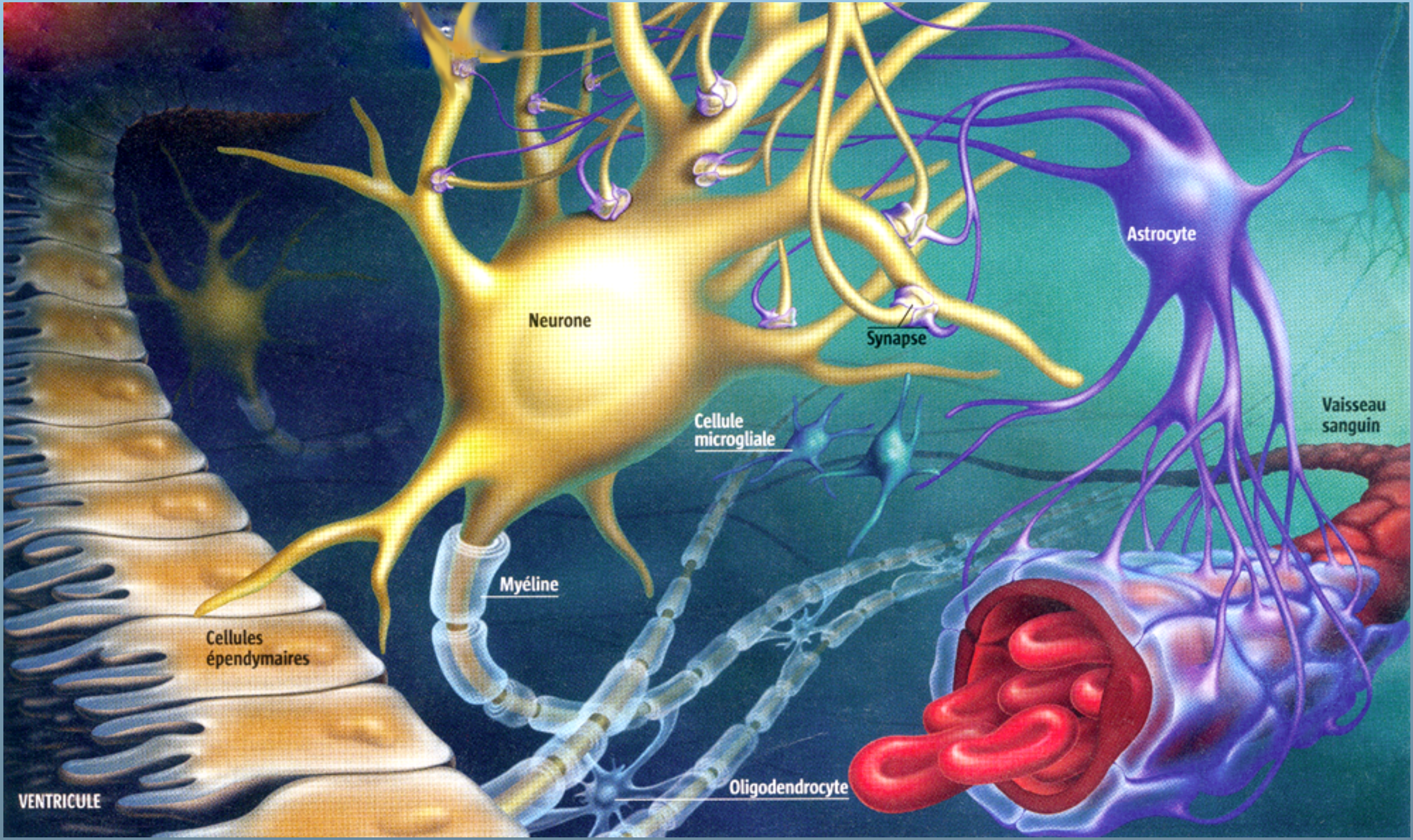

II
III
IVa
IVb
IVc-α
IVc-β
V
VI
wm
0 µm 50
100 µm


500 µm
B

Astrocytes


B


pial surface
cell bodies
(8-12 µm)
processes
(50-70 µm)
C
capillary



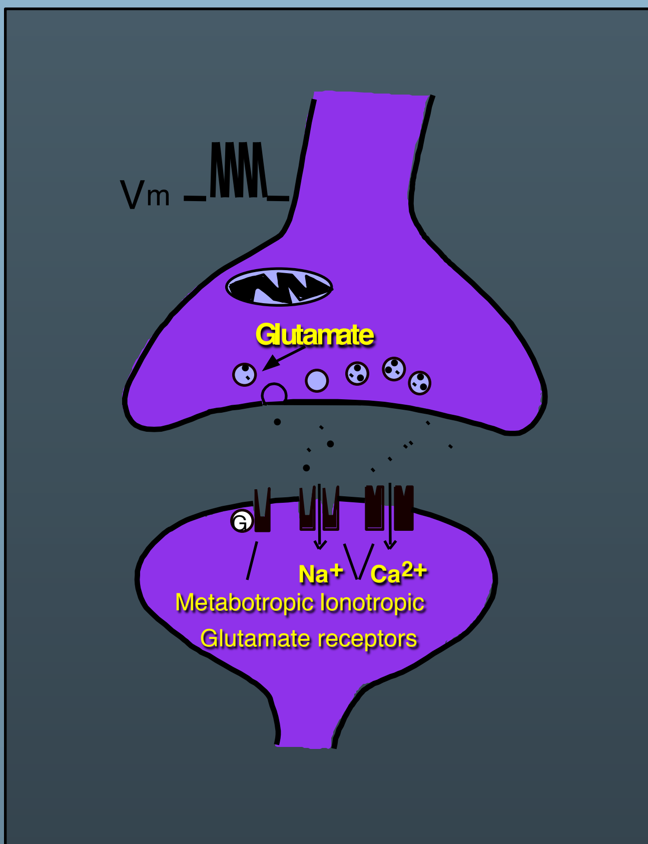
from F. Pfrieger and C. Steinmetz, La recherche, 2003 (361)

Which are the cellular and molecular mechanisms that underlie the coupling of synaptic activity with metabolic and vascular responses ?

NEURONAL ACTIVITY

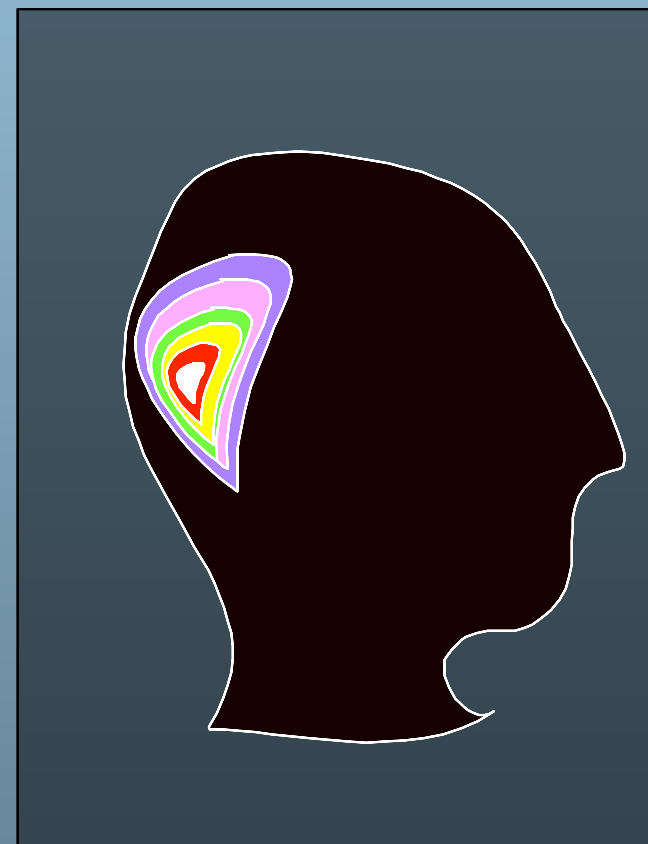
METABOLIC AND VASCULAR RESPONSES

FUNCTIONAL BRAIN IMAGING

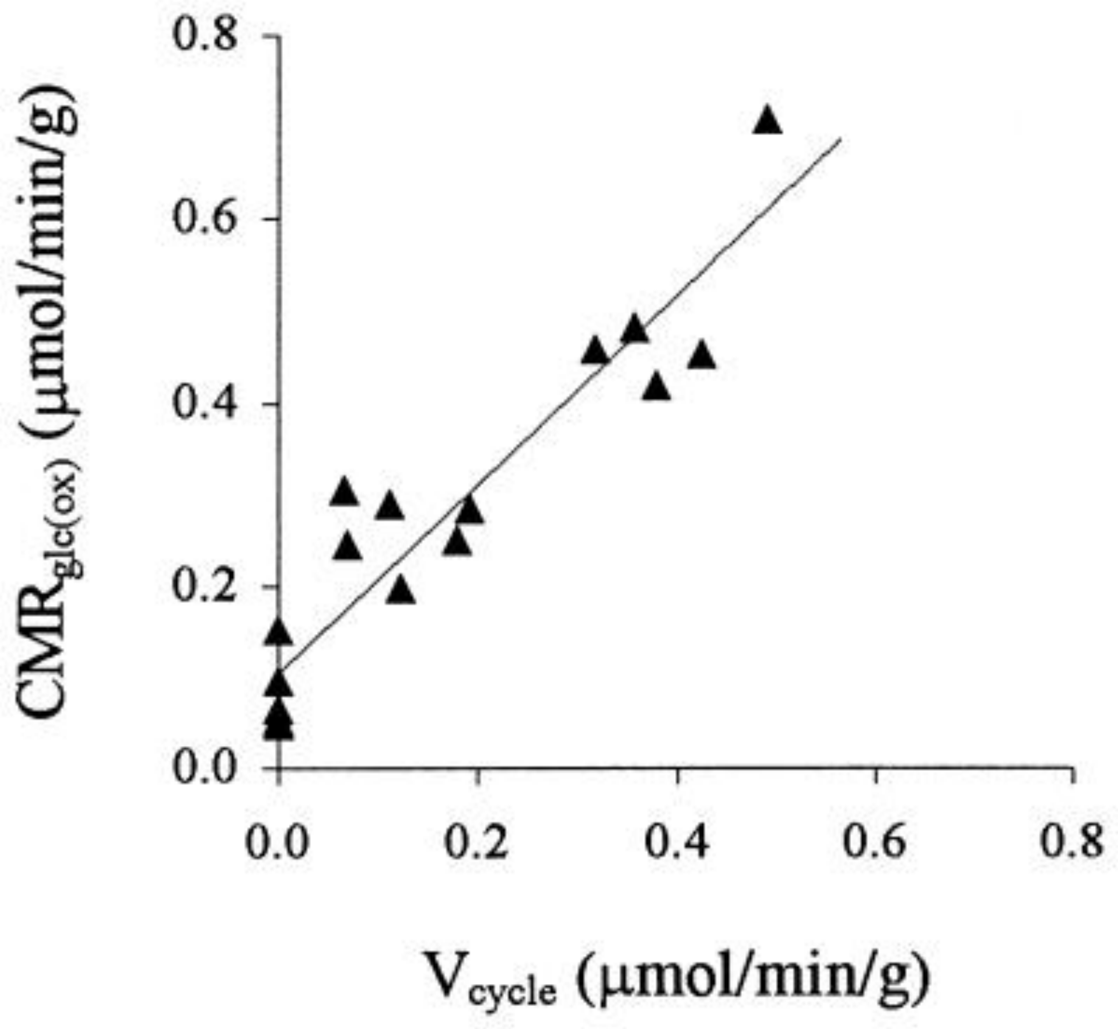


"Coupling"

?

