Flow-Metabolism Coupling –PET vs. fMRI- Debate, Modeling and Application

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Outline

- Debate (PET vs. fMRI)
- Modeling (fMRI)
  - Validation of the fMRI BOLD Model
- Application (PET+ fMRI)
- Future Directions
- Summary
Debate
Cerebral Blood Flow (CBF) vs. Brain Function

(A) Forearm; (C) Brain

By Angelo Mosso, late 19 century
The Roy-Sherrington principle has been interpreted to mean that CBF changes reflect a tight coupling between cellular energy requirements and the supplies of glucose and oxygen.

Roy and Sherrington, J. Physiology 1890

![Fig. 2. Quantitative maps of blood flow (Upper) and oxygen consumption (Lower) in the subjects from group I while they rested quietly but awake with their eyes closed. The quantitative hemisphere mean values for these images are presented in Table 1. Note the large variation in blood flow and oxygen consumption across regions of the brain. These vary most widely between gray and white matter. Despite this variation, blood flow and oxygen consumption are closely matched, as also reflected in the image of the oxygen extraction fraction (i.e., the ratio of oxygen consumption to blood flow; see Fig. 4).](#)
Visual Stimulation

CBF: 50%
CMR$_{\text{Glc}}$: 51%

CBF: 50%
CMRO$_2$: 5%

Fox and Raichle, PNAS 1986; Fox et al., Science 1988
Glucose → Glycolysis (10 successive reactions) → 2 Pyruvate → Anaerobic conditions → 2 Lactate + 2 ATP → 2 Acetyl-CoA → Aerobic conditions → O₂ → Citric acid cycle → O₂ → 4CO₂ + 4H₂O + 38 ATP → Cells under aerobic conditions.

Prichard et al., PNAS 1991
Increased lactate/pyruvate ratio augments blood flow in physiologically activated human brain

Mark A. Mintun*, Andrei G. Vlassenko, Melissa M. Rundle, and Marcus E. Raichle
Mallinckrodt Institute of Radiology, Washington University School of Medicine, 510 South Kingshighway Boulevard, St. Louis, MO 63110
Contributed by Marcus E. Raichle, November 10, 2003

Mintun et al., PNAS 2004
Oxidative or non-oxidative metabolism?

- **Energy Demand**
  - ATP production ($J_{\text{ATP}}$) of task-induced neuronal activation

- **CBF Increases**
PET: Rate-dependent flow-metabolism coupling

Vafaee et al., JCBFM 1999

Vafaee and Gjedde, JCBFM 2000
PET: Duration-dependent flow-metabolism coupling

Mintun et al., Neuroimage 2002
Flow-metabolism coupling is non-linear
  - Rate-dependent
  - Duration-dependent

The increase in CBF associated with physiological activation is regulated by factors other than local requirements in oxygen (Fox et al., Science 1988; Mintun et al., PNAS 2001).

Energy demand (ATP production) can be met through non-oxidative metabolism (glycolysis)
BOLD biophysical model

\[
\frac{\Delta \text{BOLD}}{\text{BOLD}_0} = M \left(1 - \left(\frac{\text{CMR}_{O_2}}{\text{CMR}_{O_2}|_0}\right)^\beta \left(\frac{\text{CBF}}{\text{CBF}_0}\right)^{\alpha - \beta}\right).
\]

\[
M = TE \cdot A \cdot \text{CBV}_0 \cdot [\text{dHb}]_v^\beta.
\]

\[
\frac{\Delta \text{BOLD}}{\text{BOLD}_0} = M \left(1 - \left(\frac{\text{CBF}}{\text{CBF}_0}\right)^{\alpha - \beta}\right).
\]

Calibrated by Hypercapnia

\[
\frac{\text{CBV}}{\text{CBV}_0} = \left(\frac{\text{CBF}}{\text{CBF}_0}\right)^\alpha.
\]

