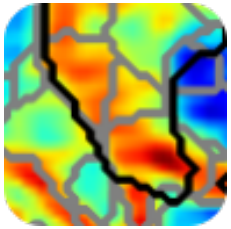

Arterial Spin Labelling: Non-invasive measurement of perfusion

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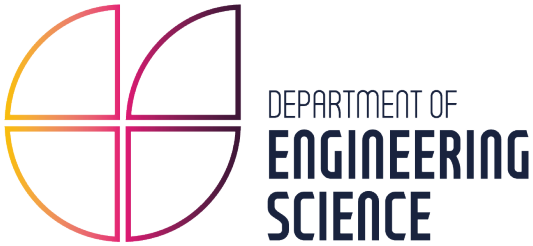
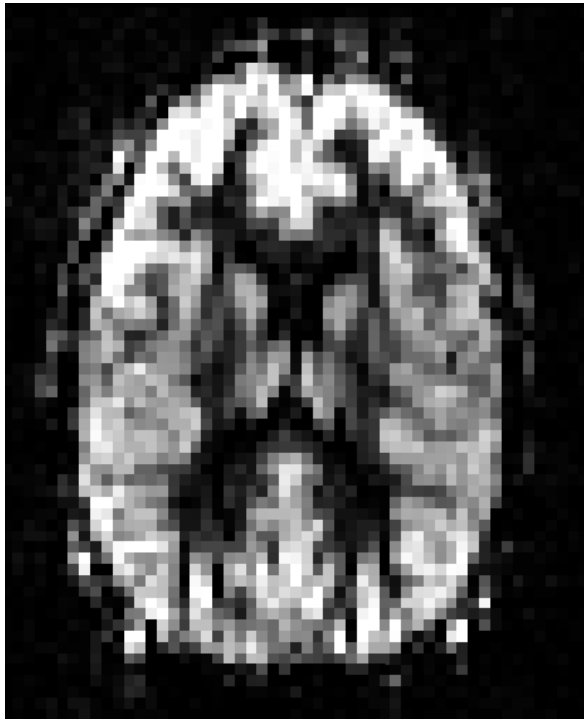
University of Oxford.



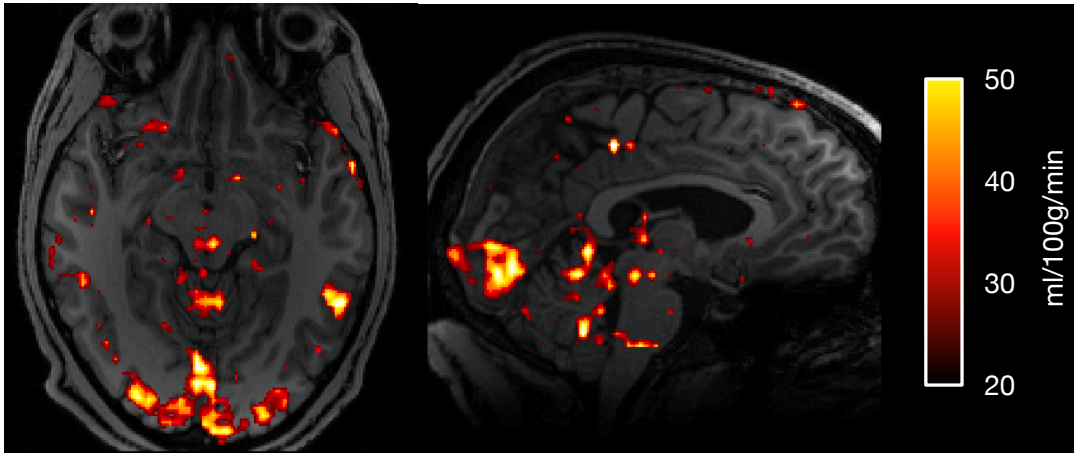
Perfusion

- 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'.

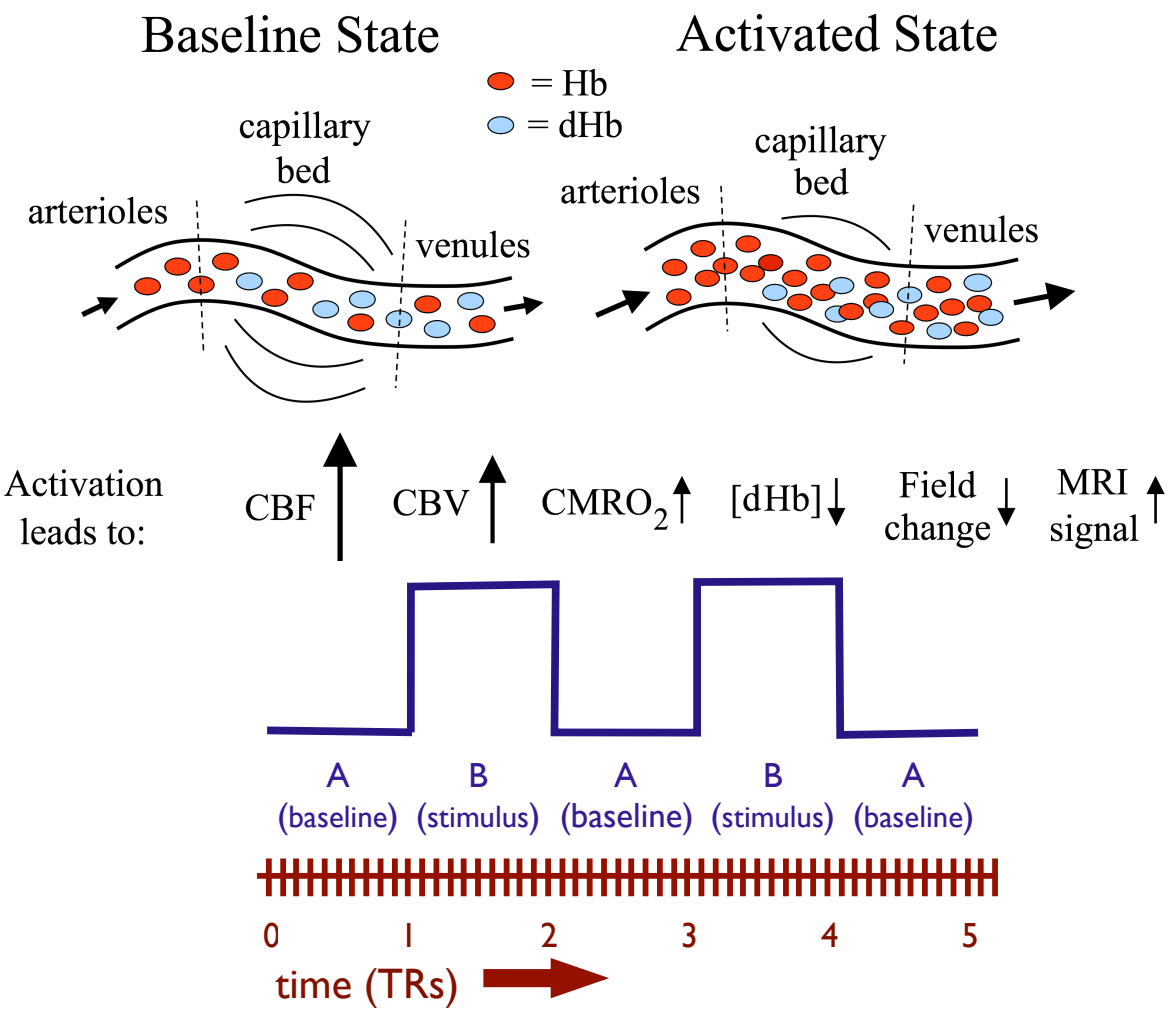


- What are the challenges?
  - ➡ SNR
  - ➡ Temporal sampling - TR and the need for label and control scans.

Perfusion

- ASL is not BOLD!
  - ➡ CBF change is a component of the BOLD signal.
  - ➡ ASL can make absolute measurements under different conditions.
  - ➡ You DONT 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 (mutli-) echo ASL/BOLD

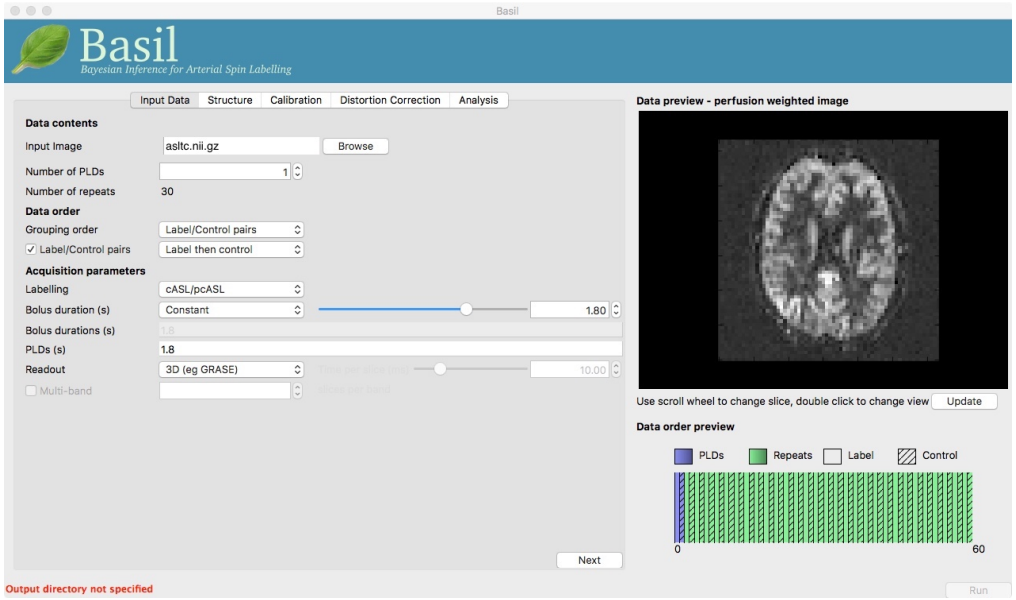


Arterial Spin Labelling : M.A. Chappell

FSL for Arterial Spin Labelling

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

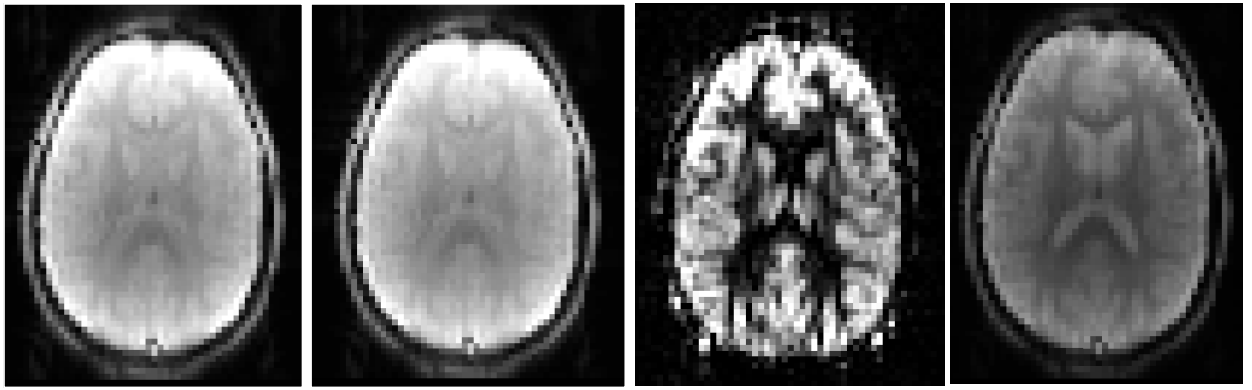
  - ➡ Command line tools
    oxford_asl, basil, asl_reg, asl_calib
  - ➡ Graphical User Interface
    asl_gui



- Make sure you are using FSL v 6.0.1 at home!

