Arterial Spin Labelling: Non-invasive measurement of perfusion

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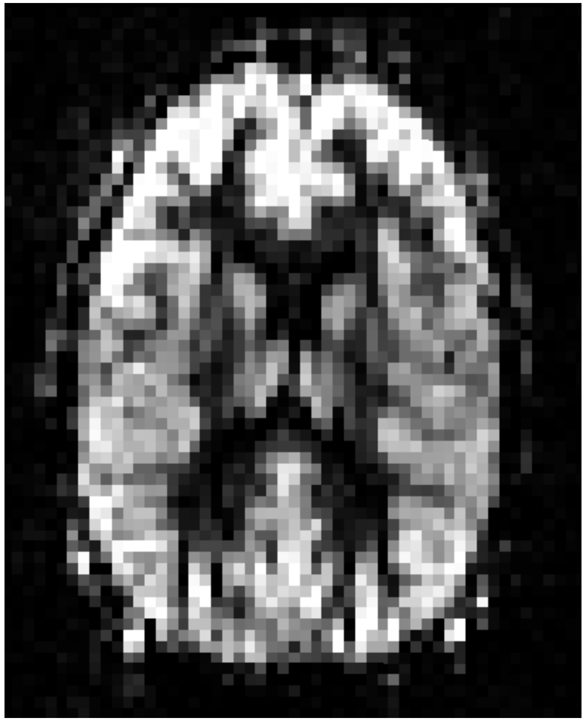
PERFUSION

- 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.



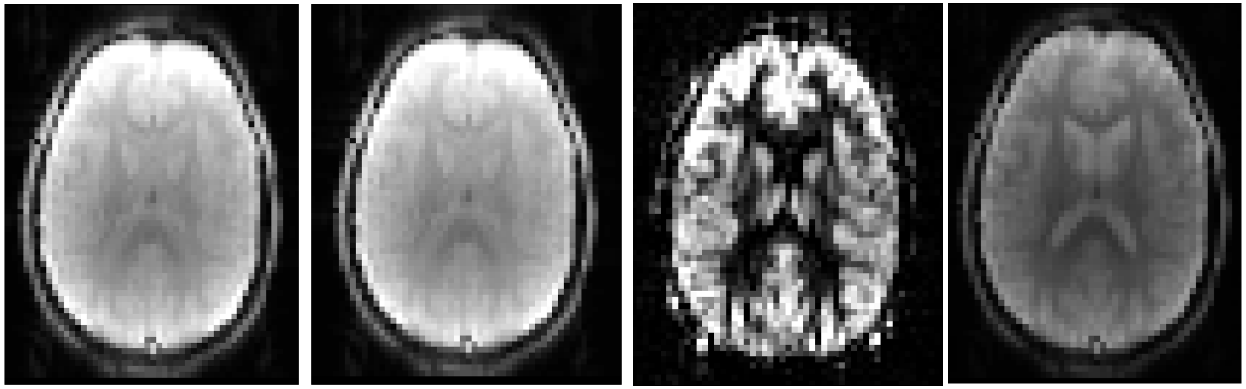
FSL for Arterial Spin Labelling

- 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 (beta)
      Asl / Asl_gui

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)

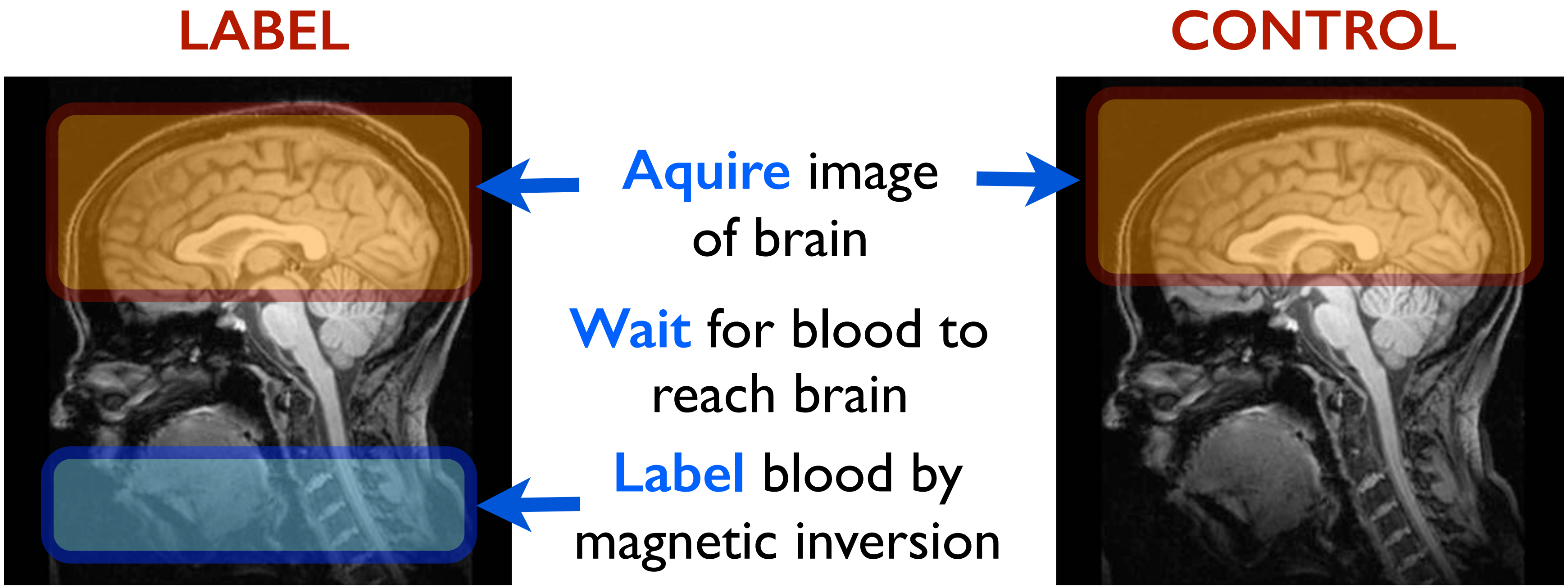
Command line instructions here for future reference...

OUTLINE

- Acquisition
- Keep it simple!
    - ➡ Perfusion weighted images.
    - ➡ Perfusion fMRI.
- Quantitative perfusion:
    - ➡ A short course in tracer kinetics.
    - ➡ Measuring arterial blood magnetization.
- Preparing for group analysis.
- Advanced quantification:
    - ➡ Macro vascular contamination
    - ➡ Partial Volume Correction

Arterial Spin Labelling

- A tracer experiment with an endogenous tracer - **blood water**.



LABEL

CONTROL

Aquire image of brain

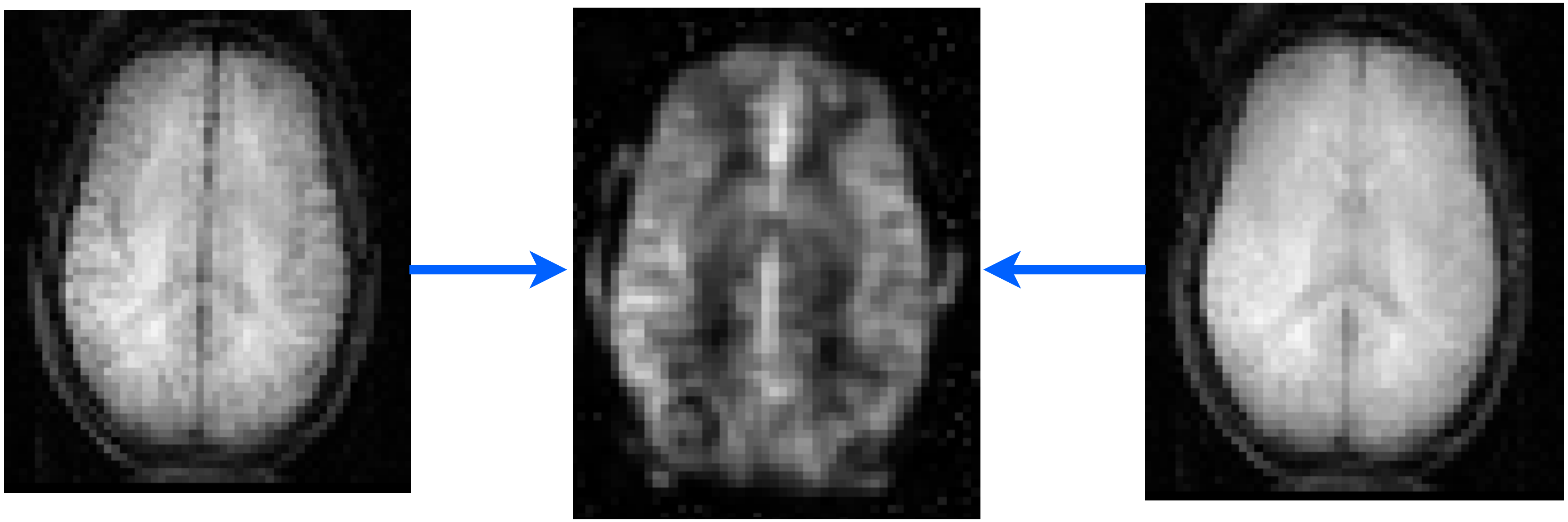
Wait for blood to reach brain

Label blood by magnetic inversion

ASL ACQUISITION

- Spot the difference?

LABEL **CONTROL**

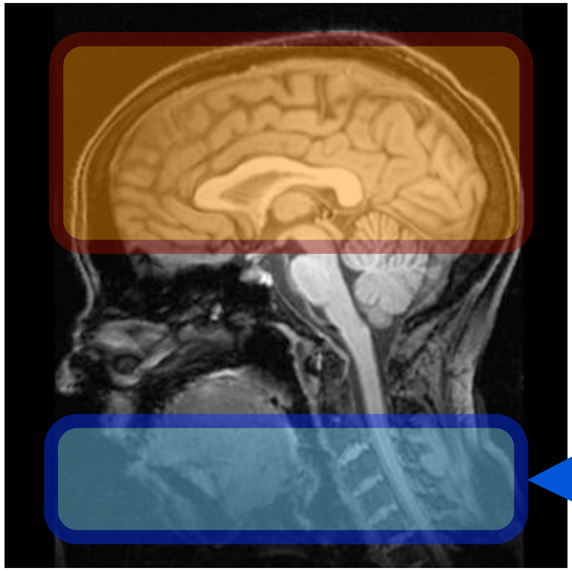


Perfusion is ~60 ml/100g/min = 0.01 s^{-1}
Signal is ~ 1-2%

ASL ACQUISITION

- Nuts & bolts: Labelling

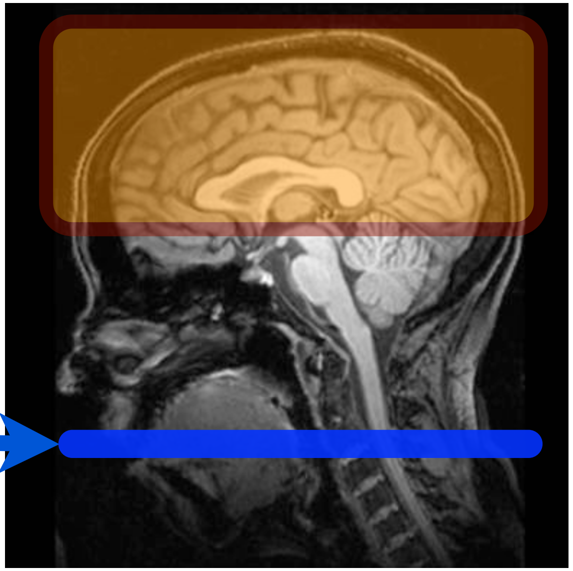
pASL: Pulsed ASL



Label a region in a single pulse

Label blood by magnetic inversion

cASL: Continuous ASL
pcASL: psuedo-continous ASL

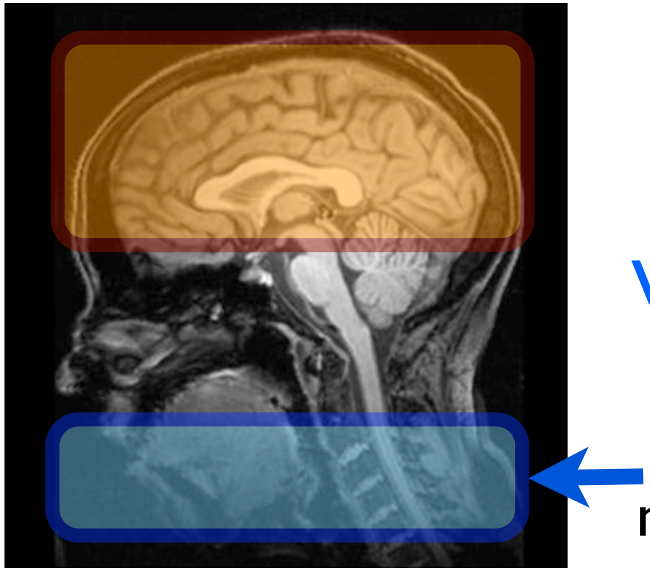


Label blood flowing through a plane for some time

pcASL uses pulses and is more widely available

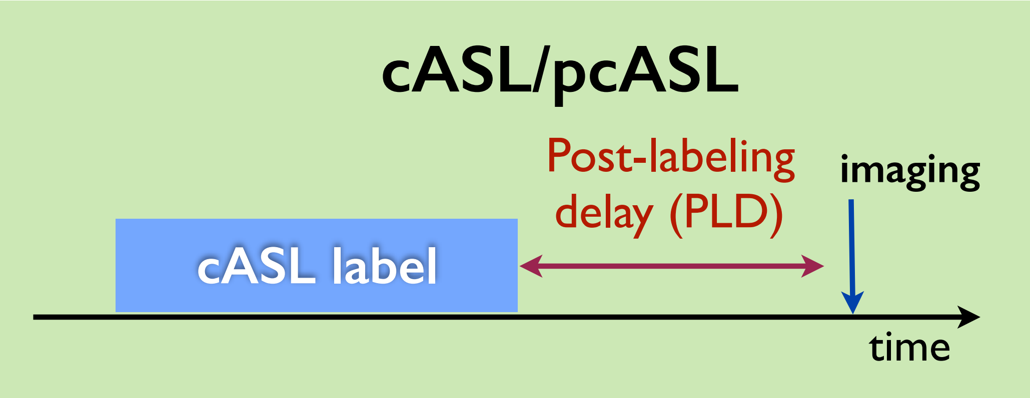
ASL Acquisition

- Nuts & bolts: Inflow time

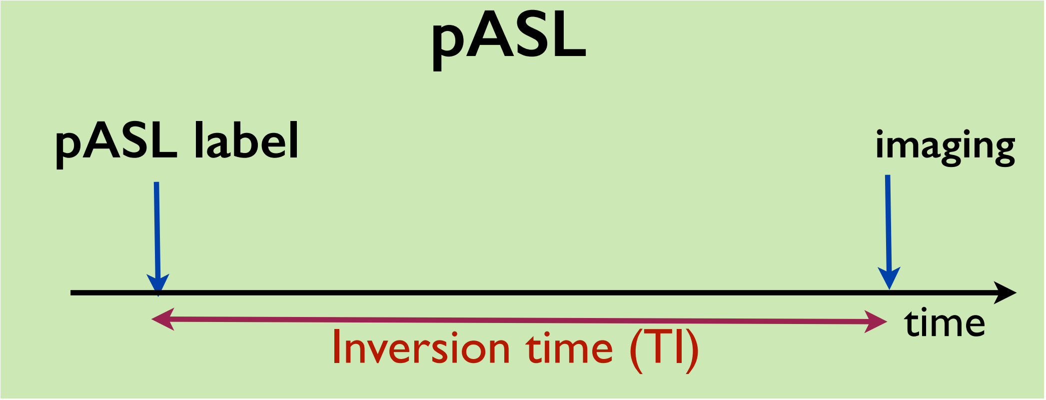


Wait for blood to reach brain

Label blood by magnetic inversion



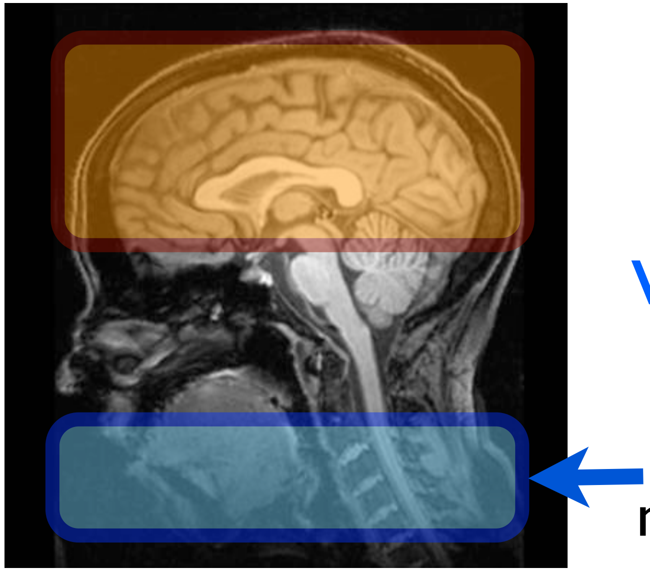
cASL/pcASL



pASL

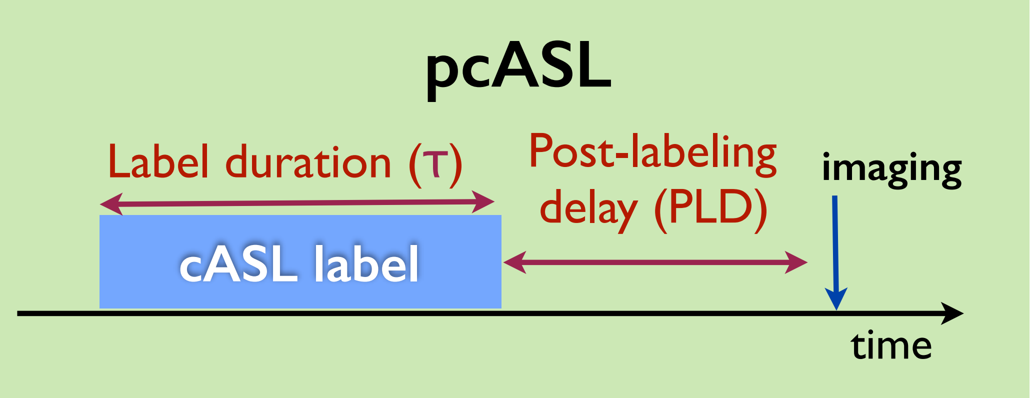
ASL ACQUISITION

- Nuts & bolts: Bolus/label duration



Wait for blood to reach brain

Label blood by magnetic inversion



pcASL

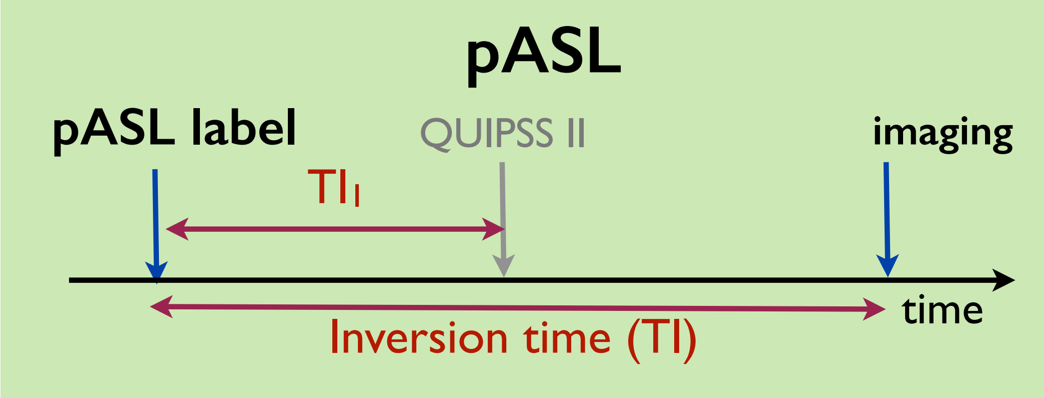
Label duration (τ)

Post-labeling delay (PLD)

imaging

cASL label

time



pASL

pASL label

QUIPSS II

imaging

TI_1

time

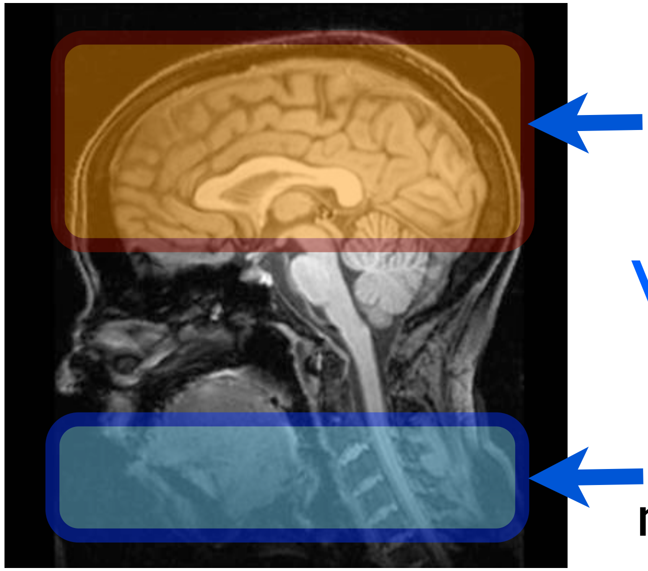
Inversion time (TI)

pASL

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

ASL ACQUISITION

- Nuts & Bolts: Readout



Aquire image of brain

Wait for blood to reach brain

Label blood by magnetic inversion

EPI
(stack of 2D slices)
Different PLD/TI for each slice

GRASE/RARE (3D)
Higher SNR
Long echo-train: blurring

Pre-saturation
Saturate static signal at start of TR

Background suppression
Null static signal - reduce physiological noise

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

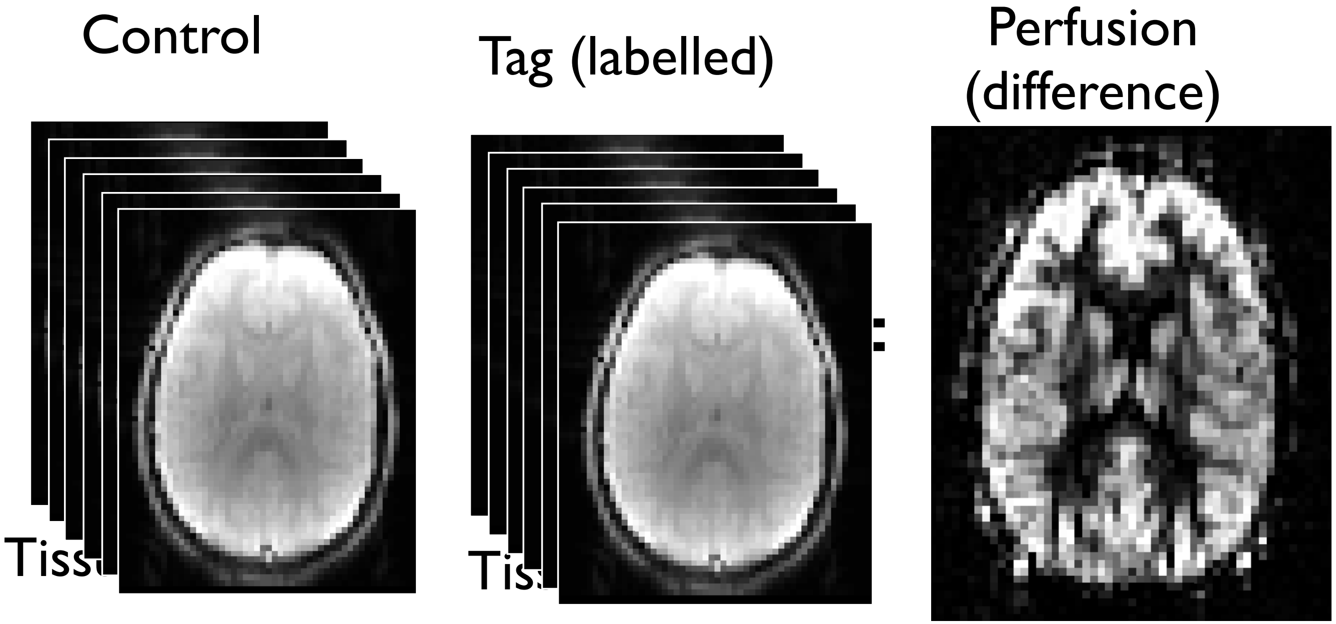
Magnetic Resonance in Medicine - 73 (1) p102-116, 2015.