Davis et al., PNAS 1998
fMRI: Rate-independent flow-metabolism coupling

- Flow-metabolism coupling is rate-independent
- Coupling ratio (%CBF/%CMRO$_2$) = 2-3
- Increase in CBF is needed to meet the oxygen demand

Hoge et al., PNAS 1999
<table>
<thead>
<tr>
<th>Flow-metabolism coupling</th>
<th>PET</th>
<th>fMRI</th>
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<tbody>
<tr>
<td>is non-<em>linear</em></td>
<td>Rate-dependent</td>
<td>Rate-<em>independent</em></td>
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<td></td>
<td>Duration-dependent</td>
<td>Duration-<em>independent</em></td>
</tr>
<tr>
<td>CBF increase $\rightarrow$ O$_2$ demand</td>
<td>Coupling ratio = 2-10</td>
<td>CBF increase $\rightarrow$ O$_2$ demand</td>
</tr>
<tr>
<td>Energy demand: met through both <em>aerobic</em> and <em>anaerobic</em> metabolism</td>
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<td>Energy demand: met through <em>aerobic</em> metabolism</td>
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<td></td>
<td>Support Roy-Sherrington principle?</td>
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</table>
Debate: PET vs. fMRI
1986-2006

Energy Demand

- Oxidative or non-oxidative metabolism?
- Brain: 2% body weight; 20% oxygen consumption
- $5\% \text{ CMRO}_2 \rightarrow 64\% \text{ ATP production}$ (Mangia)
- $\geq 97\% \text{ ATP is produced aerobically}$ (Mangia et al., JCBFM 2009)
- $> 90\% \text{ ATP is produced aerobically}$ (Hoge et al., PNAS 1999)

CBF Increases

- Oxidative or non-oxidative metabolism?
Modeling
Validation of PET studies

- Six adult baboons
- Intracarotid injection of $^{15}\text{O}$-labeled blood
- $^{15}\text{O}$ inhalation PET method

$E = \frac{S_{aO_2} - S_{vO_2}}{S_{aO_2}}$

**FIG. 8.** Comparison of oxygen extraction ($E$) in baboons measured by intracarotid injection of $O^{15}\text{O}$ (true) and by our PET method. Twenty-two sequential measurements of $E$ were done in six animals over a range of 0.08 to 0.58. Results show close correlation (dashed line) that is not statistically different from unity (solid line).

Mintun et al., J Nucl Med, 1984
fMRI BOLD Modeling – revisit

\[
\frac{\Delta \text{BOLD}}{\text{BOLD}_0} = M \left( 1 - \left( \frac{\text{CMR}_{O_2}}{\text{CMR}_{O_2,0}} \right)^\beta \left( \frac{\text{CBF}}{\text{CBF}_0} \right)^\alpha \right).
\]

\[
M = \text{TE} \cdot A \cdot \text{CBV}_0 \cdot [\text{dHb}]_v^\beta.
\]

\[
\frac{\text{CBV}}{\text{CBV}_0} = \left( \frac{\text{CBF}}{\text{CBF}_0} \right)^\alpha
\]

M: 0.22 (Hoge et al., PNAS 1999)
0.07 (Davis et al., PNAS 1998)
0.05-0.10 (Gauthier et al., NI 2011)

Long TE (50 ms): increase BOLD signal; decrease in CBF signal
\[ \alpha = 0.38? \]

Lin et al., ONIJ 2011, in press
fMRI BOLD Modeling – revisit

Rate-varying experiment

Evaluation of MRI Models in the Measurement of CMRO₂ and Its Relationship With CBF

Ai-Ling Lin,¹ Peter T. Fox,¹ Yihong Yang,² Hanzhang Lu,³ Li-Hai Tan,⁴ and Jia-Hong Gao⁵*

Duration-varying experiment

Time-dependent correlation of cerebral blood flow with oxygen metabolism in activated human visual cortex as measured by fMRI

