Arterial Spin Labelling:
Non-invasive measurement
of perfusion

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Perfusion

• Perfusion is a measurement of delivery of blood to capillary bed
  ➔ Related to nutrient delivery to cells and waste removal.
  ➔ Altered by task activity.
  ➔ Changes in disease.

• Quantity of blood *delivered* per unit of tissue per unit of time
  ➔ ml blood / 100g tissue / min
  ➔ (Dimensions of [T]⁻¹)
  ➔ Grey matter ‘magic’ number: 60 ml/100g/min

• Cerebral Blood Flow (CBF) is a misleading name!

• To image perfusion we need a tracer
  ➔ ASL uses blood-water as an endogenous tracer.
Perfusion

- Why use ASL?
  - A direct measure of perfusion changes - physiological response.
  - (Potentially) fully quantitative - possible to calculate absolute perfusion.
  - Good for low frequency or ‘one-off’ designs.
  - Large ‘effect size’.

- What are the challenges?
  - SNR
  - Temporal sampling - TR and the need for label and control scans.
• ASL is not BOLD!
  ➡ CBF change is a component of the BOLD signal.
  ➡ ASL can make absolute measurements under different conditions.
  ➡ You DON'T need a interleaved design with ASL.
  ➡ ‘Rest’ and ‘task’ don’t even need to be in the same session.

• ASL and BOLD can be combined
  ➡ Dual (multi-) echo ASL/BOLD

**Perfusion**

[Diagram showing baseline and activated states with blood flow changes indicated]

**Simple paradigm design:**
- stimulus vs baseline
- constant stimulus “intensity”
- constant block lengths
- many repetitions: ABABA

Need baseline (rest) condition to measure change:

A (baseline) A (baseline) A (baseline)
B (stimulus) B (stimulus) A (baseline)

Time (TRs): 0 1 2 3 4 5

Stimulus example: flashing chequerboard

Arterial Spin Labelling : M.A. Chappell
FSL for Arterial Spin Labelling

- **BASIL**: a toolset for resting ASL quantification:
  - CBF quantification.
  - Calibration / M0 estimation
  - Registration.
  - Partial volume correction.

- Command line tools
  - oxford_asl, basil, asl_reg, asl_calib

- Graphical User Interface
  - asl_gui

- **NEW VERSION!** available as a ‘pre-release’ - you will be using this version on the course.
What Have I Got Here!? 

- What I have...

- What I want...

- What should I do?

I just want to do something simple/easy!

I must have absolute perfusion (ml/100g/min)

Command line instructions here for future reference...
Outline

• Acquisition

• Keep it simple!
  ➡ Perfusion weighted images.

• Quantitative perfusion:
  ➡ Kinetics: A short course in tracer kinetics.
  ➡ Calibration: Measuring arterial blood magnetization.

• Preparing for group analysis.

• Advanced quantification:
  ➡ Distortion Correction
  ➡ Macro vascular contamination
  ➡ Partial Volume Correction
A tracer experiment with an endogenous tracer - **blood water**.

**Arterial Spin Labelling**

- Label blood by magnetic inversion
- Wait for blood to reach brain
- Acquire image of brain

**LABEL**

**CONTROL**
Spot the difference?

**LABEL**

**CONTROL**

Perfusion is $\sim 60 \text{ ml/100g/min} = 0.01 \text{ s}^{-1}$

Signal is $\sim 1\text{-}2\%$
ASL Acquisition

- Nuts & bolts: Labelling

**pASL: Pulsed ASL**
- Label a region in a single pulse

**cASL: Continuous ASL**
- Label blood flowing through a plane for some time

**pcASL: Pseudo-Continuous ASL**
- pcASL uses pulses and is more widely available

Label blood by magnetic inversion
ASL Acquisition

- Nuts & bolts: Inflow time

Wait for blood to reach brain
Label blood by magnetic inversion

pcASL

- Post-labeling delay (PLD)

pASL

- Inversion time (TI)
ASL Acquisition

- Nuts & bolts: Bolus/label duration

**pcASL**
- Label duration (τ)
- Post-labeling delay (PLD)

**pASL**
- Label duration is undefined in pASL.
- QUIPSSII pulses ‘cut off’ the end of the labeled bolus.

**Wait** for blood to reach brain

**Label** blood by magnetic inversion
ASL Acquisition

- Nuts & Bolts: Background Suppression

**pcASL**

- **cASL label**
- Background suppression pulse(s)
- Imaging

**Wait** for blood to reach brain

**Label** blood by magnetic inversion

- Suppress signal from static tissue
- Reduce subtraction artefacts
- Reduce sensitivity to motion and physiological noise
ASL Acquisition

