Non-BOLD Methods: Arterial Spin Labeling

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Lecture Goals

• Other non-BOLD techniques (T2 weighted, Mn contrast agents, SSFP, Dynamic Diffusion, ASL)

• Understand Basic Principles in Spin labeling: spin inversion, flow vs. perfusion,

• ASL variations

• Quantification of perfusion from ASL data

• Functional ASL analysis: Detection and Quantification

• Some Examples

• The niche for functional ASL
The BOLD Effect

(Figure courtesy of Doug Noll)
Drawbacks of BOLD imaging

- Not a quantitative physiological parameter
- Non-linear function of neuronal activity
- Signal drifts ("1/f noise")
- Susceptibility artifacts
- Small contrast / noise ratio
Alternatives to BOLD


Alternatives to BOLD


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**Results**

**Fig.1:** SPM activation map from a $b=2400 \, \text{s/mm}^2$ diffusion-sensitized data set showing areas of increased signal (decreased diffusion).

**Fig.2:** Diffusion-derived swelling (red) and normalized BOLD (blue) time courses for subject CH. Arrows: landmarks of interest showing the time lag between swelling and BOLD. Dark blue: activation paradigm.

**Fig.3** Plot of $X^2(\Delta t)$ against $\Delta t$ between diffusion and time-shifted BOLD (blue) time courses, and $\Delta t$ derivative (black) to peak up minimum.

**Fig.4:** Diffusion-derived swelling (red) and normalized BOLD (blue) time courses of subjects YA... and NA...
Alternatives to BOLD


Alternatives to BOLD

- $T_{1\rho}$: also sensitive to blood volume and oxygenation, but not to magnetic susceptibility.

Alternatives to BOLD

- A Novel Method for Direct Detection and Spatial Mapping of Neuronal Activity
  Jeongtaek Lee, Seung-Kyun Lee, and Jang-Yeon Park
  Proc ISMRM 2018 #703

- Mapping Neural Circuitry at High Speed (10Hz) using functional Magnetic Resonance Elastography (fMRE)
  Samuel Patz, Daniel Fovargue, Katharina Schregel, Navid Nazari, Miklos Palotai, Paul E. Barbone, Ben Fabry, Alexander Hammers, Sverre Holm, Sebastian Kozerke, David Nordsletten, and Ralph Sinkus
  Proc ISMRM 2018, 704
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Enter Arterial Spin Labeling:

- Traditional Perfusion measurements are based on the injection of a tracer.


- Apply what we know from PET, …etc.
Obvious advantages
(fine print: there are drawbacks too)

• Completely non-toxic
• No injections!
• Easy to deliver a good input function to the tissue of interest.
• Quick decay = Quickly repeatable.
Arterial Spin Labeling

Inflow of labeled blood reduces signal intensity at the target tissue

Label is “injected” upstream of the target tissue: RF pulses produce inversion of the spins
Quick Review: The MR signal

The MR signal is proportional to the *net* magnetization vector

\[ \sum \longleftrightarrow \bigg\uparrow \]
Flow contrast

Inflowing spins are inverted!
A generic ASL pulse sequence

Some Options
- Pulsed vs. Continuous
- Delays
- Saturation Pulses
- 2D, 3D …
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Simplest case: Continuous ASL
Example: Baseline Perfusion Image
High Res. Perfusion Image
The Inversion Label

Flow Driven Adiabatic Pulses

- Effective field ($B_{\text{eff}}$) in Rotational Frame of Reference
- Frequency Sweep
- Effective Field: $B_{\text{eff}} = \Delta \omega / \gamma + B_1$
- “Spin Locking”
- Flow: $z(t) = v \times t + z_0$
  $\Delta \omega / \gamma = z(t) * G_z$
Inversion and Decay (different velocities)
Side effect at the imaging slice: Magnetization Transfer (MT)

\[ K_f M_f = K_b M_b \]

- On-Resonance spins affected by off-resonance pulses
- Can be used as a form of contrast
MT solution:
two-Coil AST scheme
MT Solutions:
Pseudo-continuous inversion

• Tag is achieved by a train of RF pulses: steady state inversion
• Control case: steady state is disrupted
• Both cases produce the same amount of MT

Continuous ASL
Pulsed ASL
Velocity Selective ASL
Consensus for clinical ASL

- PCASL
- Long post labeling delay
- 3D GRASE acquisition
- Background suppression

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The ASL signal

Arterial signal

Dispersion: \((t \, e^{-kt})\)
Relaxation: \((e^{-t/T1a})\)