OUTLINE

- Acquisition
- Keep it simple!
  - ➡ Perfusion weighted images.
  - ➡ Perfusion fMRI.
- Quantitative perfusion:
  - ➡ A short course in tracer kinetics.
  - ➡ Measuring arterial blood magnetization.
- Preparing for group analysis.
- Advanced quantification:
  - ➡ 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?
  - ➡ Tag-control subtraction
  - ➡ Average



```
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}
```

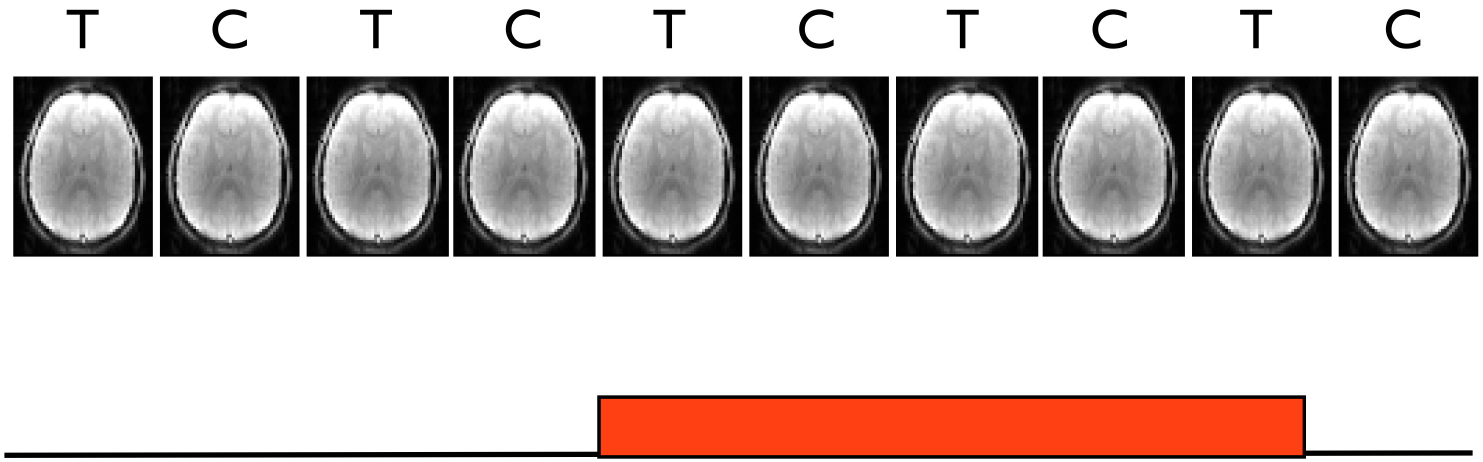
TASK-BASED ASL

- 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).

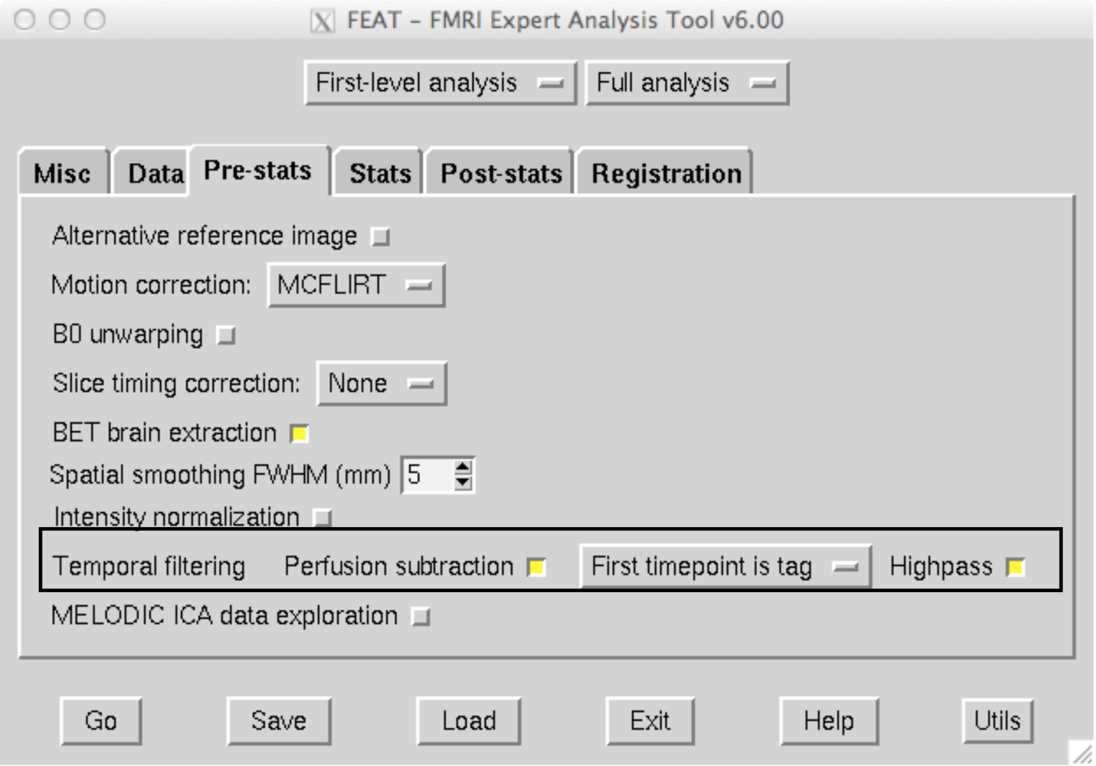
TASK-BASED ASL



- What I have...
  - ➡ ASL data during a functional task.
- What I want...
  - ➡ Activations
- What should I do?
  - ➡ Tag-control subtraction
  - ➡ GLM

TASK-BASED ASL

- Two options in FEAT
  - ➡ Do subtraction before GLM
  - ➡ (FILM prewhitening OFF)
  - ➡ ONLY considers the perfusion contribution, subtraction removes BOLD signal.



First-level analysis
Full analysis

Alternative reference image ☐
Motion correction: MCFLIRT
B0 unwarping ☐
Slice timing correction: None
BET brain extraction ☑
Spatial smoothing FWHM (mm) 5
Intensity normalization ☐
Temporal filtering Perfusion subtraction ☑ First timepoint is tag Highpass ☑
MELODIC ICA data exploration ☐

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

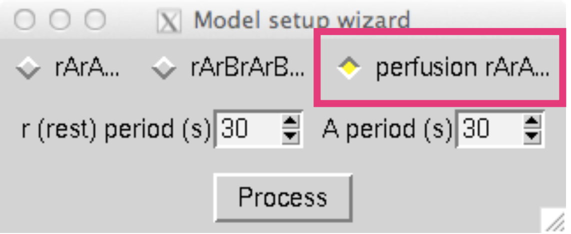
TASK-BASED ASL

- Two options in FEAT
  - ➡ Full model

    Includes perfusion and BOLD contributions

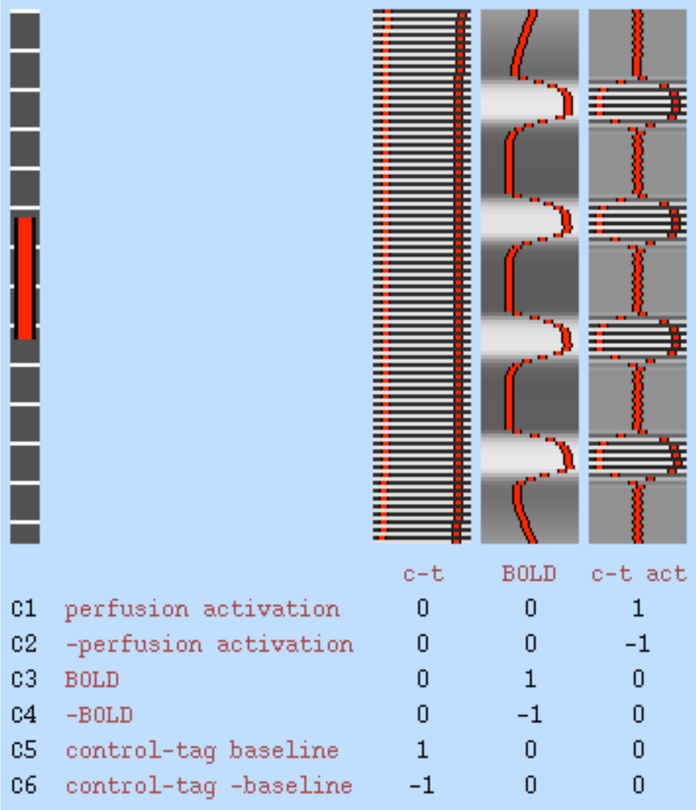
  - ➡ EV1 - Tag vs. Control

    -1 1 -1 1 -1 1 -1 1
  - ➡ EV2 - BOLD
  - ➡ EV3 - Interaction



r (rest) period (s) 30

A period (s) 30



		c-t	BOLD	c-t act
C1	perfusion activation	0	0	1
C2	-perfusion activation	0	0	-1
C3	BOLD	0	1	0
C4	-BOLD	0	-1	0
C5	control-tag baseline	1	0	0
C6	control-tag -baseline	-1	0	0

OUTLINE

- Acquisition
- Keep it simple!
  - ➡ Perfusion weighted images.
  - ➡ Perfusion fMRI.
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- Preparing for group analysis.
- Advanced quantification:
  - ➡ Macro vascular contamination
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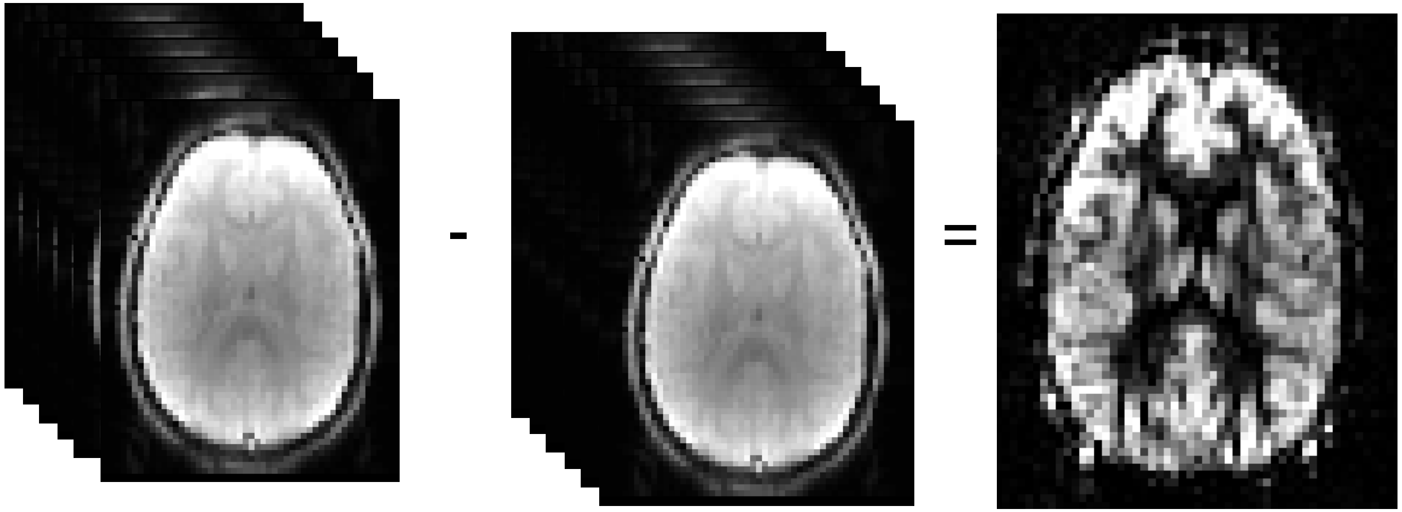
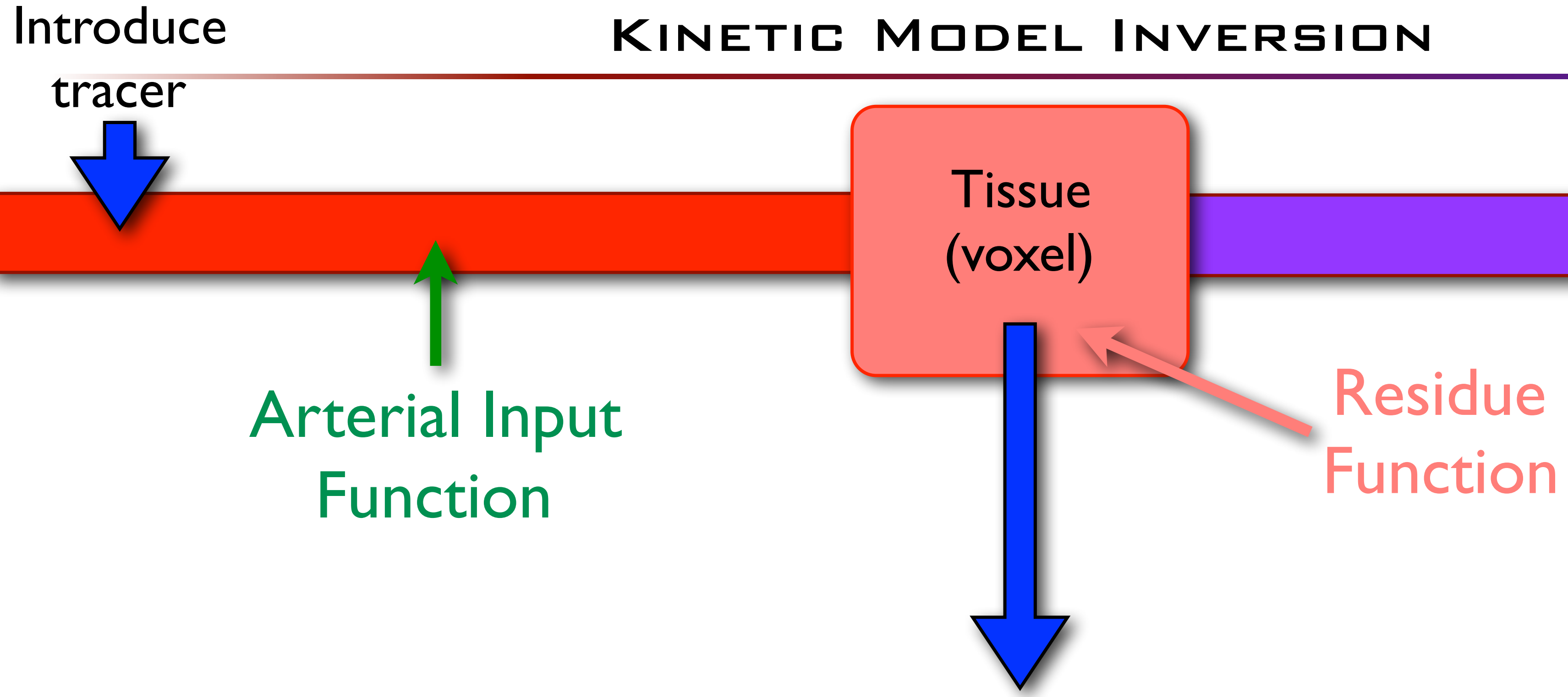
EXAMPLE



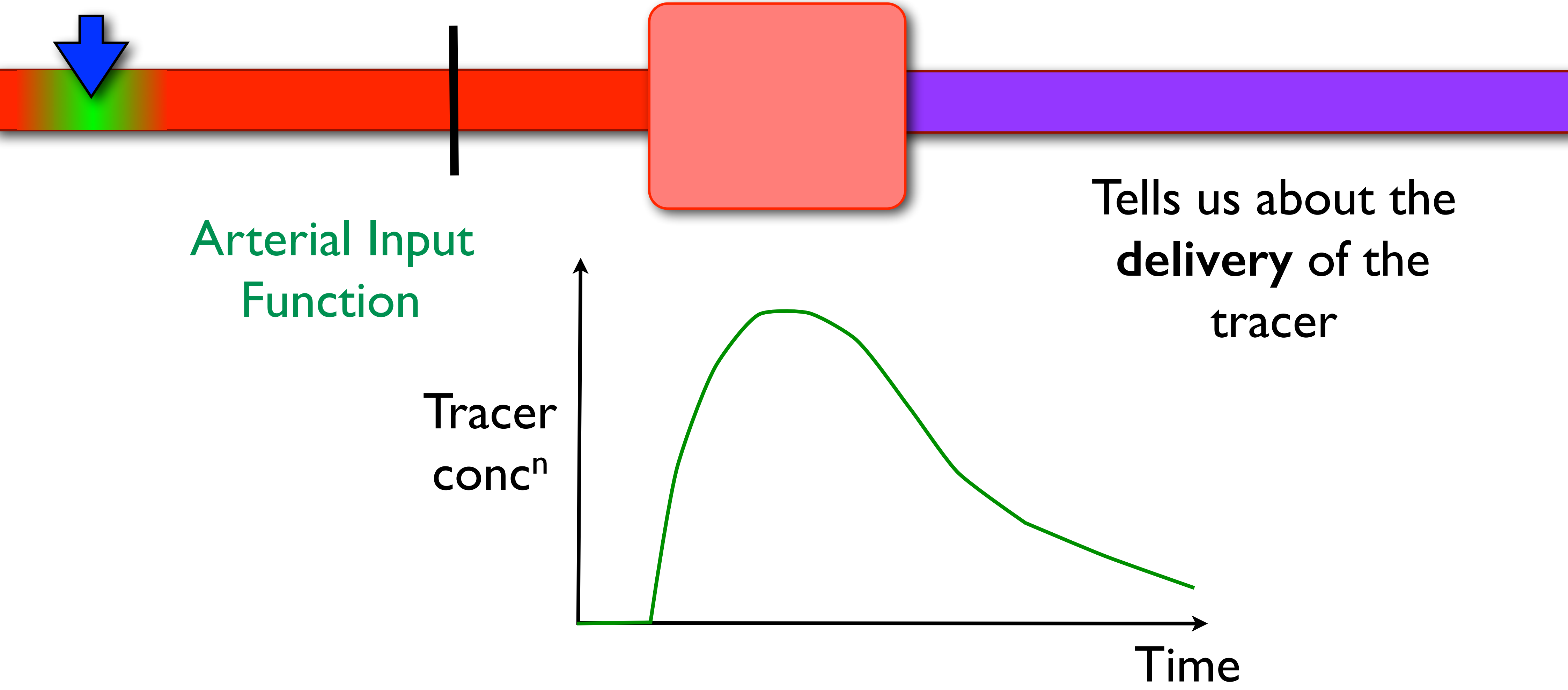
- What I have...
  - ASL data
  - (calibration images)
- What I want...
  - Perfusion in ml/100g/min
- What should I do?
  - Tag-control subtraction. ✓
  - Kinetic model inversion. ←
  - M0 calculation.