- **Nuts & Bolts: Readout**

  **Label** blood by magnetic inversion

  **Wait** for blood to reach brain

  **Aquire** image of brain

**3D: GRASE/RARE**

- Higher SNR
- Long echo-train: blurring
- Muti-shot/segmented approaches

**2D: EPI (Multi-slice)**

- Different PLD for each slice
ASL Acquisition

- The ASL ‘white paper’ - a good place to begin:
  - **Use pcASL where possible**
    - Label duration 1800 ms
    - Post labeling delay ~1800 ms
  - **Otherwise pASL with QUIPSSII**
    - Inversion time ~1800 ms
    - TI1 of 800 ms
    - Slab thickness 15-20 cm
  - **Ideally 3D readout.**
    - 2D EPI an acceptable alternative.
  - **Resolution:**
    - 3-4 mm in plane.
    - 4-8 mm through plane.
  - **Use background suppression.**

Recommended Implementation of Arterial Spin Labeled Perfusion MRI for Clinical Applications: A consensus of the ISMRM Perfusion Study Group and the European Consortium for ASL in Dementia

**Outline**

- Acquisition
- Keep it simple!
  - Perfusion weighted images.
- Quantitative perfusion:
  - Kinetics: A short course in tracer kinetics.
  - Calibration: Measuring arterial blood magnetization.
- Preparing for group analysis.
- Advanced quantification:
  - Distortion Correction
  - Macro vascular contamination
  - Partial Volume Correction
**Example (simple)**

- **What I have...**
  - ➔ ASL data!

- **What I want...**
  - ➔ A perfusion image (in this subject).

- **What should I do?**
  - ➔ Label-control subtraction
  - ➔ Average

```bash
asl_file --data={ASLdata.nii.gz} --ntis=1 --iaf=tc --diff --out={diffdata.nii.gz}
asl_file --data={ASLdata.nii.gz} --ntis=1 --iaf=tc --diff --mean={diffdata_mean.nii.gz}
```
• Acquisition

• Keep it simple!
  ➡️  Perfusion weighted images.

• Quantitative perfusion:
  ➡️  Kinetics: A short course in tracer kinetics.
  ➡️  Calibration: Measuring arterial blood magnetization.

• Preparing for group analysis.

• Advanced quantification:
  ➡️  Distortion Correction
  ➡️  Macro vascular contamination
  ➡️  Partial Volume Correction
**Example**

- **What I have...**
  - ASL data
  - (calibration images)

- **What I want...**
  - Perfusion in ml/100g/min

- **What should I do?**
  - Label-control subtraction. ✓
  - Kinetic model inversion. ←
  - Calibration
Introduce tracer

Arterial Input Function

Tissue (voxel)

Residue Function

\[ \Delta M(t) = F \cdot \text{AlF}(t) \cdot r(t) \]
Kinetic Model Inversion

Arterial Input Function

Tracer concentration tells us about the delivery of the tracer

Tracer concentration over time
Kinetic Model Inversion

Parameters:
- Arterial Transit time
- Label duration
- T1 decay (in blood)

pcASL

AIF

LABEL

T1 decay

Tissue (voxel)
Residue Function

Tells us what happens to the tracer after it has arrived.

Tracer Remaining

100%

‘time’
Kinetic Model Inversion

‘Well mixed’ T1 decay

- Rapid exchange: single well mixed compartment
- No spins leave the compartment
- Decay with T1

Parameters:
Arterial Transit Time
Label duration
T1 decay (in blood)
\[ \Delta M(t) = F \cdot \text{AIF}(t) \ast r(t) \]

**Parameters:**
- Perfusion - \( F \)
- Arterial Transit Time
- Label duration
- T1 decay (in blood)
Kinetic Model Inversion

Arterial Input Function

Residue Function

Concentration time curve
The ‘simple’ model
- Only one $T_1$ value (blood)
- Spins never leave tissue

The ‘standard’ model:
- Separate $T_1$ for blood and tissue ($T_{1b} < T_{1t}$).
- Spins leave voxel at rate determined by perfusion and partition coefficient.

