

UCLA NITP
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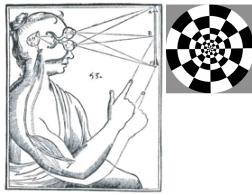
Relating Neurophysiology and Imaging Signals

Richard B. Buxton
University of California, San Diego

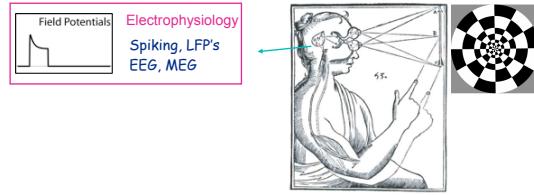
Signals Reflecting Brain Activity



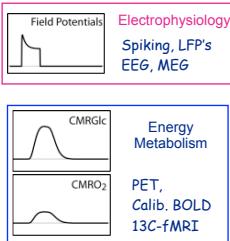
Signals Reflecting Brain Activity



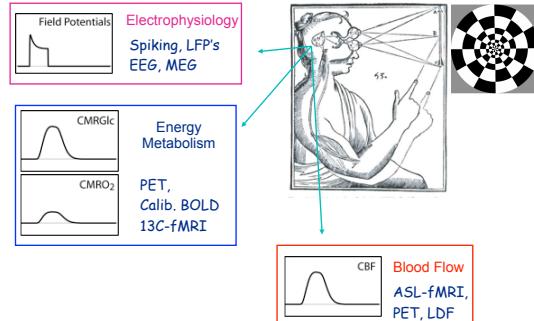
Signals Reflecting Brain Activity



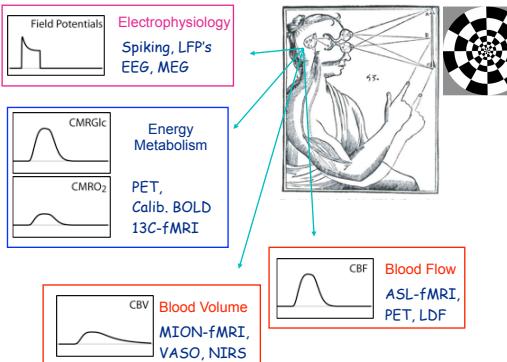
Signals Reflecting Brain Activity



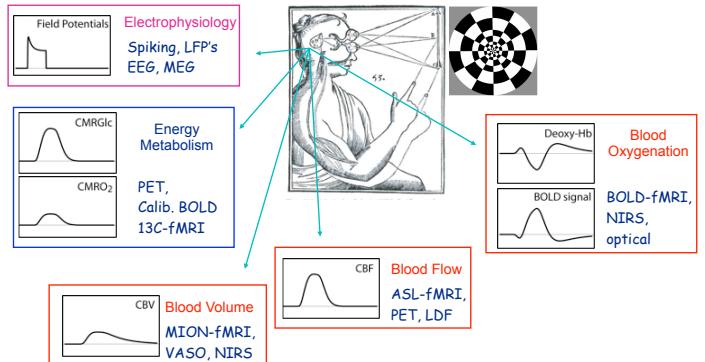
Signals Reflecting Brain Activity



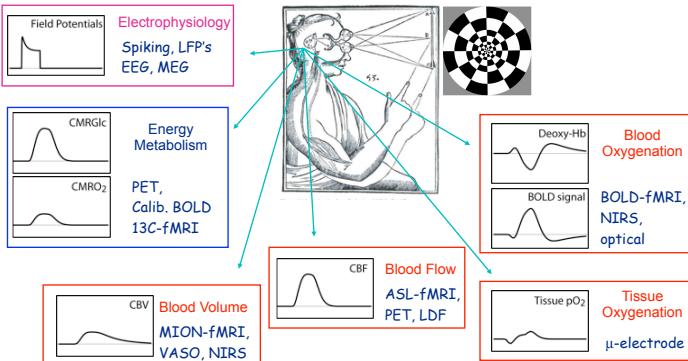
Signals Reflecting Brain Activity



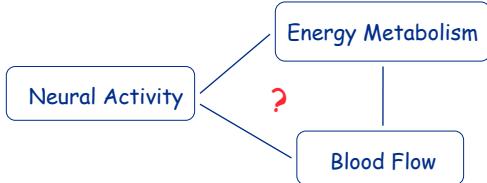
Signals Reflecting Brain Activity



Signals Reflecting Brain Activity



How does it all fit together?