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...
```

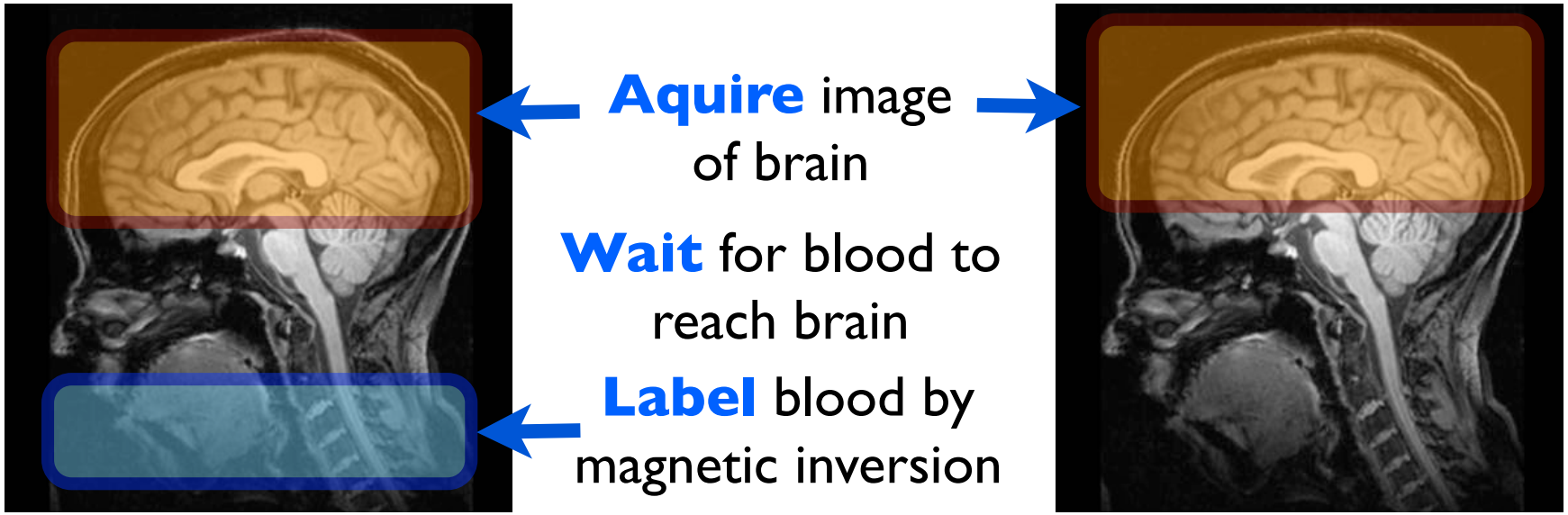
Outline

- 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:
  - ➡ Motion, Distortion & Artefacts
  - ➡ Cerebrovascular Reactivity/Reserve
  - ➡ Macro Vascular Contamination
  - ➡ Partial Volume Effects

Arterial Spin Labelling

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

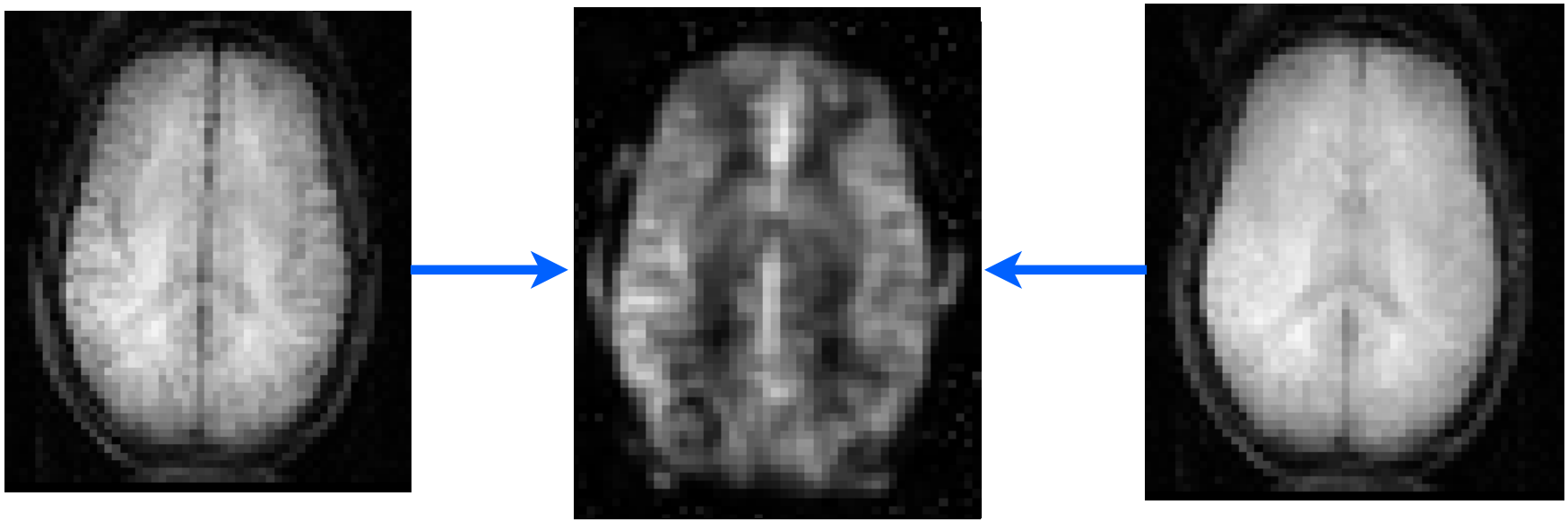
LABEL **CONTROL**



ASL Acquisition

- Spot the difference?

LABEL **CONTROL**



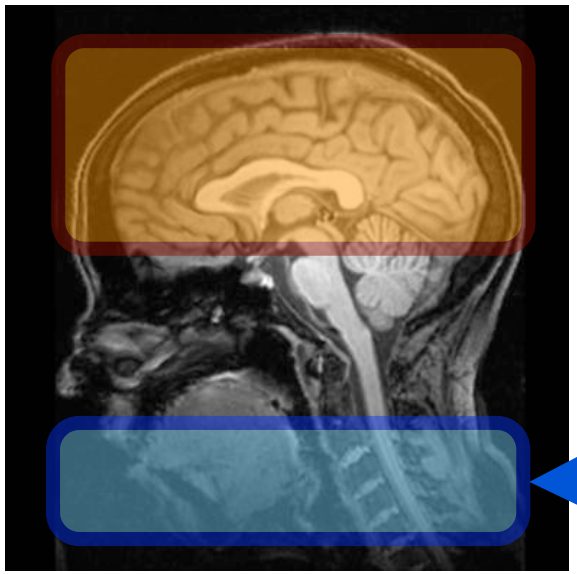
Perfusion is ~60 ml/100g/min = 0.01 s^{-1}

Signal is ~ 1-2%

ASL Acquisition

- Nuts & bolts: Labelling

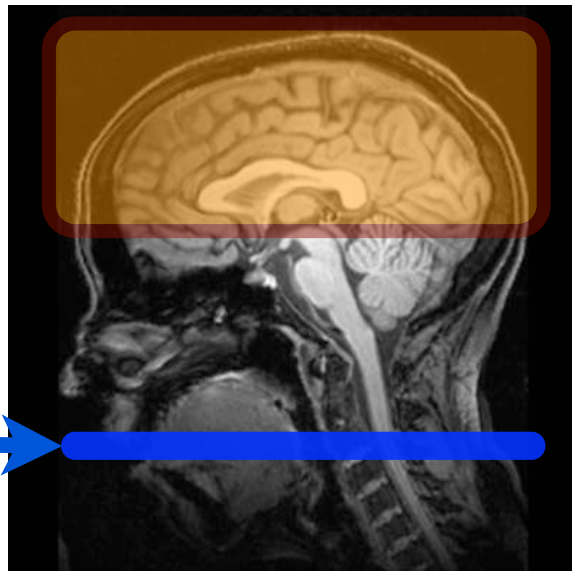
pASL: Pulsed ASL



Label a region in a single pulse

Label blood by magnetic inversion

cASL: Continuous ASL
pcASL: psuedo-continous ASL

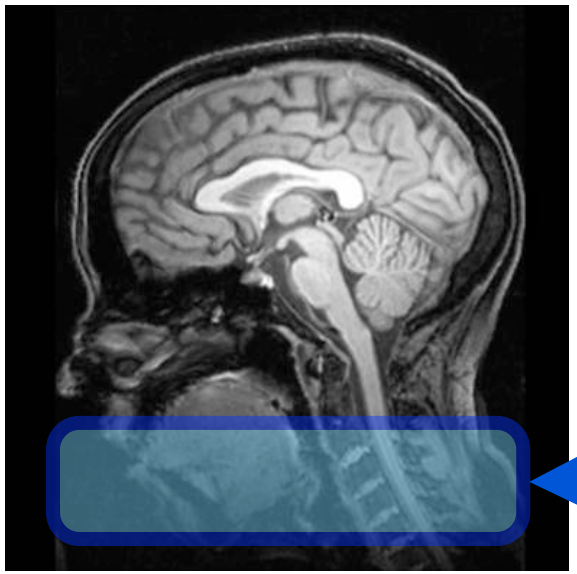


Label blood flowing through a plane for some time

pcASL uses pulses and is more widely available

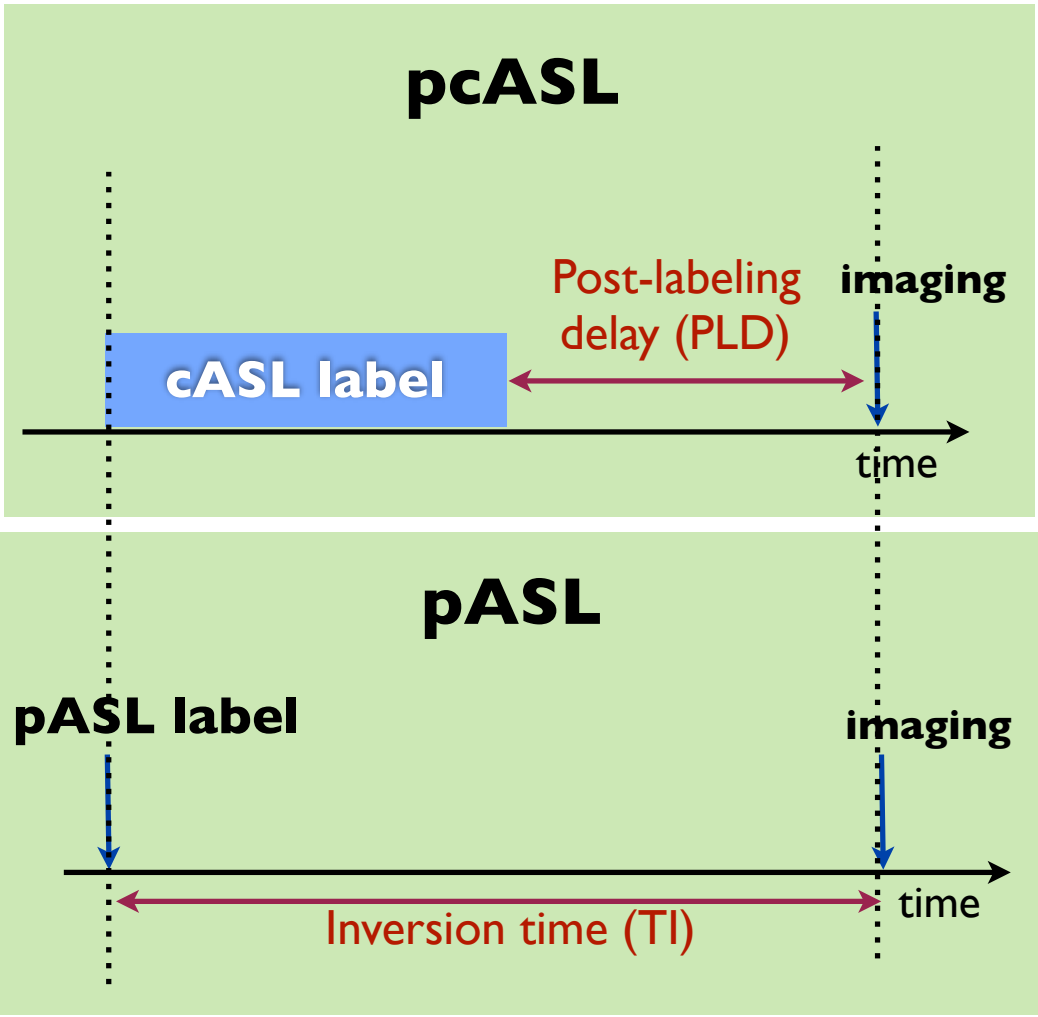
ASL Acquisition

- Nuts & bolts: Inflow time



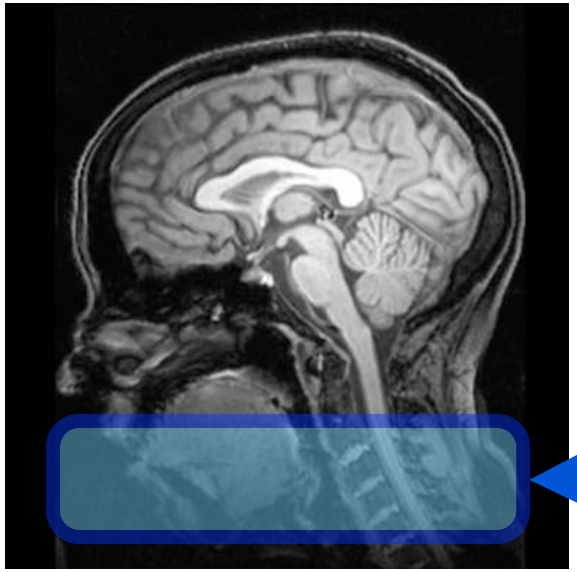
Wait for blood to reach brain

Label blood by magnetic inversion



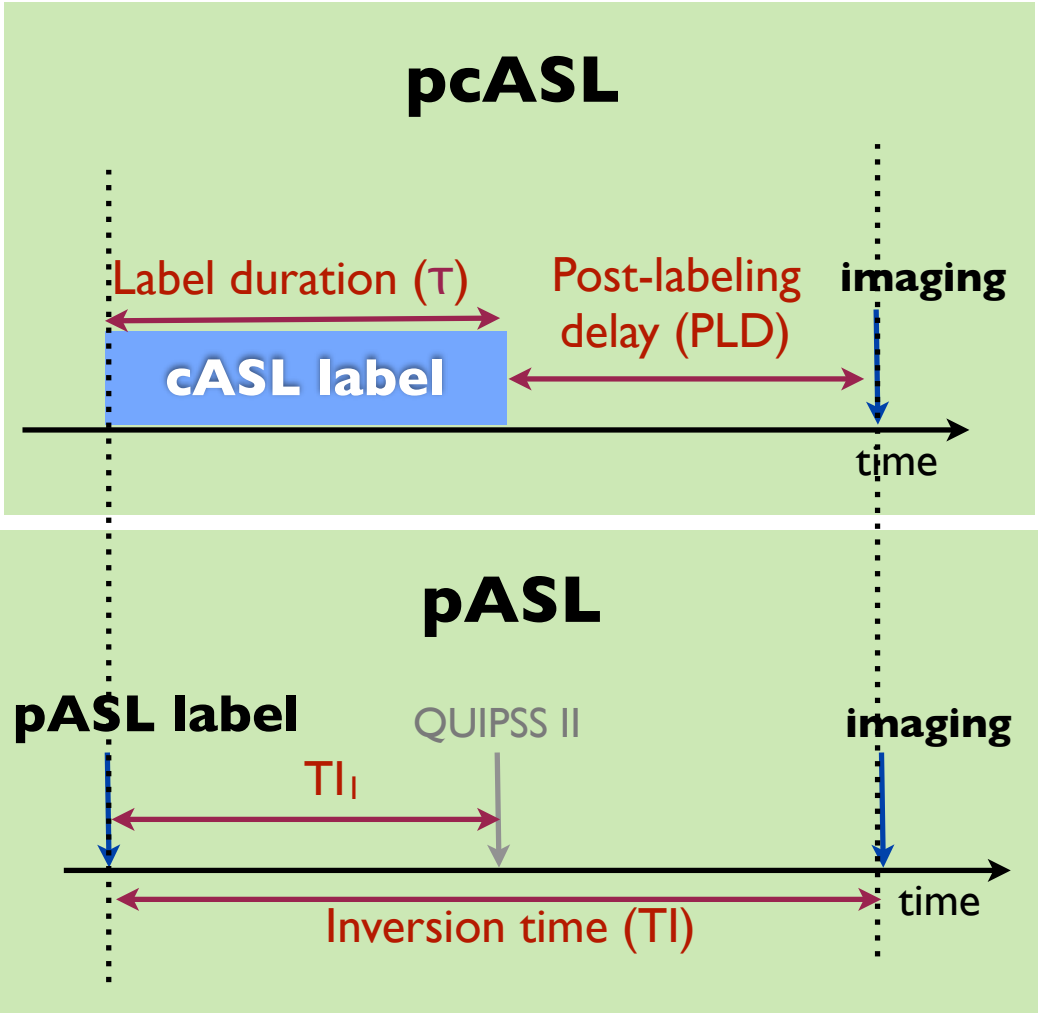
ASL Acquisition

- Nuts & bolts: Bolus/label duration



Wait for blood to reach brain

Label blood by magnetic inversion

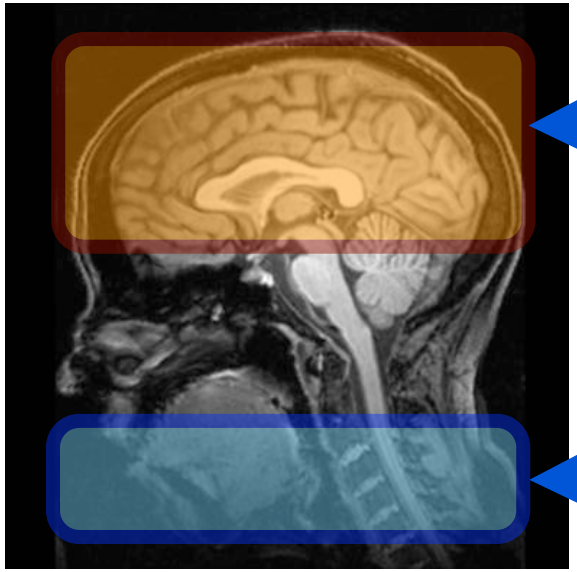


pASL