KINETIC MODEL INVERSION



$$\Delta M(t) = F \cdot AIF(t) * r(t)$$

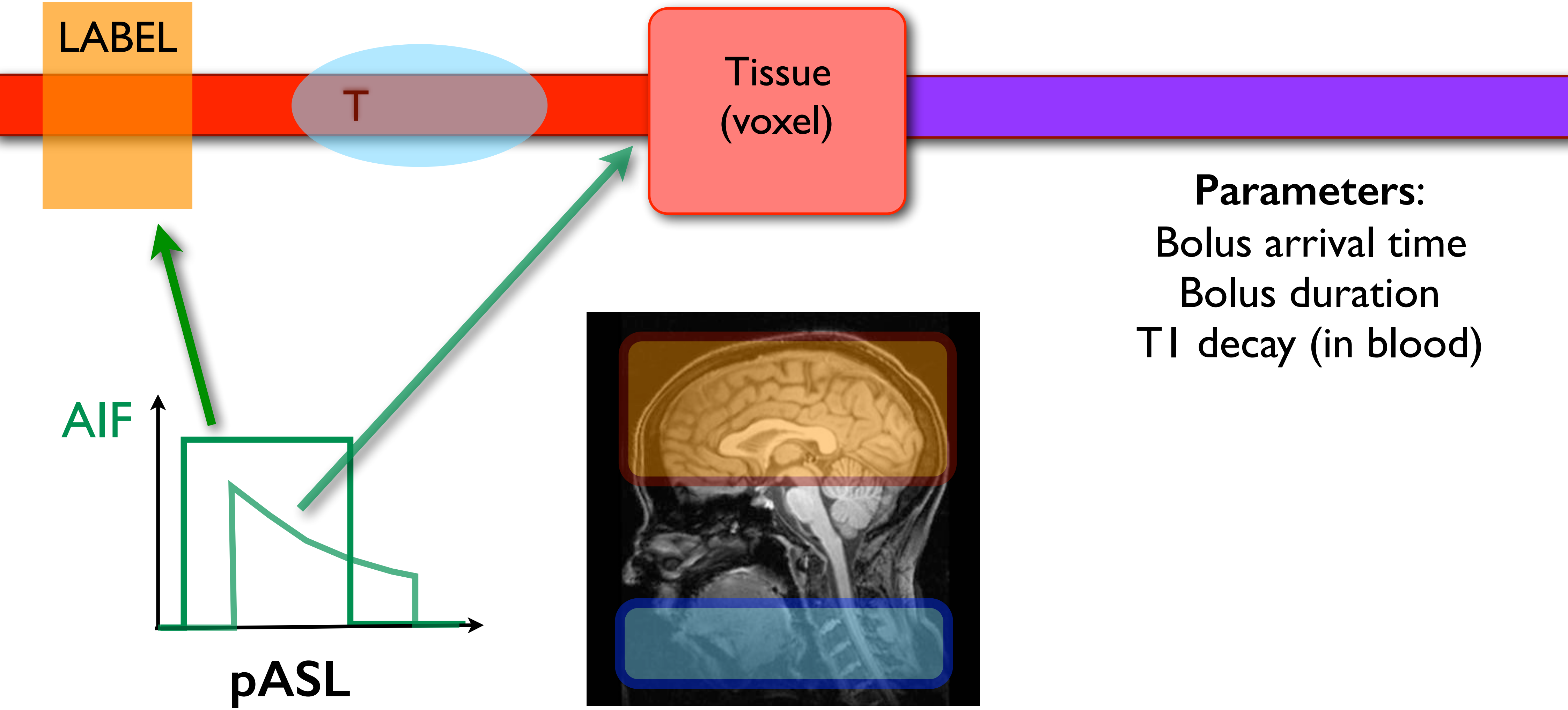
KINETIC MODEL INVERSION



Arterial Input Function

Tells us about the **delivery** of the tracer

KINETIC MODEL INVERSION



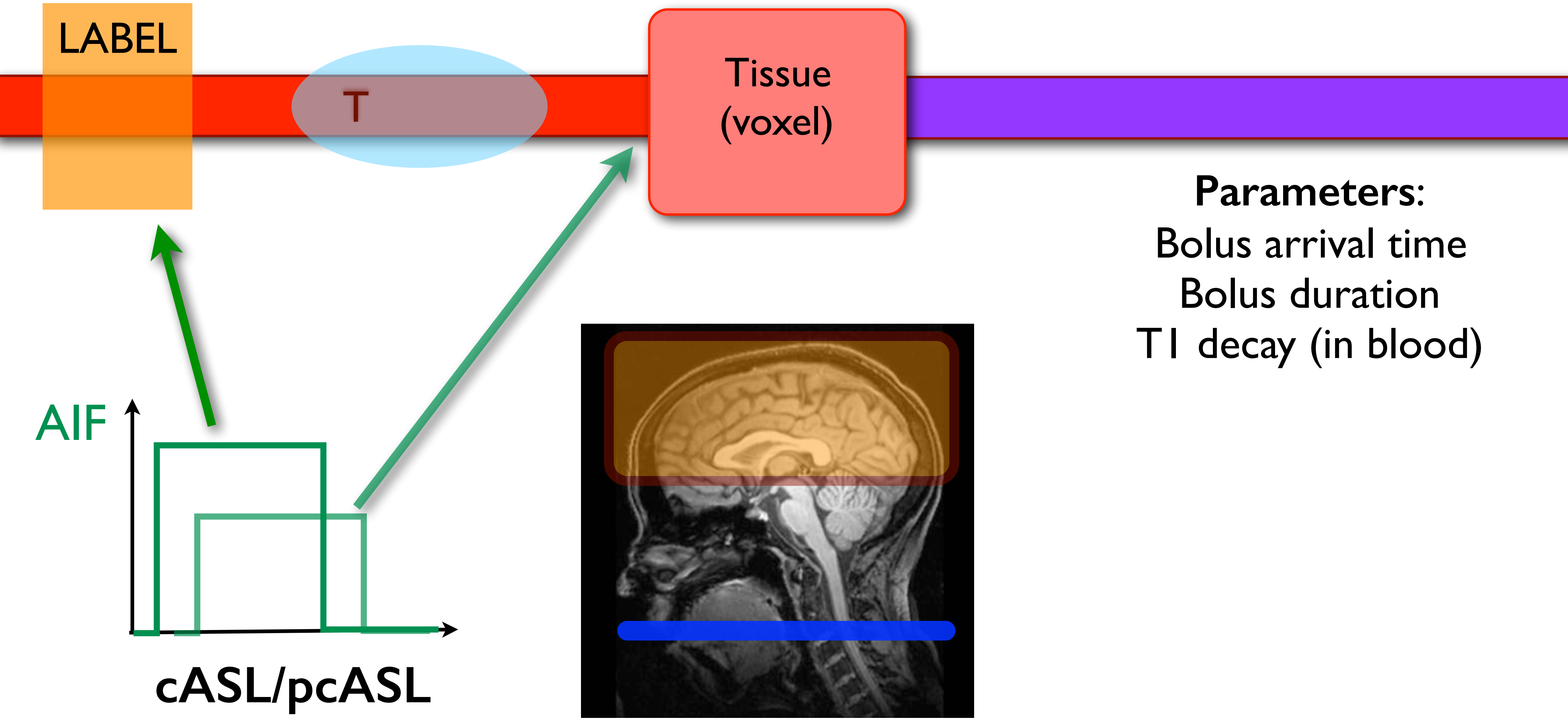
Parameters:

Bolus arrival time

Bolus duration

T1 decay (in blood)

KINETIC MODEL INVERSION



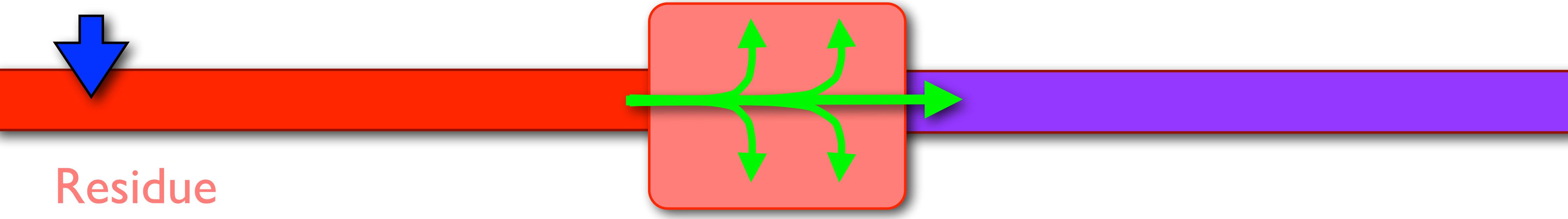
Parameters:

Bolus arrival time

Bolus duration

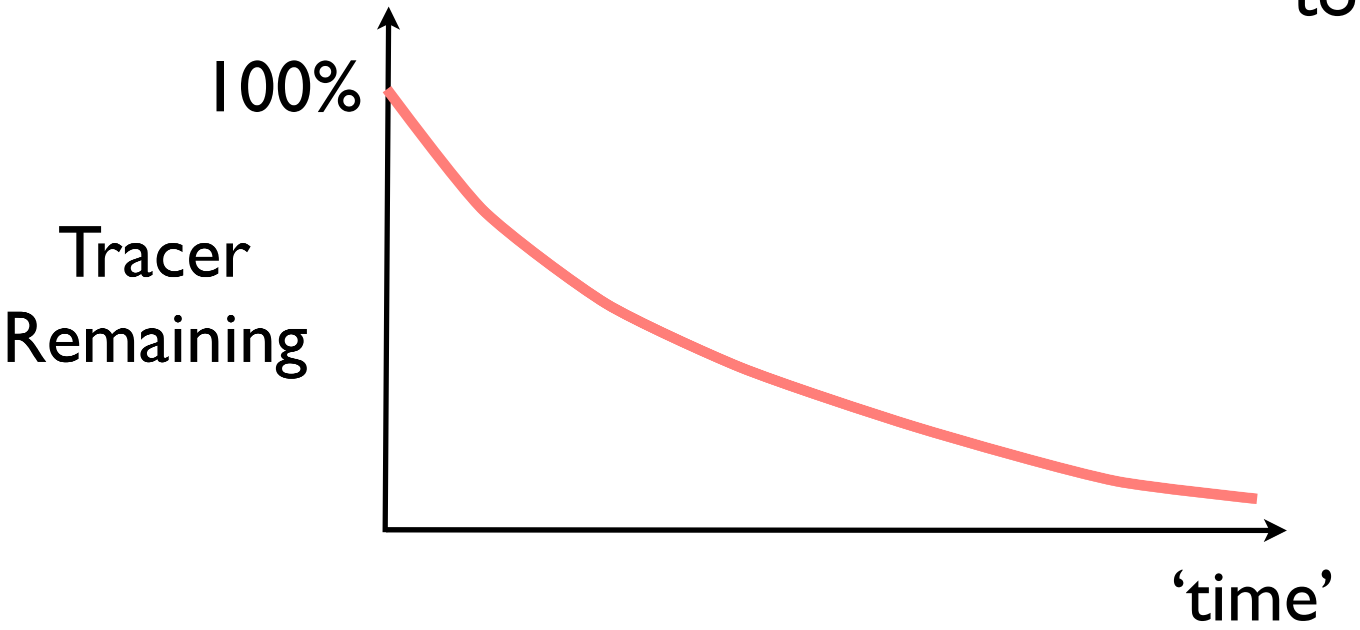
T1 decay (in blood)

KINETIC MODEL INVERSION



Residue Function

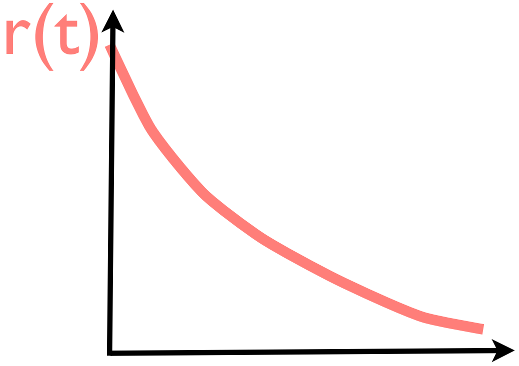
Tells us what happens to the tracer after is has arrived.



KINETIC MODEL INVERSION

'Well mixed'
T1 decay

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



Parameters:
Bolus arrival time
Bolus duration
T1 decay (in blood)

Kinetic Model Inversion

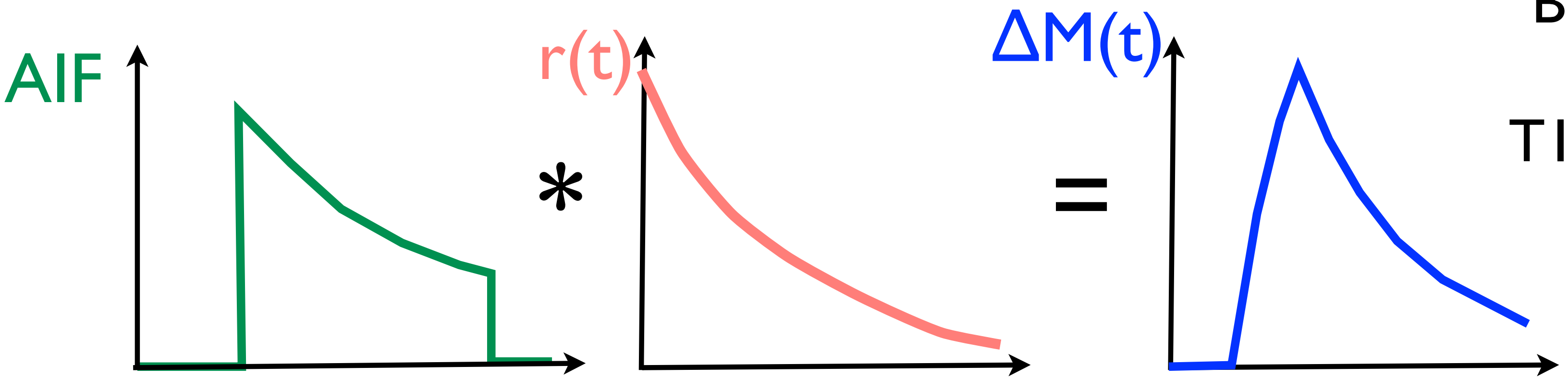
Parameters:

Perfusion - F

Bolus arrival time

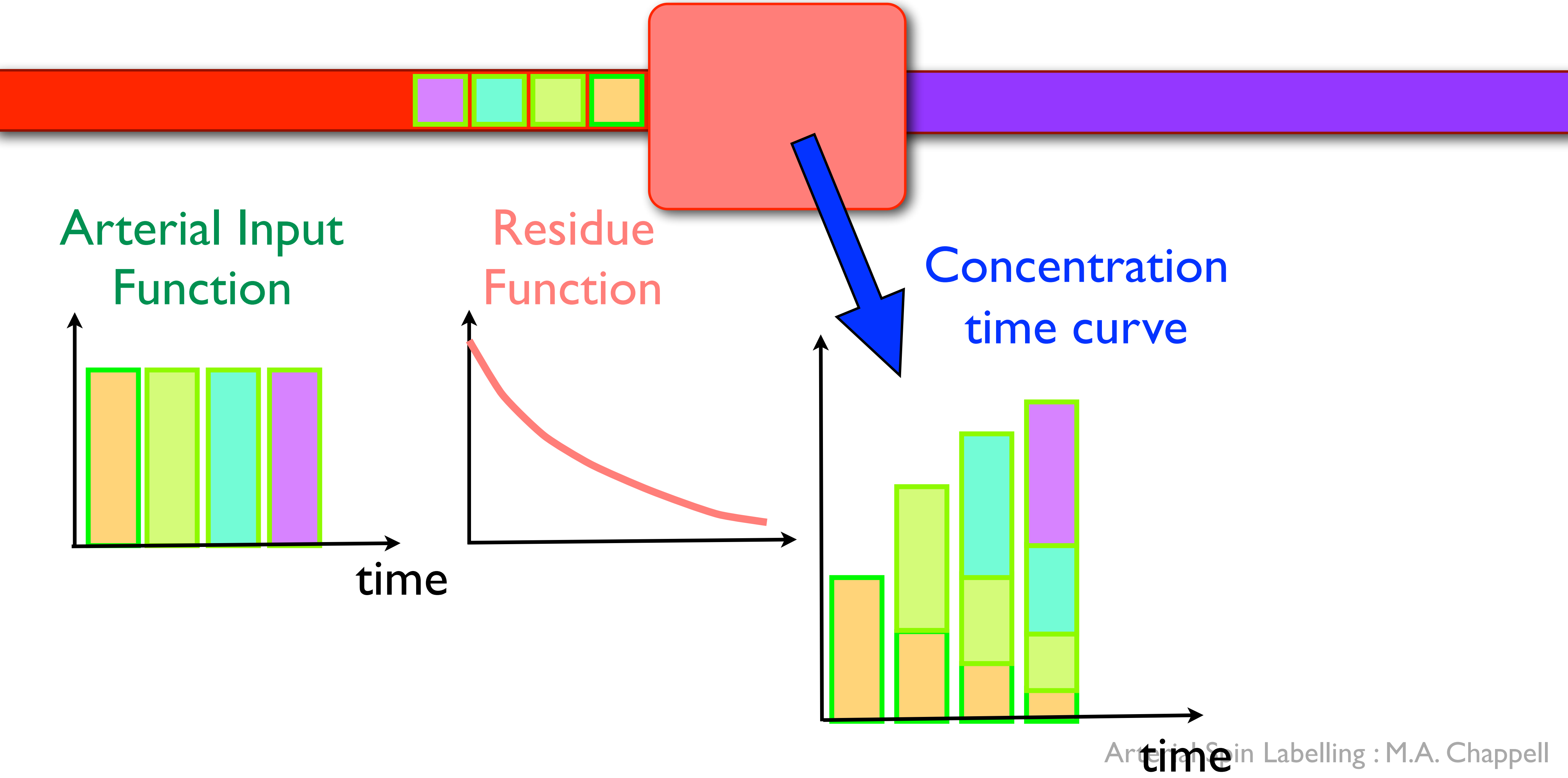
Bolus duration

T1 decay (in blood)



$$\Delta M(t) = F \cdot AIF(t) * r(t)$$

KINETIC MODEL INVERSION

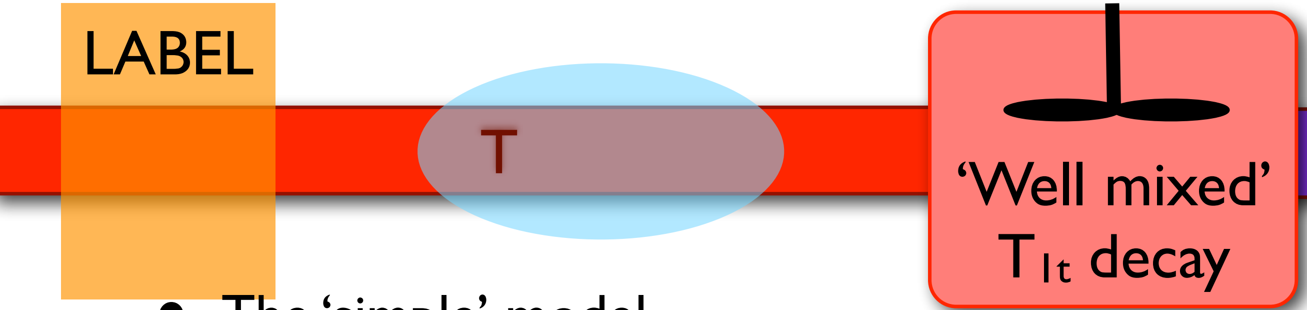


Arterial Input Function

Residue Function

Concentration time curve

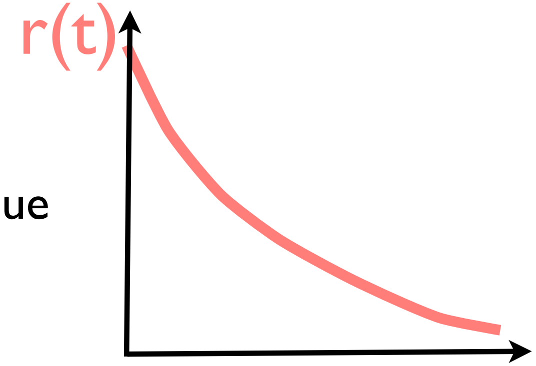
KINETIC MODEL INVERSION

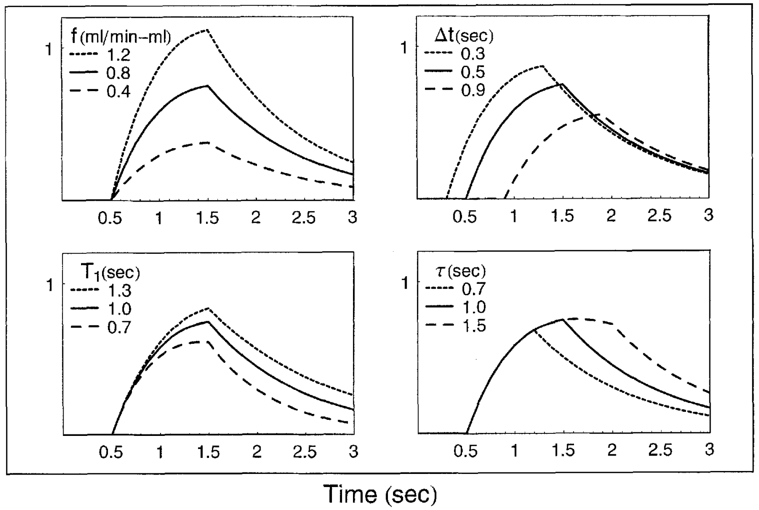

LABEL

T

‘Well mixed’ T_{1t} decay

- The ‘simple’ model
  - ➡ Only one T1 value (blood)
  - ➡ Spins never leave tissue
- The ‘standard’ model:
  - ➡ Separate T_1 for blood and tissue ($T_{1t} < T_{1b}$).
  - ➡ Spins leave voxel at rate determined by perfusion and partition coefficient.