"The view that the hemodynamic response is coupled to signaling processes represents a conceptual shift from the traditional idea that the energy demands of the tissue directly determine the flow increase associated with neural activation."
Attwell and Iadecola (2002)

"Future issues to be resolved: 1) What function(s) does regional brain-blood flow perform when neuronal activity changes?"
Raichle and Mintun (2006)

Outline

- Energy metabolism
- Neural activity
- Cerebral blood flow
- Current ideas

Energy Metabolism

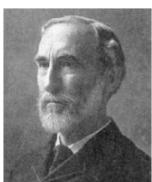
Gibbs Free Energy Change

Gibbs free energy (ΔG) encompasses both energy and entropy changes: in any transformation the net ΔG must be negative.

Any system far from equilibrium will have a negative ΔG if it moves toward equilibrium.

A process that increases ΔG in one system can occur if it is coupled to another system with a larger decrease in ΔG .

The brain needs sources of free energy to drive uphill reactions and for signaling.



J. Willard Gibbs

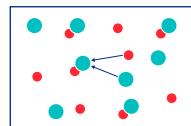
Sources of ΔG

Systems far from equilibrium

Chemical imbalance:

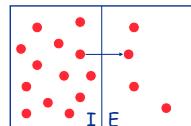


$$\Delta G \sim -\ln \frac{[A][B]}{[C]}$$



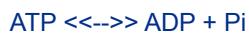
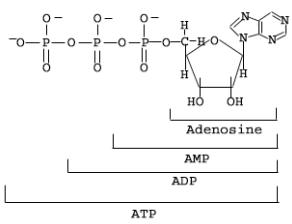
Gradients across a membrane:

$$\Delta G \sim -\ln \frac{[C_I]}{[C_E]}$$



For ions, ΔG depends on potential as well as concentration gradient

Adenosine Triphosphate (ATP)



At equilibrium,

$$\frac{[ATP]}{[ADP]} \ll 1$$

But in the brain

$$\frac{[ATP]}{[ADP]} \approx 10$$

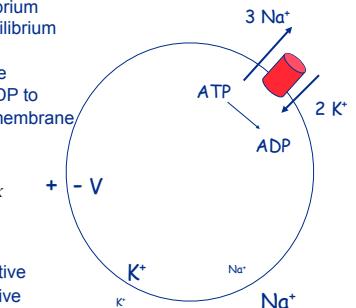
ΔG depends on the phosphorylation potential: $\ln \frac{[ATP]}{[ADP][P_i]}$

Ion Distributions and the Sodium/Potassium Pump

Ion distributions (intra- vs extra-cellular):
Sodium (Na^+) is far from equilibrium
Potassium (K^+) is closer to equilibrium

Sodium pump: The Na/K ATPase couples conversion of ATP \rightarrow ADP to moving Na^+ and K^+ across the membrane

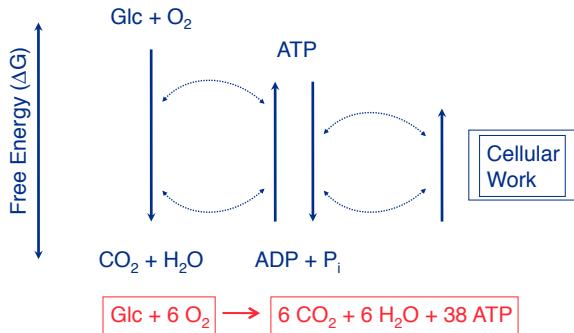
$$\Delta G = \Delta G_{ATP} + \Delta G_{Na} + \Delta G_K$$



ΔG :