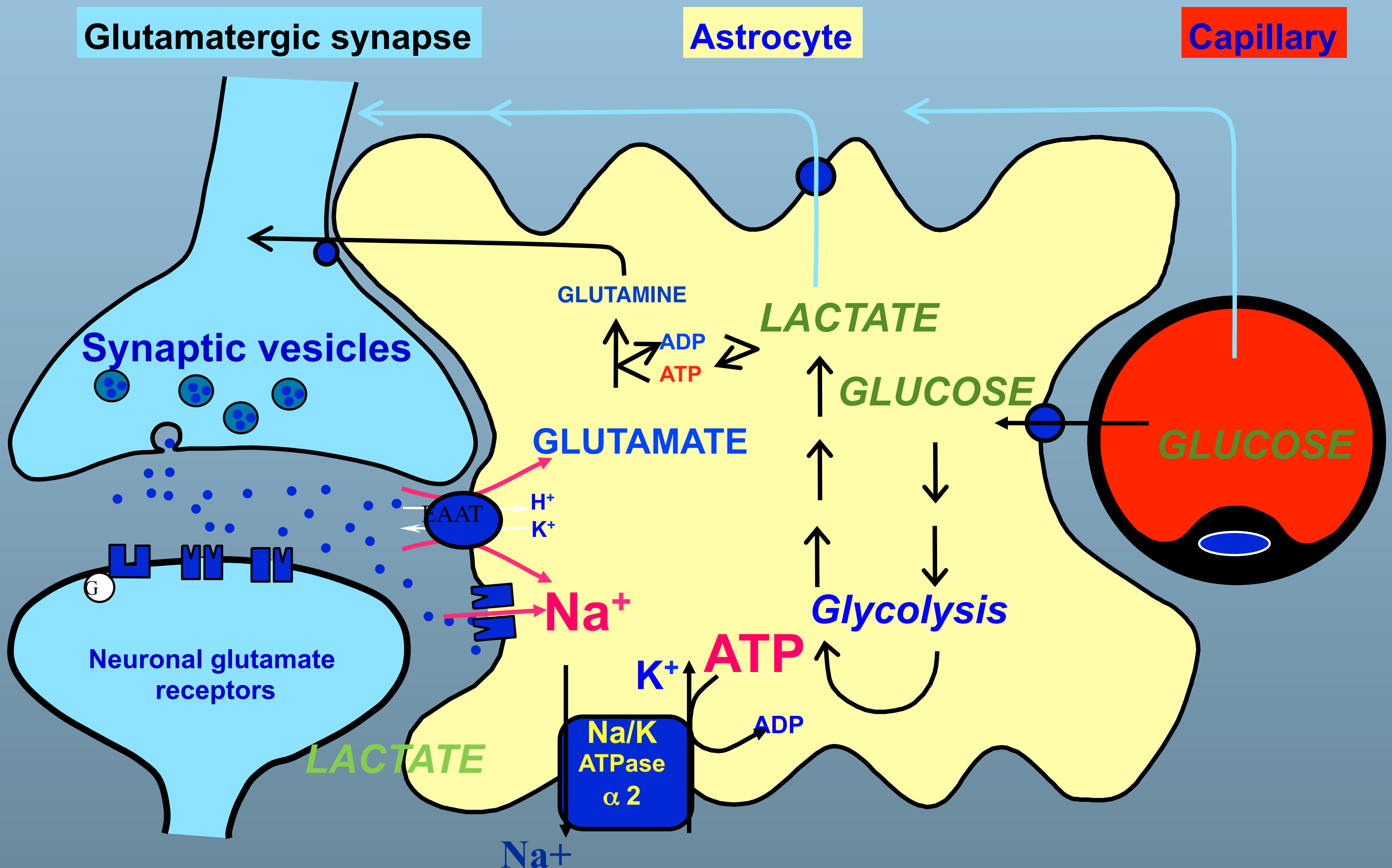


Linear relationship between glutamatergic neurotransmission and glucose utilization (in vivo MRS)



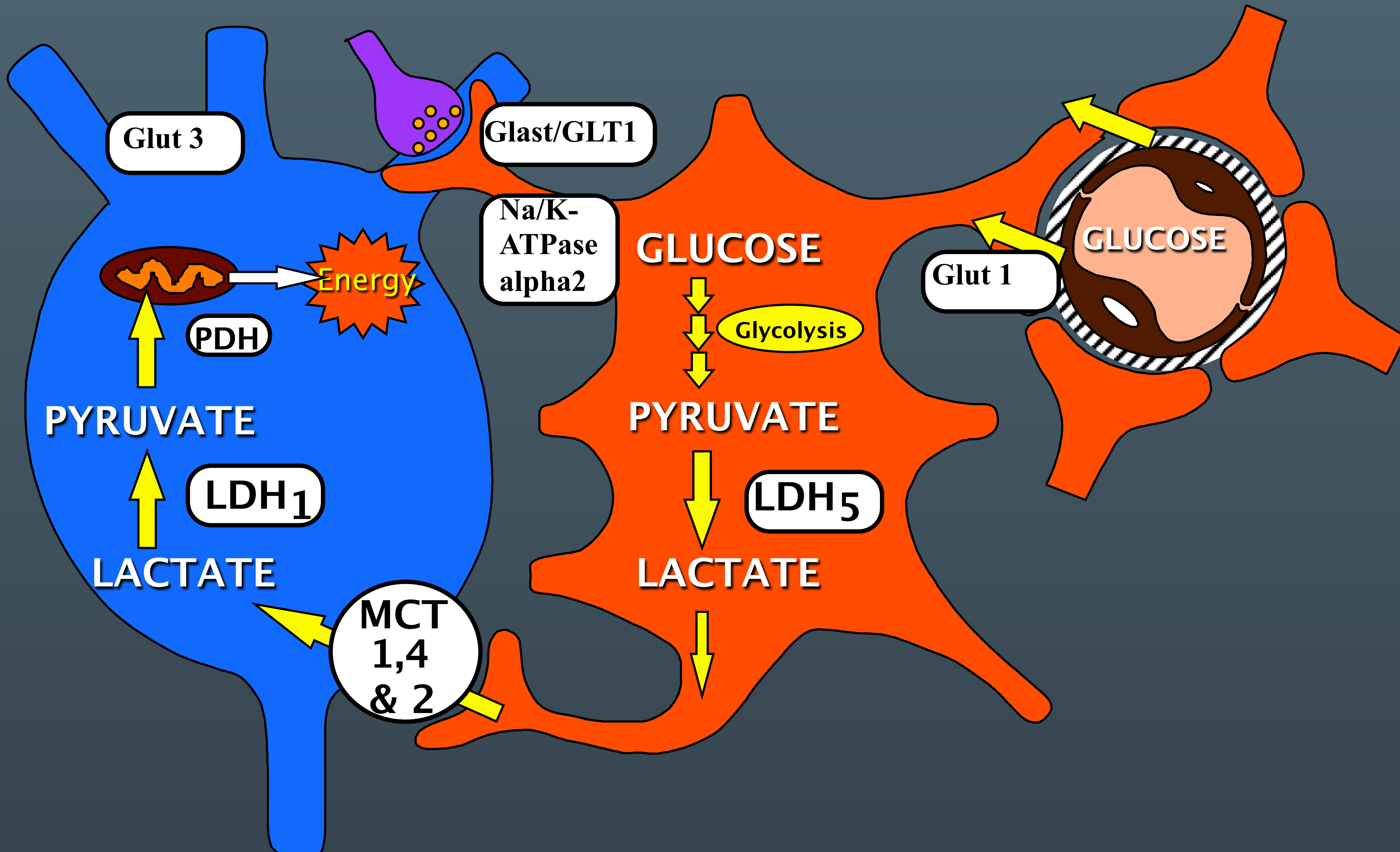
Sibson et al, 1998

Mechanism for Coupling Neuronal Activity to Glucose Utilization



Reviewed in Magistretti et al 1999;
Magistretti 2006

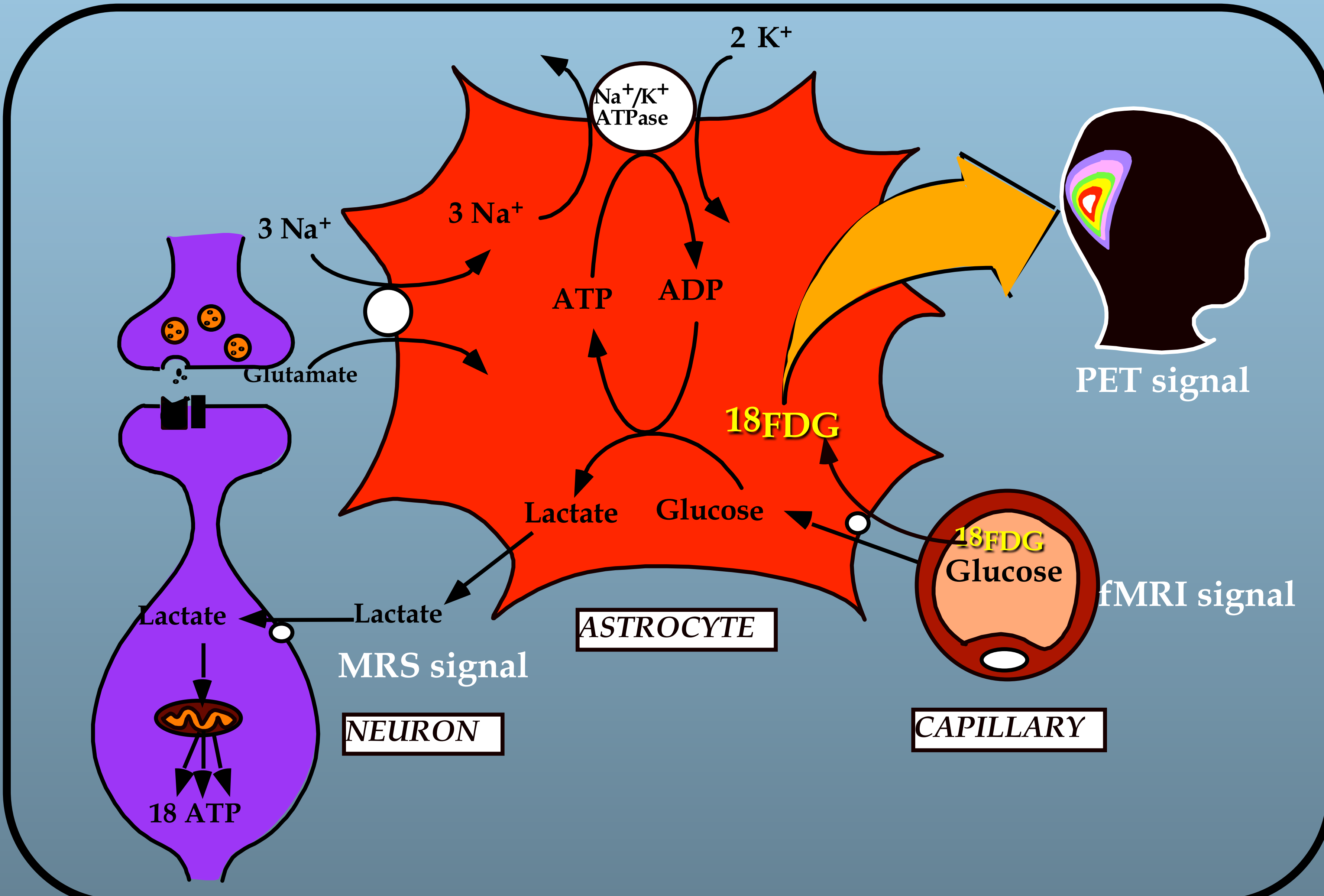
ASTROCYTE-NEURON LACTATE SHUTTLE (ANLS)