Buxton *et al.*, MRM 40(3), 1998.

EXAMPLE

- 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. ←
  - ➡ M0 calculation.

What you need to know about your data:

Labeling

pASL (pulsed)	or	pcASL (continuous)
Inversion time(s) Bolus duration (if QUIPSS/Q2TIPS)		Post-labeling delay(s) Labeling duration

Model

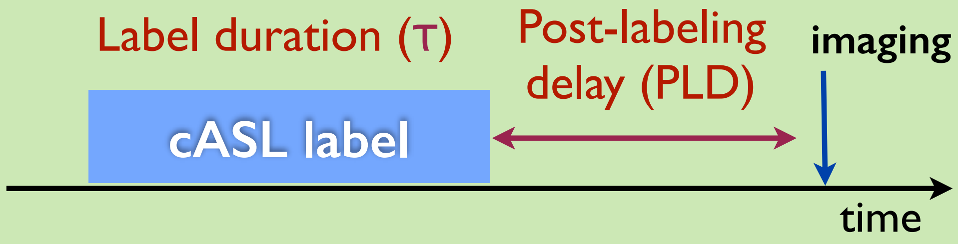
T1 (tissue and blood?)
Bolus arrival time

Kinetic Model Inversion

Analytical solutions - Simple model (ASL 'white paper'):

pcASL

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



Label duration (τ)

Post-labeling delay (PLD)

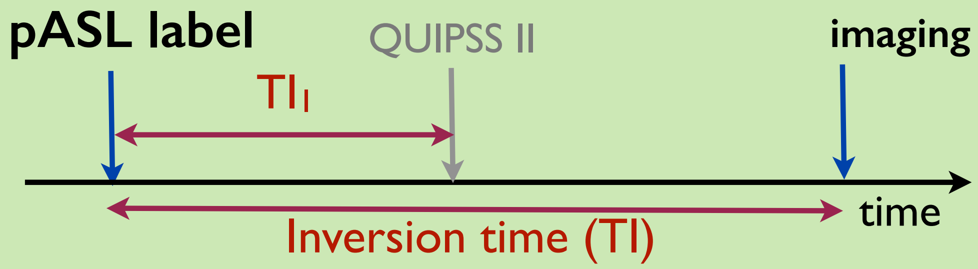
imaging

cASL label

time

pASL QUIPSS II

$$\mathrm{CBF} = \frac{6000 \cdot \lambda \cdot (\mathrm{SI}_{\mathrm{control}} - \mathrm{SI}_{\mathrm{label}}) \cdot e^{\frac{\mathrm{TI}}{T_{1,\mathrm{blood}}}}}{2 \cdot \alpha \cdot \mathrm{TI}_1 \cdot \mathrm{SI}_{\mathrm{PD}}}$$



pASL label

QUIPSS II

imaging

TI_1

time

Inversion time (TI)

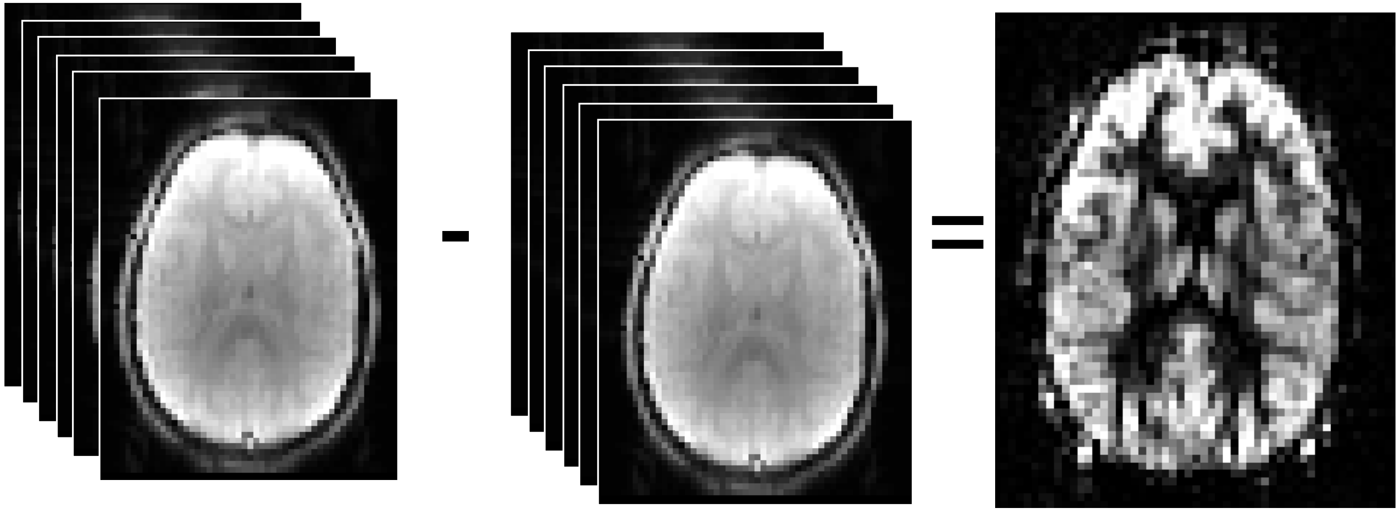
Fixed value:

T_{1blood} = 1650 ms (3T)

Assumes that BAT = 0

EXAMPLE 1

- 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. ←
    - ➡ M0 calculation.



pcASL with
labeling duration: 1.4 s
post-label delay: 1.0 s

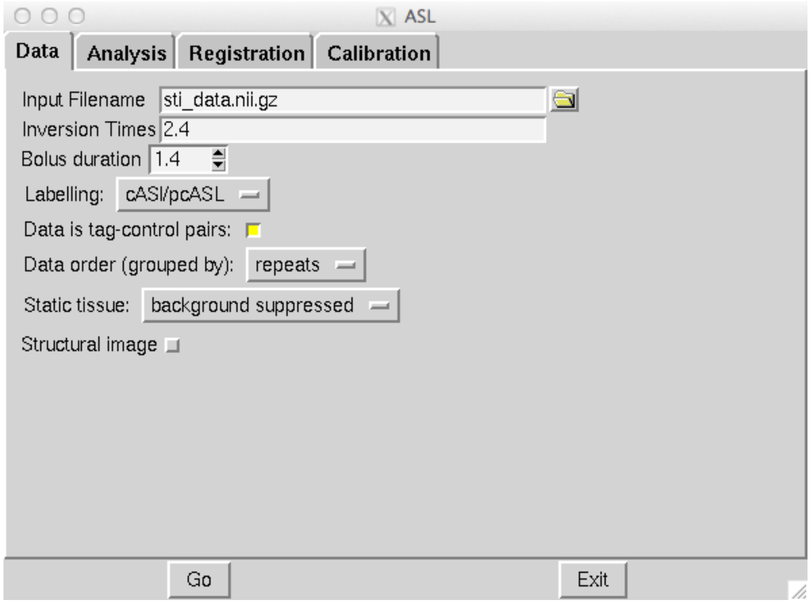
Assume
T1 (blood): 1.6 s
T1 (tissue): 1.3 s
BAT : 1.3 s

```
oxford_asl -i {ASL_diff_data.nii.gz} -o {result_dir}
  --casl --tis 2.4 --bolus 1.4 --bat 1.3 --artoff --fixbolus
```

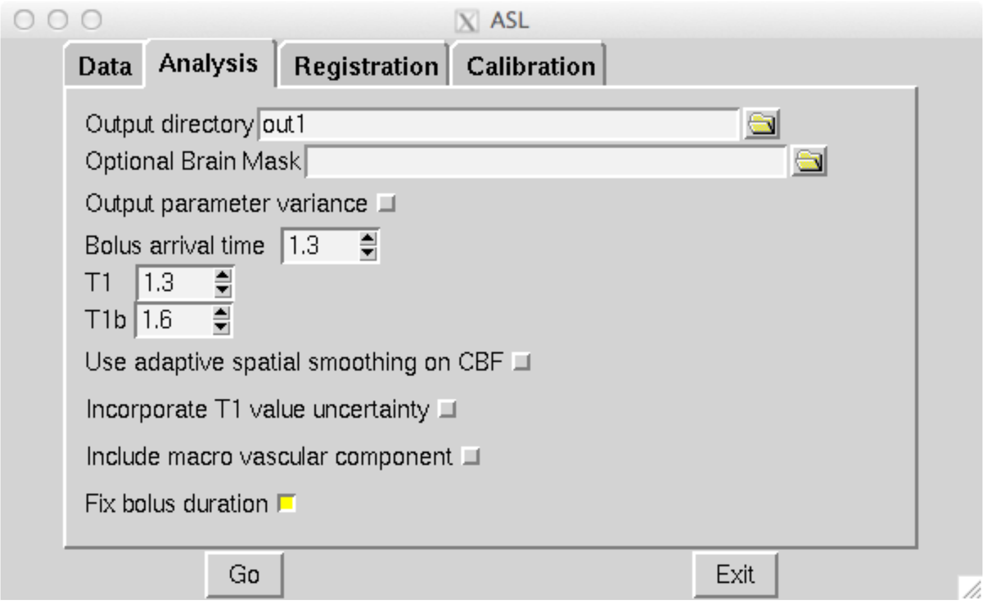
EXAMPLE 1

pcASL with
- tagging duration: 1.4 s
- post-label delay: 1.0 s

Assume
- T1 (blood): 1.6 s
- T1 (tissue): 1.3 s
- BAT : 1.3 s



Input Filename: sti_data.nii.gz
Inversion Times: 2.4
Bolus duration: 1.4
Labelling: cASl/pcASL
Data is tag-control pairs: ☑
Data order (grouped by): repeats
Static tissue: background suppressed
Structural image ☐

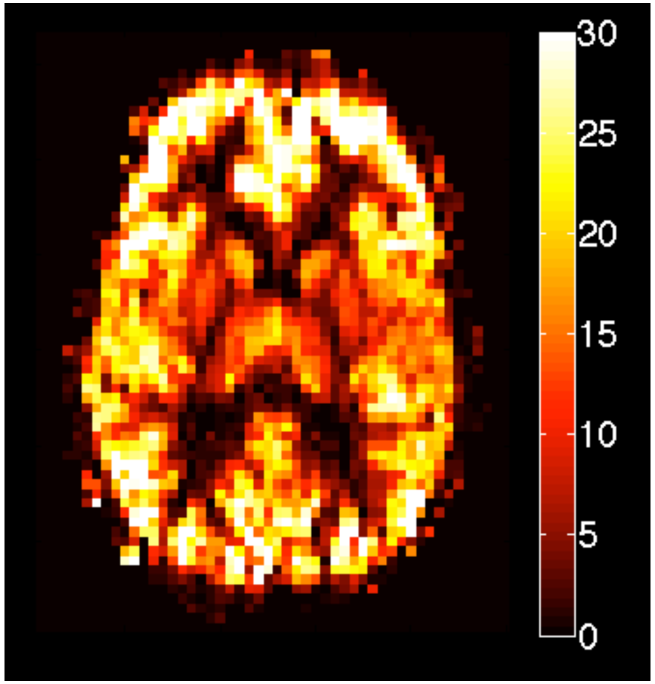


Output directory: out1
Optional Brain Mask:
Output parameter variance ☐
Bolus arrival time: 1.3
T1: 1.3
T1b: 1.6
Use adaptive spatial smoothing on CBF ☐
Incorporate T1 value uncertainty ☐
Include macro vascular component ☐
Fix bolus duration ☑

```
> asl_file --data=sti_data.nii.gz --ntis=1 --iaf=tc --diff --out=sti_diffdata.nii.gz
> oxford_asl -i sti_diffdata.nii.gz -o out1
   --casl --tis 2.4 --bolus 1.4 --bat 1.3 --artoff --fixbolus
```

EXAMPLE 1

Perfusion (arbitrary units)

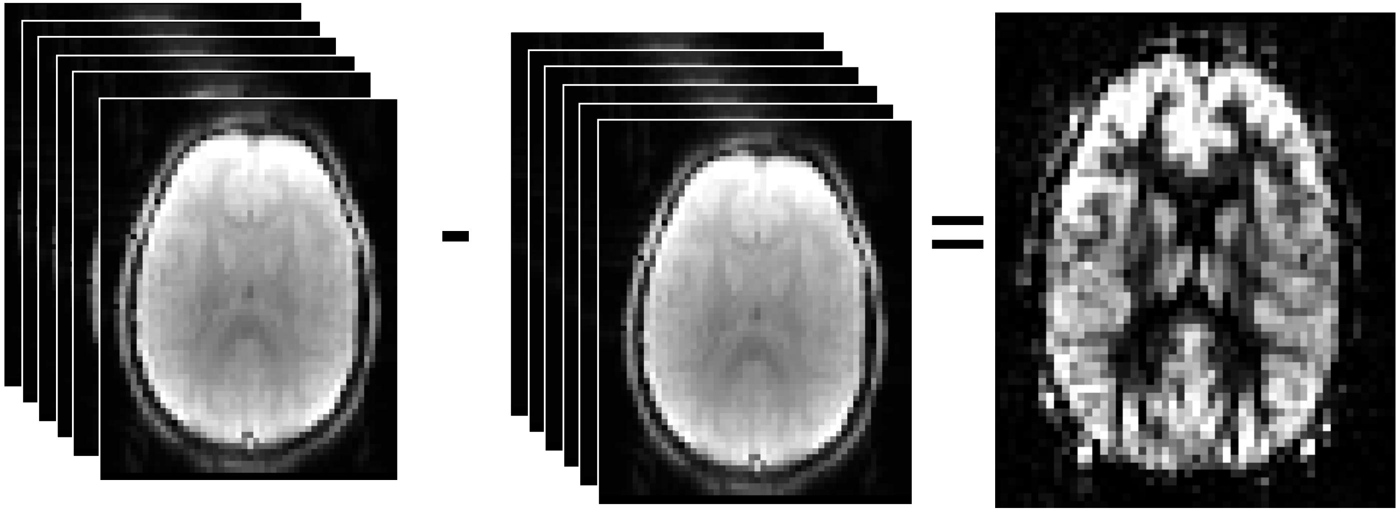


out1/native_space/perfusion.nii.gz

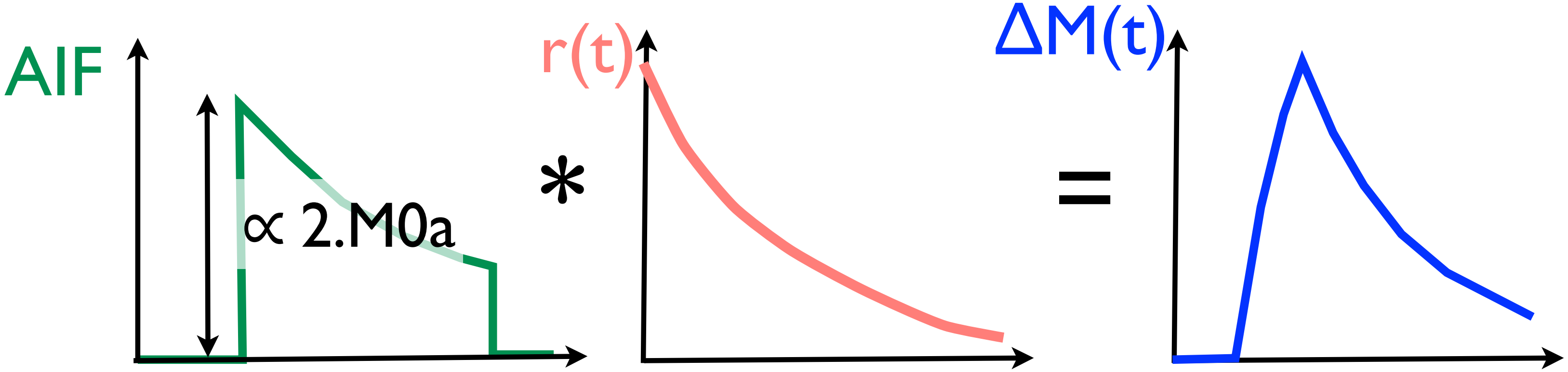
```
> asl_file --data=sti_data.nii.gz --ntis=1 --iaf=tc --diff --out=sti_diffdata.nii.gz
> oxford_asl -i sti_diffdata.nii.gz -o out1
   --casl --tis 2.4 --bolus 1.4 --bat 1.3 --artoff --fixbolus
```

EXAMPLE

- 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. ✓
  - ➡ M0 calculation. ←



M0 Calculation



$$\Delta M(t) = 2 \cdot M0a \cdot CBF \cdot AIF(t) * r(t)$$

M0 CALCULATION

- Cannot measure M0a directly.
- indirect via brain 'tissue' magnetization.

➡ Calculate M0t.

(M0 of 'tissue')

➡ M0t to M0a.

Steady state magnetization

$$S = M_0\left(1 - e^{-TR/T_1}\right)$$

With pre-saturation:

$$S = M_0\left(1 - Ae^{-t/T_{1t}}\right)$$

With background suppression:

No static tissue - need separate calibration images i.e. a control image with BGS off.

Account for relative proton densities:

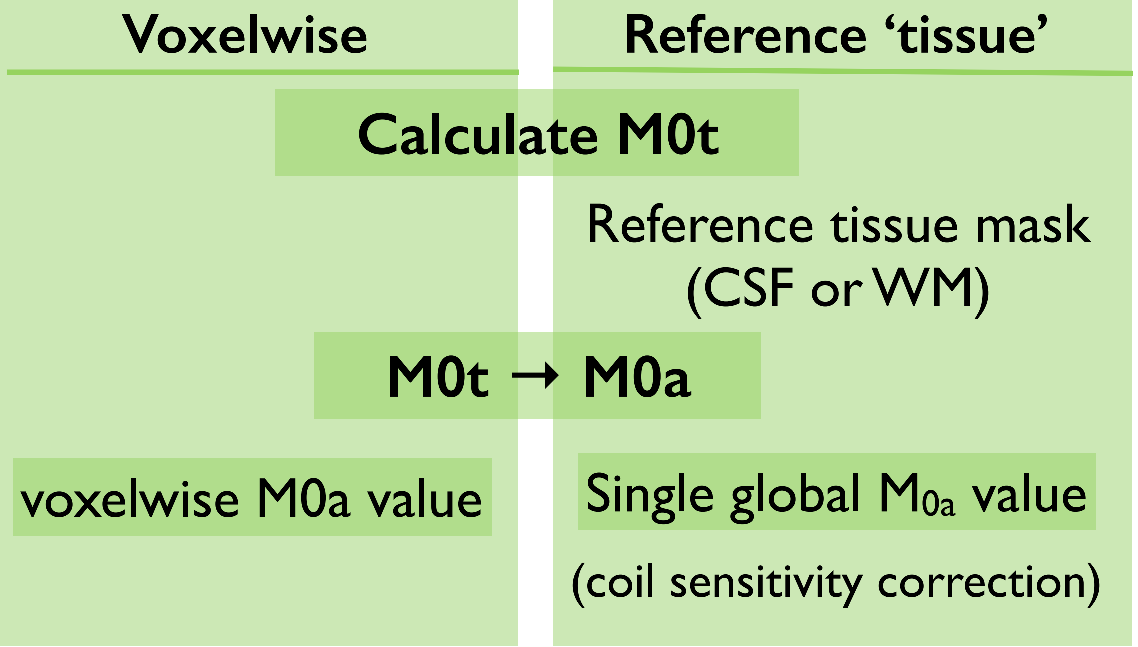
$$M_{0a} = \frac{M_{0t}}{\lambda}$$

```
oxford_asl ... -c {calibration_image.nii.gz} -s {structural_image.nii.gz}
asl_calib --mode longtr ...
asl_calib --mode satrecov ...
```

M0 CALCULATION

- Cannot measure M0a directly.
- indirect via brain 'tissue' magnetization.
  - ➡ Calculate M0t.

    (M0 of 'tissue')
  - ➡ M0t to M0a.
- Practicalities
  - ➡ Reference 'tissue'?
  - ➡ Voxelwise?