**Example**

**What you need to know about your data:**

<table>
<thead>
<tr>
<th>Labeling</th>
<th>pASL (pulsed)</th>
<th>pcASL (continuous)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inversion time(s)</td>
<td>or</td>
<td>Post-labeling delay(s)</td>
</tr>
<tr>
<td>Bolus duration</td>
<td></td>
<td>Labeling duration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model</th>
<th>3D/2D (slice timing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 (tissue and blood)</td>
<td></td>
</tr>
<tr>
<td>Arterial Transit Time</td>
<td></td>
</tr>
</tbody>
</table>

**What I have...**
- ASL data
- (calibration images)

**What I want...**
- Perfusion in ml/100g/min

**What should I do?**
- Label-control subtraction. ✓
- Kinetic model inversion. ←
- Calibration.

```
oxford_asl -i {asl_data} -o {output_dir} --iaf={tc} {--casl} --tis={list_of_TIs} --bolus={bolus_duration} --slicedt={time_per_slice} {model/analysis options}
```
Example

- What I have...
  - ASL data
  - (calibration images)

- What I want...
  - Perfusion in ml/100g/min

- What should I do?
  - Label-control subtraction. ✓
  - Kinetic model inversion.
  - Calibration

**pcASL** with
- labeling duration: 1.8 s
- post-label delay: 1.8 s

2D readout
- 45.2 ms per slice

Assume 'white paper'
- TI : 1.65 s
- ATT : 0 s

Arterial Spin Labelling : M.A. Chappell
**Example**

**pcASL** with
- labeling duration: 1.8 s
- post-label delay: 1.8 s
- 2D readout
  - 45.2 ms per slice

Assume
- ‘white paper’
- $T1 = 1.65$ s
- $ATT = 0$ s

#Do label control subtraction

```bash
> asl_file --data={ASLdata.nii.gz} --ntis=1 --iaf=tc --diff --out={asldiffdata.nii.gz} \ 
   --mean={asldiffdata_mean.nii.gz}
```
**Example**

**pcASL** with
labeling duration: 1.8 s
post-label delay: 1.8 s

**2D** readout
45.2 ms per slice

Assume
‘white paper’

T1 : 1.65 s
ATT : 0 s

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```bash
# Do label control subtraction
> asl_file --data={ASLdata.nii.gz} --ntis=1 --iaf=tc --diff --out={asldiffdata.nii.gz} \ 
  --mean={asldiffdata_mean.nii.gz}
```
**Example**

- **What I have...**
  - ASL data
  - (calibration images)

- **What I want...**
  - Perfusion in ml/100g/min

- **What should I do?**
  - Label-control subtraction.
  - Kinetic model inversion.
  - M0 calculation.

**pcASL** with
- labeling duration: 1.8 s
- post-label delay: 1.8 s
- 2D readout
  - 45.2 ms per slice

Assume
- 'white paper'
  - TI : 1.65 s
  - ATT : 0 s

---

#Do label control subtraction
asl_file --data={ASLdata.nii.gz} --ntis=1 --iaf=tc --diff --out={asldiffdata.nii.gz} \  --mean={asldiffdata_mean.nii.gz}
**Example**

pcASL with
labeling duration: 1.8 s
post-label delay: 1.8 s

2D readout
45.2 ms per slice

Assume
‘white paper’
T1 : 1.6 s
ATT : 0 s

Do motion correction

---

`# Do the analysis using oxford_asl`

```
> oxford_asl -i {ASLdata.nii.gz} -o {oxasl} --iaf=tc --casl --tis=3.6 --bolus=1.8 /
    --slicedt=0.0452 --wp --mc
```

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Example

Perfusion (arbitrary units)

oxas1/native_space/perfusion.nii.gz
• What I have...
  ➞ ASL data
  ➞ (calibration images)

• What I want...
  ➞ Perfusion in ml/100g/min

• What should I do?
  ➞ Tag-control subtraction. ✓
  ➞ Kinetic model inversion. ✓
  ➞ Calibration  ←
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**Calibration**

*Well mixed*

\[ T_1 \text{ decay} \]

\[ \Delta M(t) = 2 \cdot \alpha \cdot M_{0a} \cdot F \cdot AIF(t) * r(t) \]

**Imperfect inversion**

Inversion efficiency \( \alpha \)
Cannot measure $M_{0a}$ directly.

indirect via brain ‘tissue’ magnetization.

Calculate $M_{0t}$.

($M_{0}$ of ‘tissue’)

$M_{0t}$ to $M_{0a}$.

Calibration image:

- Proton Density weighted
- ‘Long’ TR: > 5 seconds
- No labelling or background suppression

Account for relative proton densities:

$$M_{0a} = \frac{M_{0t}}{\lambda}$$

Partition co-efficient $\lambda$

(relative concentration of water)
Calibration

- Cannot measure M0a directly.
- Indirect via brain ‘tissue’ magnetization.
  - Calculate M0t.
    - (M0 of ‘tissue’)
  - M0t to M0a.
- Practicalities
  - Voxelwise

Perfusion (ml/100g/min) = (Perfusion / M0a) × 6000

Voxelwise Calibration

\[
\text{Voxelwise Calibration} = \frac{\text{Perfusion}}{\text{M0a}} \times 6000
\]