Neurons are mainly oxidative

Astrocytes are mainly glycolytic

ROLE OF ASTROCYTES IN BRAIN IMAGING SIGNALS



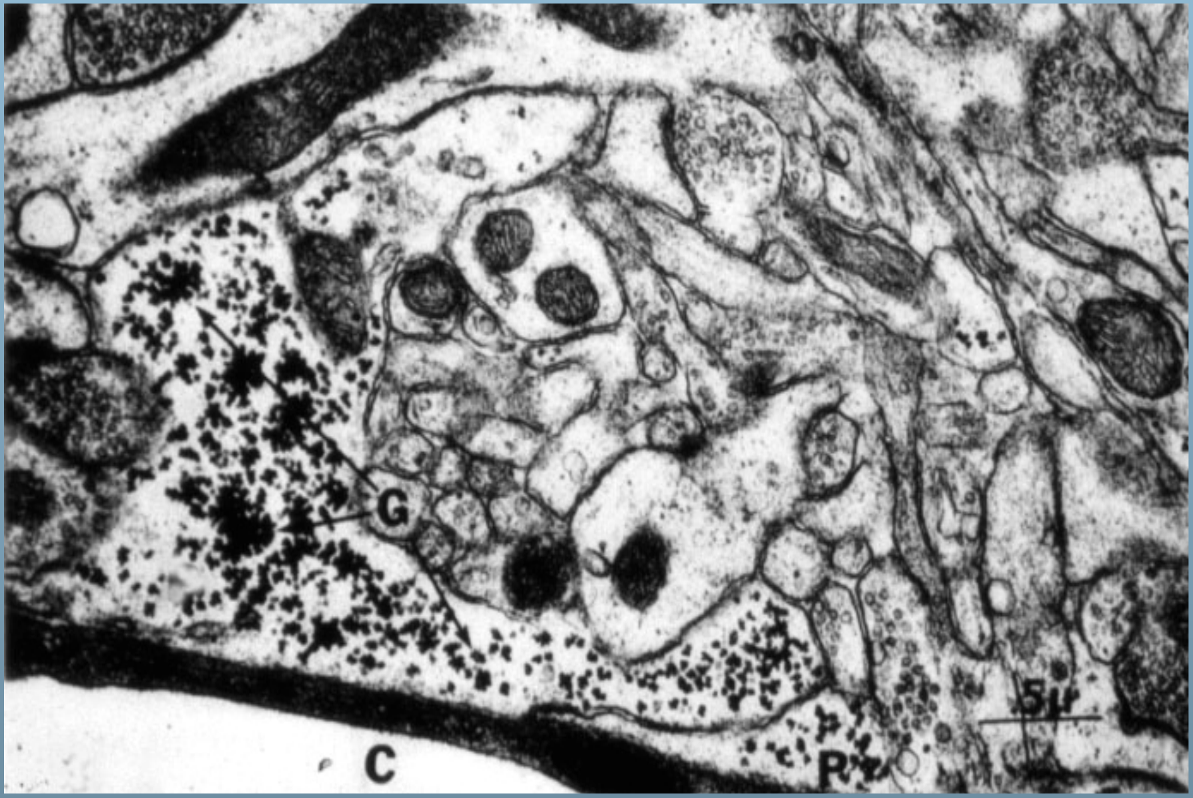
Neuroenergetics

- What costs energy ?

- How is energy delivered and produced ?

➢ Energy can also be stored and mobilized when necessary

Glycogen is exclusively localized in astrocytes



NA and VIP circuits II

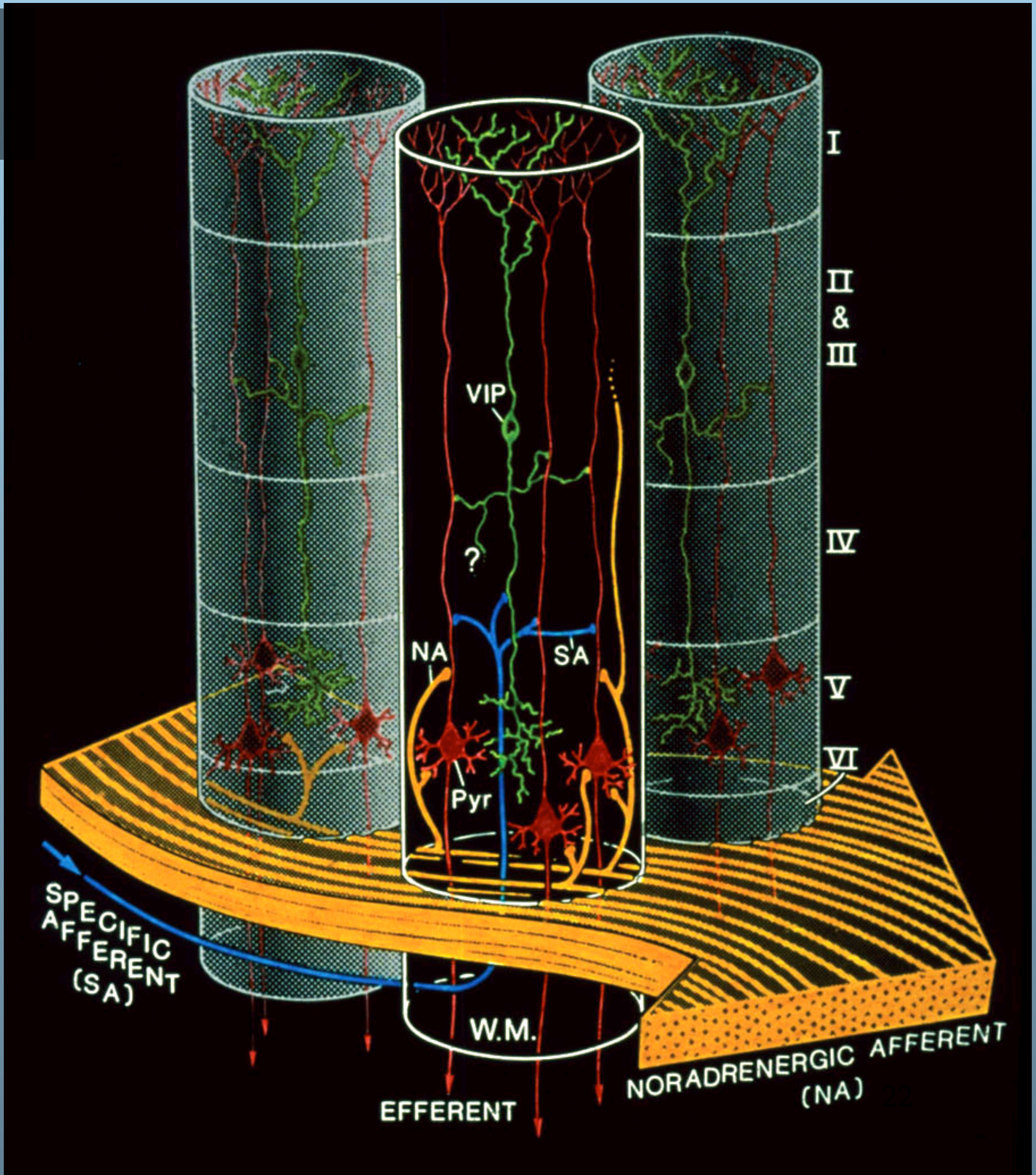
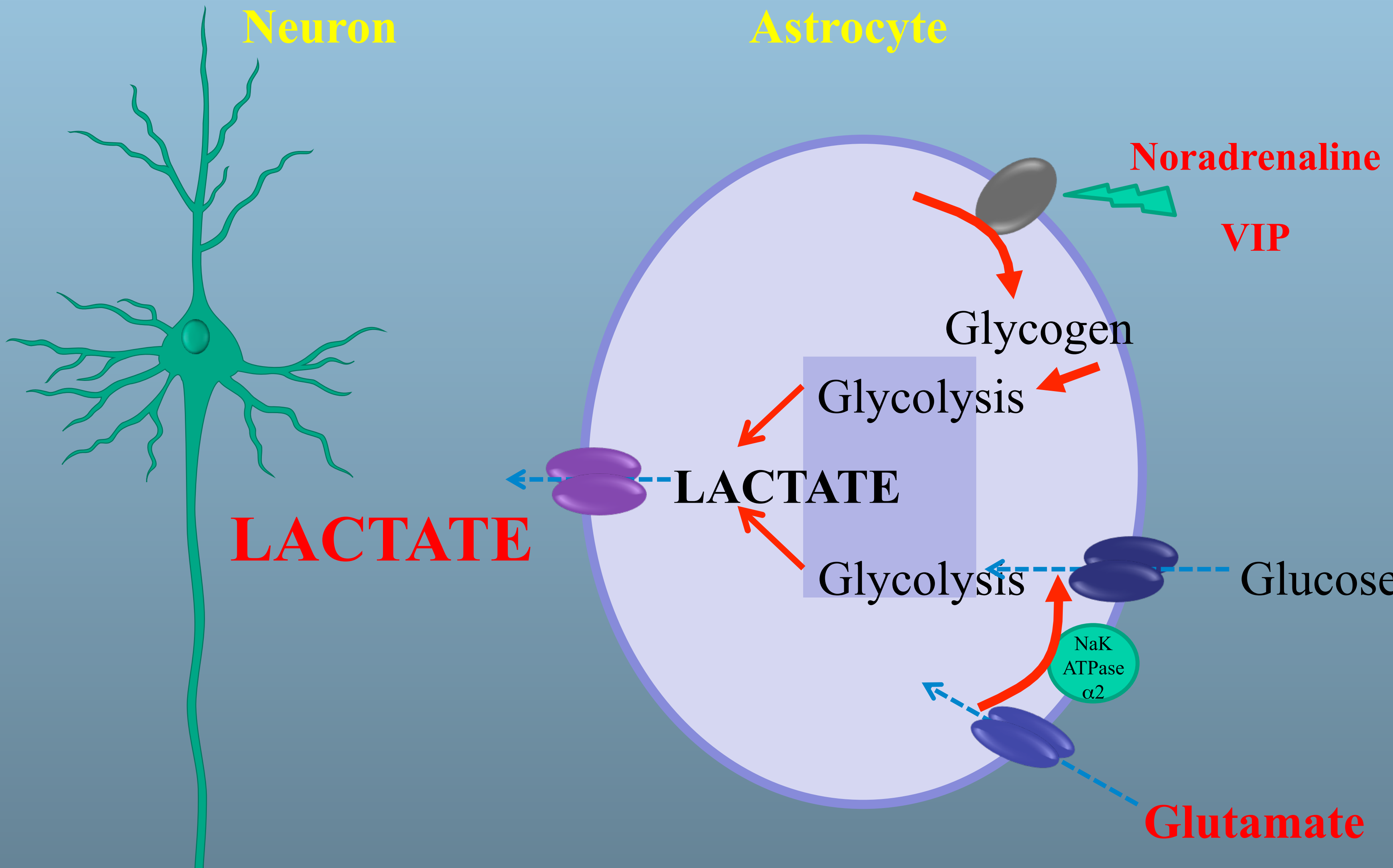