Voxelwise

Reference 'tissue'

Calculate M0t

Reference tissue mask (CSF or WM)

M0t → M0a

voxelwise M0a value

Single global M_{0a} value

(coil sensitivity correction)

$$\text{Perfusion (ml/100g/min)} = (\text{Perfusion} / M_{0a}) * 6000$$

```
oxford_asl ... -c {calibration_image.nii.gz} -s {structural_image.nii.gz}
asl_calib --mode longtr ...
asl_calib --mode satrecov ...
fslmaths {perfusion.nii.gz} -div [M0a] -mul 6000 {perfusion_calib.nii.gz}
```

M0 CALCULATION

Analytical solutions - Simple model (ASL 'white paper'):

pcASL

$$\mathrm{CBF} = \frac{6000\cdot\lambda\cdot(\mathrm{SI}_{\mathrm{control}}-\mathrm{SI}_{\mathrm{label}})\cdot e^{\frac{\mathrm{PLD}}{T_{1,\mathrm{blood}}}}}{2\cdot\alpha\cdot T_{1,\mathrm{blood}}\cdot \mathrm{SI}_{\mathrm{PD}}\cdot\left(1-e^{-\frac{\tau}{T_{1,\mathrm{blood}}}}\right)}$$

$\alpha = 0.85$

pASL QUIPSS II

$$\mathrm{CBF} = \frac{6000\cdot\lambda\cdot(\mathrm{SI}_{\mathrm{control}}-\mathrm{SI}_{\mathrm{label}})\cdot e^{\frac{\mathrm{TI}}{T_{1,\mathrm{blood}}}}}{2\cdot\alpha\cdot \mathrm{TI}_1\cdot \mathrm{SI}_{\mathrm{PD}}}$$

$\alpha = 0.98$

Perfusion (ml/100g/min) = (Perfusion / M_{0a}) * 6000

A 'voxelwise' approach:

$M_{0a} = M_{0t} / \lambda = SI_{PD} / \lambda$ with $\lambda = 0.9$ ml/g

SI_{PD} is a proton density weighted image with 'long' TR

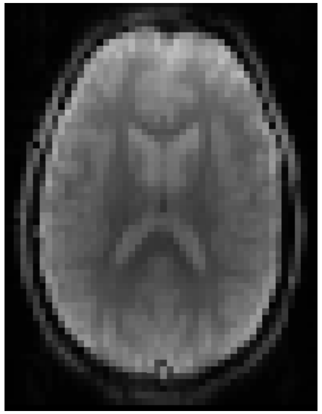
For TR < 5s correct using: $$S = M_0\left(1-e^{-TR/T_1}\right)$$

EXAMPLE 2

- 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. ✓
  - ➡ M0 calculation. ←

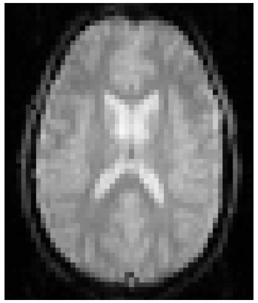
Background suppression on

Calibration image



Steady state
TR = 6 s

Calibration reference

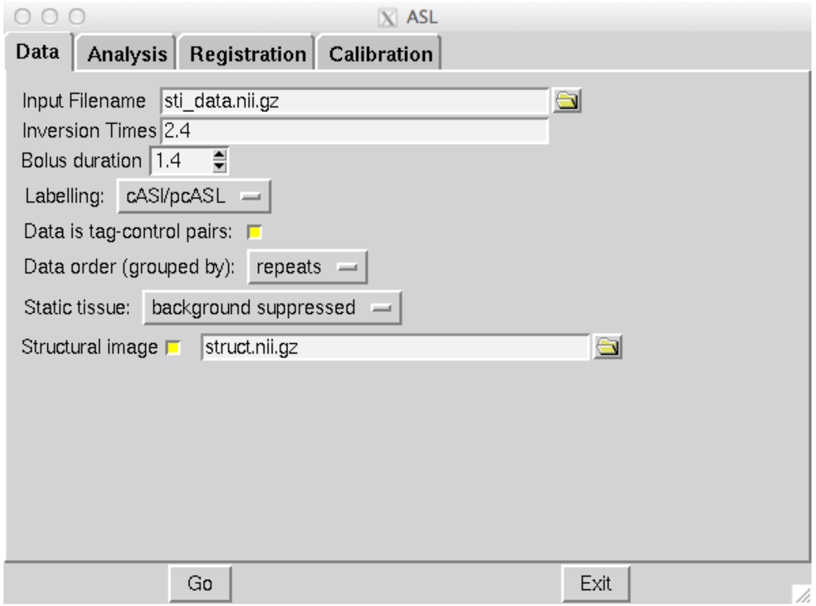


```
oxford_asl -i {ASL_diff_data.nii.gz} -o {result_dir}
  --casl --tis 2.4 --bolus 1.4 --bat 1.3 --artoff --fixbolus
  -c {calibration_image.nii.gz} --tr 6 --cref {calibration_reference.nii.gz}
  -s {structural_image} --regfrom {calibration_image)
```

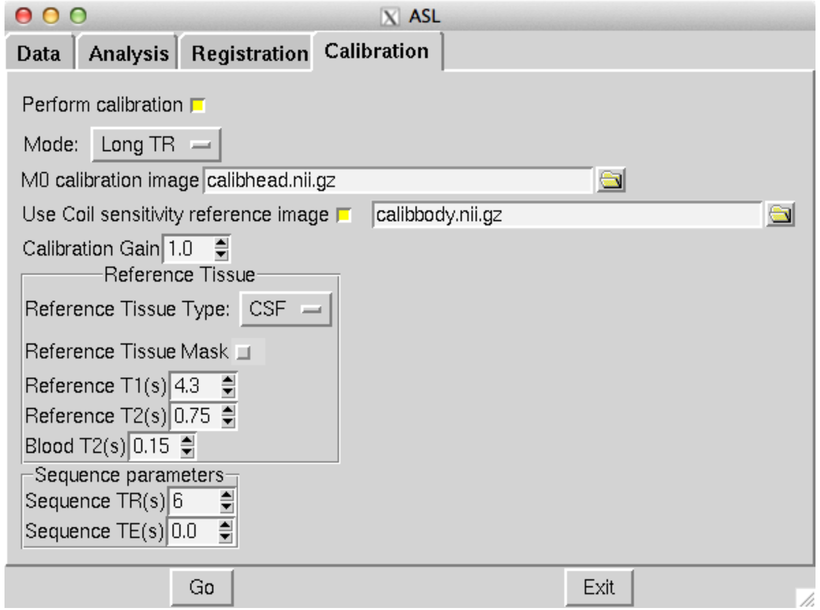
EXAMPLE 2

pcASL with
  tagging duration: 1.4 s
  post-label delay: 1.0 s

Calibration image with TR = 6 s
Calibration reference (body coil)



Input Filename: sti_data.nii.gz
Inversion Times: 2.4
Bolus duration: 1.4
Labelling: cASl/pcASL
Data is tag-control pairs: ☑
Data order (grouped by): repeats
Static tissue: background suppressed
Structural image ☑ struct.nii.gz

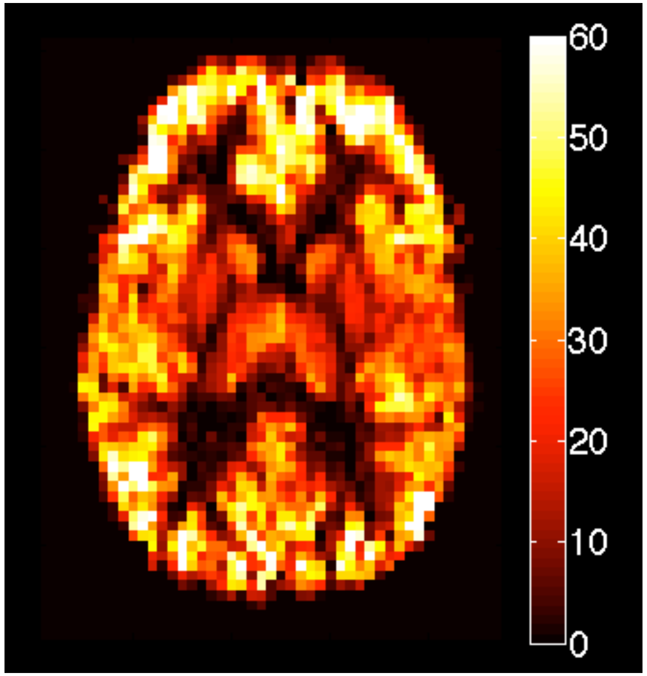


Perform calibration ☑
Mode: Long TR
M0 calibration image: calibhead.nii.gz
Use Coil sensitivity reference image ☑ calibbody.nii.gz
Calibration Gain: 1.0
Reference Tissue Type: CSF
Reference Tissue Mask ☐
Reference T1(s): 4.3
Reference T2(s): 0.75
Blood T2(s): 0.15
Sequence TR(s): 6
Sequence TE(s): 0.0

```
> oxford_asl -i sti_diffdata.nii.gz -o out2
    --casl --tis 2.4 --bolus 1.4 --bat 1.3 --artoff --fixbolus
    -c calibhead.nii.gz --tr 6 --cref calibbody.nii.gz
    -s struct.nii.gz --regfrom calibhead.nii.gz
```

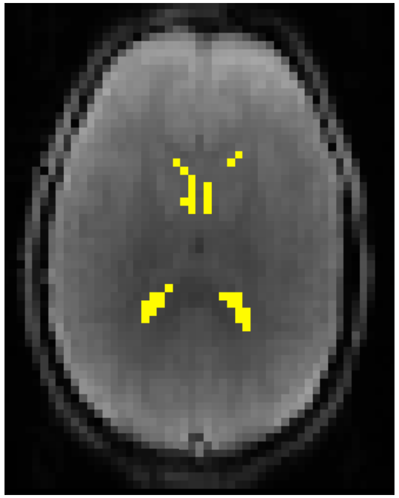
EXAMPLE 2

Perfusion (ml/100g/min)



`out2/native_space/perfusion_calib.nii.gz`

Calibration: CSF mask



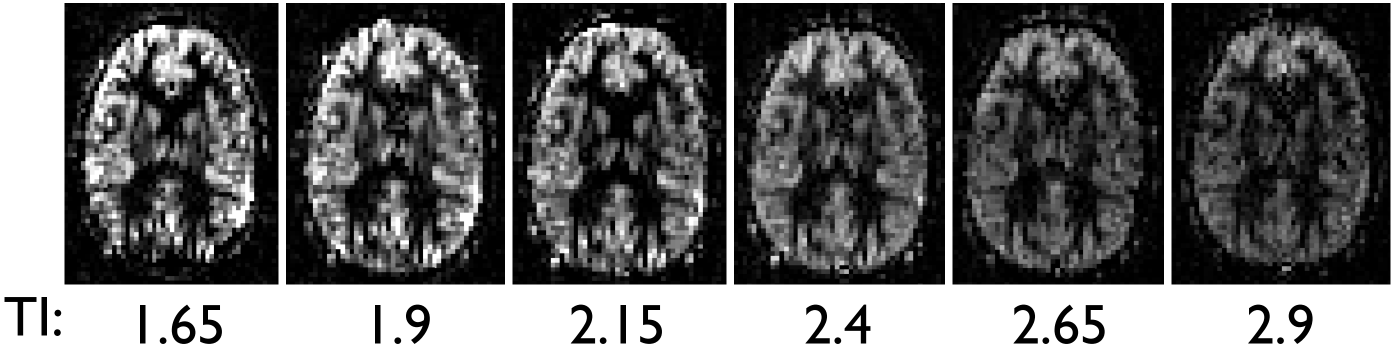
`out2/calibration/refmask.nii.gz`
(overlaid on raw data)

```
> oxford_asl -i diffdata.nii.gz -o out2
    --casl --tis 2.4 --bolus 1.4 --bat 1.3 --artoff --fixbolus
    -c calibhead.nii.gz --tr 6 --cref calibbody.nii.gz
    --s struct.nii.gz --regfrom calibhead.nii.gz
```

EXAMPLE 3

- What I have...
  - ➡ ASL data - multi-TI/PLD
  - ➡ (calibration images)
- What I want...
  - ➡ Perfusion in ml/100g/min
- What should I do?
  - ➡ Tag-control subtraction.
  - ➡ Kinetic model inversion.
  - ➡ M0 calculation.

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



KINETIC MODEL INVERSION

Parameters:

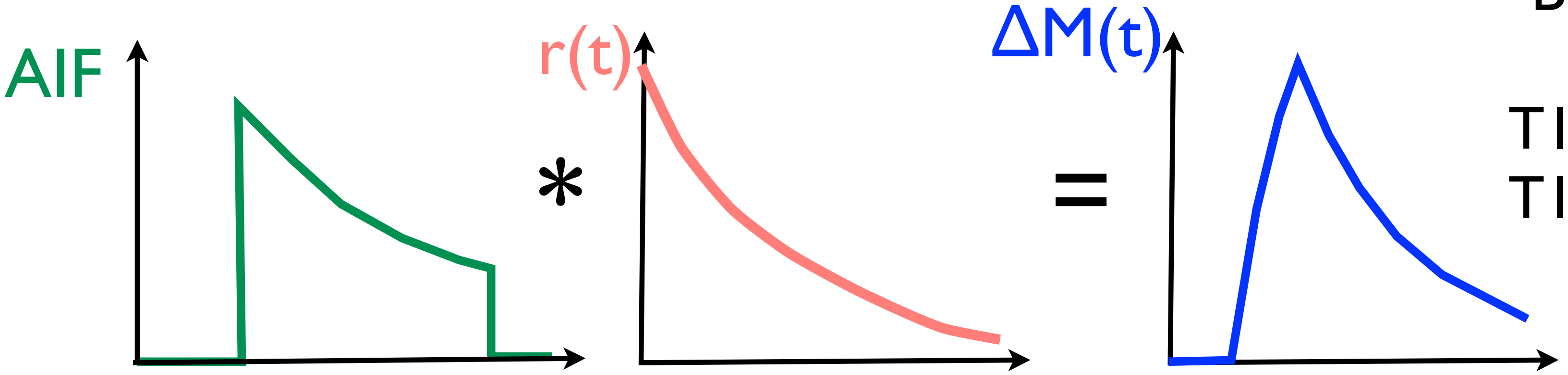
Perfusion - F

Bolus arrival time

Bolus duration

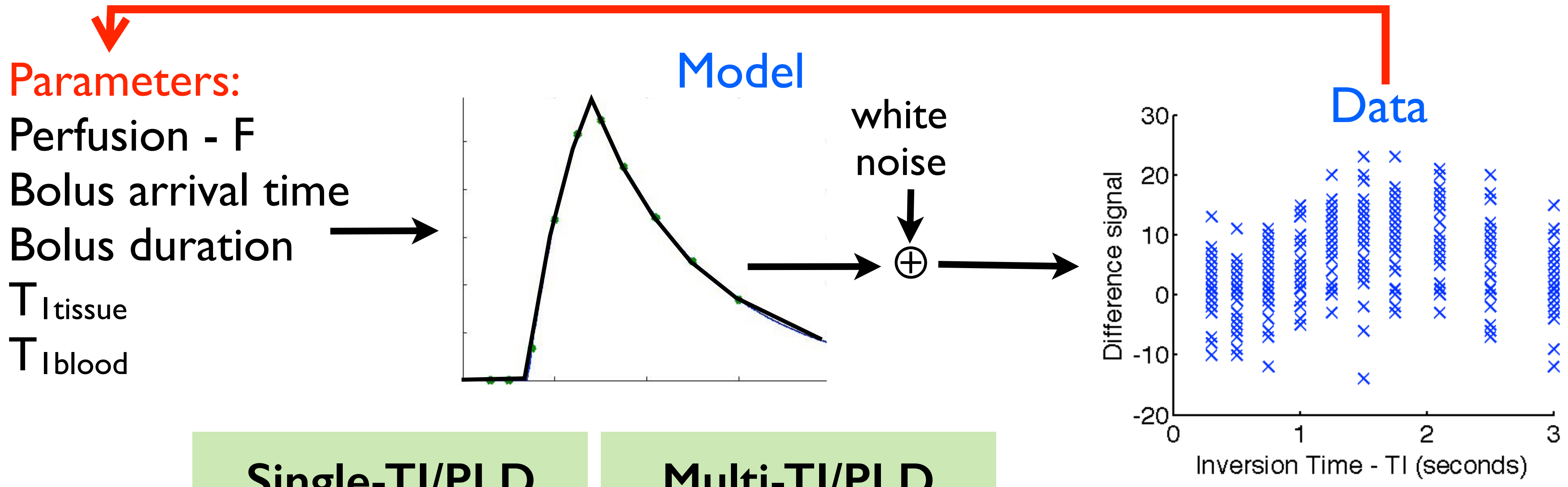
T1 decay (in blood)

T1 decay (in tissue)



$$\Delta M(t) = F \cdot AIF(t) * r(t)$$

Kinetic Model Inversion



Parameters:

Perfusion - F

Bolus arrival time

Bolus duration

$T_{1\text{tissue}}$

$T_{1\text{blood}}$

Model

white noise

Data

Single-TI/PLD

Analytic solution

Multi-TI/PLD

Non-linear fitting

(least squares)

Bayesian inference (BASIL)

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

KINETIC MODEL INVERSION

- Perfusion
  - ➡ Want to know this - **variable**
- Bolus/Arterial arrival time
  - ➡ Want to correct for this - **variable**

but limited to a sensible range

- Bolus/Label duration
  - ➡ Set by sequence - **fixed**

might not be that well fixed, pASL?

- T$_1$ tissue
  - ➡ 1.3 s at 3T - **fixed**
- T$_1$ blood
  - ➡ 1.66 at 3T - **fixed**

Doesn't T$_1$ vary a bit?

KINETIC MODEL INVERSION

Priors:

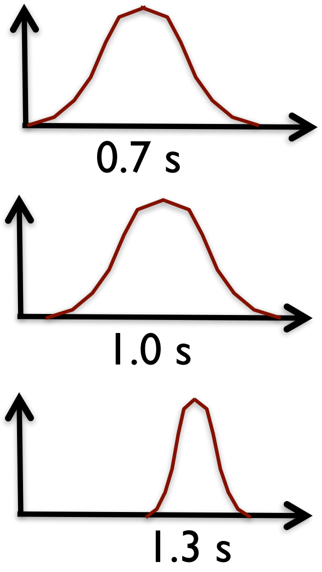
Perfusion

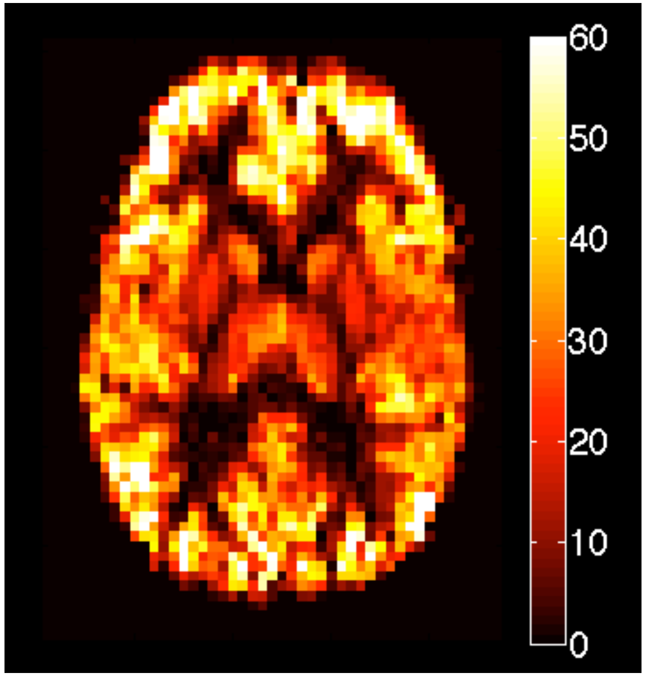
Bolus arrival time

Bolus duration

TI

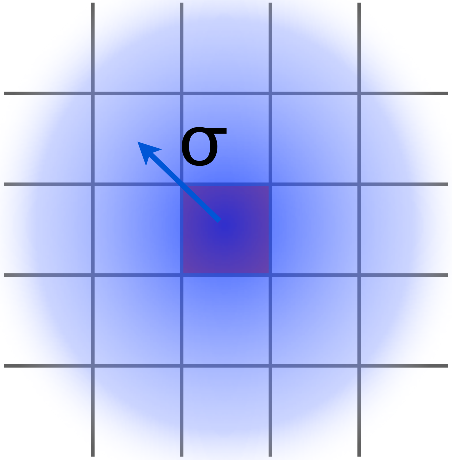
Spatial





Spatial prior:

Prior distribution for perfusion in voxel defined over its neighbours

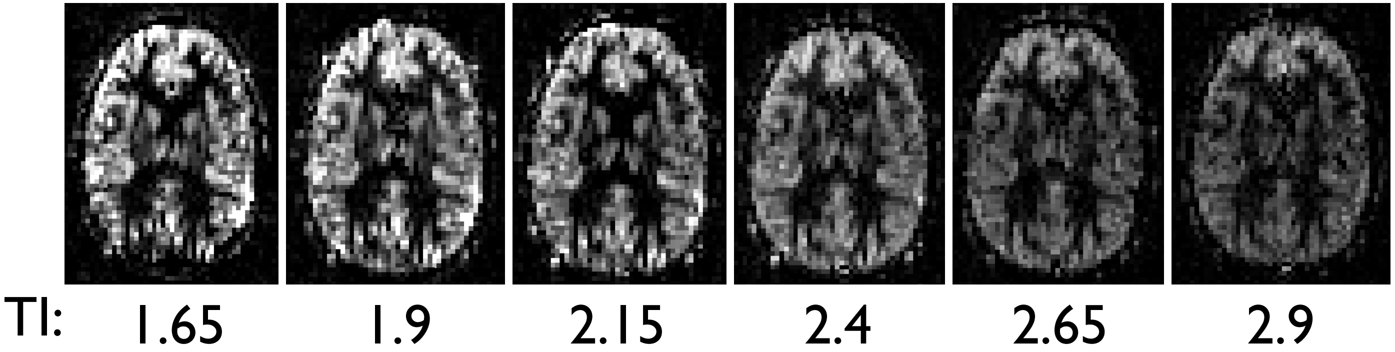


σ - spatial scale of prior (determined from the data)

EXAMPLE 3

- What I have...
  - ➡ ASL data - multi-TI/PLD
  - ➡ (calibration images)
- What I want...
  - ➡ Perfusion in ml/100g/min
- What should I do?
  - ➡ Tag-control subtraction.
  - ➡ Kinetic model inversion.
  - ➡ M0 calculation.