```
foxford_asl ... -c {calibration_image.nii.gz} --tr=[TR]
asl_calib --mode longtr ...
asl_calib --mode satrecov ...
fslmaths {perfusion.nii.gz} -div [M0a] -mul 6000 {perfusion_calib.nii.gz}
```
Calibration

- Cannot measure M0a directly.
- Indirect via brain ‘tissue’ magnetization.
  - Calculate M0t.
    - (M0 of ‘tissue’)
  - M0t to M0a.
- Practicalities
  - Reference Tissue

Perfusion (ml/100g/min) = (Perfusion / M0a) × 6000

Reference Tissue
CSF or WM

```
oxord_asl ... -c {calibration_image.nii.gz} --tr=[TR]
asl_calib --mode longtr ...
asl_calib --mode satrecov ...
fslmaths {perfusion.nii.gz} -div [M0a] -mul 6000 {perfusion_calib.nii.gz}
```
Example

- What I have...
  - ASL data
  - (calibration images)

- What I want...
  - Perfusion in ml/100g/min

- What should I do?
  - Label-control subtraction.
  - Kinetic model inversion.
  - Calibration

**pcASL** with
- labeling duration: 1.8 s
- post-label delay: 1.8 s

**2D readout**
- 45.2 ms per slice

Assume
- T1 (blood) : 1.6 s
- T1 (tissue) : 1.3 s
- ATT : 1.3 s
- $\alpha$ : 0.85
**Calibration image**

No background-suppression
TR: 4.8 s
# Do the analysis using oxford_asl

```
oxford_asl -i {ASLdata.nii.gz} -o {oxasl} --iaf=tc --casl --tis=3.6 --bolus=1.8 / --slicedt=0.0452 --wp --mc --c {calibration_image.nii.gz} --tr=4.8
```

**Calibration image**
TR: 4.8 s

**Calibration mode**
Voxelwise
Example

Perfusion (ml/100g/min)

Correct for ‘edge effects’ (and distortion)

oxasl/native_space/perfusion_calib.nii.gz
Do the analysis using oxford_asl

```bash
# oxford_asl -i {ASLdata.nii.gz} -o {oxasl} --iaf=tc --casl --tis=3.6 --bolus=1.8 / --slicedt=0.0452 --wp --mc --c {calibration_image.nii.gz} --tr=4.8 / --fslanat=T1.anat
```

**Example**

**Calibration image**

TR: 4.8 s

**Calibration mode**

- Reference region
  - CSF (ventricles)

**Calibration mask**

(derived automatically from structural image)
Example

**Perfusion (ml/100g/min)**

**Voxelwise**

**Reference region**

oxas1/native_space/perfusion_calib.nii.gz

**Ventricular mask**

(automatically generated)
Summary

- The ASL ‘white paper’ quantification formula (pcASL):

\[
\text{CBF} = \frac{6000 \cdot \lambda \cdot (\text{SI}_{\text{control}} - \text{SI}_{\text{label}})}{2 \cdot \alpha \cdot T_{1,\text{blood}} \cdot \text{SI}_{\text{PD}} \cdot (1 - e^{-\frac{\text{PLD}}{T_{1,\text{blood}}}})} e^{\frac{T_{1,\text{blood}}}{\tau}}\]

**Subtraction**

**Kinetic Model Inversion**

**M0 Calculation** (Calibration)

**Values:**
- \( T_{1,\text{blood}} = 1650 \text{ ms (3T)} \)
- \( \alpha = 0.85 \)
- \( \lambda = 0.9 \text{ ml/g} \)

**Assumptions:**
- Voxelwise calibration (\( M_{0t} = \text{SI}_{\text{PD}} \))
- \( T_{1,\text{tissue}} = T_{1,\text{blood}} \)
- ATT = 0

Recommended Implementation of Arterial Spin Labeled Perfusion MRI for Clinical Applications: A consensus of the ISMRM Perfusion Study Group and the European Consortium for ASL in Dementia

**EXAMPLE**

- **What I have...**
  - ASL data - multi-PLD
  - (calibration images)

- **What I want...**
  - Perfusion in ml/100g/min

- **What should I do?**
  - Label-control subtraction.
  - Kinetic model inversion.
  - Calibration

---

pcASL with

- labeling duration: 1.4 s
- post-label delays: 0.25, 0.5, 0.75, 1.0, 1.25, 1.5 s

TI: 1.65, 1.9, 2.15, 2.4, 2.65, 2.9

---

# Label control subtraction for each PLD individually