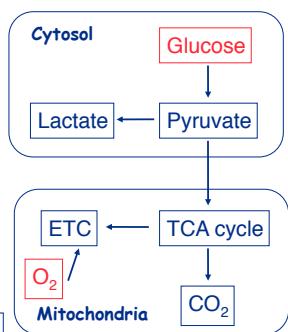
$ATP \rightarrow ADP$	strongly negative
$Na^+(I) \rightarrow Na^+(E)$	strongly positive
$K^+(E) \rightarrow K^+(I)$	weakly positive

Bioenergetics

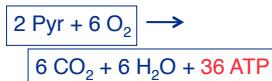


Generation of ATP

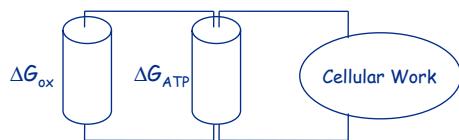
Glycolysis



Oxidative Metabolism



Biological Batteries



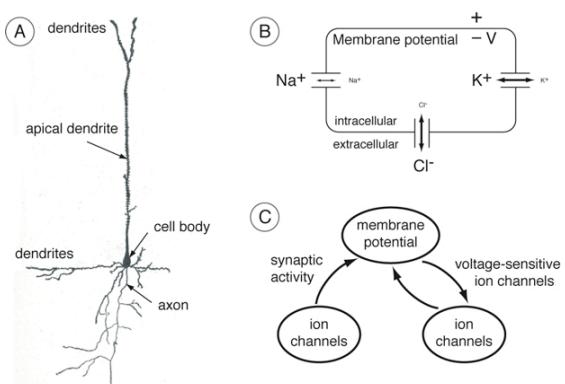
Free energy, either to drive uphill reactions or for signaling, is available from subsystems that are far from equilibrium:

$$\frac{[Pyr][O_2]^3}{[CO_2]^3} \quad \frac{[H^+]_o}{[H^+]_i} \quad \frac{[ATP]}{[ADP][P_i]} \quad \frac{[Na^+]_E}{[Na^+]_i} \quad \frac{[Ca^{++}]_E}{[Ca^{++}]_i}$$

Environment Mitochondria Cell Cell Membrane

Neural Activity

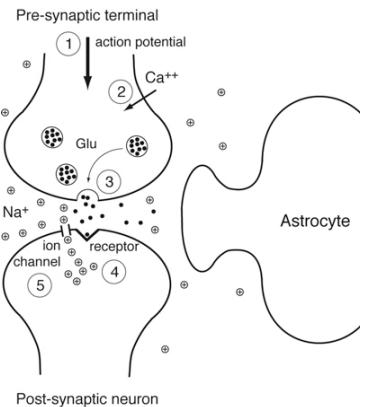
Neuronal Signaling



Synaptic activity initiates ion fluxes

Pre-synaptic Activity:
Arrival of an action potential (1) opens Ca⁺⁺ channels, and Ca⁺⁺ influx (2) causes vesicles to release glutamate into the synaptic cleft (3).

Post-synaptic Activity:
Glutamate binds to post-synaptic receptors (4) opening Na⁺ channels allowing many sodium ions to flow down their gradient into the post-synaptic neuron (5).

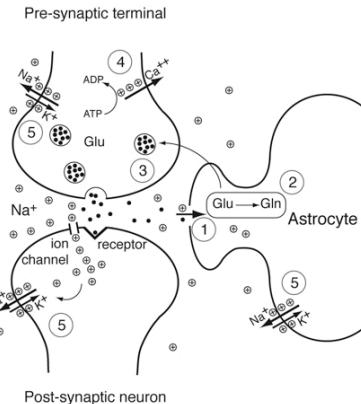


Recovery from signaling requires free energy

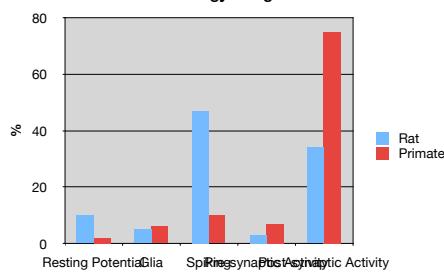
Astrocyte Activity:
Glutamate is taken up by the astrocyte (1 – Na⁺ gradient), and converted to glutamine (2 – ATP).