Parenchymal signal

Capillary Bed Retention
\((f \, e^{-(f/l)t})\)

Relaxation \((e^{-t/T1})\)

Venous signal

Input Function (Label)

Blood from the Heart

Artery

Blood to the Heart

Vein
Two Compartment Model

FIG. 1. Diagram of the two-compartment perfusion model and the flow encoding arterial spin tagging (FEAST) technique. In the original ASL technique with a postlabeling delay time (a), the perfusion signal acquired without bipolar gradients has two source contributions from the vascular and capillary/tissue compartments. By applying appropriate bipolar gradients to spoil the vascular signal (b), only ASL signal in the capillary/tissue compartment is acquired. Tissue transit time can be obtained by the ratio between the ASL signals acquired with and without bipolar gradients. Note that the premise of this model is that the postlabeling delay time is greater than vascular transit time but less than tissue transit time.
Quantification of perfusion
(the model)

\[
\frac{dM_{\text{tissue}}(t)}{dt} = f \times M_{\text{art}}(t) - \frac{f}{T_1} \times M_{\text{tissue}}(t)
\]

- \( M_{\text{tissue}} \): accumulated tissue magnetization tag (subtraction of control and tagged images)
- \( M_{\text{art}} \): incoming arterial magnetization tag - must account for inversion efficiency and decay \( (2\alpha e^{-\Delta T_1/\text{art}}) M_{\text{art}}(0)) \)
- \( \lambda \): blood brain partition coefficient
- \( f \): perfusion rate
- \( T_1 \): longitudinal relaxation rate of the tissue

Another way to look at it

\[
M_{\text{tissue}}(t) = f \times M_{\text{art}}(t) \times [r(t)m(t)]
\]

- \( r(t) \): tissue retention function \( (e^{ft}) \)
- \( m(t) \): T1 decay of tag in the tissue \( (e^{-t/T_1}) \)

Quantification of perfusion

- Continuous ASL: steady state solution yields a “simple” equation

- Pulsed ASL: not as simple. You really need to fit the equation for the different stages of the passage... There are approximations, such as assuming that you sample during the uptake portion of the passage:

- references
  - Yang, MRM, 39, 1998, p.825
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Example: Functional ASL
A Linear Model for ASL

- Base image
- BOLD effects
- ASL at rest
- ASL during activation
Analyzing ASL based FMRI signals

• It is very common to difference the data and/or apply filters.

• To difference or not to difference?
  – Warning: AR noise is still present
  – Differencing Amplifies (high frequency noise) transitions.
  – Short Answer: It is preferable to model the sources than to modify the data. Greater estimation efficiency and power.

Analyzing ASL based FMRI signals

- **Differencing the timecourse**: perfusion is proportional to the difference between control and tag
- **Differencing schemes** help you clean up the data

**pairwise**

$$y_2[m] = y_c[m] \quad y_t[m] \iff D_2 = \begin{bmatrix} 1 & 1 & 0 \\ 0 & 1 & 1 \end{bmatrix}$$

**running**

$$y_3[n] = (1^n \cdot (y[n] \quad y[n+1]) \iff D_3 = \begin{bmatrix} 1 & 1 & 0 \\ 0 & 1 & 1 \end{bmatrix}$$

**surround**

$$y_4[n] = (1^n \cdot (2y[n] \quad y[n+1] \quad y[n+2]) \iff D_4 = \begin{bmatrix} 1 & 2 & 1 \\ 1 & 2 & 1 \end{bmatrix}$$
Effect of Differencing ASL Data (frequency content)
The GLM Equations in ASL

• Simple GLM:
  \[ Y = X\beta + \varepsilon \]

• Differencing the data (and the design matrix)
  \[ DY = DX\beta + D\varepsilon \]

• Prewhitening : Generalized Least Squares
  \[ WY = WX\beta + W\varepsilon \]
GLS Analysis of un-differenced data vs. OLS Analysis of differenced data
Quantifying *dynamic* perfusion changes

“Simple” Approach:

2. Calculate difference in perfusion between conditions.
3. Calculate means and variances

GLM Approach:

1. Translate GLM parameters (betas) into perfusion.
2. Translate variance estimates (sigmas) into perfusion effects variance

Quantifying *dynamic* perfusion changes

\[
\hat{f}_{\text{effect}} = \frac{\hat{b}_{\text{effect}} \times R_{1\text{app}}}{0 \times 2 \times \hat{\lambda} \times R_{1a} \left( e^{(w)R_{1\text{app}}} e^{(w)R_{1\text{app}}} \right)}
\]