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

ASL Acquisition

- Nuts & Bolts: Readout

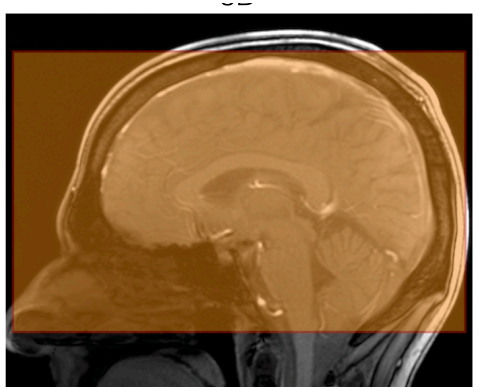


Aquire image of brain

Wait for blood to reach brain

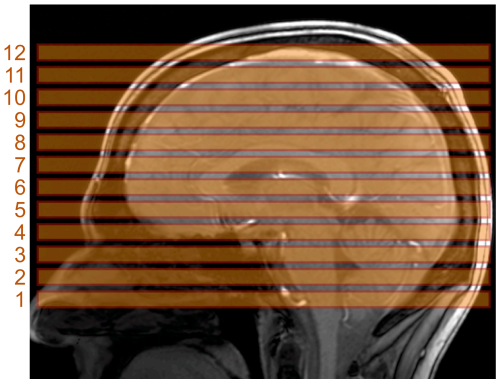
Label blood by magnetic inversion

3D: GRASE/RARE



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

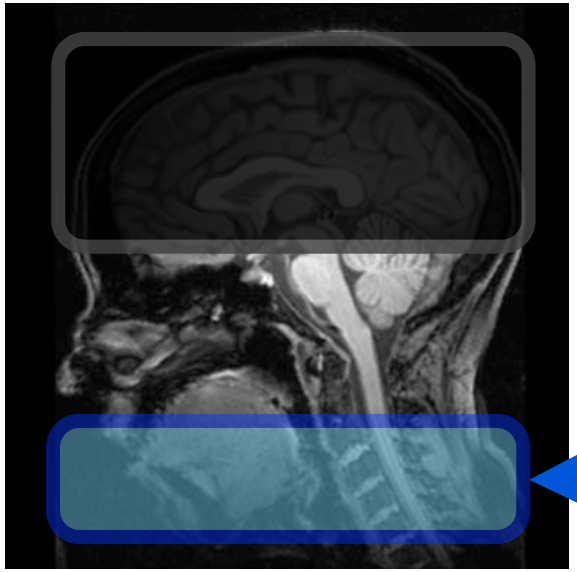
2D: EPI (Multi-slice)



Different PLD for each slice

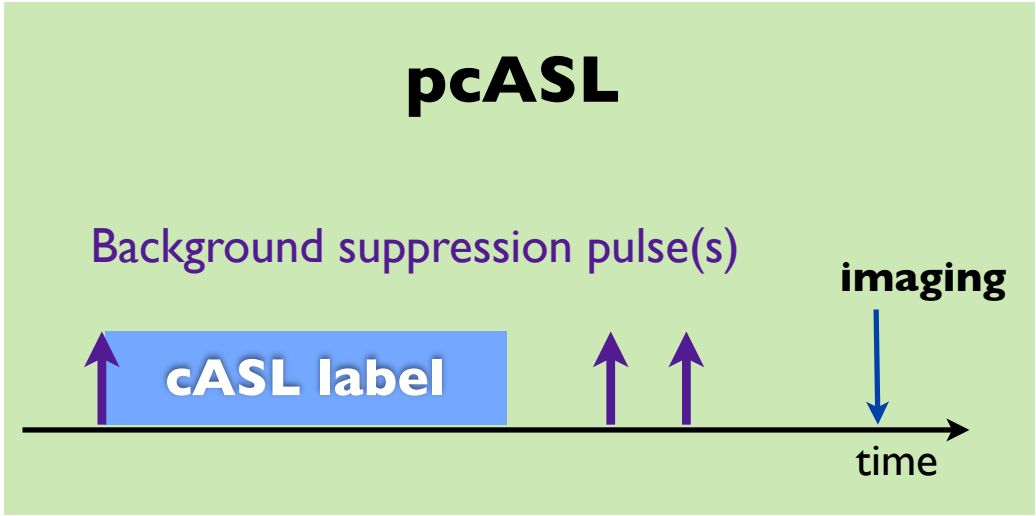
ASL Acquisition

- Nuts & Bolts: Background Suppression



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

- 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
  T11 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

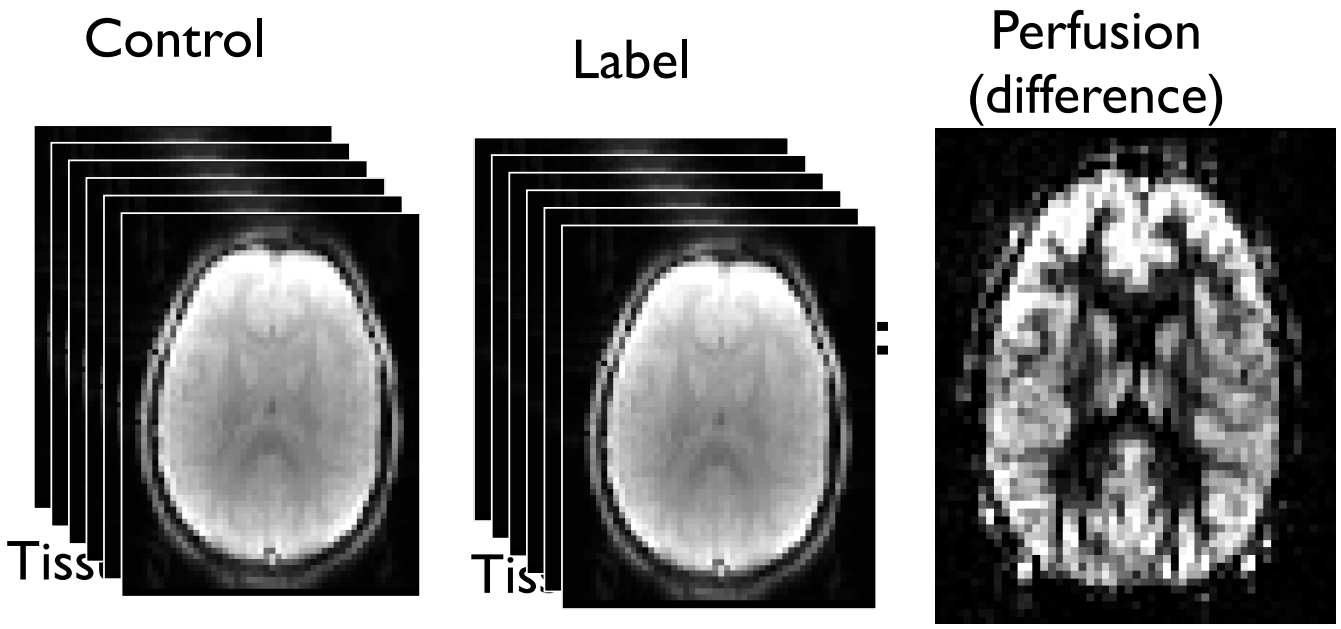
Magnetic Resonance in Medicine - 73 (1) p102-116, 2015.

Outline

- Acquisition
- Keep it simple!
  - ➡ Perfusion weighted images.
- Quantitative perfusion:
  - ➡ Kinetics: A short course in tracer kinetics.
  - ➡ Calibration: Measuring arterial blood magnetization.
- Preparing for group analysis.
- Advanced quantification:
  - ➡ Motion, Distortion & Artefacts
  - ➡ Cerebrovascular Reactivity/Reserve
  - ➡ Macro Vascular Contamination
  - ➡ Partial Volume Effects

Example (simple)

- What I have...
  - ➡ ASL data!
- What I want...
  - ➡ A perfusion image (in this subject).
- What should I do?
  - ➡ Label-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}
```