```bash
> asl_file --data={ASLdata.nii.gz} --ntis=6 --iaf=tc --ibf=rpt --diff --split \ 
  --mean={asldiffdata_mean_at_each_PLD.nii.gz}
```
**Kinetic Model Inversion**

`'Well mixed'`

![Diagram](image)

**Parameters:**
- Perfusion - $F$
- Arterial Transit Time
- Label duration
- $T_1$ decay (in blood)
- $T_1$ decay (in tissue)

\[
\Delta M(t) = F \cdot AIF(t) \ast r(t)
\]
Kinetic Model Inversion

Parameters:
- Perfusion - \( F \)
- Arterial Transit Time
- Label duration
- \( T_{1\text{tissue}} \)
- \( T_{1\text{blood}} \)

Model

Data

Single-TI/PLD
- Analytic solution
- Bayesian inference (BASIL)

Multi-TI/PLD
- Non-linear fitting (least squares)

Chappell et al., IEEE TSP 57(1), 2009.
Kinetic Model Inversion

- Perfusion
  - Want to know this - variable

- Arterial Transit Time
  - Want to correct for this - variable

- Label duration
  - Set by sequence - fixed
  - but limited to a sensible range
  - (might not be that well fixed, pASL?)

- $T_1$ tissue
  - 1.3 s at 3T - fixed

- $T_1$ blood
  - Doesn't $T_1$ vary a bit?
  - 1.65 at 3T - fixed
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Kinetic Model Inversion

Priors:

- Perfusion
- Bolus arrival time
- Bolus duration
- T1

Spatial prior:

Prior distribution for perfusion in voxel defined over its neighbours

σ - spatial scale of prior (determined from the data)
EXAMPLE

• What I have...
  ➔ ASL data - multi-TI/PLD
  ➔ (calibration images)

• What I want...
  ➔ Perfusion in ml/100g/min

• What should I do?
  ➔ Label-control subtraction.
  ➔ Kinetic model inversion.
  ➔ Calibration.

**pcASL** with
  labeling duration: 1.4 s
  post-label delays: 0.25, 0.5, 0.75, 1.0, 1.25, 1.5 s

TI: 1.65 1.9 2.15 2.4 2.65 2.9

# Label control subtraction for each PLD individually
> asl_file --data={ASLdata.nii.gz} --ntis=6 --iaf=tc --ibf=rpt --diff --split \
  --mean={asldiffdata_mean_at_each_PLD.nii.gz}
Example

pcASL with
labeling duration: 1.4 s
post-label delays: 0.25, 0.5, 0.75, 1.0, 1.25, 1.5 s

> oxford_asl -i {ASLdata.nii.gz} -o {oxasl} --iaf=tc --ibf=rpt --casl --tis=1.65,1.9,2.15,2.4,2.65,2.9 --bolus=1.4 --slicedt=0.0452 --fixbolus --artoff --mc --c {calibration_image.nii.gz} --tr=4.8
**Example**

- **Data:**
  - pcASL
    - Single-PLD
      - label duration: 1.8 s
      - post-label delay: 1.8 s
      - Assume ATT of 1.3 s
    - Multi-PLD
      - label duration: 1.4 s
      - PLDs: 0.25, 0.5, 0.75, 1.0, 1.25, 1.5 s

oxasl/native_space/perfusion_calib.nii.gz
oxasl/native_space/arrival.nii.gz
Single- vs. Multi-PLD

- Which is better in a fixed scan duration?

Single-PLD

\[ \Delta M(t) \]

\[ \times 6 \]  

Multi-PLD

\[ \Delta M(t) \]

Woods et al. MRM 2018 in press
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• Quantitative perfusion:
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• Preparing for group analysis.

• Advanced quantification:
  ➡ Distortion Correction
  ➡ Macro vascular contamination
  ➡ Partial Volume Correction
Preparing for Group Analysis

• Group analysis and quantitative comparisons between individuals requires consistent representation

• **Consistent geometry:**
  ➡ ‘Spatial’ normalization (registration)
  ➡ Transform perfusion map to a common space, e.g. MNI152

• **Consistent intensity:**
  ➡ Quantitative maps - perfusion in ml/100g/min.
  ➡ Intensity normalization to a reference.
Preparing for Group Analysis

• Registration to ‘standard’ space
  ➔ ASL → Structural
    linear - 6 DOF
  ➔ Structural → Standard
    linear - 12 DOF
    non-linear

oxford_asl ... --s {structural_image.nii.gz}

See also: asl_reg, flirt, fnirt
Run fsl_anat on structural image

BASIL will then do registration and transformation to:
structural space
standard space

> fsl_anat {T1.nii.gz}
> oxford_asl -i {ASLdata.nii.gz} -o {oxasl} --iaf=tc --casl --tis=3.6 --bolus=1.8 /
--slicedt=0.0452 --wp --mc -c {calibration_image.nii.gz} --tr=4.8 /
--fslanat=T1.anat
Preparation for Group Analysis

- **Quantitative maps**
  - Requires estimate of M0a - ‘calibration’ data.
  - Pros:
    - An absolute scale - can potentially relate to physiology
    - Ought to be able to set consistent thresholds
      - e.g. perfusion < 20 ml/100g/min is ischaemia
  - Cons:
    - Requires calibration information.
    - Global perfusion appears to be quite variable between individuals.

- **Intensity normalization:**
  - Requires a ‘reference’.
    - e.g. a brain structure: thalamus
    - e.g. a ‘global’ value: mean in GM or WM
  - Pros:
    - No need for calibration.
    - Removes inter subject variability in ‘global’ perfusion.
  - Cons:
    - Relies on a consistent reference.
Preparing for Group Analysis

- Intensity normalization:
  ➡ Pick a ROI:
    Manually
    From atlas
    From a segmentation
  ➡ Calculate mean within ROI.
  ➡ Scale perfusion maps.

- Transform ROI into perfusion space or vice versa?
  ➡ ROI in high-res -> perfusion space
    Interpolation on ROI mask: sharp boundaries in high-res become ‘soft’ requiring thresholding - possible bias.
  ➡ Perfusion image -> high-res
    Interpolation occurs on perfusion values, ROI untouched.

- Exception is ‘soft’ segmentations
  e.g. GM/WM on a structural image.
  ➡ Transform ‘soft’ segmentations first and THEN threshold to create ROI.
Preparing for Group Analysis

GM PVE

Transform

Threshold at 0.7

High res GM mask

Transform

Threshold at 0.7

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Preparing for Group Analysis

- ROI
  - GM / WM (?)
    - partial volume issues
  - Structures
- Voxelwise

- Designs
  - Group mean
  - Group differences/paired differences

**Absolute perfusion:**
A direct physiological measurement
- e.g. Asllani et al., JCBFM, 28, 2008.
A consistent baseline (c.f BOLD)
- e.g. Wang et. al, MRM, 49, 2003.
Inter subject and inter session variability
- e.g Gevers et al., JCBFM, 31, 2011.
- Petersen et al., NeuroImage, 49(1), 2011.

**Arrival time (multi-TI/PLD):**
Potential confound
An extra quantitative measurement
- e.g. Bokkers et al., AJNR, 29(9), 2008.
- MacIntosh et al, AJNR, 33(10), 2012.

Feat (higher-level analysis)
Randomise
EXAMPLE

• What I have...
  ➔ ASL perfusion in multiple sessions/subjects
  ➔ Structural images

• What I want...
  ➔ Perfusion change/difference (in ml/100g/min)

• What should I do?
  ➔ Registration.
  ➔ GLM

pcASL with
labeling duration: 1.4 s
post-label delays: 0.25, 0.5, 0.75, 1.0, 1.25, 1.5 s

> oxford_asl -i {ASLdata.nii.gz} -o {oxasl} --iaf=tc --ibf=rpt --casl --tis=1.65,1.9,2.15,2.4,2.65,2.9 --bolus=1.4 --slicedt=0.0452 --fixbolus --artoff --mc --fslanat=T1.anat --c {calibration_image.nii.gz} --tr=4.8
- **Data:**
  - pcASL, Multi-PLD
    - label duration: 1.4 s
    - PLDs: 0.25, 0.5, 0.75, 1.0, 1.25, 1.5 s
  - 8 individuals
    - task - finger tapping and visual stimulation

- **Paired t-test**