\(f_{\text{effect}}\) is the perfusion change due to the effect of interest,

- \(\alpha\) is the inversion efficiency,
- \(\beta_{\text{effect}}\) is the parameter estimate of the regressor representing the effect of interest,
- \(\lambda\) is the blood brain partition coefficient,
- \(R_1, R_{1a}, R_{1\text{app}}\) are longitudinal relaxation rates of arterial blood, tissue, and tissue in the presence of perfusion.
- \(\delta\) is the arterial transit time,
- \(TR, w, \text{ and } \tau\) are repetition time, post labeling delay, and labeling duration.
Quantifying the variance of those *dynamic* perfusion changes

\[ \hat{s}^2_{\text{effect}} = \hat{s}^2_{0} \frac{\left( \hat{f}_{\text{effect}} \right)^2}{0} + \hat{s}^2_{\text{effect}} \frac{\left( \hat{f}_{\text{effect}} \right)^2}{\text{effect}} + 2 \times \text{COV}\left( \hat{b}_0, \hat{b}_{\text{effect}} \right) \]

\[
\hat{f}_{\text{effect}} = \frac{\hat{b}_0 \times R_{1\text{app}}}{1 - e^{-TR \times R_1}} \times 2 \times e^{-R_1a \left( e^{(w)\times R_{1\text{app}}} - e^{(w)\times R_{1\text{app}}} \right)}
\]

\[
\hat{f}_{\text{effect}} = \frac{\hat{s}^2_{0} \times R_{1\text{app}}}{1 - e^{-TR \times R_1}} \times 2 \times e^{-R_1a \left( e^{(w)\times R_{1\text{app}}} - e^{(w)\times R_{1\text{app}}} \right)}
\]
Maps of Perfusion Effects and their Variance
Estimates and their Variance
The whole ASL Processing Stream
Software you can use

**BASIL:**
http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/BASIL

**f-ASL**
http://www.eecs.umich.edu/~hernan/Public/Programs

**ASLtbx**
https://cfn.upenn.edu/~zewang/ASLtbx.php
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Real Time F-ASL (pCASL)
Motor Visual Paradigm

Current Raw image

Current Subtracted image

Statistical Map

Time courses
Example: Working memory training study

M. Buschkuehl, et al “Neural effects of short-term training on working memory.”

• How does cognitive training affect performance?
• What happens to your brain when you practice?
  • Resting
  • Activation
Working memory training study: the experiment

Paradigm: blocks of rest, 4-back and 1-back
Imaging with pseudo-continuous ASL
Working Memory Load: 4-back – 1-back

1. Test Performance (while collecting ASL images)
2. Train for one week, 20 mins. per day
3. Test Performance (while collecting ASL images)
Working memory training study:

Effect of training: bigger activations

Fig. 4 Task-related perfusion in the 4-back minus 1-back contrast. The numbers next to each slice represent the z-coordinates in MNI space. This figure corresponds to the data reported in Table 1
Working memory training study

Effect of training: Resting Perfusion Change

Note: there was a correlation between performance and resting CBF in frontal regions!
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Why ASL?
Quantification.

- **Quantification:**
  - **BOLD:** a complicated mix of parameters
  - **Perfusion:** Single physiological parameter

- **Real Time neuro-feedback:** How do you evaluate whether subject’s brain is doing the “right thing”?
  1. Brain activity matches a specific **spatial** pattern
  2. Brain activity matches a specific **temporal** pattern
  3. **Amount** of activity in a given region
Why ASL?
The BOLD Signal Drift

• Autoregressive structure
• BOLD signals are inherently “drifty” because:
  – Physiological effects
    • Respiration
    • Heart beat
  – Scanner effects
  – Temperature
ASL Perfusion vs. BOLD
Very Low Task Frequency


Treatment effects START in this range!
Event Related BOLD

An FMRI signal with Gaussian noise

An FMRI signal with AR noise
Blocked Design BOLD: Slow Paradigm

An FMRI signal with Gaussian noise

An FMRI signal with AR noise
Blocked Design FASL: Slow Paradigm

An ASL signal with Gaussian noise

An ASL signal with AR noise
Blocked Design FASL: Slow Paradigm
ASL Perfusion fMRI vs. BOLD (sensitivity)

ASL’s niche

Applications

- Drug Studies
- Attention
- Cognitive Training
- Slow paradigms
- Mental State studies
- Population Studies
- … anything SLOW or requiring Quantification!

- Current ASL techniques have lower SNR and Speed than BOLD

- BOLD breaks down in slow paradigms because of autoregressive drifts
Some References