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



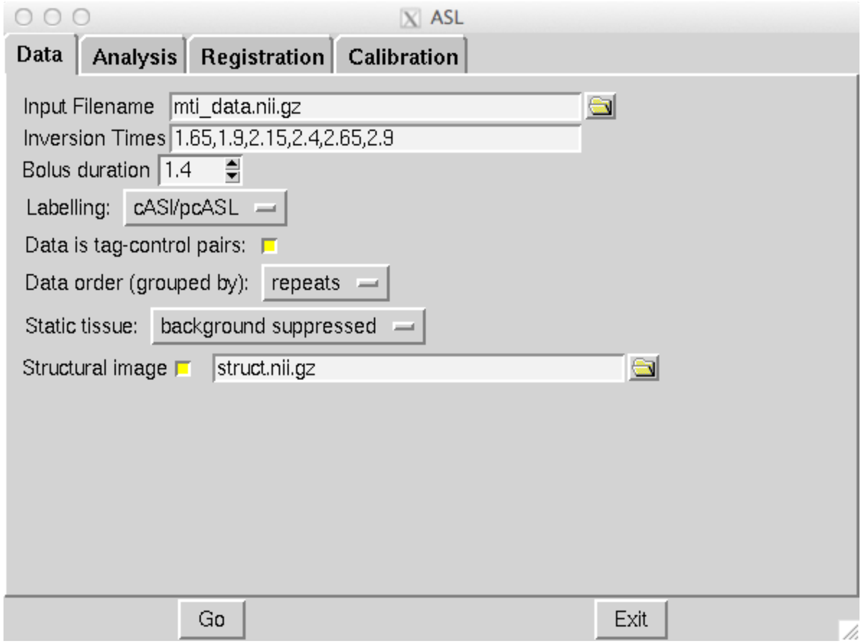
```
oxford_asl -i {ASL_diff_data.nii.gz} -o {result_dir}
  --casl --tis 1.65,1.9,2.15,2.4,2.65,2.9 --bolus 1.4 --bat 1.3 --artoff --fixbolus
  -c {calibration_image.nii.gz} --tr 6 --cref {calibration_reference.nii.gz}
  -s {structural_image.nii.gz} --regfrom {calibration_image.nii.gz)
```

Example 3

pcASL with

tagging duration: 1.4 s

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



Input Filename mti_data.nii.gz

Inversion Times 1.65,1.9,2.15,2.4,2.65,2.9

Bolus duration 1.4

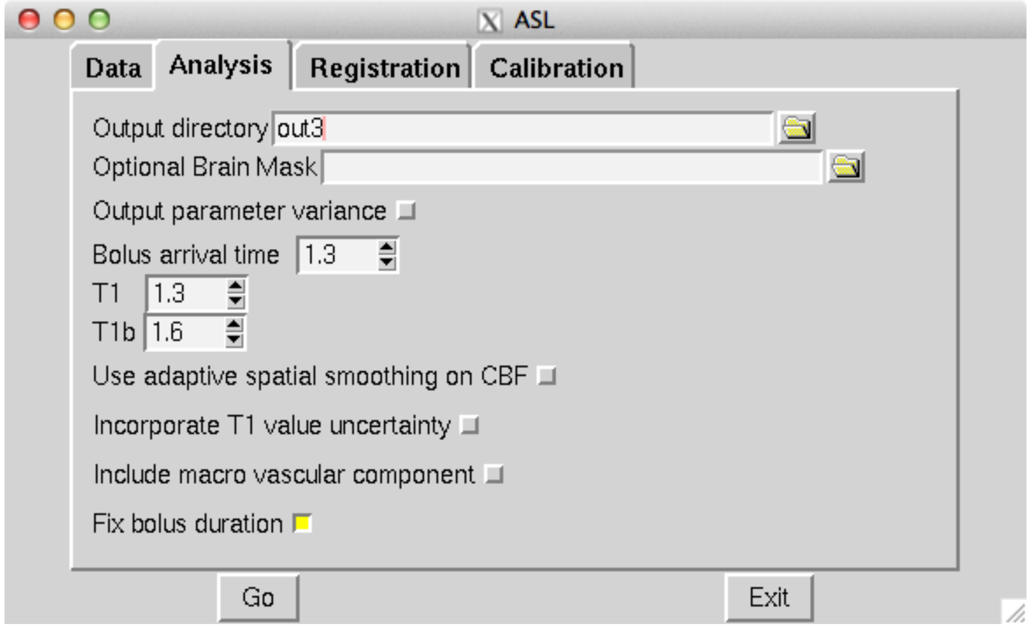
Labelling: cASl/pcASL

Data is tag-control pairs: ☑

Data order (grouped by): repeats

Static tissue: background suppressed

Structural image ☑ struct.nii.gz



Output directory out3

Optional Brain Mask

Output parameter variance ☐

Bolus arrival time 1.3

T1 1.3

T1b 1.6

Use adaptive spatial smoothing on CBF ☐

Incorporate T1 value uncertainty ☐

Include macro vascular component ☐

Fix bolus duration ☑

```
> asl_file --data=mti_data.nii.gz --ntis=6 --iaf=tc --diff --out=mti_diffdata --obf=rpt
> oxford_asl -i diffdata.nii.gz -o out3 --casl --tis 1.65,1.9,2.15,2.4,2.65,2.9
  --bolus 1.4 --bat 1.3 --artoff --fixbolus -c calibhead.nii.gz --tr 6
  --cref calibbody.nii.gz -s struct.nii.gz --regfrom calibhead.nii.gz
```

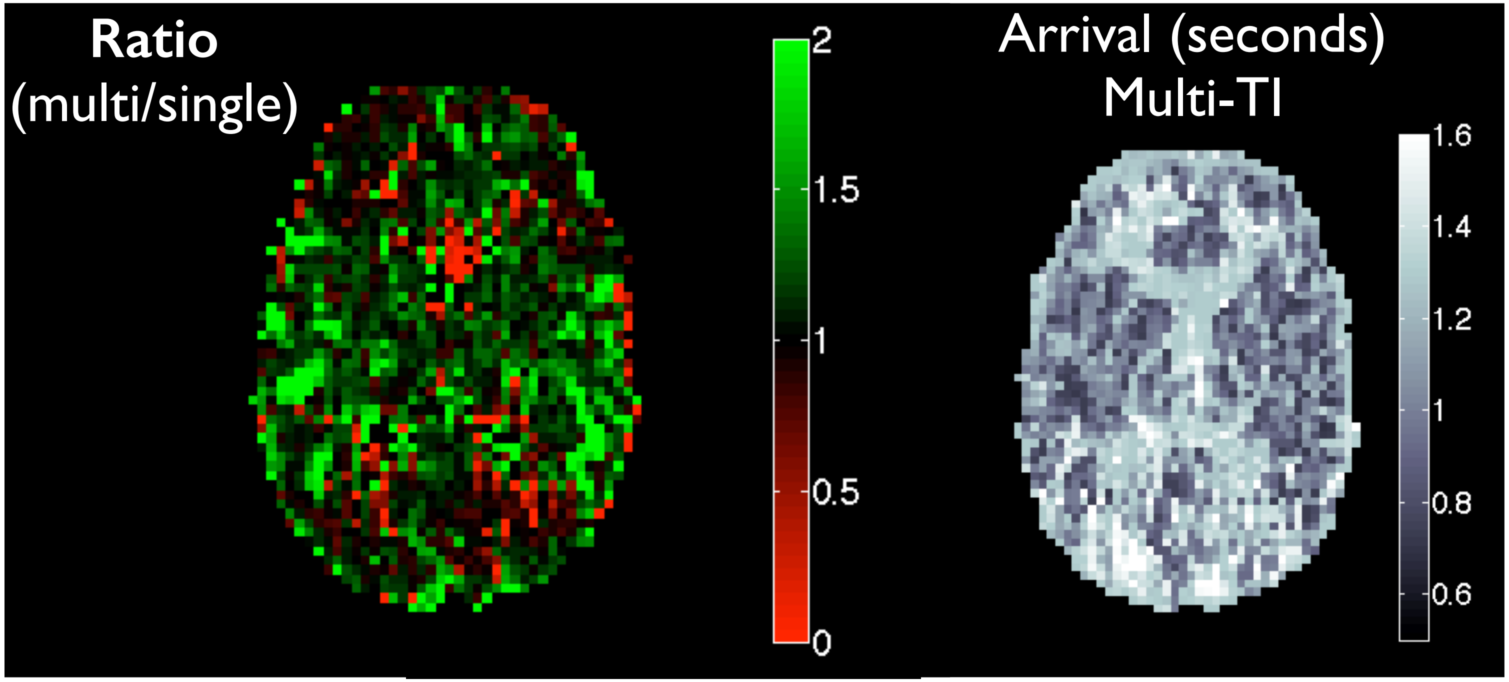
SINGLE-TI VS MULTI-TI

- Data:
  - ➡ pcASL
  - ➡ tagging duration: 1.4 s

  - ➡ Single-TI
  - ➡ post-label delay: 1.5 s
  - ➡ Assume BAT of 1.3 s

  - ➡ Multi-TI

    PLDs: 0.25, 0.5, 0.75, 1.0, 1.25, 1.5 s



```
out1/native_space/perfusion_calib.nii.gz
out3/native_space/perfusion_calib.nii.gz
out3/native_space/arrival.nii.gz
```

OUTLINE

- Acquisition
- Keep it simple!
    - ➡ Perfusion weighted images.
    - ➡ Perfusion fMRI.
- Quantitative perfusion:
    - ➡ A short course in tracer kinetics.
    - ➡ Measuring arterial blood magnetization.
- Preparing for group analysis.
- Advanced quantification:
    - ➡ Macro vascular contamination
    - ➡ Partial Volume Correction

PREPARING FOR GROUP ANALYSIS

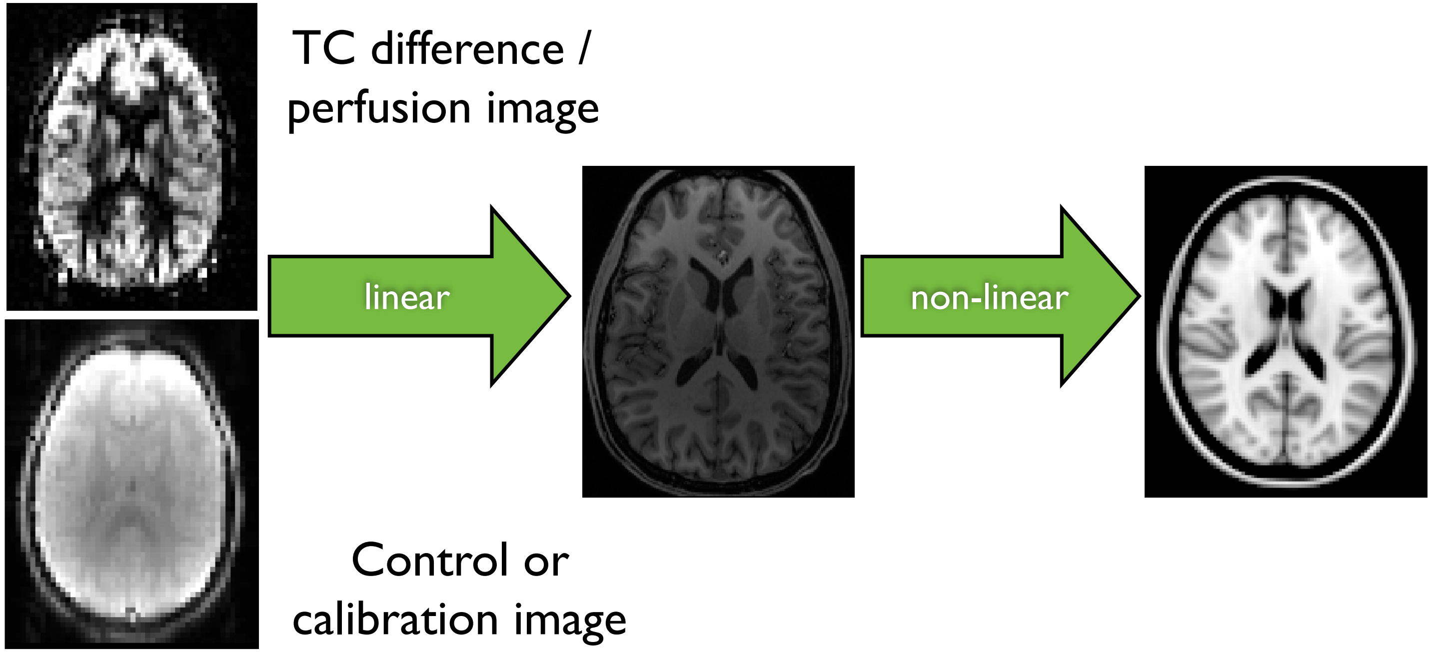
- Group analysis and quantitative comparisons between individuals requires consistent representation

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

- **Consistent intensity:**
  - ➡ Quantitive 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



TC difference / perfusion image

Control or calibration image

```
oxford_asl ... --s {structural_image.nii.gz} -t {struct2std.mat}
  --regfrom {control/calibration_image.nii.gz)
```

See also: `asl_reg`, `flirt`, `fnirt`

PREPARING 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.

    NB still might want coil sensitivity correction.
  - ➡ 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

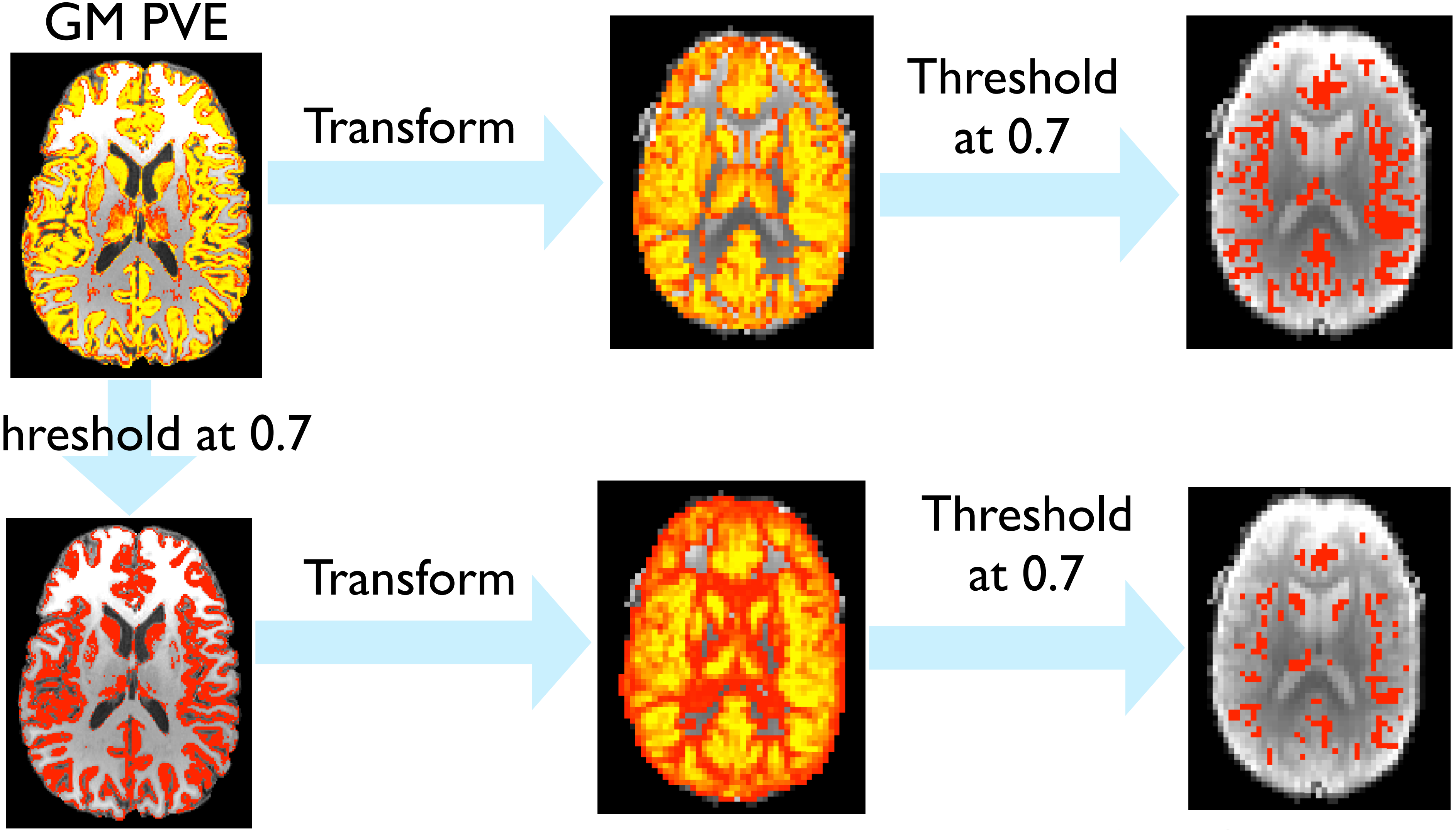
    Interpolation occurs on perfusion values, ROI untouched.

- Exception is 'soft' segmentations

  e.g. GM/WM on a structural image.
  - ➡ Transform 'soft' segmentations first and THEN threshold to create ROI.

```
oxford_asl ... --norm
oxford_asl ... --report
```

Preparing for Group Analysis



GM PVE

Transform

Threshold at 0.7

Threshold at 0.7

Transform

Threshold at 0.7

High res GM mask

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
```

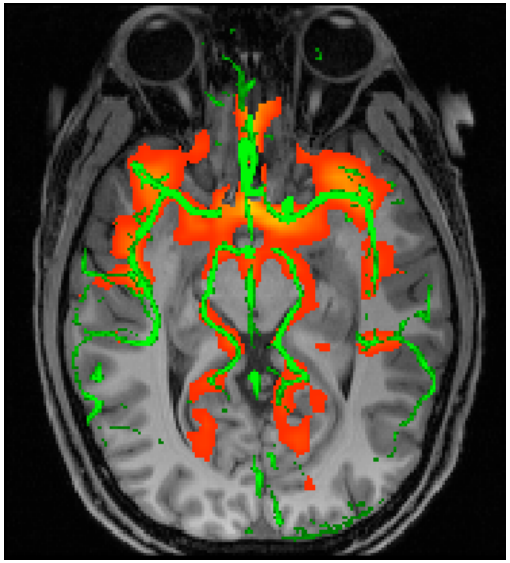
OUTLINE

- Acquisition
- Keep it simple!
  - ➡ Perfusion weighted images.
  - ➡ Perfusion fMRI.
- Quantitative perfusion:
  - ➡ A short course in tracer kinetics.
  - ➡ Measuring arterial blood magnetization.
- Preparing for group analysis.
- Advanced quantification:
  - ➡ Macro vascular contamination
  - ➡ Partial Volume Correction

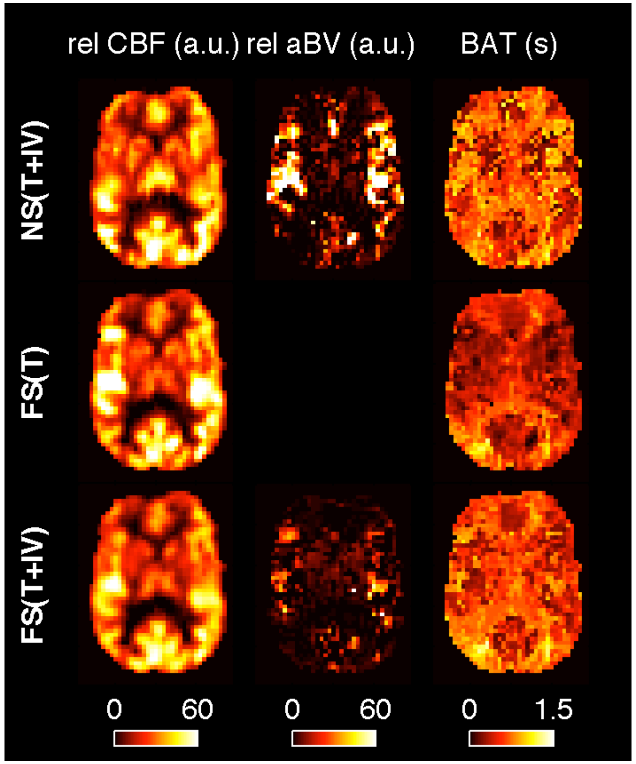
ADVANCED: MACRO VASCULAR CONTAMINATION

- 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



aBV and TOF MIP



`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.

ADVANCED: MACRO VASCULAR CONTAMINATION

- An extended model for ASL:

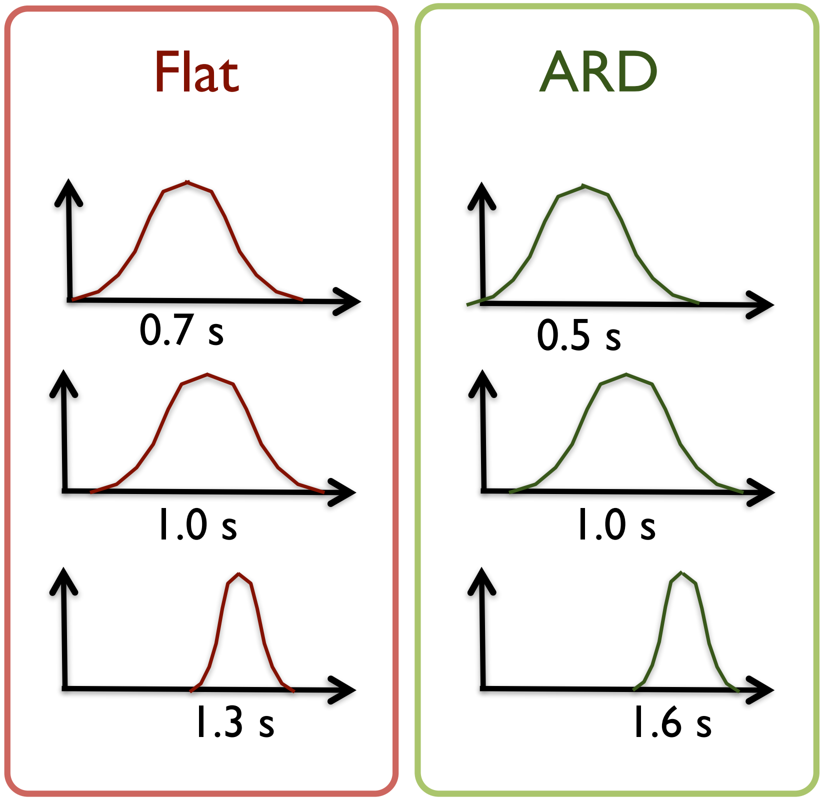
$$\Delta M(t) = \text{CBF}\,\Delta M_{tiss}(t) + \text{aBV}\,\Delta M_{IV}(t)$$

CBF/aBV

Bolus arrival time

Bolus duration

TI



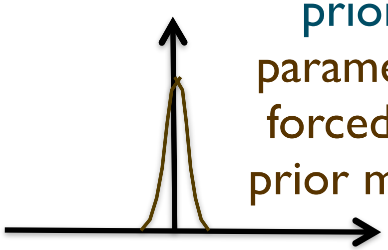
ARD prior: ~N(0,*v*)

v determines the **relevance** of the prior.

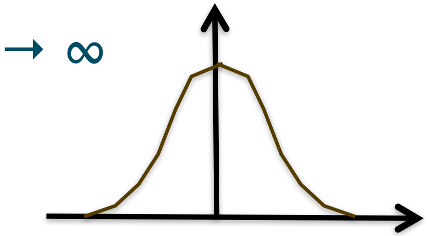
v is determined from the data.

$v \rightarrow 0$

Restrictive prior: parameter forced to prior mean



$v \rightarrow \infty$

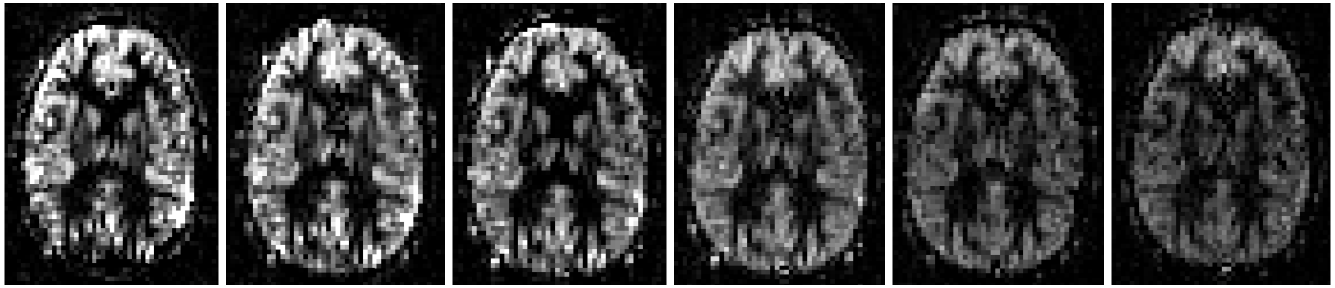


Liberal prior: parameter free to be estimated from data

EXAMPLE 4

- 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.

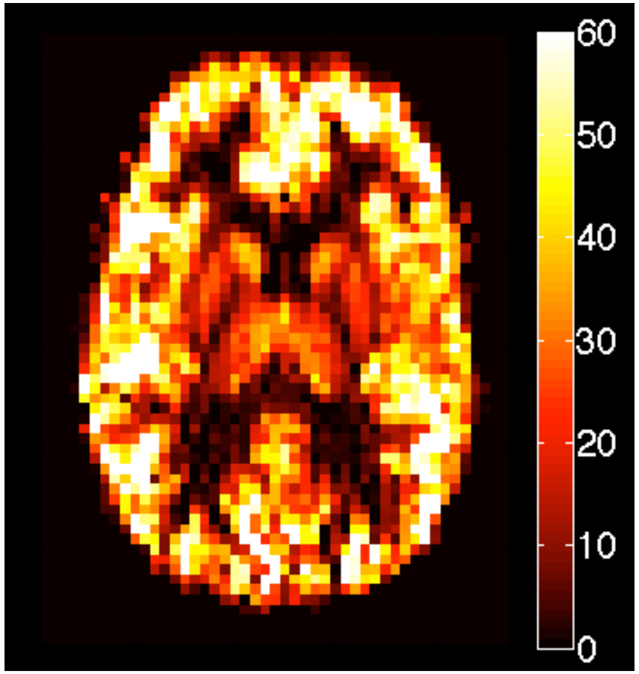
pcASL with
labeling duration: 1.4 s
post-label delays: 0.25, 0.5, 0.75,1.0, 1.25, 1.5 s