Pre-synaptic Activity:
Glutamine diffuses to pre-synaptic terminal, converted to glutamate and concentrated in vesicles (3 – ATP), and Ca⁺⁺ ions are pumped out (4 – ATP).

Post-synaptic Activity:
Na⁺ ions are pumped out and K⁺ ions are pumped in by the Na/K pump (5 – ATP).

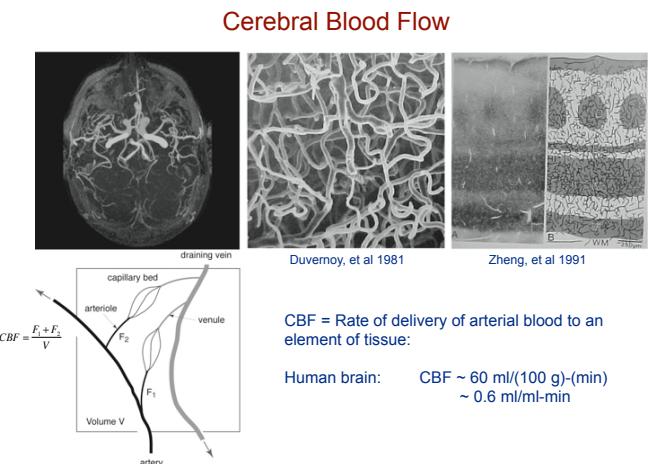


Brain Energy Budget



Most of the energy is consumed by the Na/K pump in recovering from post-synaptic excitatory activity

Cerebral Blood Flow



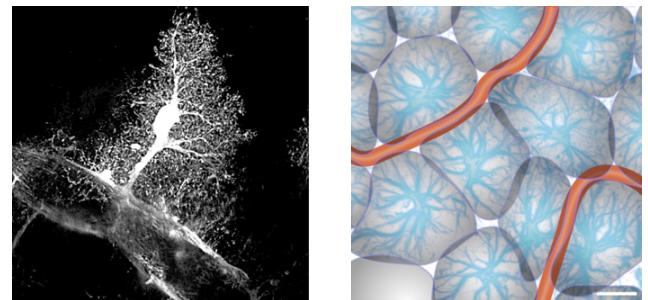
Control of CBF

Systemic: hormonal and neural effects control the distribution of blood flow to different parts of the body while maintaining CBF

Autoregulation: If blood pressure drops, cerebrovascular resistance decreases to maintain CBF

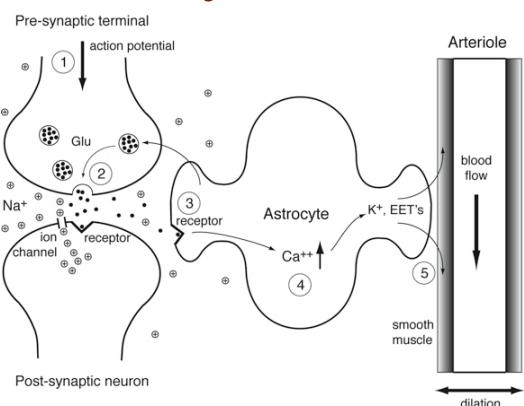
Functional activity: Local neural activity increases CBF, but function is still unclear