```
> flameo --cope=perfusion_study.nii.gz \
   --mask=${FSLDIR}/data/standard/MNI152_T1_2mm_brain_mask.nii.gz \
   --dm=design.mat --tc=design.con --cs=design.grp --runmode=ols --ld=flameout
```
**Data:**
- pcASL, Multi-PLD
  - label duration: 1.4 s
  - PLDs: 0.25, 0.5, 0.75, 1.0, 1.25, 1.5 s
- 8 individuals
  - task - finger tapping and visual stimulation

**Paired t-test**

**Perfusion change (effect size)**
Example

- Data:
  pcASL, Multi-PLD
  label duration: 1.4 s
  PLDs: 0.25, 0.5, 0.75, 1.0, 1.25, 1.5 s

- Paradigm
  Monitoring response to painful stimulus

Segerdahl et al. Nat Neuroscience 2015
Outline

- Acquisition

- Keep it simple!
  - Perfusion weighted images.

- Quantitative perfusion:
  - Kinetics: A short course in tracer kinetics.
  - Calibration: Measuring arterial blood magnetization.

- Preparing for group analysis.

- Advanced quantification:
  - Distortion Correction
  - Macro vascular contamination
  - Partial Volume Correction
**Advanced: Distortion Correction**

- EPI readout will include distortion in regions of field inhomogeneity
  - cf BOLD fMRI
- Need to correct for:
  - geometric distortion
  - AND intensity
- Need:
  - field map OR
  - phase encode reversed image