Outline

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  - ➡ Perfusion weighted images.
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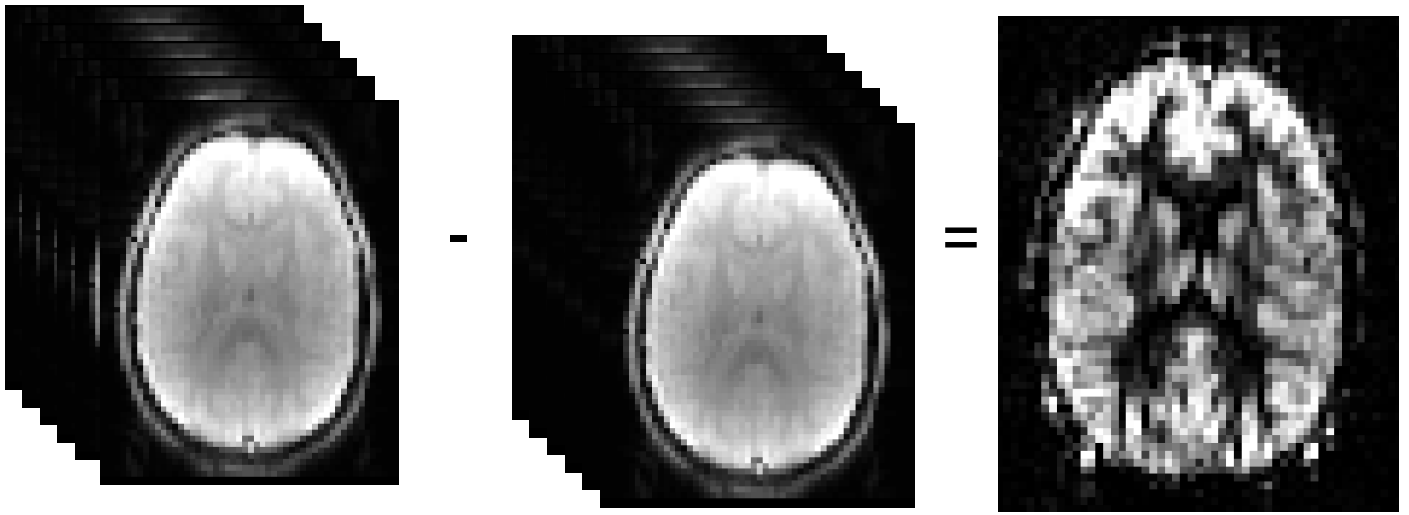
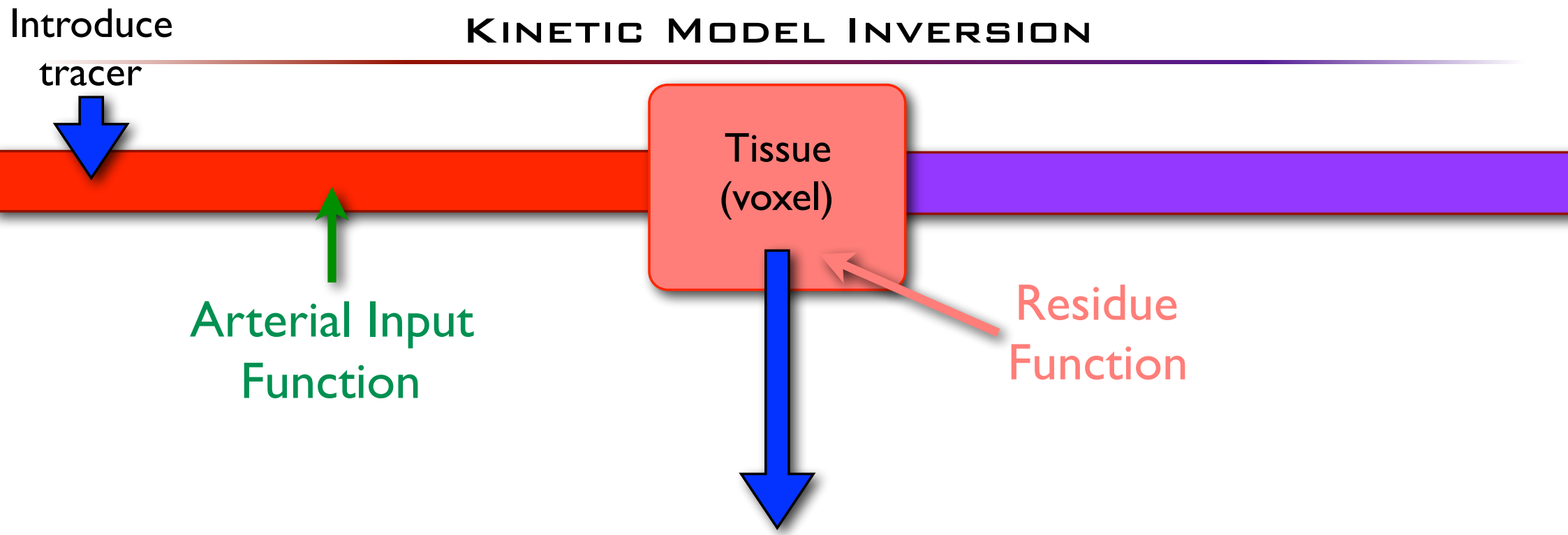
  - ➡ Macro Vascular Contamination
  - ➡ Partial Volume Effects