Astrocytes bridge neurons and vessels

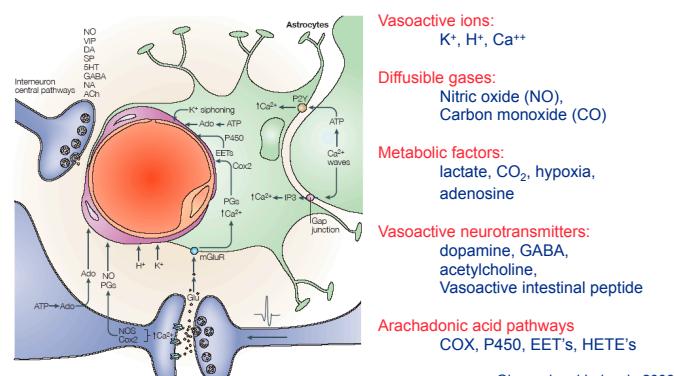


Nedergaard et al, 2003

Blood flow changes with neural activation

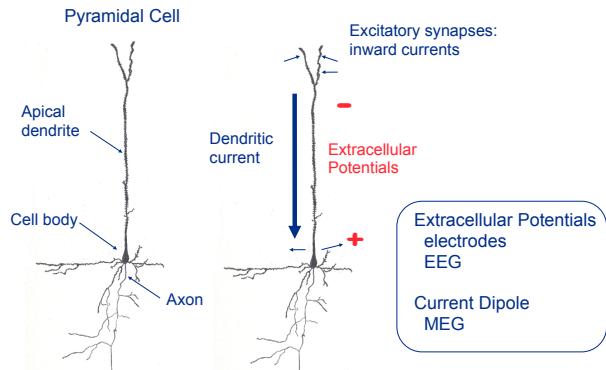


Mechanisms of CBF Control

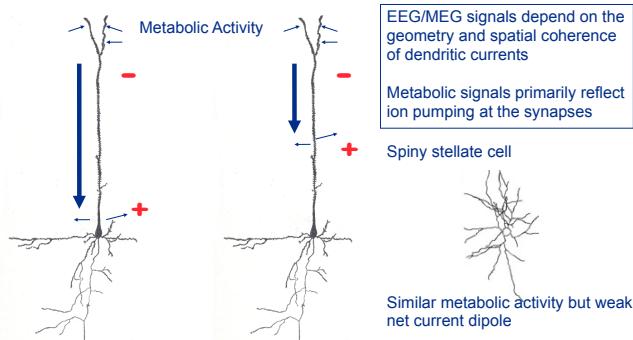


Current Ideas and Speculations

Electrophysiology Signals



EEG/MEG and fMRI reflections of neural activity



BOLD response reflects synaptic activity

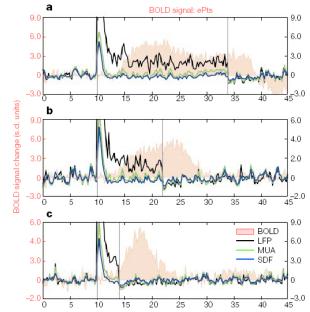
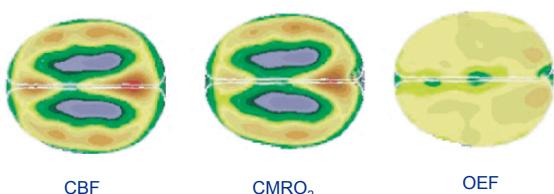


Figure 3 Simultaneous neural and haemodynamic recordings from a cortical site showing transient neural responses. **a–c**, Response to a pulse stimulus of 24, 12 and 4 s. Both single- and multi-unit responses adapt a couple of seconds after stimulus onset, with LFP remaining the only signal correlated with the BOLD response. SDF, spike-density function (see text); d.f.s., electrode ROI—positive time series.

Logothetis, 2001

Metabolic baseline state: uniform O₂ extraction

Coupled CBF, CMRGlc, and CMRO₂ with uniform O₂ extraction fraction when resting quietly with eyes open



Does OEF provide an absolute distinction between activation (OEF<40%) and deactivation (OEF>40%)?

Gusnard, 2001

Glucose metabolism increases more than oxygen metabolism during activation

Lactate Shuttle Hypothesis (Magistretti, et al): Glycolysis increase is more prominent in astrocytes, producing lactate that is transported to the neurons as fuel for oxidative metabolism

Key questions:

Do CBF and Glucose metabolism always vary together? (usually, but not always)

Does CBF need to increase to support Glucose metabolism? (no)