```bash
oxford_asl ... --cblip=ASL_calibration_phase_reversed pedir=[direction] \ --echospacing=[value]
oxford_asl ... --fmap=fieldmap_image --fmapmag=fieldmap_magnitude_image \ --fmapmagbrain=brain_extracted_fmapmag --pedir=[direction] --echospacing=[value]
```
**pcASL** with
labeling duration: 1.8 s
post-label delay: 1.8 s

**2D** readout
45.2 ms per slice

**Calibration images**
TR: 4.8 s

(1) AP encoding
(2) PA encoding
echo spacing (dwell time): 0.06 ms

# Do the analysis using oxford_asl

```
> oxford_asl -i {ASLdata.nii.gz} -o {oxasl} --iaf=tc --casl --tis=3.6 --bolus=1.8 /
--slicedt=0.0452 --wp --mc -c {calibration_image.nii.gz} --tr=4.8 /
--cblip={calibration_PA.nii.gz} --pedir=y --echospacing=0.06
```
Example

Perfusion (ml/100g/min)

oxas1/native_space/perfusion_calib.nii.gz
Advanced: Macro Vascular Contamination

- Early TIs may contain label still within larger arteries.
  ➞ perfusion overestimation

- Use long TI/PLD(s)
- Use flow suppressing gradients
- Include in model - multi-TI data
  ➞ provides estimate of arterial blood volume

oxford_asl: MV component included by default, use --artoff to turn off

Ye et al., MRM 37(2), 1997.
Chappell et al., MRM 63(5), 2010.

Arterial Spin Labelling: M.A. Chappell
An extended model for ASL:

$$\Delta M(t) = CBF \Delta M_{\text{tiss}}(t) + aBV \Delta M_{\text{IV}}(t)$$

**ARD prior:** $\sim N(0, \nu)$

- $\nu$ determines the relevance of the prior.
- $\nu$ is determined from the data.

$\nu \rightarrow 0$

Restrictive prior: parameter forced to prior mean

$\nu \rightarrow \infty$

Liberal prior: parameter free to be estimated from data
EXAMPLE

- **What I have...**
  - ASL data - multi-TI/PLD
  - (calibration images)

- **What I want...**
  - Perfusion in ml/100g/min
  - Arterial blood volume in ml/ml.

- **What should I do?**
  - Tag-control subtraction.
  - Kinetic model inversion.
  - M0 calculation.

```
> oxford_asl -i {ASLdata.nii.gz} -o {oxasl} --iaf=tc --ibf=rpt --casl --tis=1.65,1.9,2.15,2.4,2.65,2.9 --bolus=1.4 --slicedt=0.0452 --fixbolus --artoff --mc -c {calibration_image.nii.gz} --tr=4.8
```
Example

Perfusion ml/100g/min  Arterial cerebral blood volume % (ml/ml * 100)

middle slice  lower slice ~ Circle of Willis

oxasl/native_space/perfusion_calib.nii.gz
oxasl/native_space/aCBV_calib.nii.gz
Partial voluming of grey and white matter inevitable.

Leads to GM perfusion underestimation

- WM perfusion < GM
- WM blood arrival > GM

Correction

- PV estimates from segmentation of structural image.
  Note: partial volume estimates NOT a hard segmentation or probabilities.
- Make separate GM and WM perfusion estimates in every voxel.
  An under determined problem.
• Does it matter that much?
  ➔ Resolution of ASL ~ 3 x 3 x 5 mm
  ➔ Cortical thickness ~ 2 - 4 mm

• Unlikely to have many pure GM or WM voxels in the cortex

**Advanced: Partial Volume Correction**

**Structural resolution**

Partial Volume Estimate  
Threshold at 90%

**ASL resolution**

Partial Volume Estimate  
Threshold at 90%
Advanced: Partial Volume Correction

- Does it matter that much?
  - Resolution of ASL $\sim 3 \times 3 \times 5$ mm
  - Cortical thickness $\sim 2 - 4$ mm

- What is this?

\[ 60 \times PVE_{GM} + 10 \times PVE_{WM} \]  
Estimated perfusion from ASL
What do we mean when we report GM or WM perfusion?

- GM
- WM
- Whole brain

Perfusion $\text{ml/100g/min}$

Threshold on % PVE

**GM mask threshold at 90%**
Partial volume correction exploiting kinetic data:

- CBF: GM > WM
- Bolus arrival: WM > GM
Advanced: Partial Volume Correction

- Multi-component model:

\[
\Delta M(t) = PV_{GM}\Delta M_{GM}(t) + PV_{WM}\Delta M_{WM}(t) + PV_{CSF}\Delta M_{CSF}(t) + aBV \Delta M_{MV}(t)
\]

Grey matter

White matter

CSF

Macro vasc.

- Spatial priors on CBF for GM and WM
**EXAMPLE**

- **What I have...**
  - ASL data - multi-TI/PLD
  - (calibration images)

- **What I want...**
  - Grey matter perfusion in ml/100g/min

- **What should I do?**
  - Tag-control subtraction.
  - Kinetic model inversion.
  - M0 calculation.
  - Partial volume correction

---

**pcASL with**

- **labeling duration:** 1.4 s
- **post-label delays:** 0.25, 0.5, 0.75, 1.0, 1.25, 1.5 s

Segmented **structural image**, e.g. fsl_anat output

---