Illustration by Jamie Simon


Neuron
Astrocyte
Noradrenaline
VIP
Glycogen
Glycolysis
LACTATE
LACTATE
Glycolysis
Glucose
NaK
ATPase
α2
Glutamate

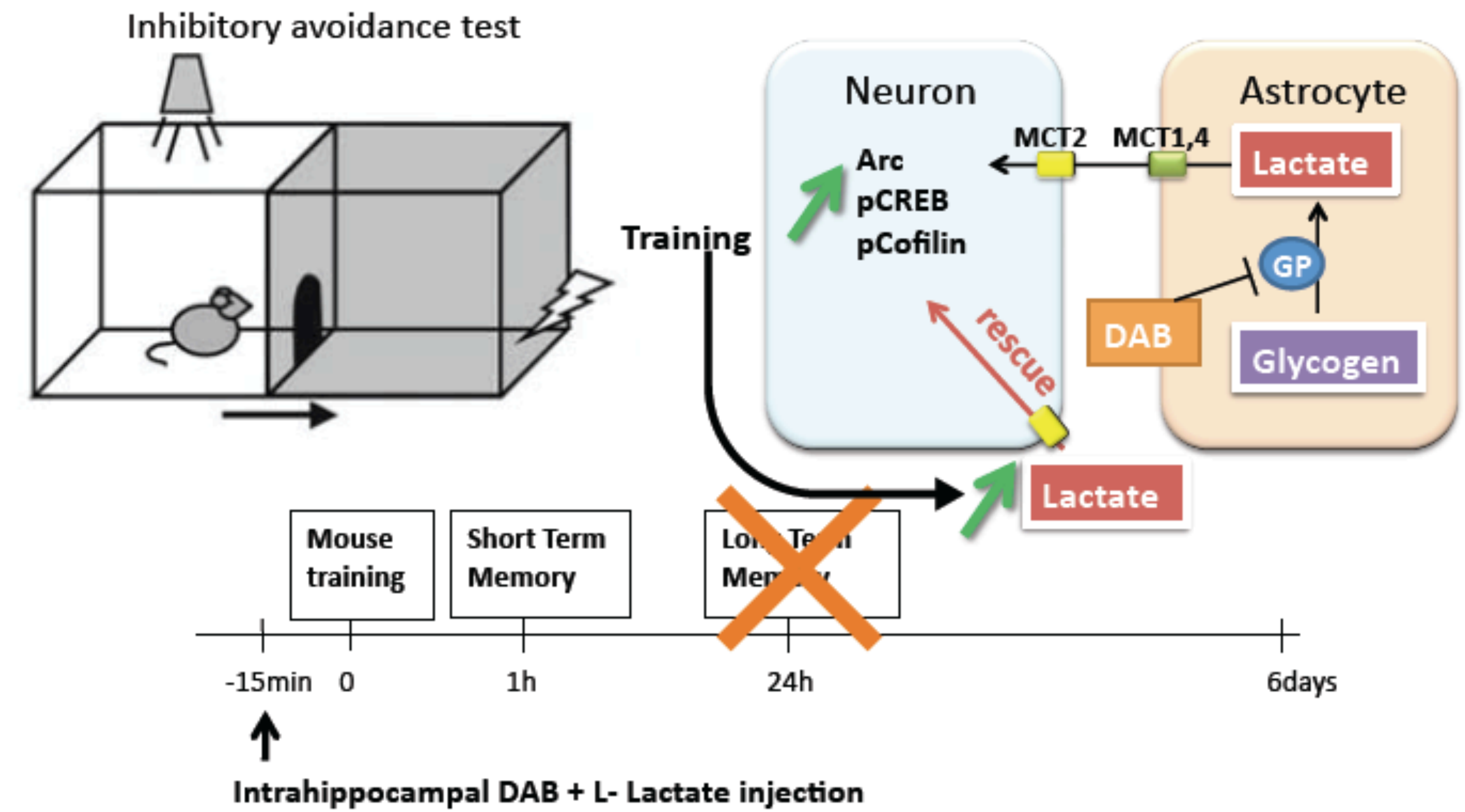
Neuroenergetics

Energy can signal information

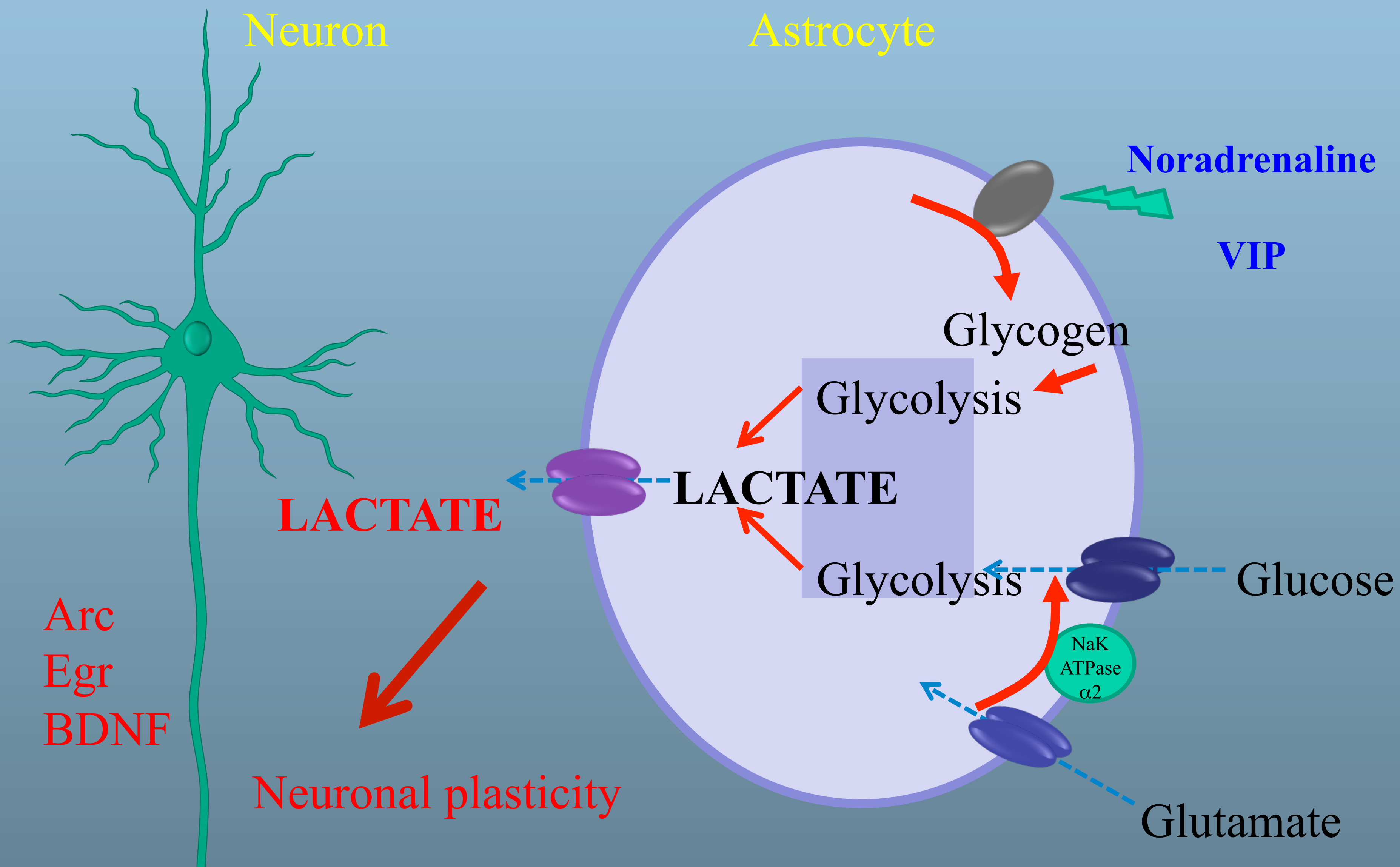

Cell

Astrocyte-Neuron Lactate Transport Is Required for Long-Term Memory Formation

Akinobu Suzuki,[1] Sarah A. Stern,[1,6] Ozlem Bozdagi,[1,2,6] George W. Huntley,[1] Ruth H. Walker,[3,4] Pierre J. Magistretti,[5,*] and Cristina M. Alberini[1,2,*]



Inhibitory avoidance test
Training
Neuron
Arc
pCREB
pCofilin
MCT2
MCT1,4
Astrocyte
Lactate
GP
DAB
Glycogen
rescue
Lactate
Mouse training
Short Term Memory
Long Term Memory
-15min
0
1h
24h
6days
Intrahippocampal DAB + L- Lactate injection



Neuron
Astrocyte
Noradrenaline
VIP
Glycogen
Glycolysis
LACTATE
Glycolysis
Glucose
NaK
ATPase
α2
Glutamate
LACTATE
Arc
Egr
BDNF
Neuronal plasticity

Differential gene expression analysis

47 differentialy expressed transcripts are selected using the following cutoff

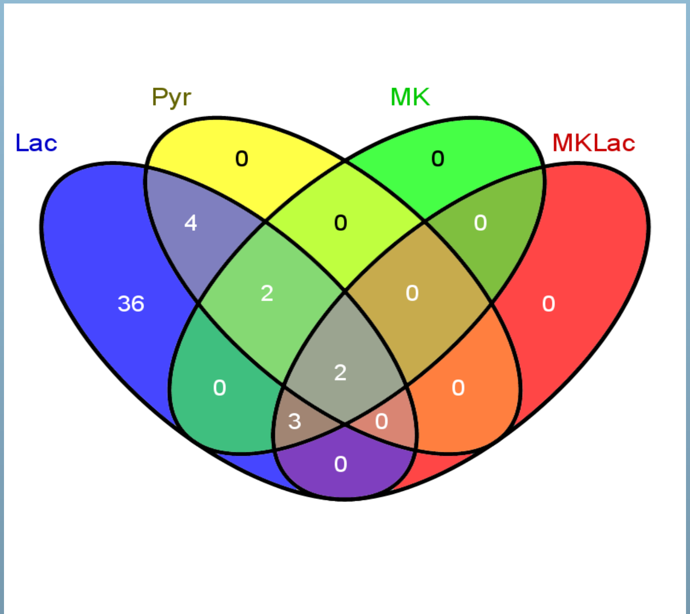
1. Average Fold change between control and Treatment >2