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



Kinetic Model Inversion

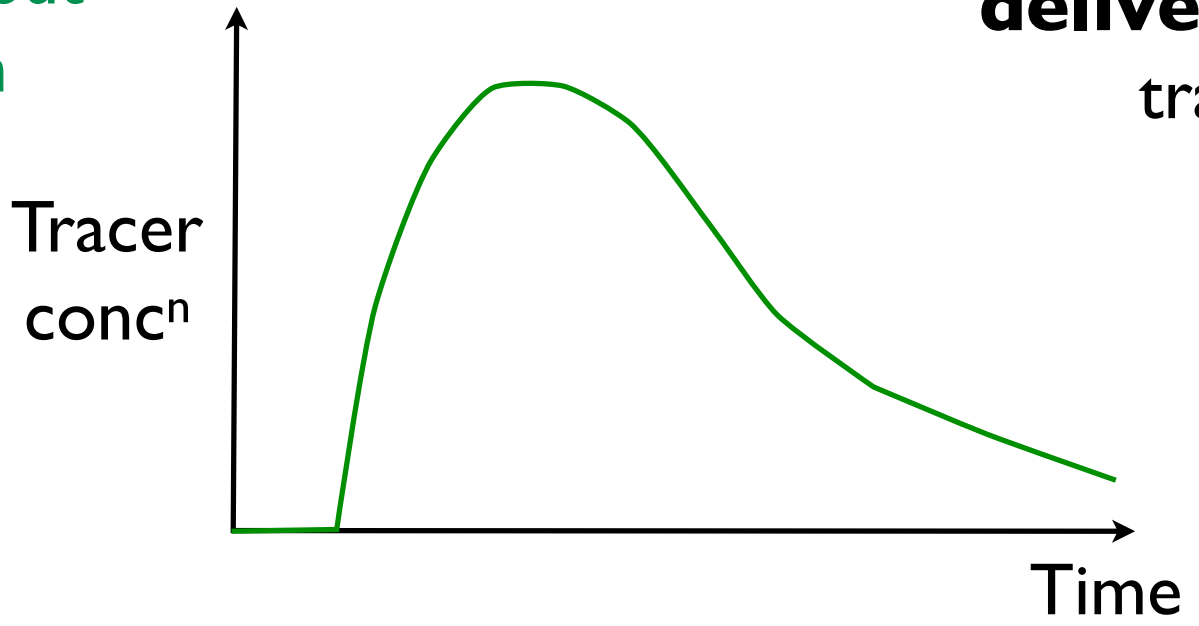


$$\Delta M(t) = F \cdot AIF(t) * r(t)$$

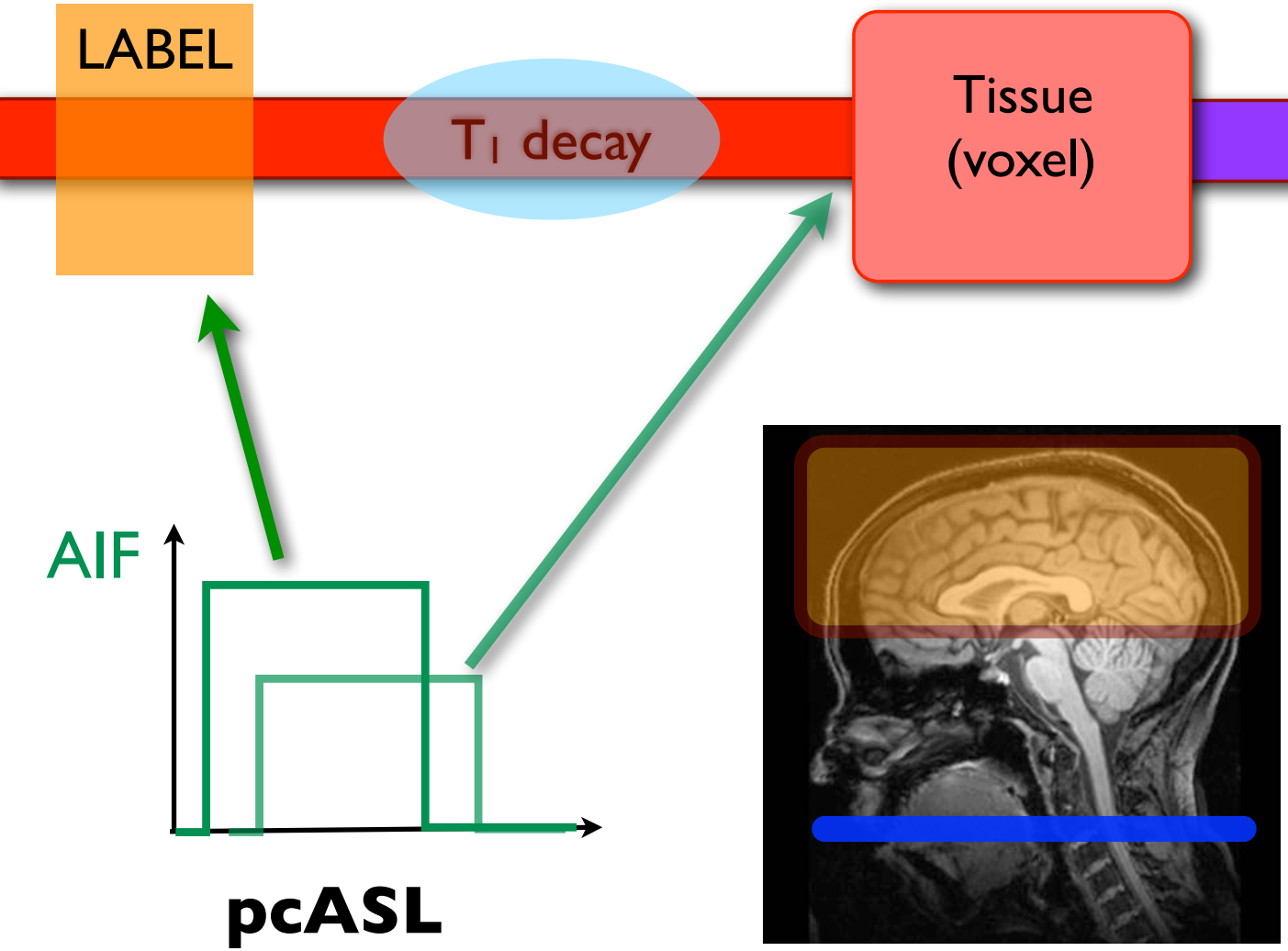
Kinetic Model Inversion

Arterial Input Function

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

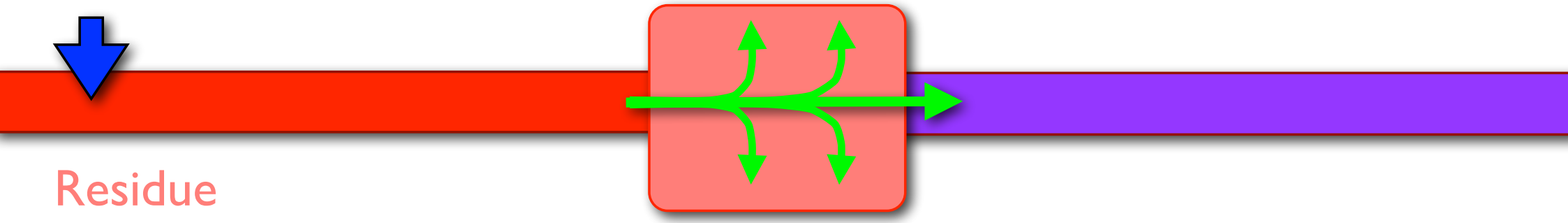


Kinetic Model Inversion



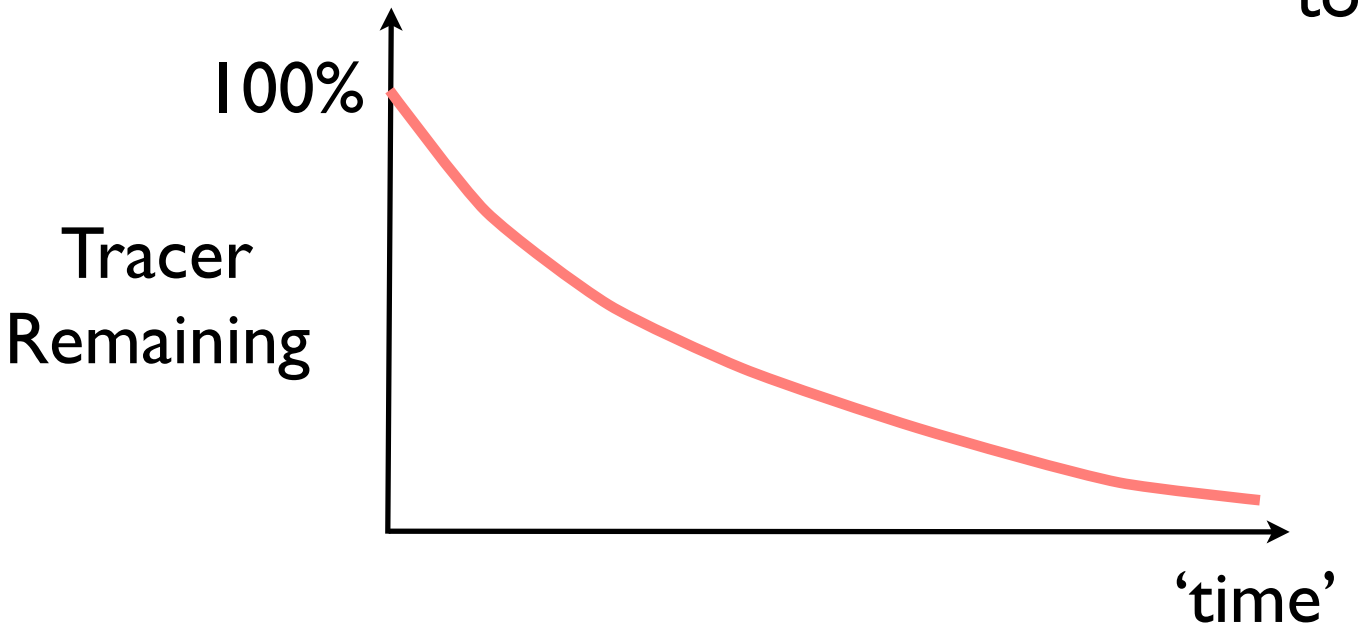
Parameters:
Arterial Transit Time
Label duration
T1 decay

Kinetic Model Inversion



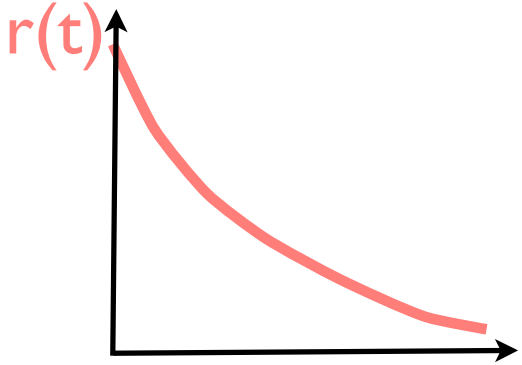
Residue Function

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



Kinetic Model Inversion

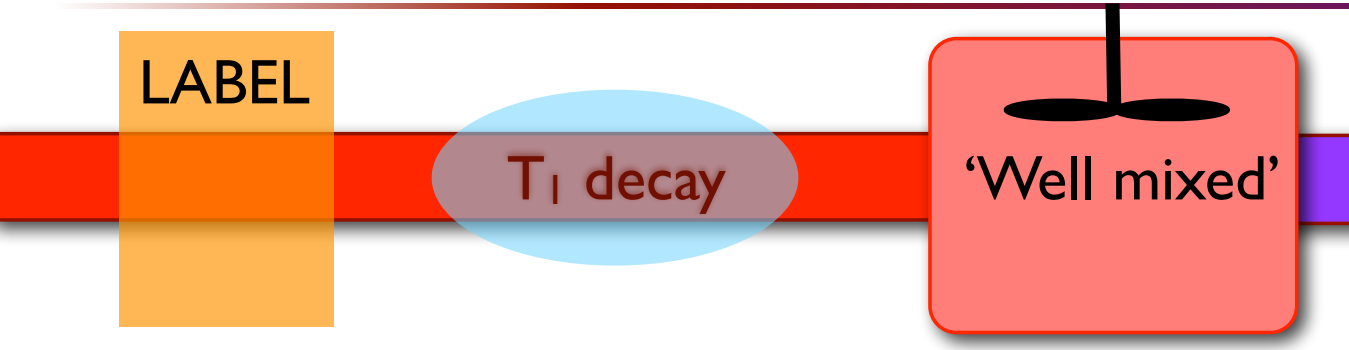
- Rapid exchange
- Single well mixed compartment
- No spins leave the compartment
- Decay with T1



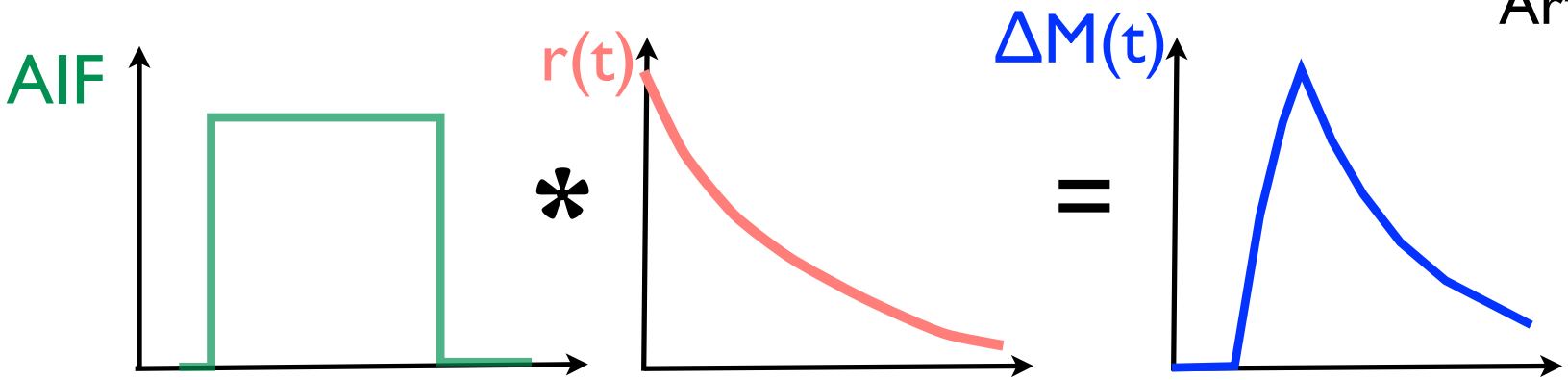
'Stays & decays'