```
oxford_asl -i {ASL_diff_data.nii.gz} -o {out4}
  --casl --tis 1.65,1.9,2.15,2.4,2.65,2.9 --bolus 1.4 --bat 1.3 ~~--artoff~~ --fixbolus
  -c {calibration_image.nii.gz} --tr 6 --cref {calibration_reference.nii.gz}
  -s {structural_image.nii.gz} --regfrom {calibration_image.nii.gz)
```

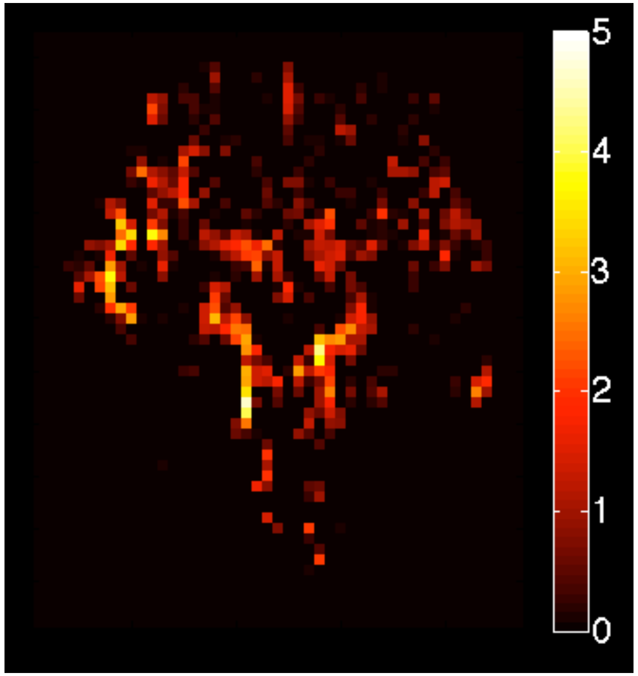
EXAMPLE 4

Perfusion ml/100g/min



middle slice

Arterial blood volume % (ml/ml * 100)



lower slice ~ Circle of Willis

```
out2/native_space/perfusion_calib.nii.gz
out4/native_space/aCBV_calib.nii.gz
```

ADVANCED: PARTIAL VOLUME CORRECTION

- Partial voluming of grey and white matter inevitable.
- Leads to GM perfusion underestimation
  - ➡ WM perfusion < GM
  - ➡ WM blood arrival > GM

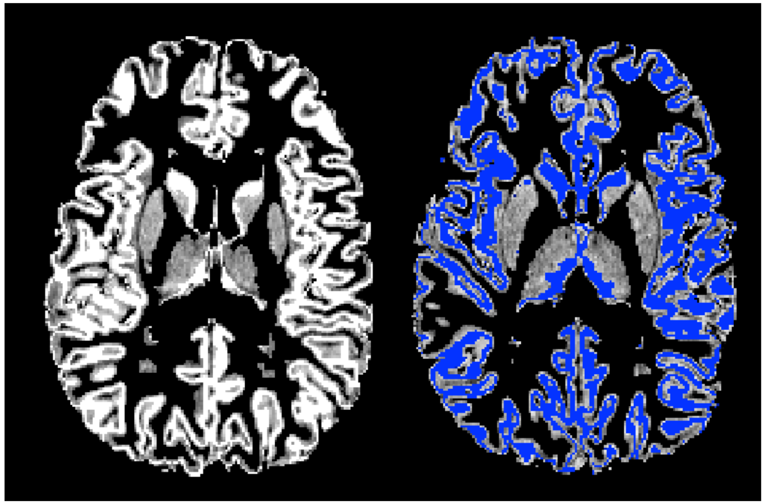
- Correction
  - ➡ PV estimates from segmentation of structural image.

    Note: partial volume estimates NOT a hard segmentation or probabilities.
  - ➡ Make separate GM and WM perfusion estimates in every voxel.

    An under determined problem.

ADVANCED: PARTIAL VOLUME CORRECTION

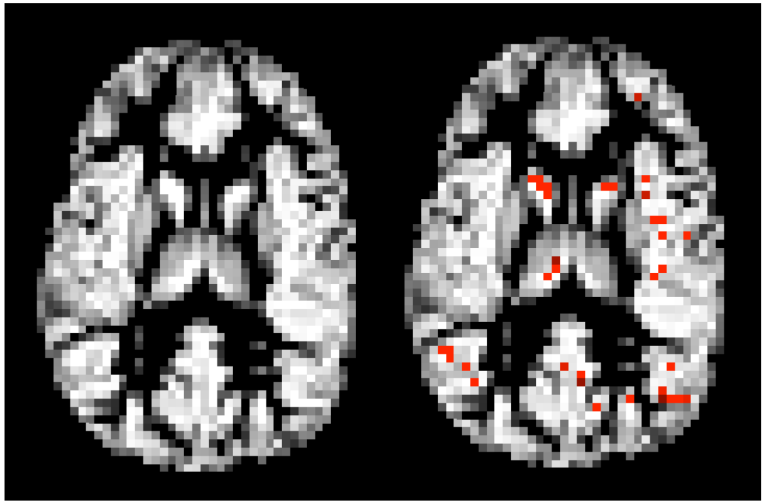
- Does it matter that much?
  - ➡ Resolution of ASL ~ 3 x 3 x 5 mm
  - ➡ Cortical thickness ~ 2 - 4 mm
- Unlikely to have many pure GM or WM voxels in the cortex



Structural resolution

Partial Volume Estimate

Threshold at 90%



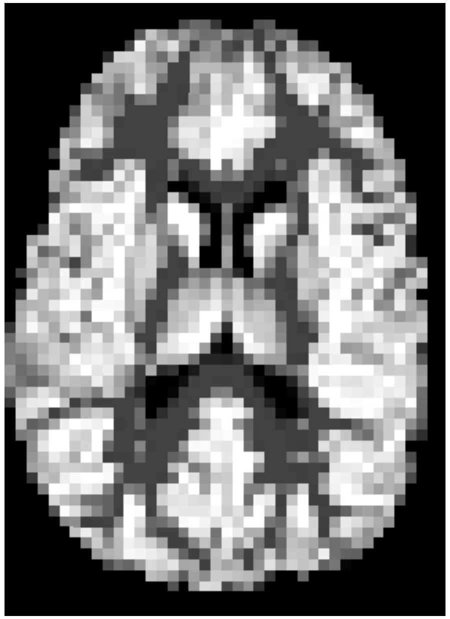
ASL resolution

Partial Volume Estimate

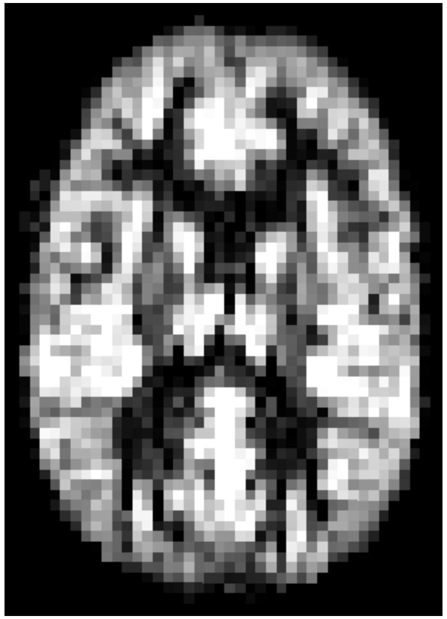
Threshold at 90%

ADVANCED: PARTIAL VOLUME CORRECTION

- Does it matter that much?
  - ➡ Resolution of ASL ~ 3 x 3 x 5 mm
  - ➡ Cortical thickness ~ 2 - 4 mm
- What is this?



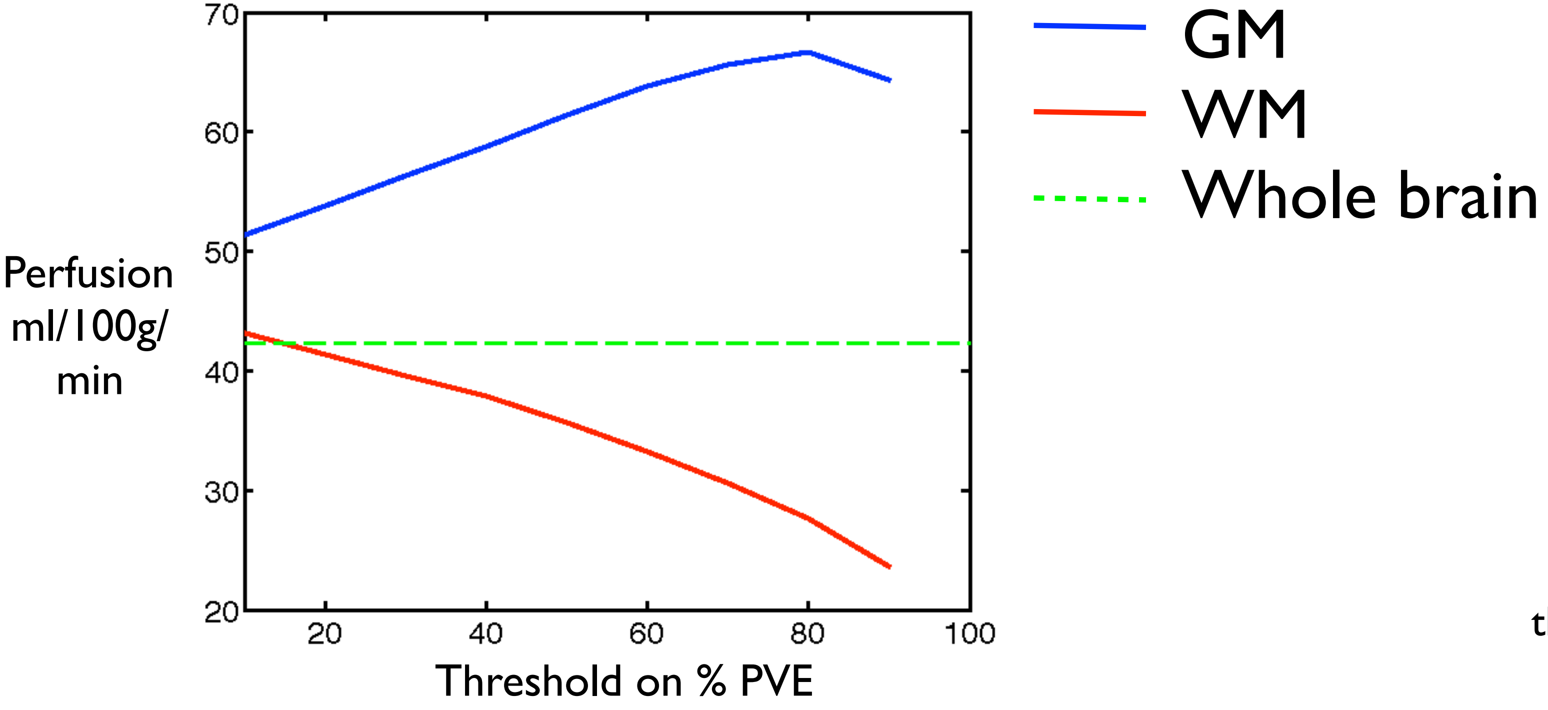
$60 * PVE_{GM} + 10 * PVE_{WM}$

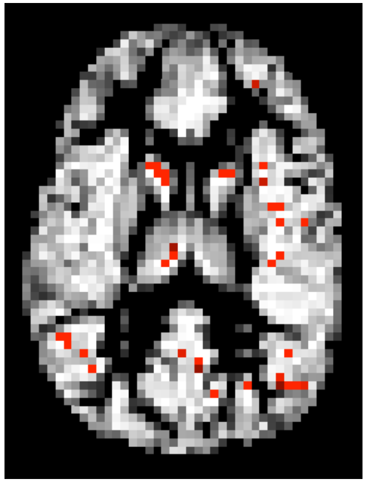


Estimated perfusion from ASL

ADVANCED: PARTIAL VOLUME CORRECTION

- What do we mean when we report GM or WM perfusion?



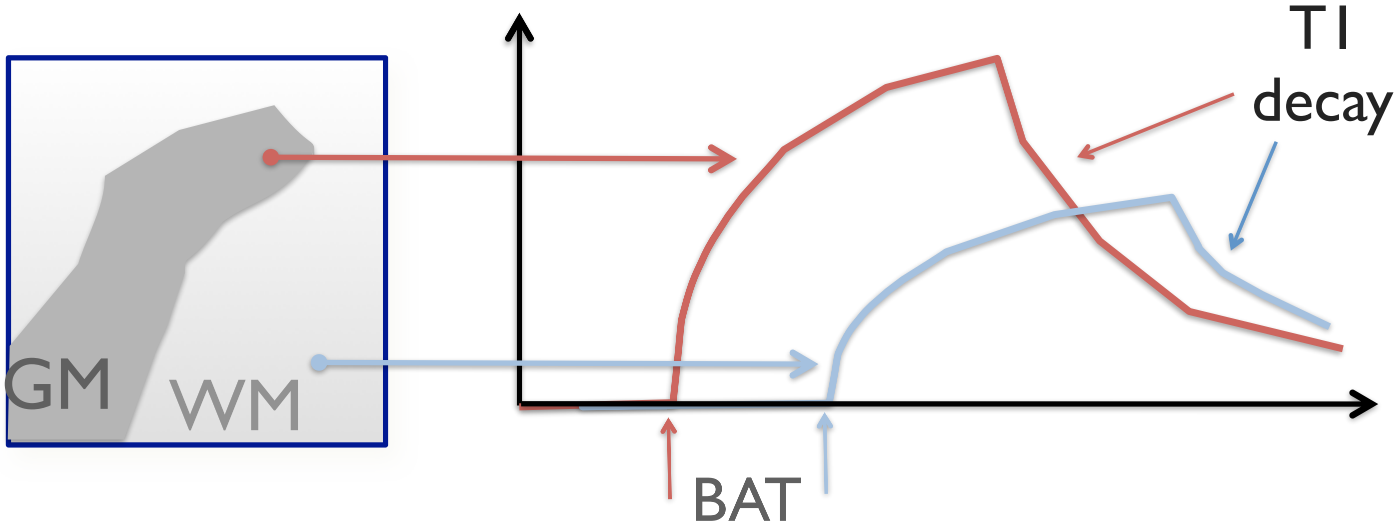


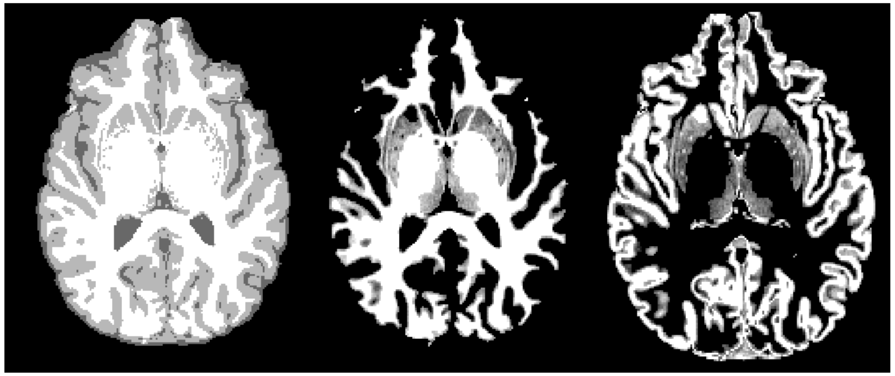
GM mask threshold at 90%