2. Fold change in each Treatment replicate >= average fold change of three Treatment replicates

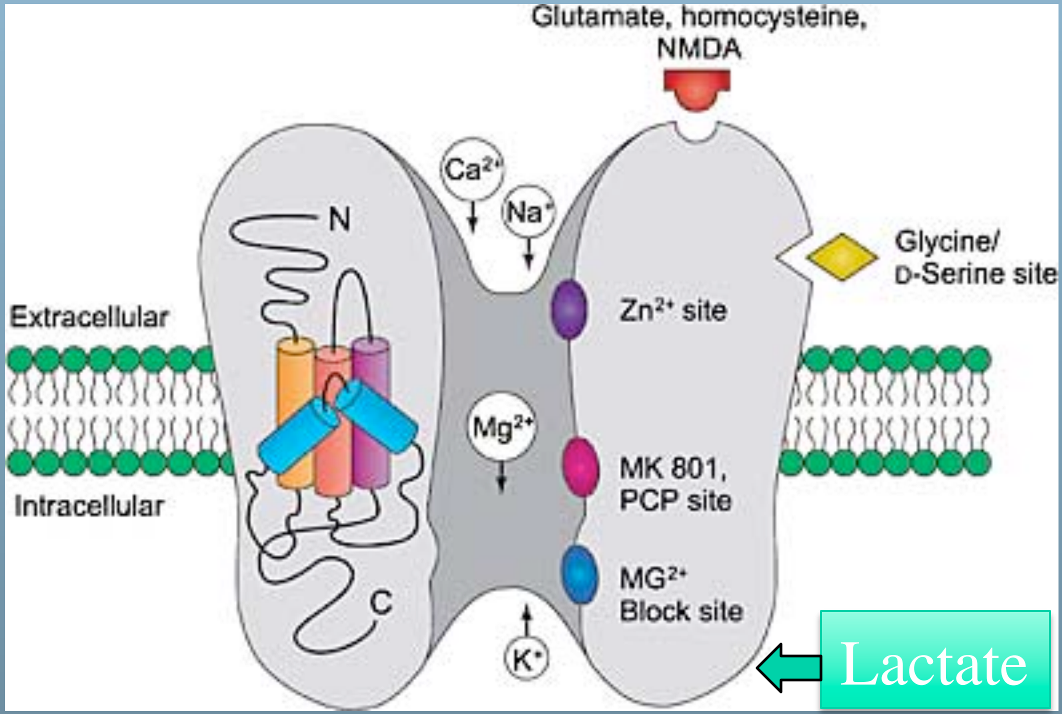
AvgFC=FC(Lac1-Lac2)+FC(Lac1-Lac3)+FC(Lac2-Lac3)/3

FC (Lac1-Lac2) >=AvgFC
FC (Lac1-Lac3) >=AvgFC
FC (Lac2-Lac3) >=AvgFC

3. P value <=0.02 (2% chance could be false positive)



NMDA Receptor



Lactate

An energy substrate, Lactate, acts also as an information signalling molecule.

> The same molecule provides energy and information.

Neuroenergetics and brain function

What is next ?

- **Modeling**
- **New imaging modalities**
- **Nanotechnologies for *in vivo* chemical detection**