Parameters:
Arterial Transit Time
Label duration
T1 decay

Kinetic Model Inversion

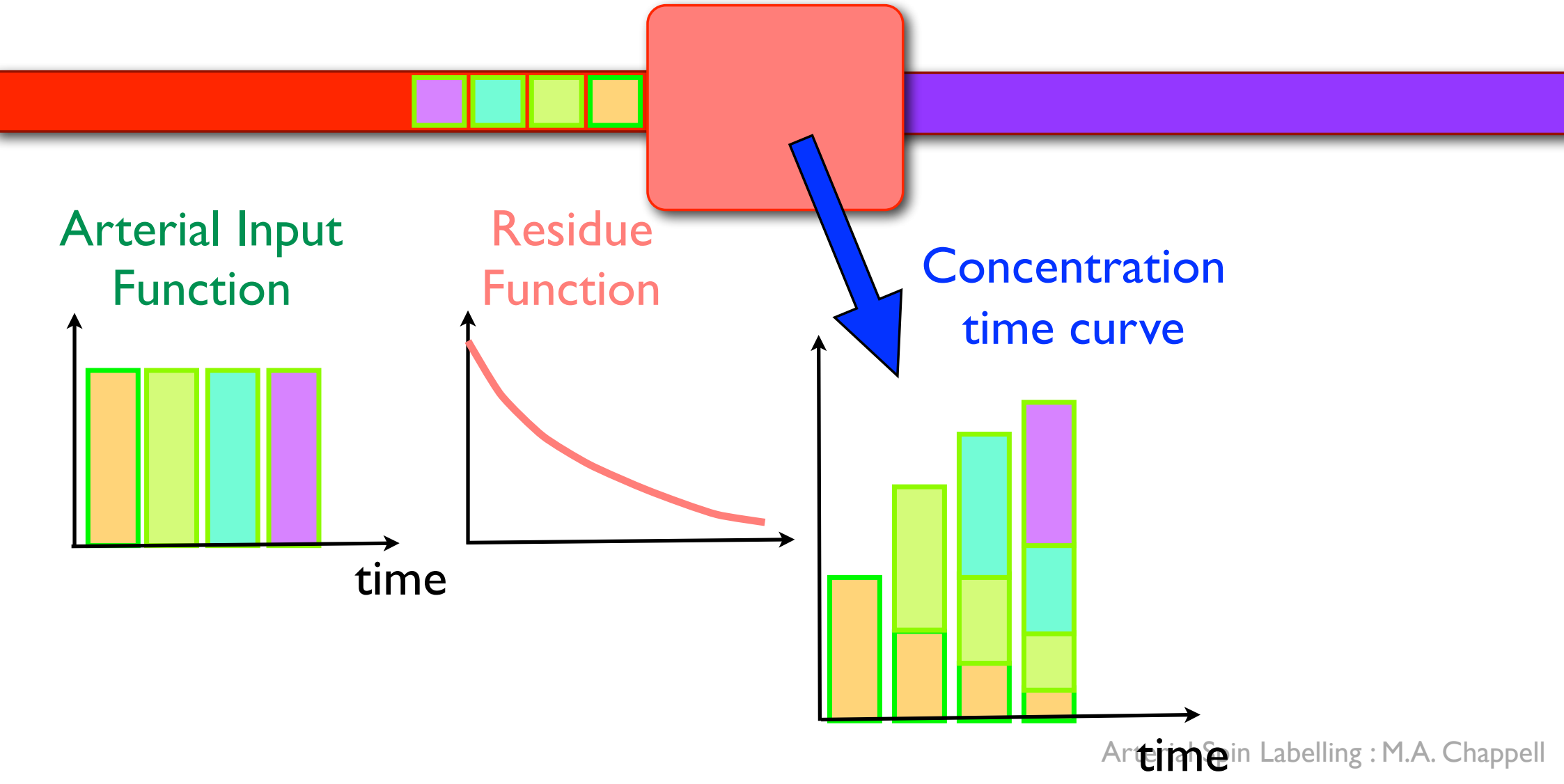


Parameters:
Perfusion - F
Arterial Transit Time
Label duration
T1 decay

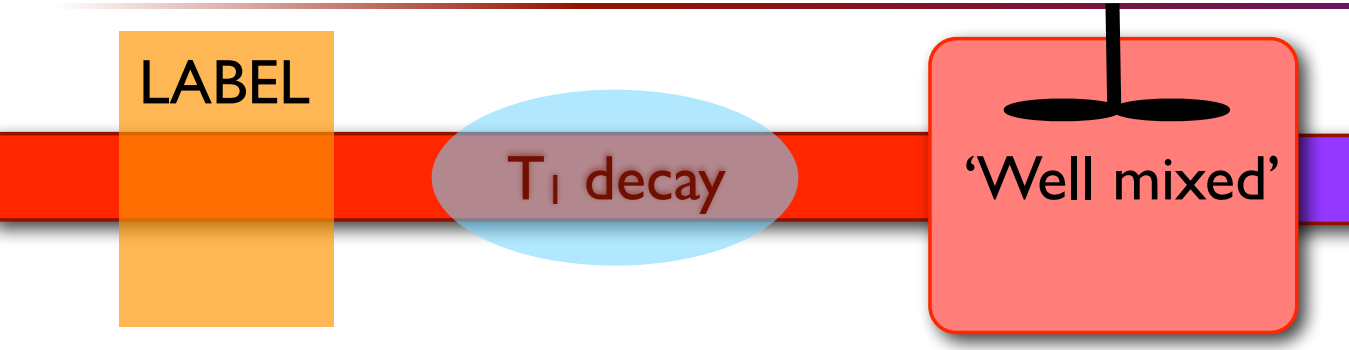


$$\Delta M(t) = F \cdot AIF(t) * r(t)$$

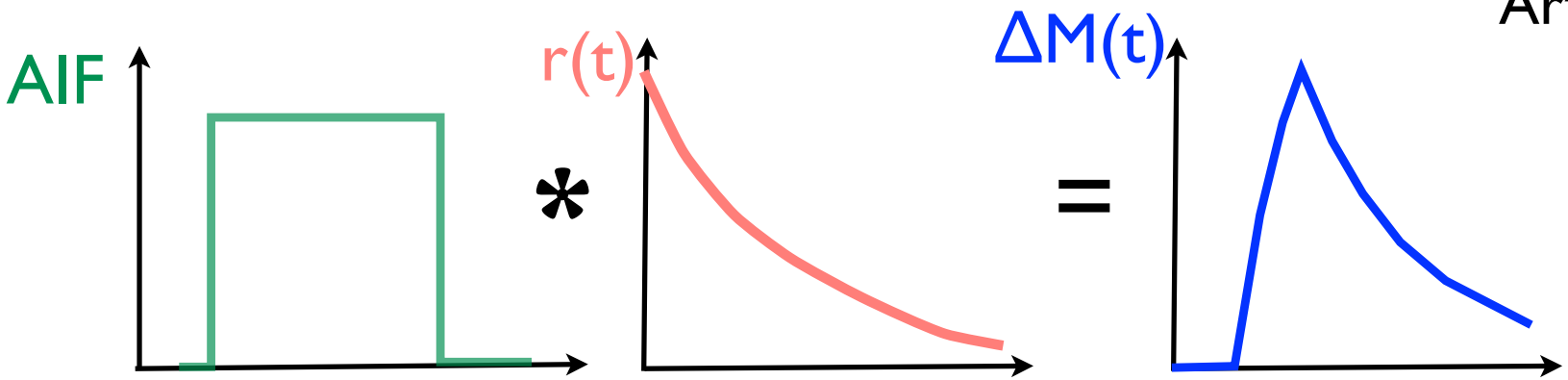
Kinetic Model Inversion



Kinetic Model Inversion



Parameters:
Perfusion - F
Arterial Transit Time
Label duration
T1 decay



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

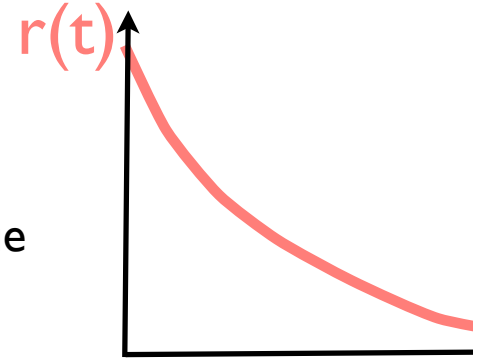
Kinetic Model Inversion

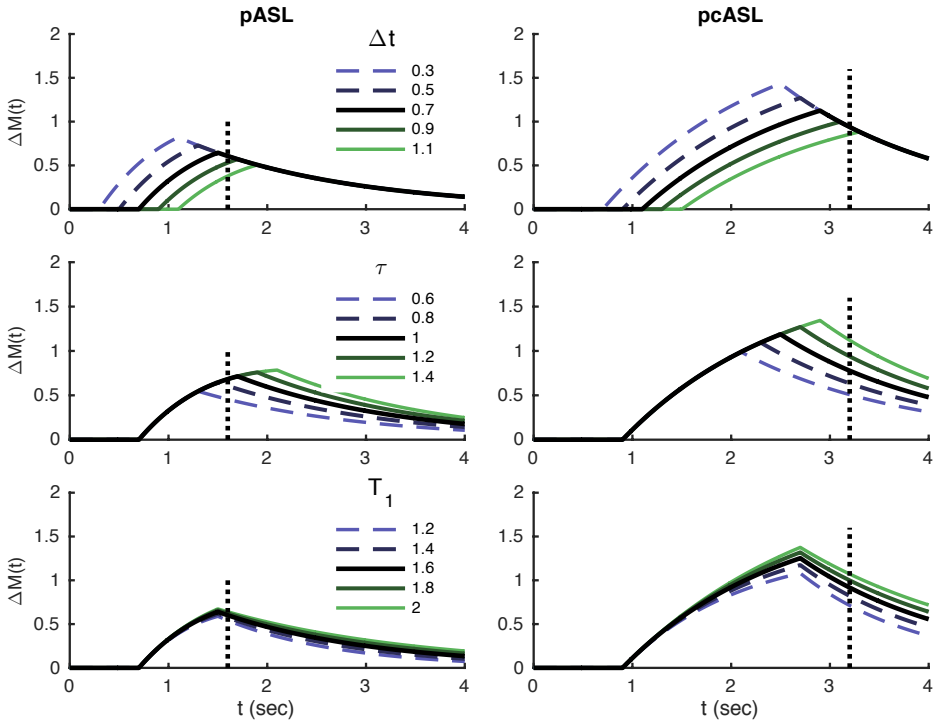
LABEL

T_{1b} decay

'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.





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.

What you need to know about your data:

Labeling	pASL (pulsed) Inversion time(s) Bolus duration (if QUIPSS/Q2TIPS)	or	pcASL (continuous) Post-labeling delay(s) Label duration
Read out	3D/2D (slice timing)		
Model	T1 (tissue and blood) Arterial Transit Time		

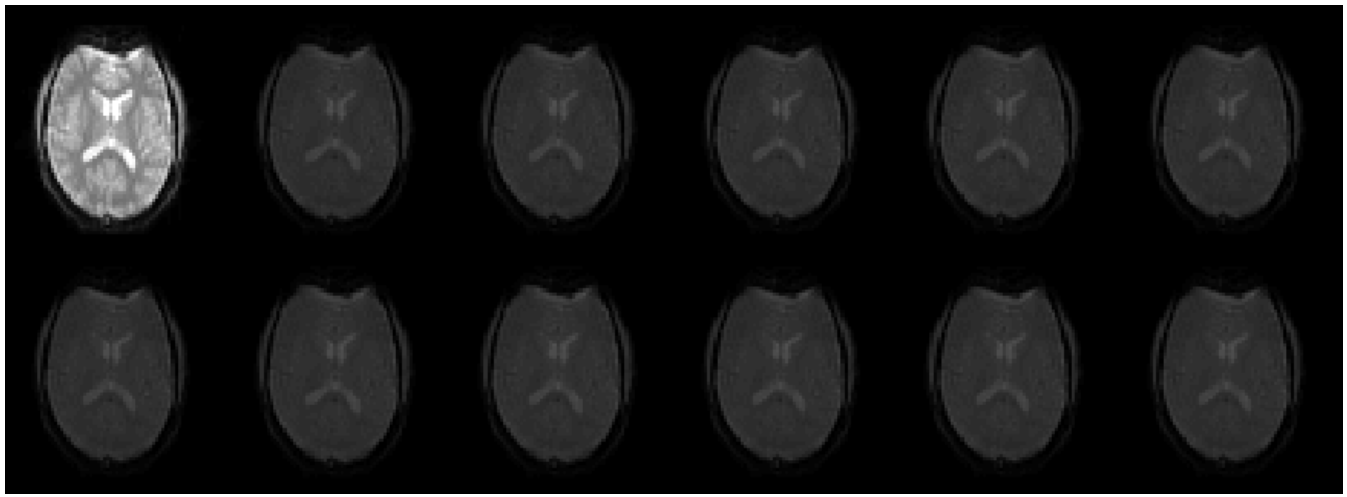
```
oxford_asl -i {asl_data} -o {output_dir} --iaf={tc} {--casl} --tis={list_of_TIs}
  –bolus={bolus_duration} –slicedt={time_per_slice} {model/analysis options}
```