```
oxford_asl ... --report
```

Advanced: Partial Volume Correction

- Partial volume correction exploiting kinetic data:





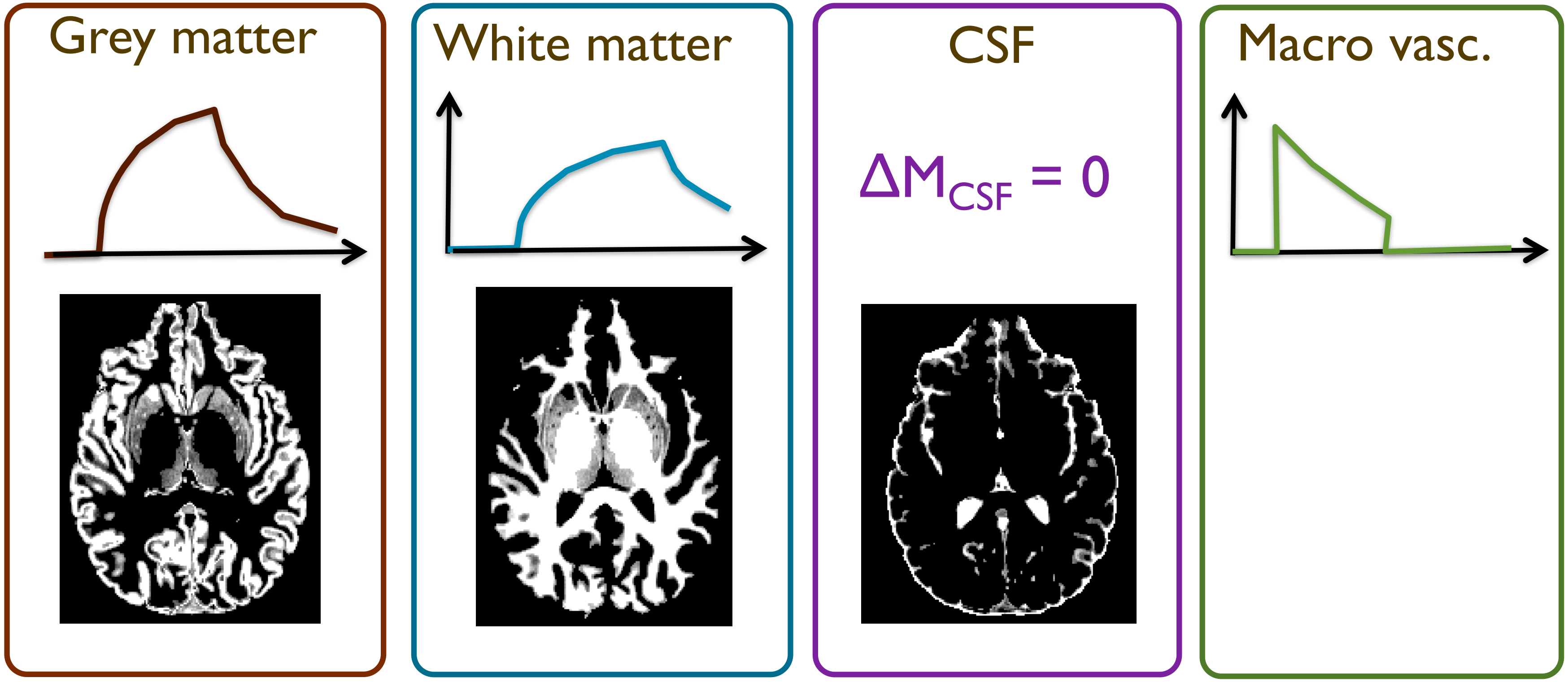
➡ CBF: GM > WM

➡ 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

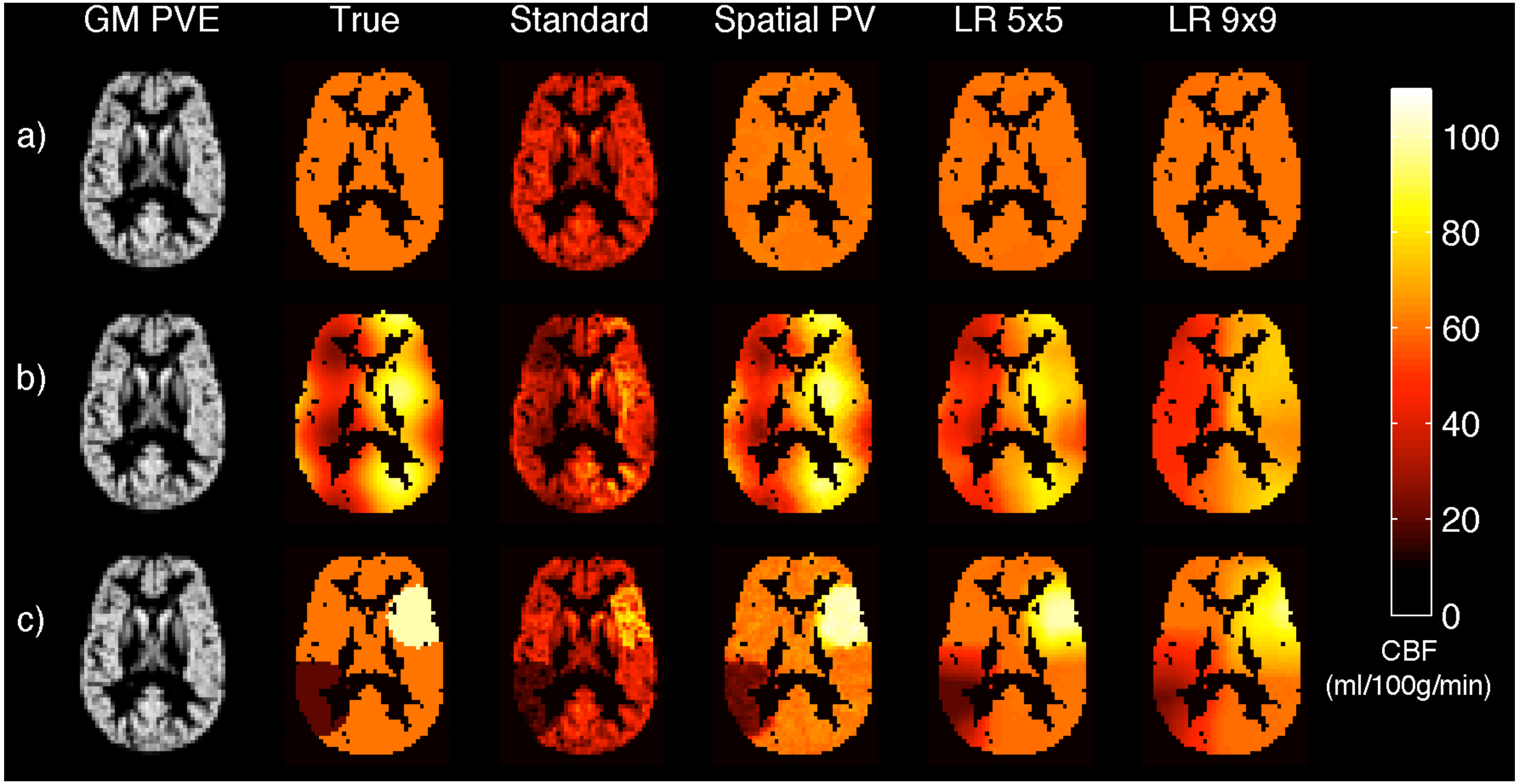
CSF

$\Delta M_{CSF} = 0$

Macro vasc.

- Spatial priors on CBF for GM and WM

ADVANCED: PARTIAL VOLUME CORRECTION

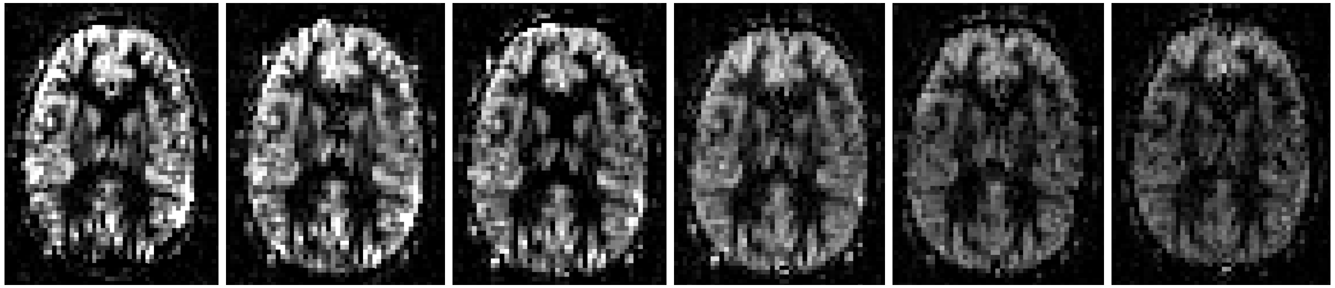


Chappell et al., MRM 65(4), 2011.

EXAMPLE 5

- 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

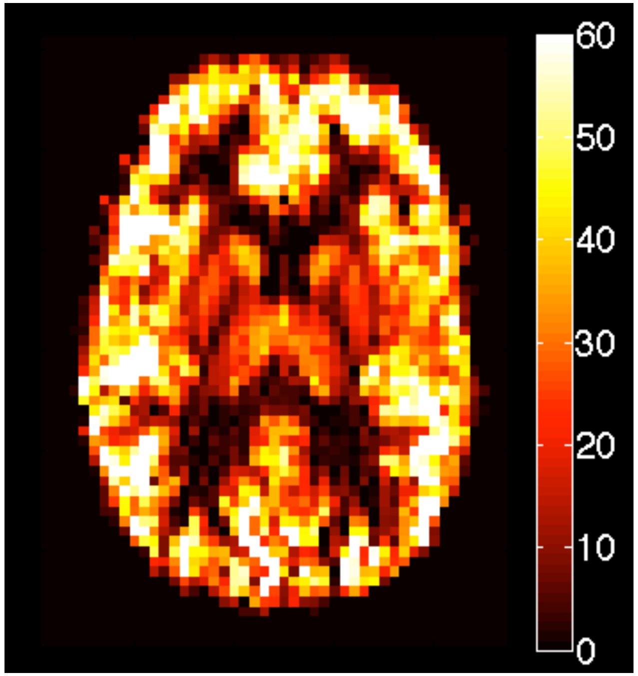
pcASL with
  labeling duration: 1.4 s
  post-label delays: 0.25, 0.5, 0.75,1.0, 1.25, 1.5 s



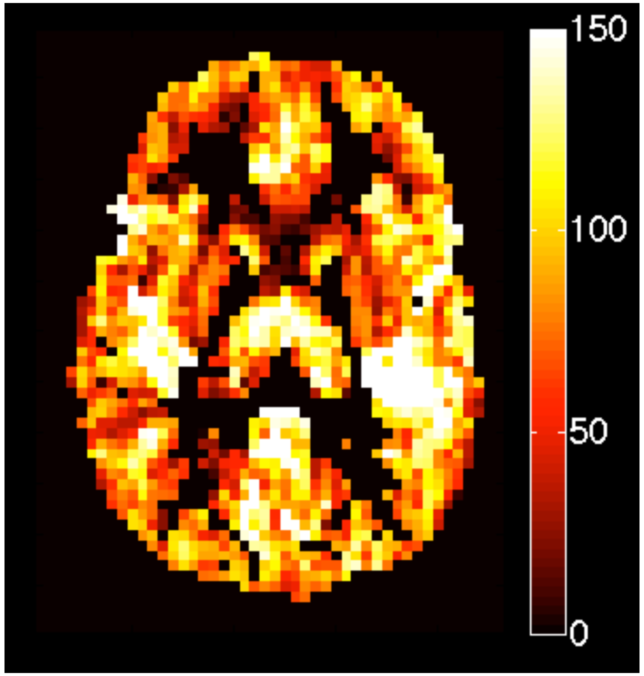
```
oxford_asl -i {ASL_diff_data.nii.gz} -o {out_dir}
  --casl --tis 1.65,1.9,2.15,2.4,2.65,2.9 --bolus 1.4 --bat 1.3 --artoff --fixbolus
  -c {calibration_image.nii.gz} --tr 6 --cref {calibration_reference.nii.gz}
  -s {structural_image.nii.gz} --regfrom {calibration_image.nii.gz) --pvcorr
```

EXAMPLE 5

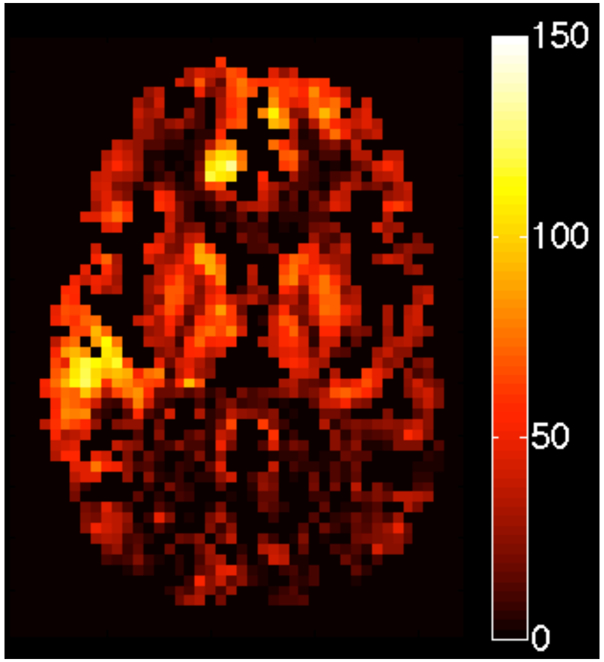
Perfusion (uncorrected)
ml/100g/min



Grey matter perfusion
ml/100g/min



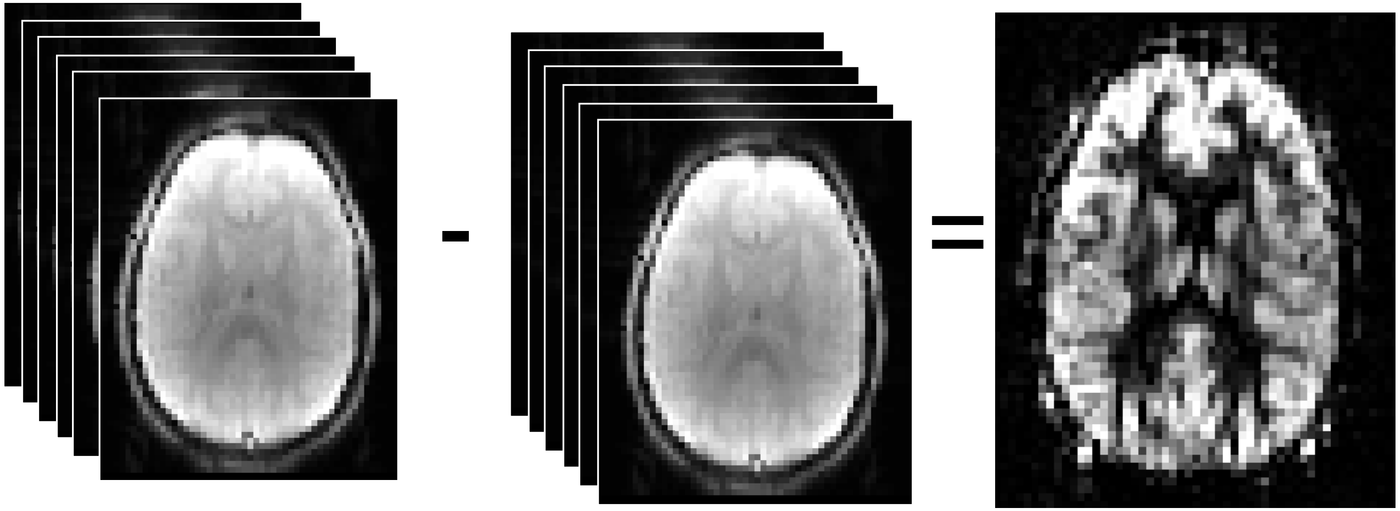
White matter perfusion
ml/100g/min



```
out2/native_space/perfusion_calib.nii.gz
out5b/native_space/perfusion_calib_masked.nii.gz
out5b/native_space/perfusion_wm_calib_masked.nii.gz
```

EXAMPLE 5B

- What I have...
  - ➡ ASL data
  - ➡ (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



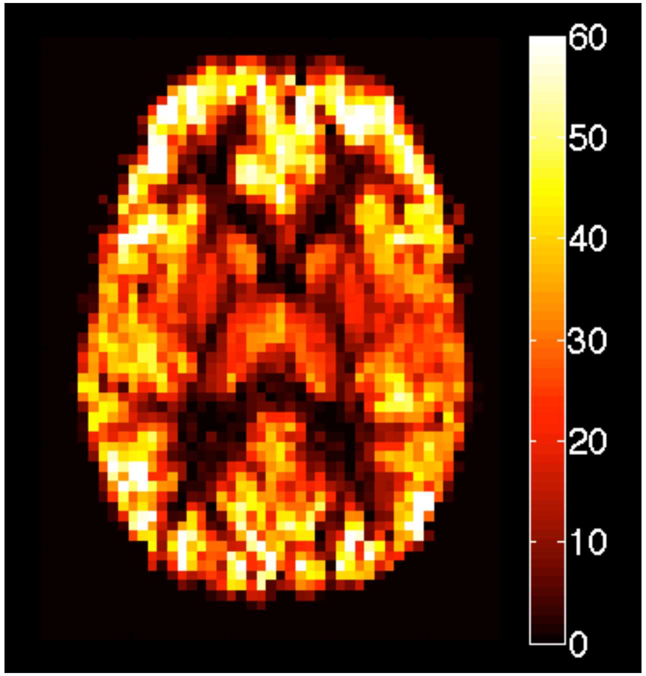
pcASL with
labeling duration: 1.4 s
post-label delay: 1.0 s

Assume
T1 (blood): 1.6 s
T1 (tissue): 1.3 s
BAT : 1.3 s

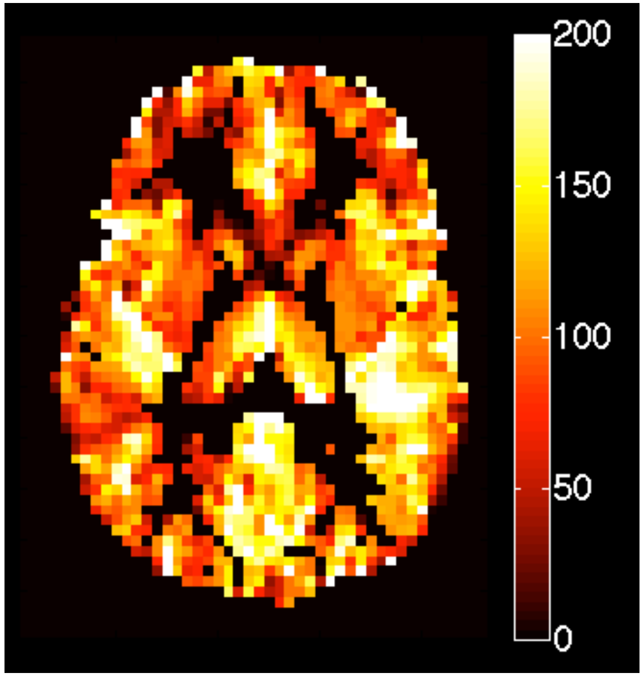
```
oxford_asl -i {ASL_diff_data.nii.gz} -o {out_dir}
  --casl --tis 2.4 --bolus 1.4 --bat 1.3 --artoff --fixbolus
  -c {calibration_image.nii.gz} --tr 6 --cref {calibration_reference.nii.gz}
  -s {structural_image.nii.gz} --regfrom {calibration_image.nii.gz) --pvcorr
```

EXAMPLE 5B

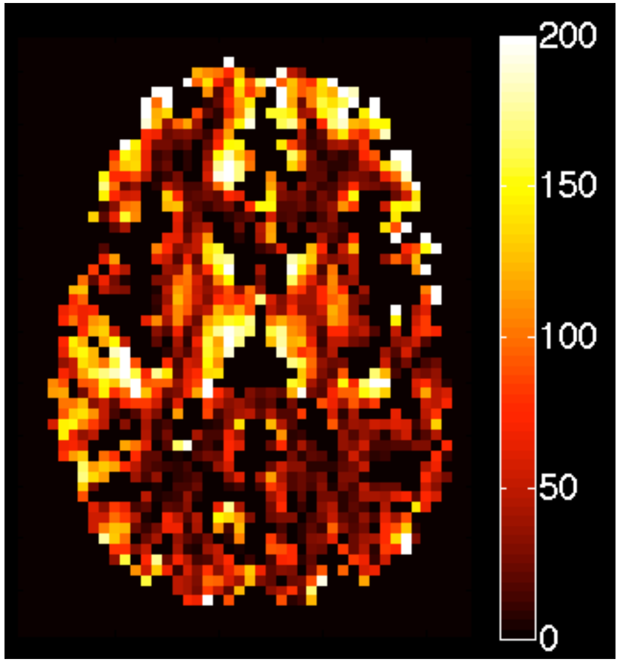
Perfusion (uncorrected)
ml/100g/min



Grey matter perfusion
ml/100g/min



White matter perfusion
ml/100g/min



```
out2/native_space/perfusion_calib.nii.gz
out5b/native_space/perfusion_calib_masked.nii.gz
out5b/native_space/perfusion_wm_calib_masked.nii.gz
```

FSL: The FMRIB Software Library (v5.0)

- ➡ BASIL: www.fmrib.ox.ac.uk/fsl/basil
  - User guide & tutorials

ACKNOWLEDGEMENTS

- FMRIB, Oxford
  - ➡ Peter Jezzard
  - ➡ Tom Okell
  - ➡ Michael Kelly
  - ➡ James Meakin
  - ➡ Matthew Webster
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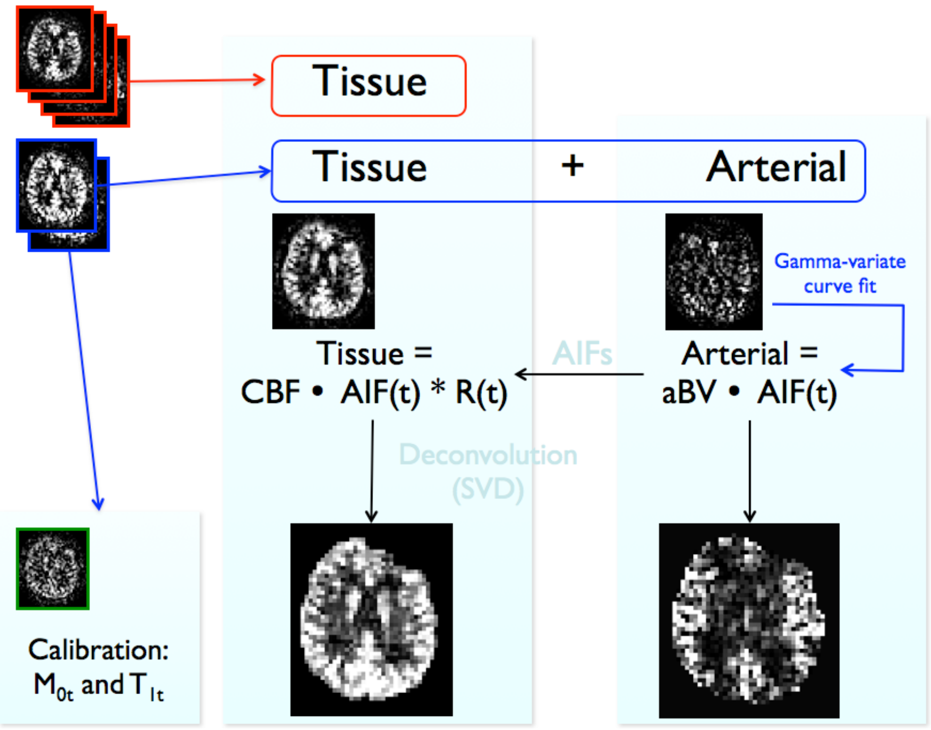
- Manus Donahue (Vanderbilt)
- Xavier Golay (UCL, London)
- Esben Petersen (Utrecht)
- Marco Castellaro (Padova)

SPECIAL: QUASAR

- 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)



Tissue

Tissue + Arterial

Gamma-variate curve fit

Tissue = CBF • AIF(t) * R(t)

AIFs

Arterial = aBV • AIF(t)

Deconvolution (SVD)

Calibration: M_{0t} and T_{1t}

```
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.