Neuroenergetics and brain function

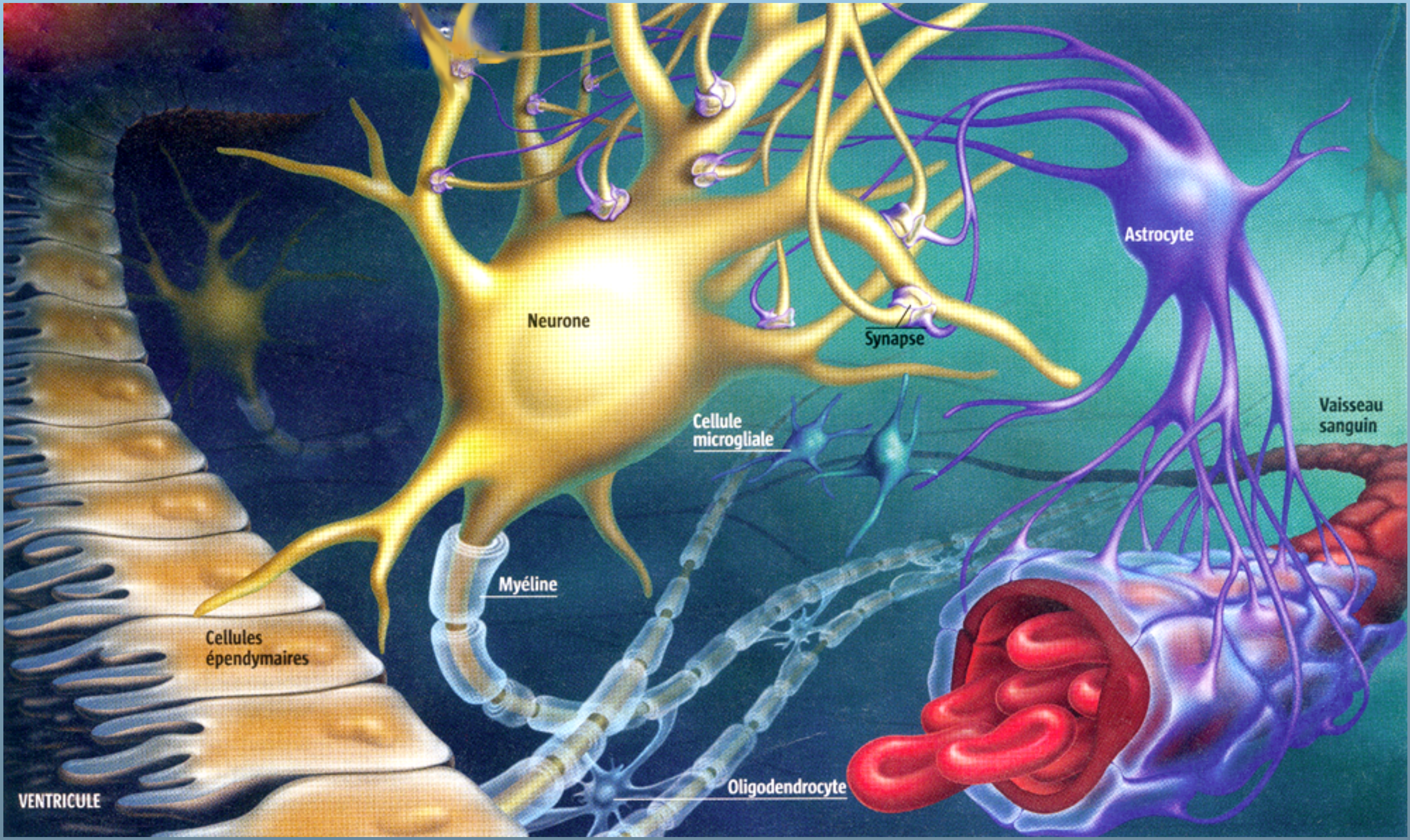
- **Modeling**

The KAUST-EPFL-HBP project on

Neuron-glia-vasculature (NGV) modeling and visualization

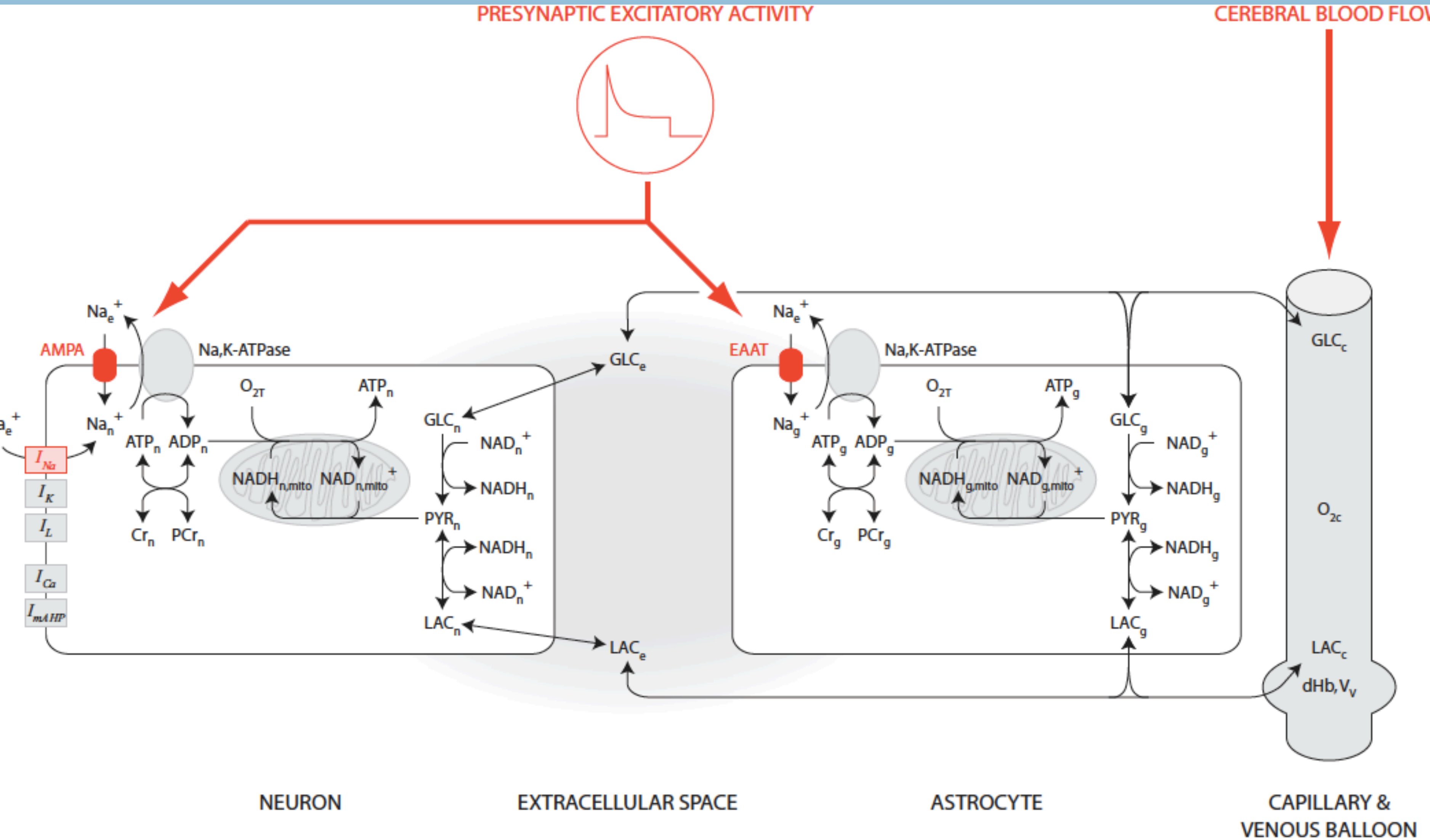
Henry Markram, Felix Schürmann, EPFL

Heikki Lehvaslaio, Madhu Srinivasan, Corrado Cali, KAUST



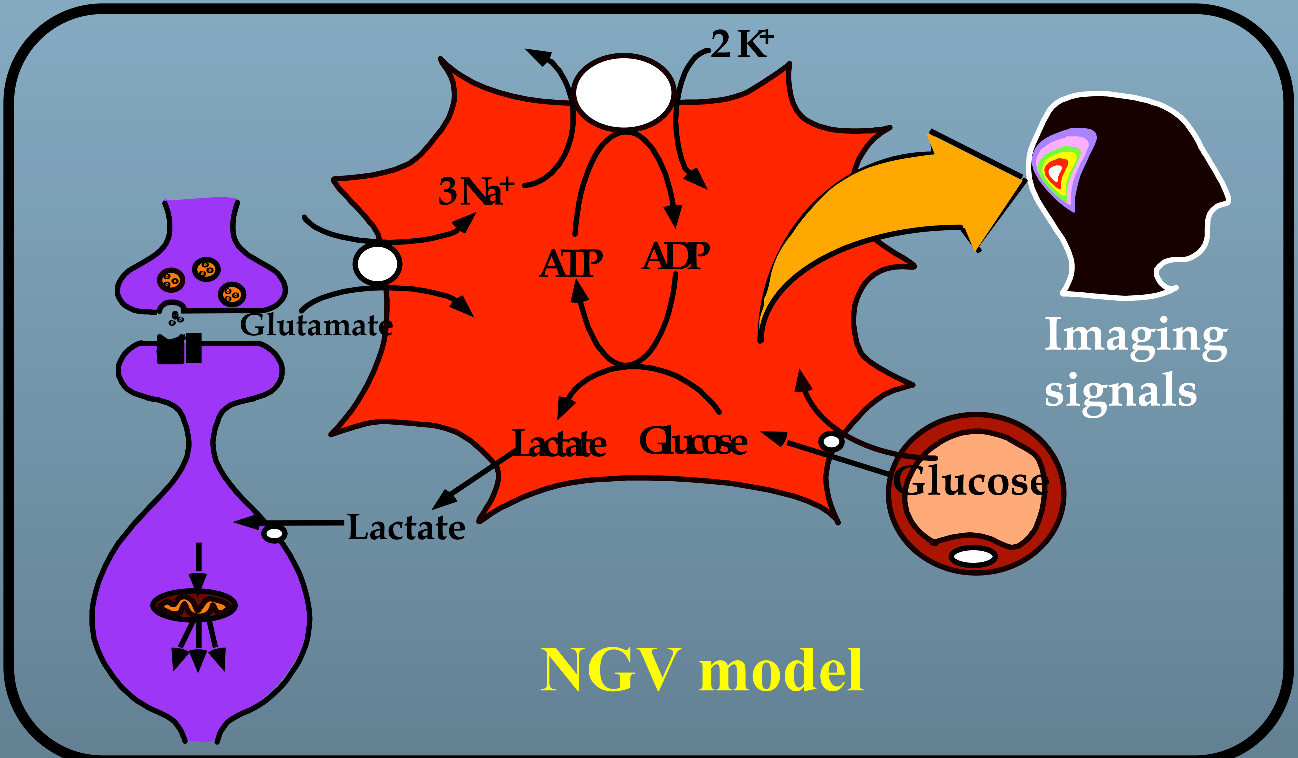
from F. Pfrieger and C. Steinmetz, La recherche, 2003 (361)

KAUST – EPFL MODELING OF NGV



In-silico imaging and visualization

- ✓Data: **Pattern extraction & rules derivation**
- ✓Building: **Constraint-based programming**
- ✓Simulation: **Multi-scale engines**
- ✓Visualization: **Visual supercomputing**
- ✓Analysis: **Interactive supercomputing**
- ✓**Virtualization:** **In-silico biology**



Neuroenergetics and brain function

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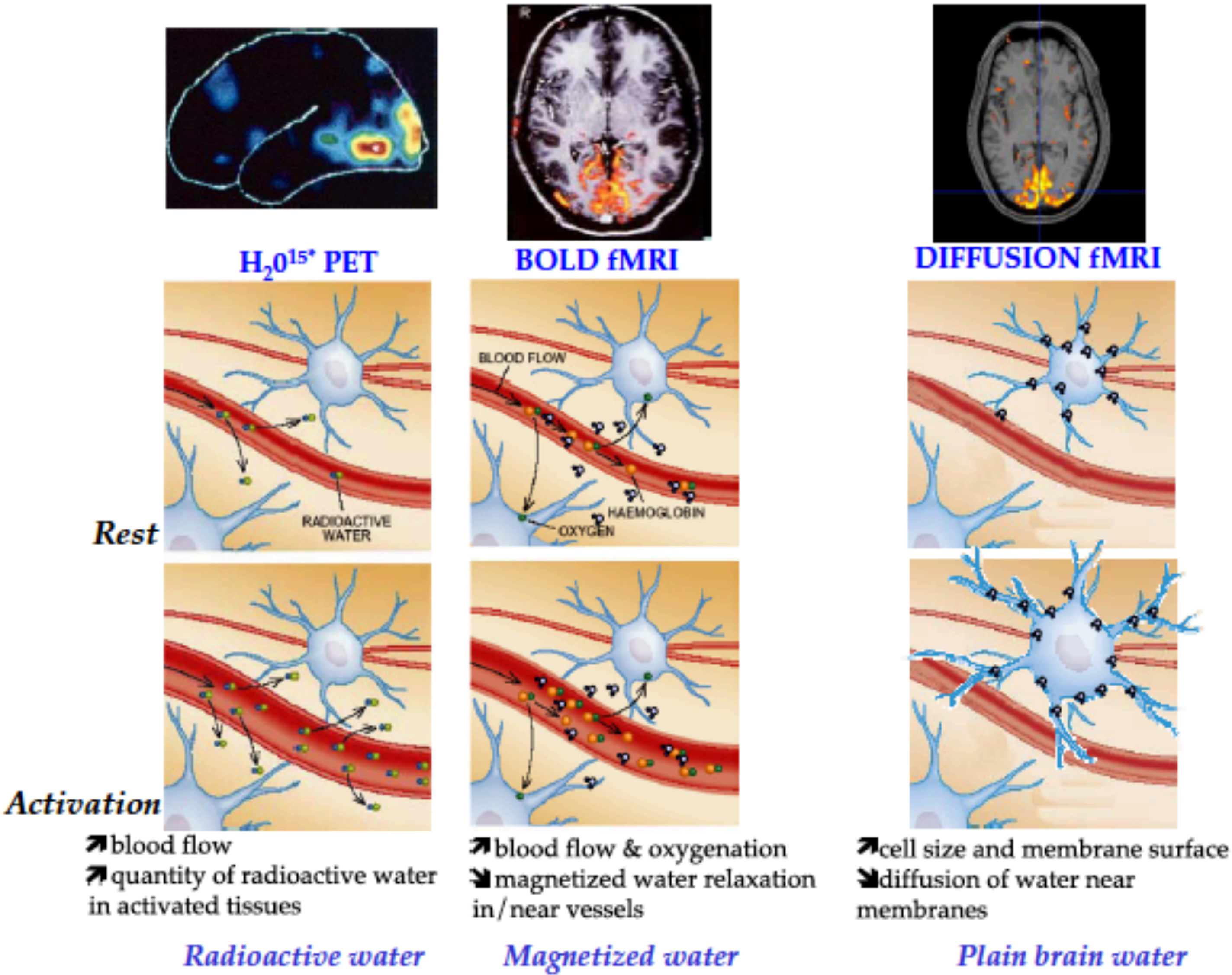
- **Nanotechnologies for *in vivo* chemical detection**

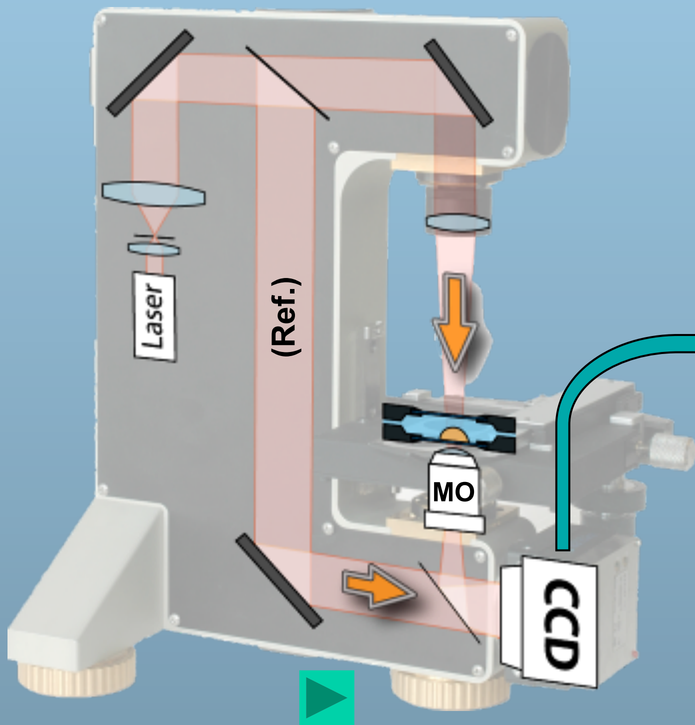
Water diffusion in brain cortex closely tracks underlying neuronal activity

Tomokazu Tsurugizawa, Luisa Ciobanu, and Denis Le Bihan[1]

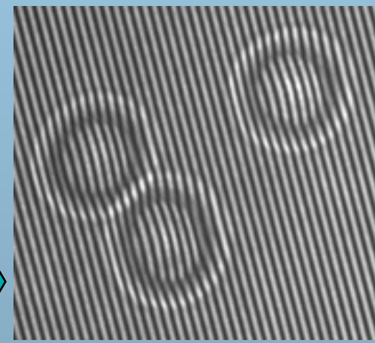
11636–11641 | PNAS | July 9, 2013 | vol. 110 | no. 28



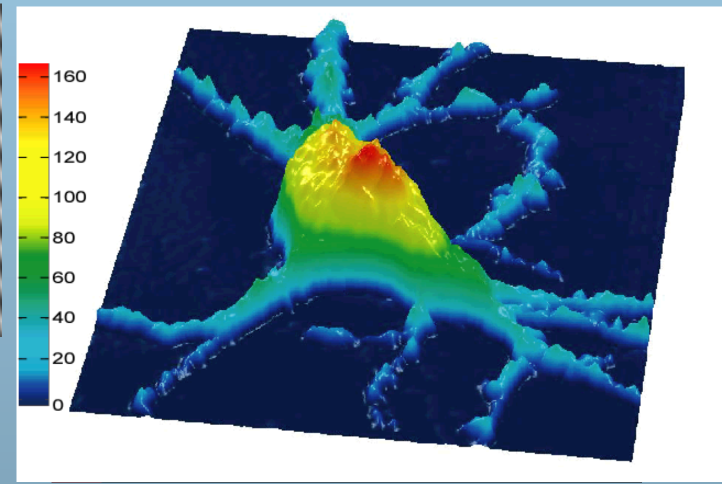
Digital Holography Microscopy



Hologram



Quantitative phase image of living cells



Phase of light: Visualization of **transparent specimen** including **Living cell** in culture