```bash
> oxford_asl -i {ASLdata.nii.gz} -o {oxasl} --iaf=tc --ibf=rpt --casl --tis=1.65,1.9,2.15,2.4,2.65,2.9 --bolus=1.4 --slicedt=0.0452 --fixbolus --mc --pvcorr --fslanat=T1.anat --c {calibration_image.nii.gz} --tr=4.8
```
EXAMPLE

Perfusion (uncorrected)  ml/100g/min
Grey matter perfusion  ml/100g/min
White matter perfusion  ml/100g/min

oxasl/native_space/perfusion_calib.nii.gz
oxasl/native_space/pvcorr/perfusion_calib_masked.nii.gz
oxasl/native_space/pvcorr/perfusion_wm_calib_masked.nii.gz
**FSL:** The FMRIB Software Library

- BASIL: [www.fmrib.ox.ac.uk/fsl/basil](http://www.fmrib.ox.ac.uk/fsl/basil)
  
  User guide & tutorials for FSL v5.0+
  
  Follow the link for the 'pre-release' and updated user guide/tutorials

**Oxford Neuroimaging Primers:**

Introduction to Perfusion Quantification using Arterial Spin Labelling

- Cover material in this lecture and more.
- [http://www.neuroimagingprimers.org](http://www.neuroimagingprimers.org)
  
  Examples using BASIL (extended from the FSL course)
Acknowledgements

- QuBlc, Engineering Science, Oxford
  - Martin Craig
  - Moss Zhao
  - Flora Kennedy McConnell
  - Tom Kirk
- WIN/FMRIB, Oxford
  - Peter Jezzard
  - Tom Okell
  - Joe Woods
  - Michael Kelly
  - James Meakin
  - Matthew Webster
  - Mark Jenkinson

- Brad MacIntosh (Univ. Toronto)
- Manus Donahue (Vanderbilt)
- Xavier Golay (UCL, London)
- Esben Petersen (Utrecht)
- Marco Castellaro (Padova)
- Ilaria Boscolo Galazzo (Verona)
Task-Based ASL

Why use ASL for a functional experiment?

- A direct measure of perfusion changes - physiological response.
- (Potentially) fully quantitative - possible to calculate absolute perfusion.
- Good for low frequency designs.

What are the challenges?

- SNR
- Temporal sampling - TR and the need for tag and control scans.
- Time series data will contain both ASL (tag-control difference) and BOLD effects (depends upon the TE used).
Task-Based ASL

- What I have...
  - ASL data during a functional task.

- What I want...
  - Activations

- What should I do?
  - Tag-control subtraction
  - GLM
• Two options in FEAT
  ➡ Do subtraction before GLM
  ➡ (FILM prewhitening OFF)
  ➡ ONLY considers the perfusion contribution, subtraction removes BOLD signal.

```
asl_file --data={ASLdata.nii.gz} --ntis=1 --iaf=tc --diff --out={diffdata.nii.gz}
perfusion_subtract {ASLdata.nii.gz} {diffdata.nii.gz}
```
Task-Based ASL

- **Two options in FEAT**
  - **Full model**
    - Includes perfusion and BOLD contributions
  - **EV1** - Tag vs. Control
    - $-1 \ 1 \ -1 \ 1 \ -1 \ 1 \ -1 \ 1$
  - **EV2** - BOLD
  - **EV3** - Interaction

```
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<th>BOLD</th>
<th>c-act</th>
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</tbody>
</table>
```
**QUASAR**

- multi-TI pASL acquisition.
- Mixture of flow suppression on and off.
- Saturation recovery control images

**Analysis**

- model-based - include MV component
- model-free - numerical deconvolution (c.f. DSC)

```bash
quasil -i {QUASAR_image} -o {out_dir}
quasil -i {QUASAR_image} -o {out_dir} --mfree
```

Petersen et al., MRM 55(2),2006.
Chappell et al., MRM e-print, 2013.