Example

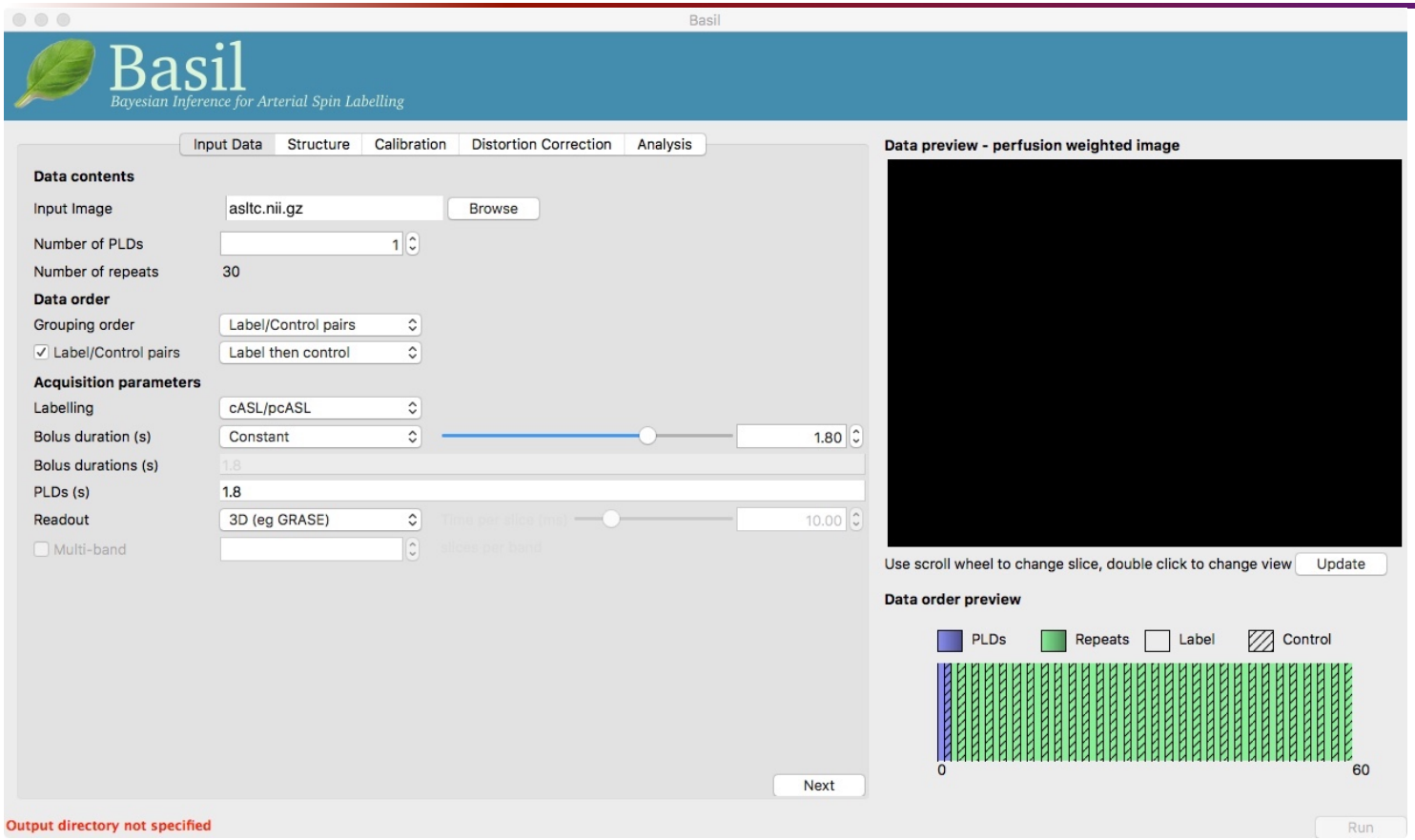
- What I have...
  - ➡ ASL data
  - ➡ (calibration images)
- What I want...
  - ➡ Perfusion in ml/100g/min
- What should I do?
  - ➡ Label-control subtraction. ✓
  - ➡ Kinetic model inversion. ←
  - ➡ Calibration

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

Assume
'white paper'
T1 : 1.65 s
ATT : 0 s



Example



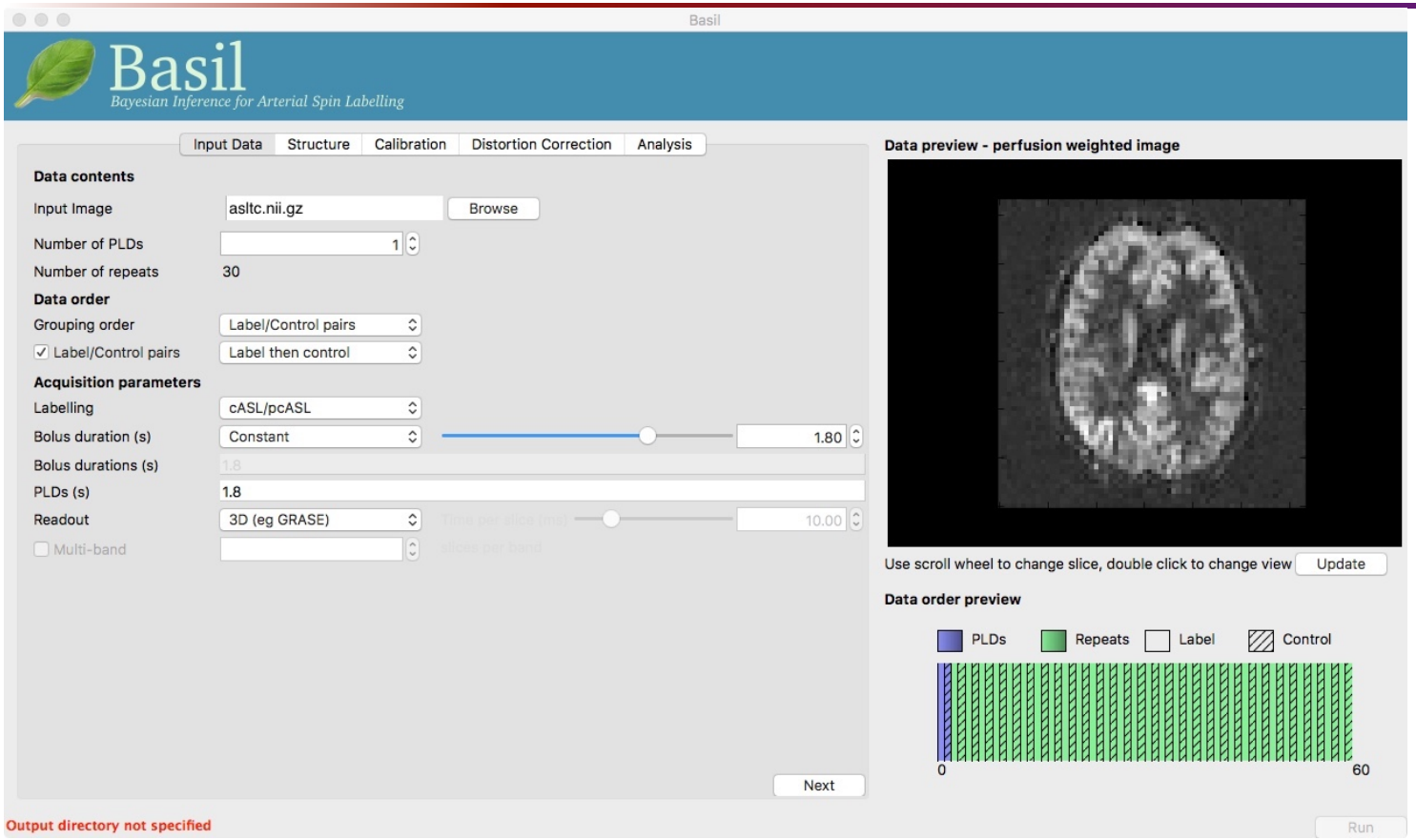
pcASL with
labeling duration: 1.8 s
post-label delay: 1.8 s

2D readout
45.2 ms per slice

Assume
'white paper'
T1 : 1.65 s
ATT : 0 s

```
#Do label control subtraction
> 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

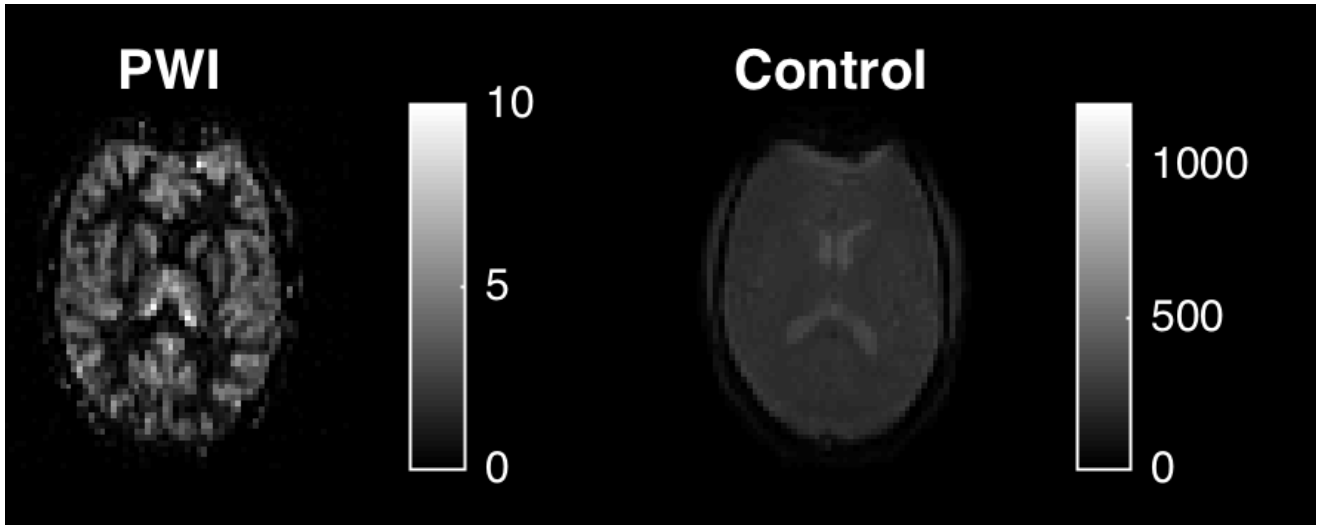
```
#Do label control subtraction
> asl_file --data={ASLdata.nii.gz} --ntis=1 --iaf=tc --diff --out={asldiffdata.nii.gz} \
    --mean={asldiffdata_mean.nii.gz}
```

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.

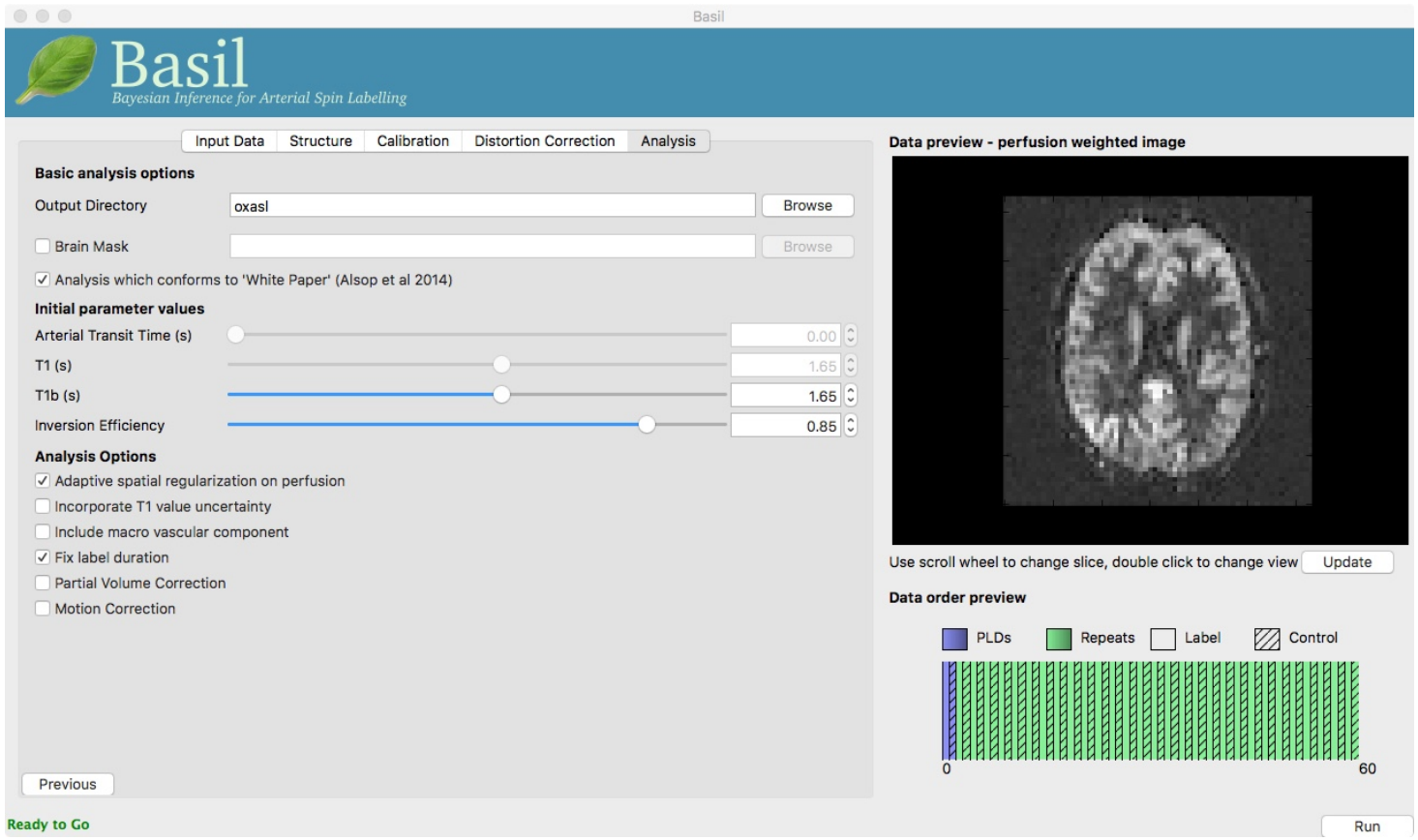
pcASL with
labeling duration: 1.8 s
post-label delay: 1.8 s
2D readout
45.2 ms per slice

Assume
'white paper'
T1 : 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

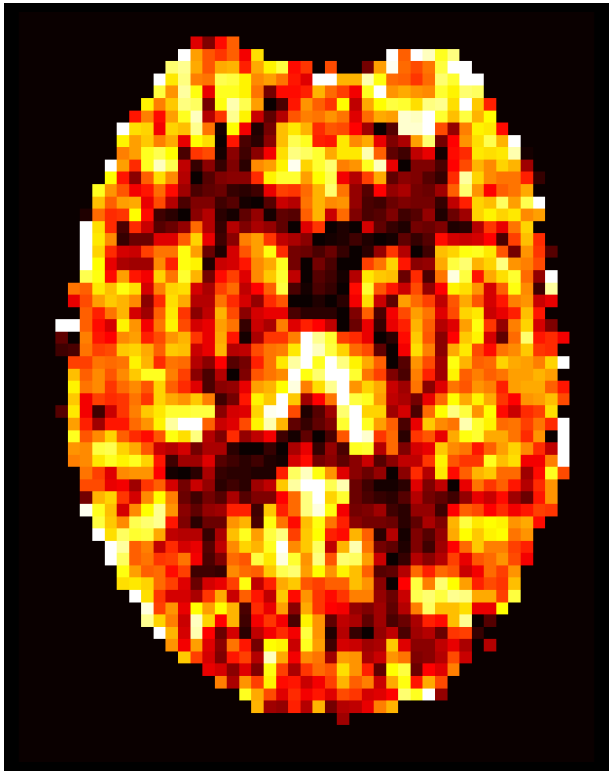
Assume
'white paper'
T1 : 1.6 s
ATT : 0 s

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
```