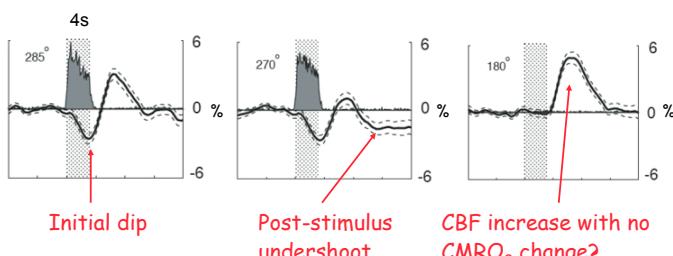
Is glycolysis preferred for providing ATP for synaptic activity? (maybe)

Do neurons primarily use lactate for oxidative metabolism? (maybe)

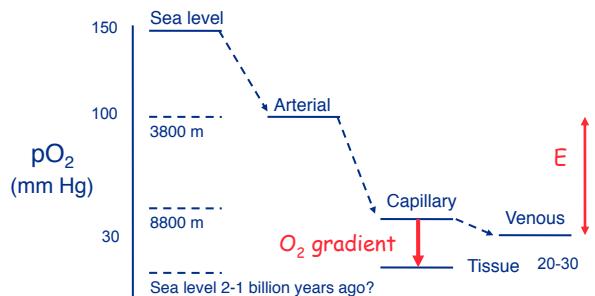
Tissue pO₂: Dynamic Responses

Thompson, et al (Science 299:1070, 2003):

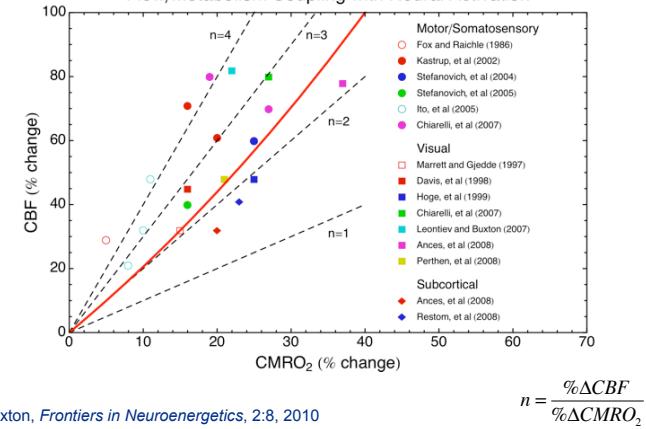
Cat model with visual stimulation
pO₂; O₂ microelectrode
spike rate: single unit electrode



Oxygen Concentration



Flow/Metabolism Coupling with Neural Activation



Does the brain try to maintain tissue pO₂ as CMRO₂ increases?

Potential answer to basic questions:

Why is the flow change so large?

CBF change needs to be ~2–3 times larger than the CMRO₂ change to maintain constant tissue pO₂.

Why is the flow change so quick?

O₂ in brain: concentration ~ 0.3 mM (mostly in blood)
metabolic rate ~ 1.6 mM/min
depletion time constant ~ 10 sec

Why does blood oxygenation change?

Allows the capillary/tissue O₂ gradient to increase without changing the tissue pO₂

But the pO₂ itself is probably not the signal for changing CBF

Current Ideas: CBF and energy metabolism responses

Initial CBF response:

Feed-forward, driven by neural activity, rather than a feed-back response to the increased energy demand.

Strongly driven by excitatory synaptic activity.

Feed-back control related to metabolism operates more slowly (?).

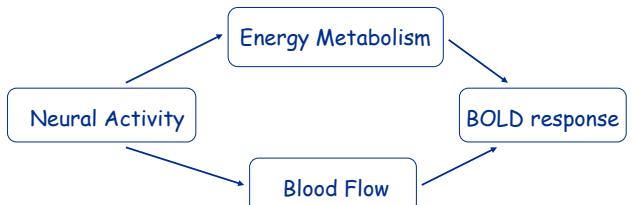
Energy metabolism response:

Major energy cost is related to pumping sodium after excitatory activity.

CMRGlc also may be strongly driven by synaptic activity to provide energy for recycling neurotransmitter.

CMRO₂ increases to cover total energy costs.

Working Hypothesis



CBF driven primarily by input synaptic activity.
CMRO₂ driven by total energy costs (synaptic plus spiking).
BOLD response depends on both!

Tissue pO_2 fluctuations and the BOLD response