Ai-Ling Lin a.*, Peter T. Fox a, Yihong Yang b, Hanzhang Lu c, Li-Hai Tan d, Jia-Hong Gao e.*
Materials and Methods

- VASO: Vascular Space Occupancy
- Two inversion time delays
- Inversion slab thickness = 100 mm
- VASO
  - TE/TI₁/TR = 9.4/610/2000 ms
- ASL
  - TE/TI₂/TR = 11.6/1200/2000 ms
- BOLD
  - TE/TR = 28.1/2000 ms
- Hypercapnia: 5% CO₂, 20% O₂ and balance N₂

Yang et al., MRM 2004
%ΔCMRO$_2$ Determination

Davis’s model (PNAS 1998)

\[ \%ΔCMRO_2 = \left(1 - \frac{(%ΔBOLD)}{M}\right)^{\frac{1}{\beta}} \cdot (1 + %ΔCBV)^{-\frac{1}{\beta}} \cdot (1 + %ΔCBF) - 1 \]

%ΔCMRO$_2$ Determination

Lu’s model (JCBFM 2004)

\[ \Delta R_{2t}^* = 0.7 \cdot \gamma \cdot B_0 \cdot \frac{4}{3} \cdot \pi \cdot \Delta \chi \cdot Hct \cdot \\
(CBV_{act} \cdot (1 - Y_v^{act}) - CBV_{rest} \cdot (1 - Y_v^{rest})) \\
(1 - Y_v) = 1 - Y_a + OEF \cdot Y_a \\
\left(1 + \frac{\Delta OEF}{OEF}\right) \cdot \left(1 + \frac{\Delta CBF}{CBF}\right) = \left(1 + \frac{\Delta CMRO_2}{CMRO_2}\right) \]
Rate-varying experiment

- 3T Siemens Trio MRI Scanner (Siemens, Erlangen, Germany)
- 8 healthy volunteers (4 men, 4 women, aged 23-36)
- 5 different levels of visual stimulation
- 3-min “stimulus” alternating with 3-min “baseline”
- Simultaneously CBV, CBF and BOLD measurement
Method [1]: \( M = 0.22; \ \alpha = 0.38 \) (Davis’ model)
Method [2]: Measured \( M \) (0.098) and CBV (Davis’ model)
Method [3]: Lu’s model
Duration-varying Experiment

- 3T Siemens Trio MRI Scanner (Siemens, Erlangen, Germany)
- 8 healthy volunteers (4 men, 4 women, aged 22-38)
- 8 Hz flashing checkerboard
- 3-min “baseline” followed by 21-min “stimulus”
- Simultaneously CBV, CBF and BOLD measurement
Matlab 7.0

Two image pairs (8 s) acquired after the onset and cessation of each task period was excluded from data analysis.
SCM\textsubscript{old}: $M=0.22$; $\alpha=0.38$ (Davis’ model)

SCM\textsubscript{new}: Measured $M$ (0.09) and CBV (Davis’ model)

MCM: Lu’s model
Flow-metabolism coupling is non-linear
- Rate-dependent
- Duration-dependent
- CBF increase $\rightarrow$ O$_2$ demand
- Coupling ratio = 2-10
- Energy demand: met through both aerobic and anaerobic metabolism

Flow-metabolism coupling is non-linear
- Rate-dependent
- Duration-dependent
- CBF increase $\rightarrow$ O$_2$ demand
- Coupling ratio = 2-8
- Energy demand: met through both aerobic and anaerobic metabolism
Physiological Debate: re-visit

- Oxidative or non-oxidative metabolism?
  - Energy Demand
    - ATP production ($J_{ATP}$) of task-induced neuronal activation
  - CBF Increases
Study Design

Visual stimulation

4, 8 and 16 Hz

which has been repeated shown to produce variable degrees of "uncoupling" between CBF and CMRO$_2$ changes (Vafaee and Gjedde, JCBFM, 2000)