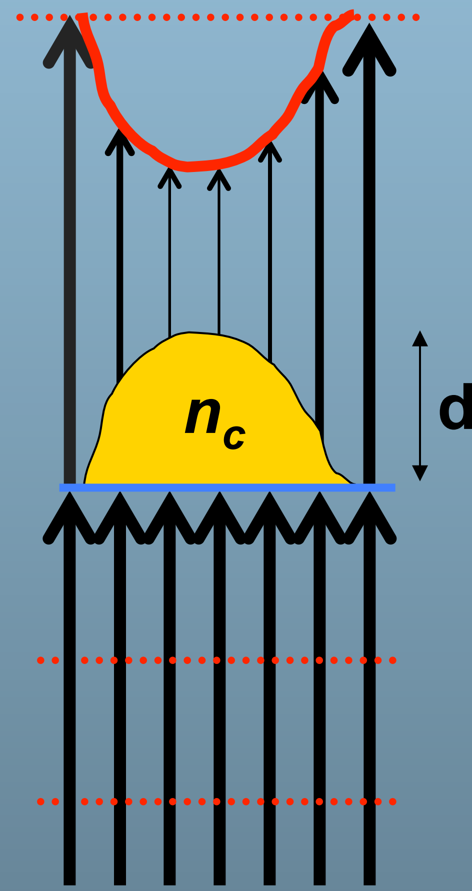
DHM Specifications and Advantages

- **No mechanical or optical scanning**
- **Short acquisition time (~20 µs)**
- **High reconstruction rate (25 im/sec)**
- **Choice of the focalization plane**
- **Sensitivity in the z-axis: ~10 nm**
- **Strictly non-invasive**
- **Phase: endogenous contrast agent**

Light - Cell interaction

Intensity absorption:

Wave front modification:



$$\varphi \propto (d, n_c)$$

Intensity contrast image

Phase contrast image

living cells = **phase** object

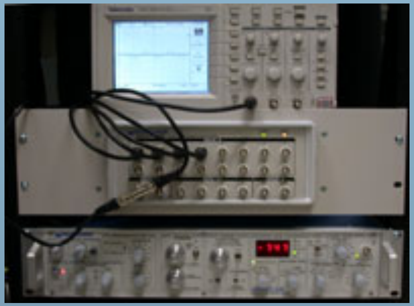
No direct detector of the phase !

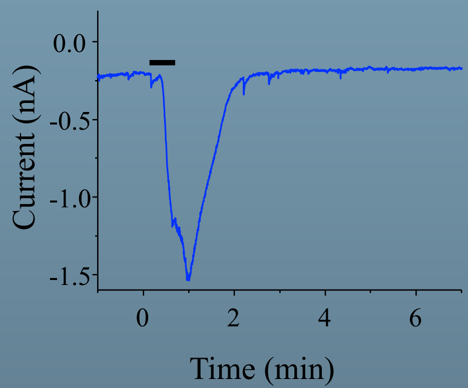
-> but can be encoded by interferometry

Electrical activity and phase signal recording

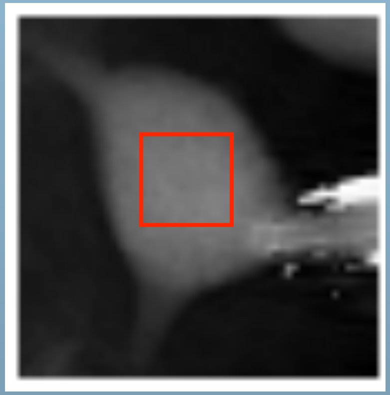
DHM/Electrophysiology set-up

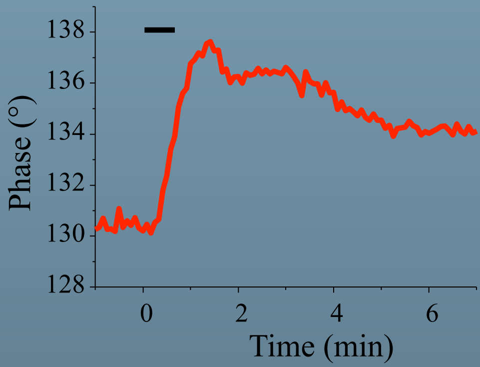
Electrophysiology



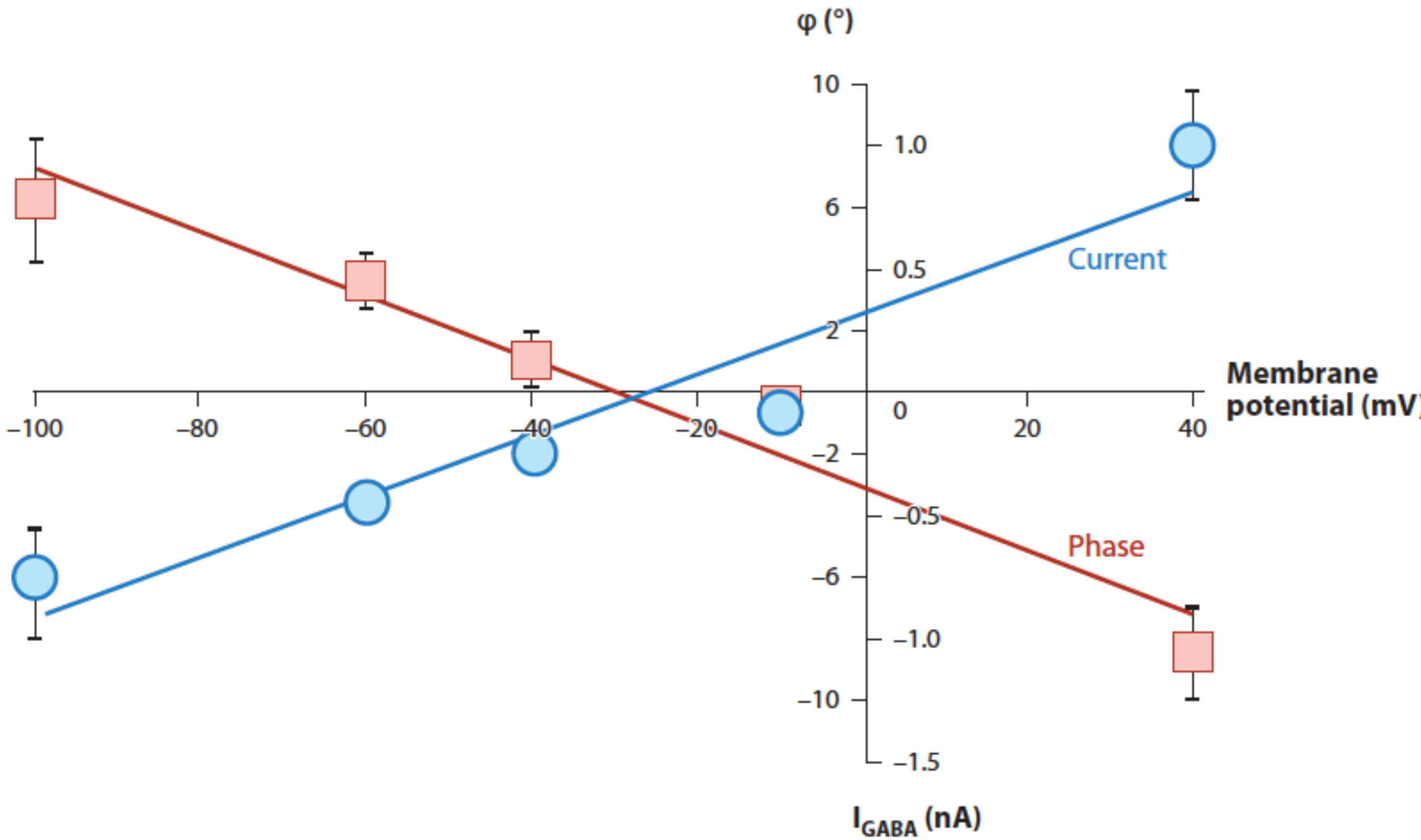


DHM





?



φ (°)
10
6
2
−2
−6
−10
1.0
0.5
0
−0.5
−1.0
−1.5
−100
−80
−60
−40
−20
20
40
Current
Phase
Membrane potential (mV)
I_{GABA} (nA)

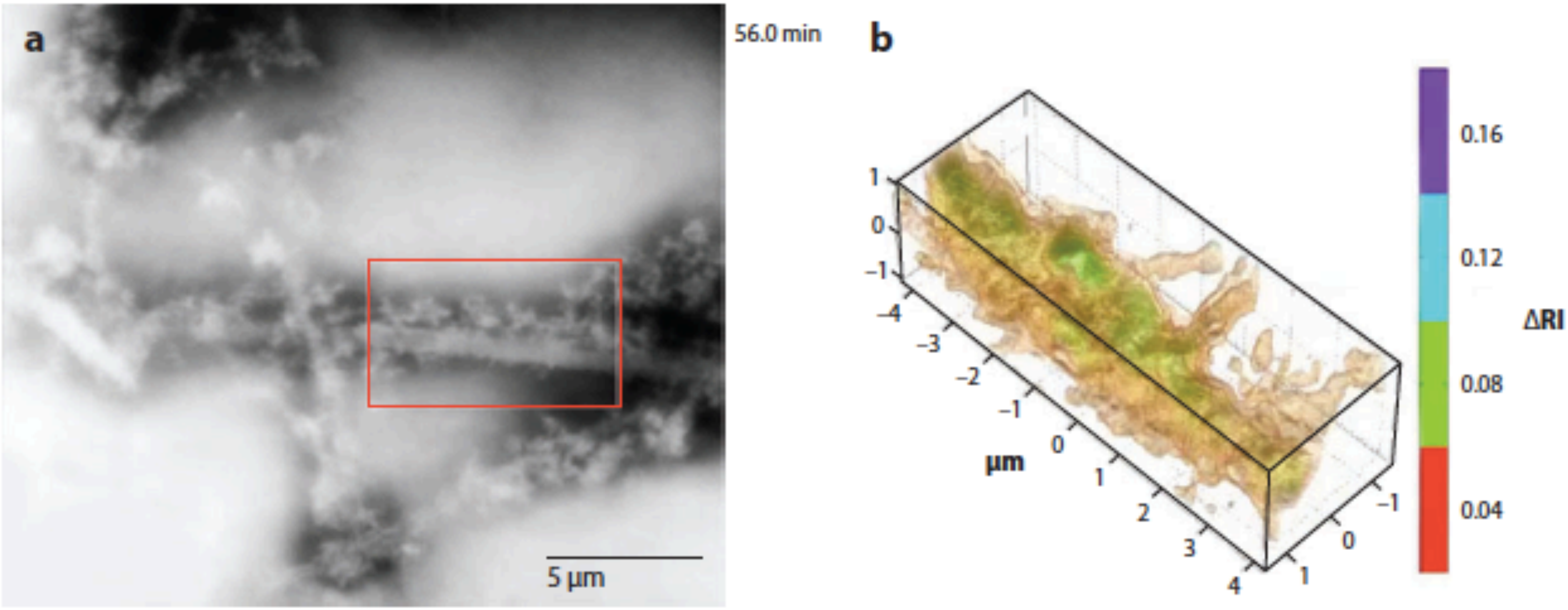


Figure 6

(*a*) Superresolved phase image of a dendrite section obtained by synthetic aperture quantitative phase image. (*b*) 3D representation of the tomographic image of an 8-µm-long section (see *inset* of panel *a*). It shows the body of the dendrite section with the details of protruding dendritic spines. Scale is in µm and the color code represents the difference in refractive index [from 0.04 (*red*) to 0.16 (*violet*)] between the dendrite and the extracellular medium. (Courtesy of Yann Cotte.)

Exploring Neural Cell Dynamics with Digital Holographic Microscopy

P. Marquet,[1,2] C. Depeursinge,[3] and P.J. Magistretti[1,2,4]

Annu. Rev. Biomed. Eng. 2013. 15:407–31

Neuroenergetics and brain function

What is next ?

- **Modeling**
- **New imaging modalities**
- **Nanotechnologies for *in vivo* chemical detection**

Nanotechnologies for *in vivo* chemical detection

<u>Currently :</u>
Microdialysis, electrochemical detection, enzyme-based probes :
Low spatial (mm) and temporal (sec, min) resolution

<u>Future :</u>
Need for new technologies with high spatial (um) , temporal (msec) and multiscale resolution : single cells within networks

Ultrasensitive Biomolecular Assays with Amplifying Nanowire FET Biosensors

Chi On Chui[a,b], Kyeong-Sik Shin[a], and Yufei Mao[a]

[a]Department of Electrical Engineering and [b]California NanoSystems Institute, University of California, Los Angeles, CA, USA 90095-1594

Nanoepitaxy: Materials and Devices V, edited by Nobuhiko P. Kobayashi, A. Alec Talin, Albert V. Davydov, M. Saif Islam, Proc. of SPIE Vol. 8820, 88200S · © 2013 SPIE

ADVANCED MATERIALS

Adv. Mater. 2008, 20, 164–167

Biospecific Recognition of Tethered Small Molecules Diluted in Self-Assembled Monolayers**

By *Mitchell J. Shuster, Amit Vaish, Matthew E. Szapacs, Mary E. Anderson, Paul S. Weiss,* and *Anne M. Andrews**

A Genetically Encoded FRET Lactate Sensor and Its Use To Detect the Warburg Effect in Single Cancer Cells

Alejandro San Martín[1,2], Sebastián Ceballo[1,2], Iván Ruminot[1,2], Rodrigo Lerchundi[1,2], Wolf B. Frommer[3], Luis Felipe Barros[1]*

PLOS | ONE

February 2013 | Volume 8 | Issue 2 | e57712

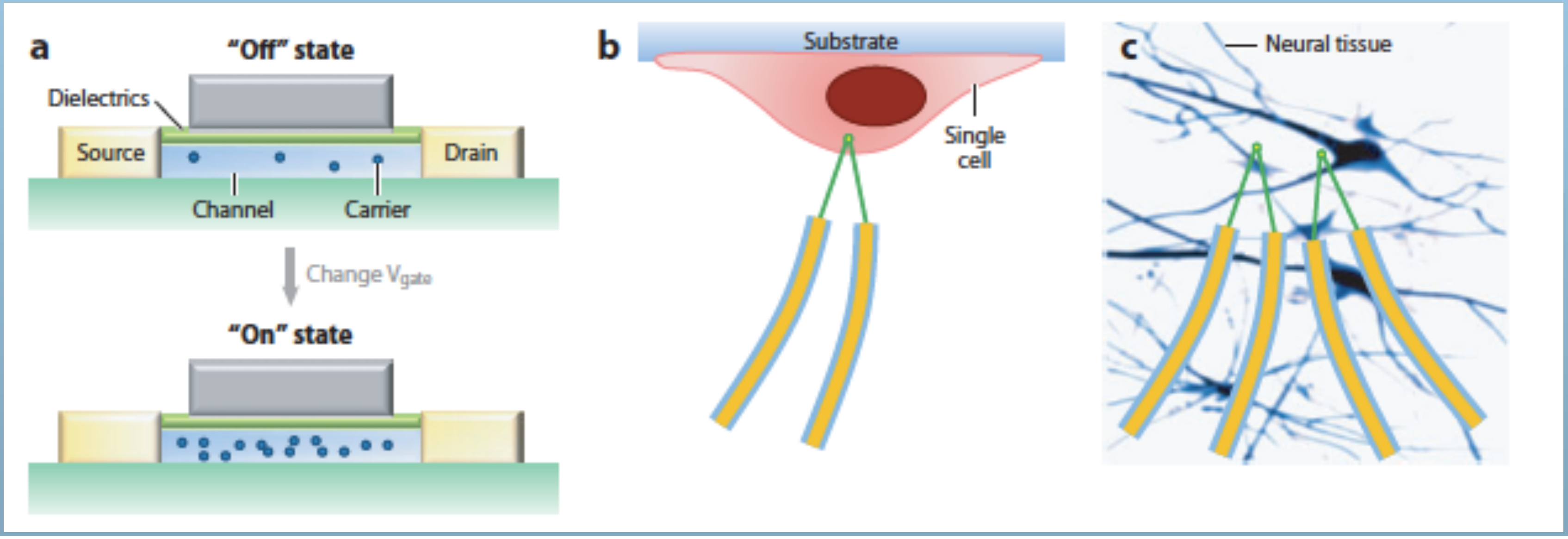
Synthetic Nanoelectronic Probes for Biological Cells and Tissues

Bozhi Tian[1] and Charles M. Lieber[2]

Annu. Rev. Anal. Chem. 2013. 6:31–51

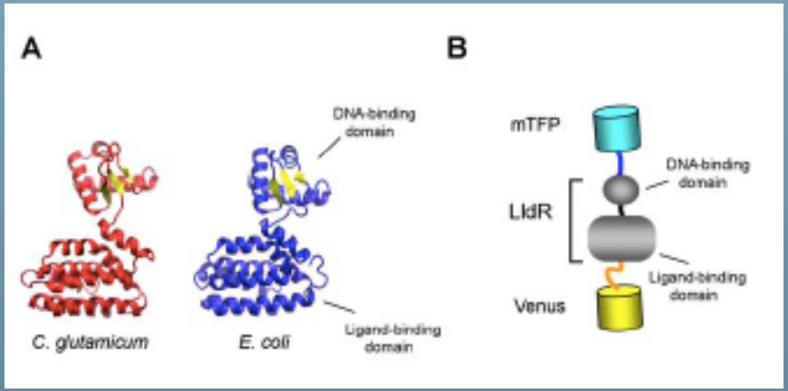
Nanoelectronics : Nanoscale FET

Tian & Lieber 2013



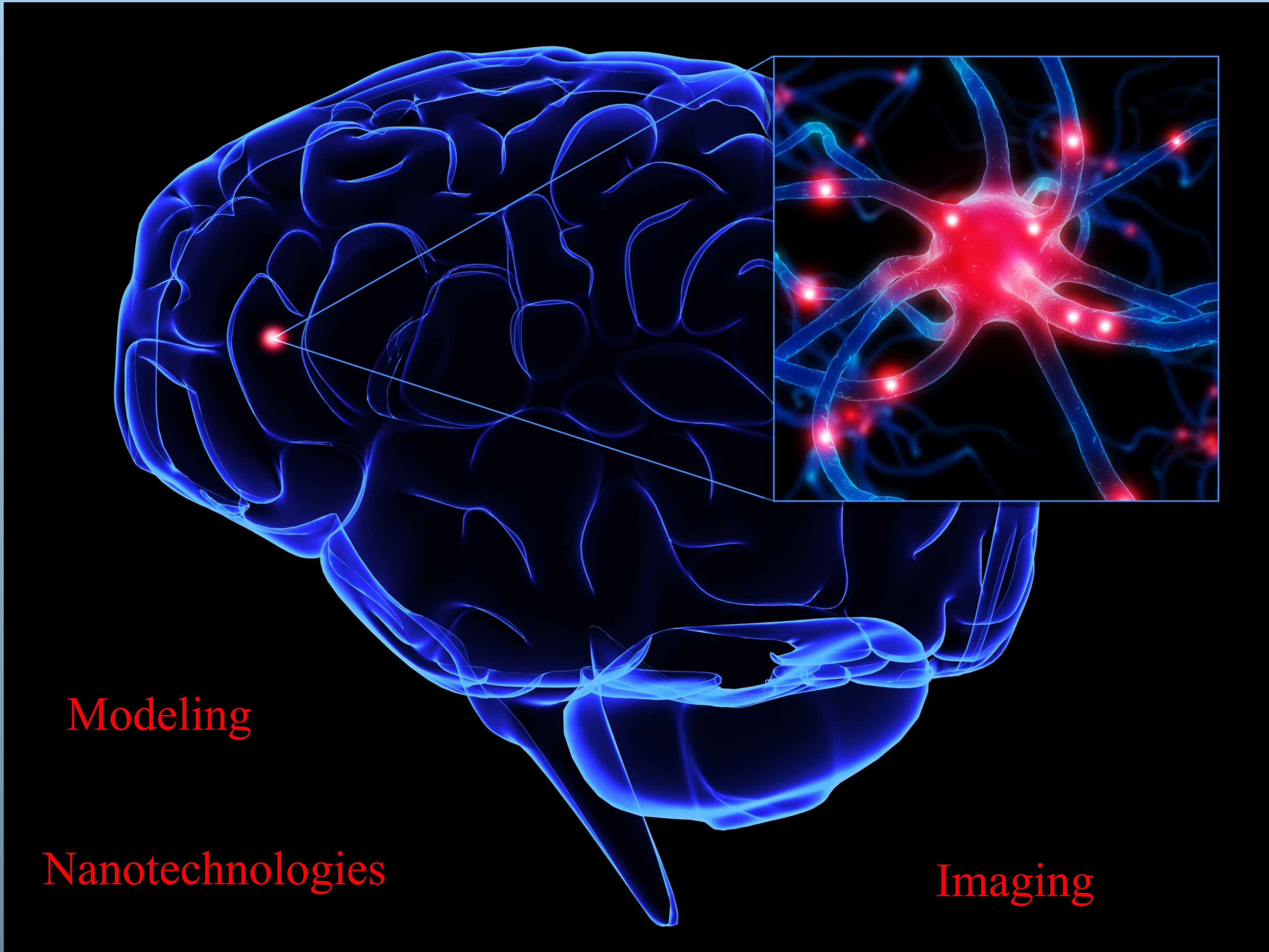
Field effect transistor (FET) basics and electrical interfaces between nanoscale FETs (nanoFETs) and biological systems.

Nanosensors : Genetically-encoded FRETs



Laconic, a FRET lactate sensor based on the transcriptional regulator LldR.

San Martin et al., 2013



A neuroenergetic perspective on brain function

... but very very low energetic cost for information processing

20 Watts !