Combined fMRI and $^1$H MRS methods

CBF – fMRI ASL method

CMRO$_2$ – fMRI BOLD model

Lactate Production ($J_{\text{Lac}}$, µmol/g/min) – $^1$H MRS

ATP production ($J_{\text{ATP}}$, µmol/g/min) calculation

Lin et al., PNAS 2010
Twelve healthy volunteers (aged 22-38)

3T Siemens Trio MR scanner

Black-white checkerboard reversing its contrast at 4, 8 and 16 Hz (4 min each)

Transmit/Receive Body/Head coil

fMRI image acquisition

- Single slice (6 mm in thickness)
- FOV=26 cm
- matrix size=64x64
- In-plane resolution= 4.1x4.1 mm²
Materials and Methods

- **1H MRS Data Acquisition**
  - Spectral width = 24 Hz
  - PRESS localization approach
  - TR/TE = 2000/30 ms
  - Voxel of Interest (VOI) = 25×21×30 mm³ (15.8 cc)

- **Data Analysis**
  - 120 averages (4 min) were summed in blocks
  - Data processing: Nuts software (Acorn NMR Inc., Livermore, CA, USA) -- Fourier transform, magnitude calculation, frequency correction, phase correction and baseline correction of the FID

Lin et al., PNAS 2010
Lactate Determination

- Ratio of intergraded intensities centered at 1.33 ppm (Lactate) and the N-acetylaspartate (NAA) resonance at 2.02 ppm
- Relative lactate concentration ($\Delta [\text{Lac}]($%)) was determined by comparing the activation states to the resting state.
- $\Delta J_{\text{Lac}}($%) was determined with $\Delta [\text{Lac}]$ divided by intergraded time period (4 min).

\[
J_{\text{ATP(a)}} = J_{\text{Lac(r)}} \times (1 + \%\Delta J_{\text{Lac}}) + \frac{19}{3} CMRO_{2(r)} \times (1 + \%\Delta CMRO_{2})
\]

Derived from Gjedde, in Cerebrovascular Disease, 1997
Lin et al., PNAS 2010
fMRI

\[ r = 1.00 \]

PET

ATP-O2 Couple

\[ y = 16.3x - 1.6 \]
\[ r^2 = 1.00 \]

Gjedde, in Cerebrovascular Disease, 1997

Lactate-CBF Couple

\[ y = 51x + 9 \]
\[ r^2 = 0.69 \]
Adapted from Vafaee and Gjedde, JCBFM 2000
Astrocyte-Neuron Lactate Shuttle (ANLS) Model

Pellerin and Magistretti, PNAS 1994; Hyder et al., JCBFM 2006
The End ?
Issues regarding M

- CMRO$_2$ does not change during hypercapnia?
  - Increase: Jones et al., 2005.
  - Decrease: Kliefoth et al., 1979; Xu et al., 2010; Bolar et al., 2010.
  - No change: Kety and Schmidt, 1948; Chen and Pike, 2010.

\[ M = TE \cdot A \cdot CBF_0^\alpha \cdot [Hct \cdot (1 - Y_{v,0})]^\beta \]
Issues regarding $\alpha$

- **Total CBV**
  \[ \frac{CBV}{CBV_0} = \left( \frac{CBF}{CBF_0} \right)^{\alpha} \]

- **Arterial CBV**
  - Optical imaging (Hillman et al., NI 2007)
  - MRI (Kim et al., MRM 2008)

\[ \Delta R_2^* = \alpha \cdot CBV_v \cdot \Delta Y \]
Issues regarding α

↓ Venous CBV

<table>
<thead>
<tr>
<th>ΔS/S (%)</th>
<th>CBF</th>
<th>CBV</th>
<th>CBV&lt;sub&gt;α&lt;/sub&gt;</th>
<th>CBV&lt;sub&gt;Pa&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breath-hold</td>
<td>60.8+/-7.2</td>
<td>54.9+/-5.8</td>
<td>53.1+/-6.2</td>
<td>54.5+/-4.9</td>
</tr>
<tr>
<td>Visual</td>
<td>62.5+/-7.5</td>
<td>28.2+/-5.2</td>
<td>53.6+/-5.5</td>
<td>22.2+/-3.8</td>
</tr>
</tbody>
</table>

15s breath-hold; Vis Stim

Hua et al., ISMRM2010
Validation of the fMRI BOLD Modeling

- **M**: Direct measurement for each component
  \[ M = TE \cdot A \cdot CBV_0 \cdot [dHb]_v^\beta. \]

- **α**: Temporal relationship of the aCBV and vCBV contribution to the BOLD signals

- In normal and disease states

- By comparison with (or include information from) other imaging techniques
  - PET, NIRS
We use the relation between baseline HbT₀ and the fraction of vascular blood V₀:

\[ HbT₀ = \frac{HGB}{MW_{Hb}} V₀ \]

\[ \frac{\Delta S}{S₀} = \frac{MW_{Hb}}{HGB} \left( \frac{k₂ + k₃}{k₁} \right) \Delta HbT - \frac{k₁ + k₂}{1 + \frac{S}{4} a₂ \left( E₀ - \frac{1}{4} \right)} \Delta HbR \]

- Linear regression to get a₁ and a₂
- We will compute E₀ from the ratio a₁/a₂ to avoid dealing with photon pathlength factors and partial volume errors as well as any bad assumptions about MW_{Hb} or HGB.
Application

Concurrent of PET-fMRI measurements

• Small Animals
• Patients
PET

- Excellent for quantitative $\text{CMR}_{\text{Glc}}$ measurement
- Difficult for quantitative CBF and CMRO$_2$ measurements

fMRI

- Opposite!

PET+ fMRI
**Surf 1 KO mouse**

- Major assembly factors:
  - Surf1, Sco1, Sco2
- 13 subunits:
  - Mutation in complex IV (cytochrome c oxidase)
  - Decreased O₂ consumption
  - 20-30% increased lifespan
Hypothesis: Metabolic pathway shifts from oxidative to non-oxidative metabolism

- Decreased CMRO$_2$ with preserved or increased CMR$_{Glc}$ will be observed in Surf1$^{−/−}$ mice as compared to the age-matched WT mice.

- This pathway shift will alter metabolite concentrations, oxygen-glucose index (OGI=CMRO$_2$/CMR$_{Glc}$), and the flow-metabolism ratio (n=CBF/CMRO$_2$) both in the resting state and during neuronal excitation by forepaw stimulation.
Surf1 KO mice increased basal CBF and glucose uptake

Cerebral Blood Flow
- Wild Type (WT): 1.09 ml/g/min
- Surf1 KO (-/-): 1.29 ml/g/min

18% increase

Brain Glucose Uptake
- Wild Type (WT): 0.0 mCi
- Surf1 KO (-/-): 4.0 mCi

85% increase
Task-Induced Changes

- Flow-Metabolism uncoupling
  - %CMR_{Glc}
  - %CBF
  - %CMRO_{2} (importance of fMRI BOLD model validation)
Future Directions

- Validation of fMRI BOLD model under various conditions
- Quantitative CMRO$_2$ measurements: $^{15}$O PET vs. MRI
  - Quantitative BOLD (qBOLD) (An and Lin 2000; He et al., 2008)
  - $^{17}$O
- PET+ fMRI—animal models
  - Surf mice
  - Caloric restriction
  - Rapamycin
  - Neurodegenerative disorders
- PET+ fMRI + NIRS
  - cytochrome c oxidase
The fMRI CMRO$_2$ measurements are consistent with PET results with proper parameters (M and $\alpha$).

The fMRI BOLD needs further validation, particularly for disease states.

The multi-metric imaging methods (PET, fMRI, NIRS) will have profound implication in translational research.
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