Example

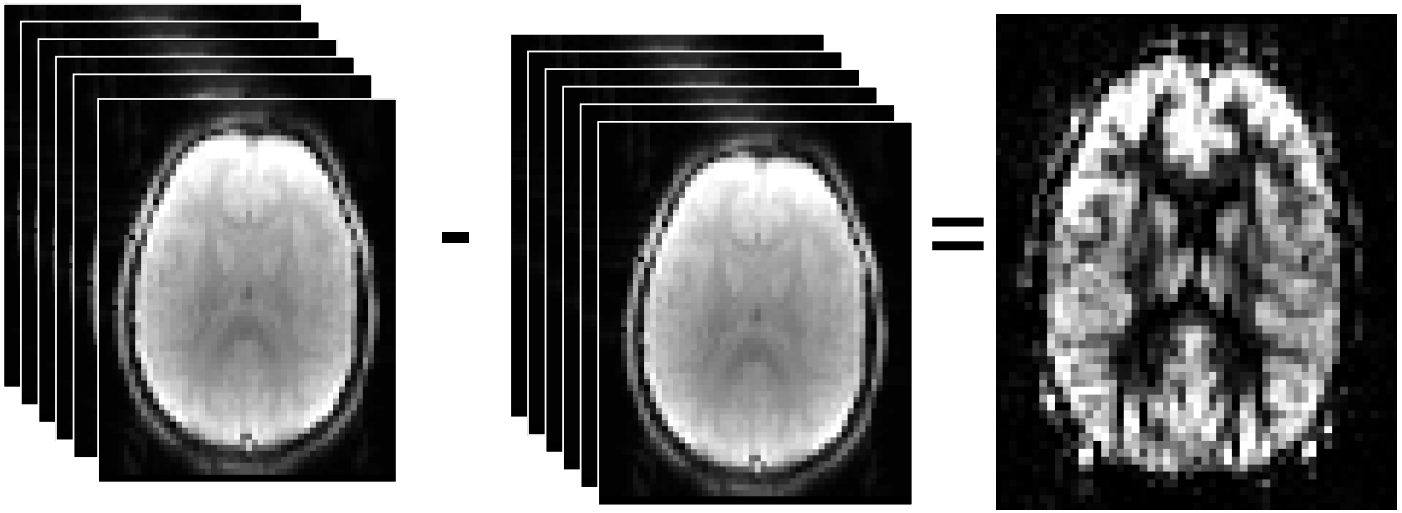
Perfusion (arbitrary units)



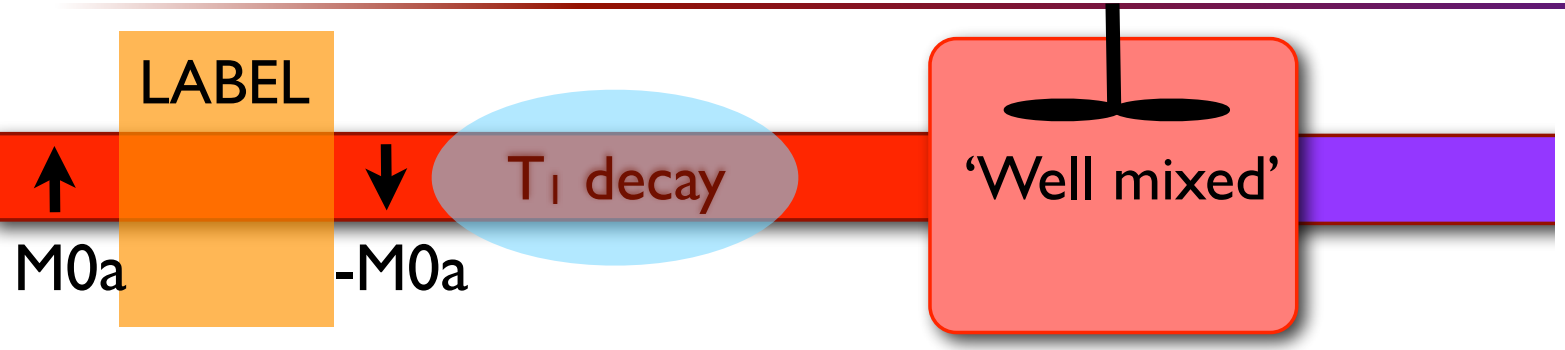
```
oxasl/native_space/perfusion.nii.gz
```

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. ✓
  - ➡ Calibration ←



Calibration

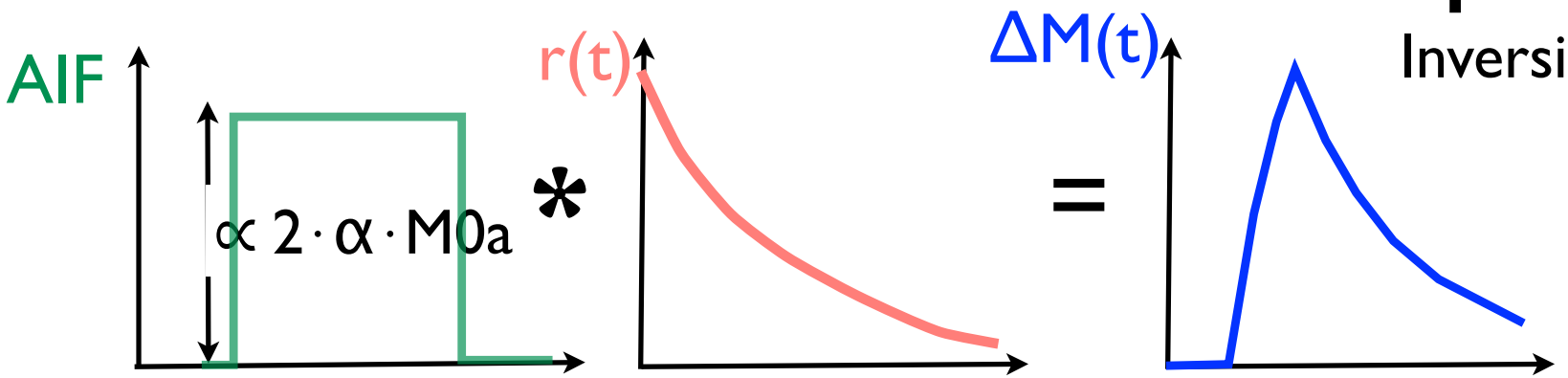


'Concentration' of the label

Magnetization of arterial blood M0a

Imperfect inversion

Inversion efficiency α



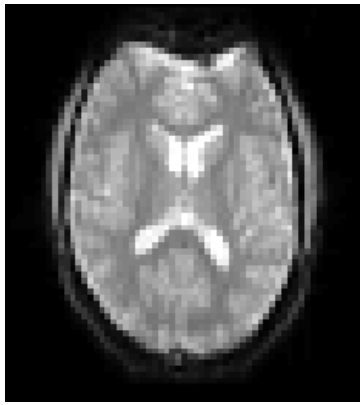
$$\Delta M(t) = 2 \cdot \alpha \cdot M0a \cdot F \cdot AIF(t) * r(t)$$

Calibration

- Cannot measure M0a directly.
- indirect via brain 'tissue' magnetization.
  - ➡ Calculate M0t.
    (M0 of 'tissue')
  - ➡ M0t to M0a.

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 λ
(relative concentration of water)

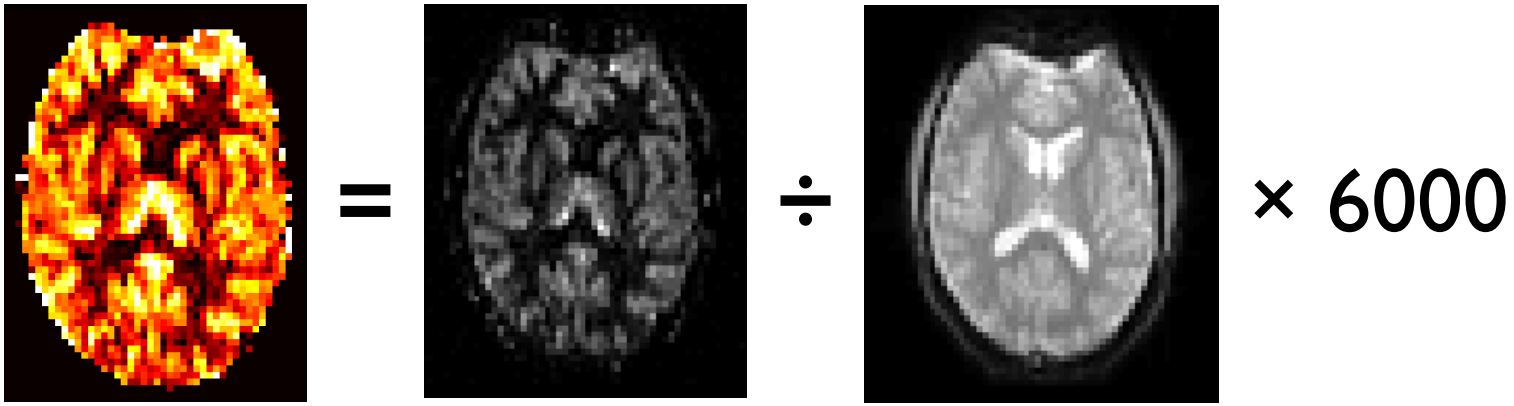
```
oxford_asl ... -c {calibration_image.nii.gz} --tr={TR}
```

Calibration

- Cannot measure M0a directly.
- indirect via brain 'tissue' magnetization.
  - ➡ Calculate M0t.
    (M0 of 'tissue')
  - ➡ M0t to M0a.
- Practicalities
  - ➡ Voxelwise

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

Voxelwise Calibration



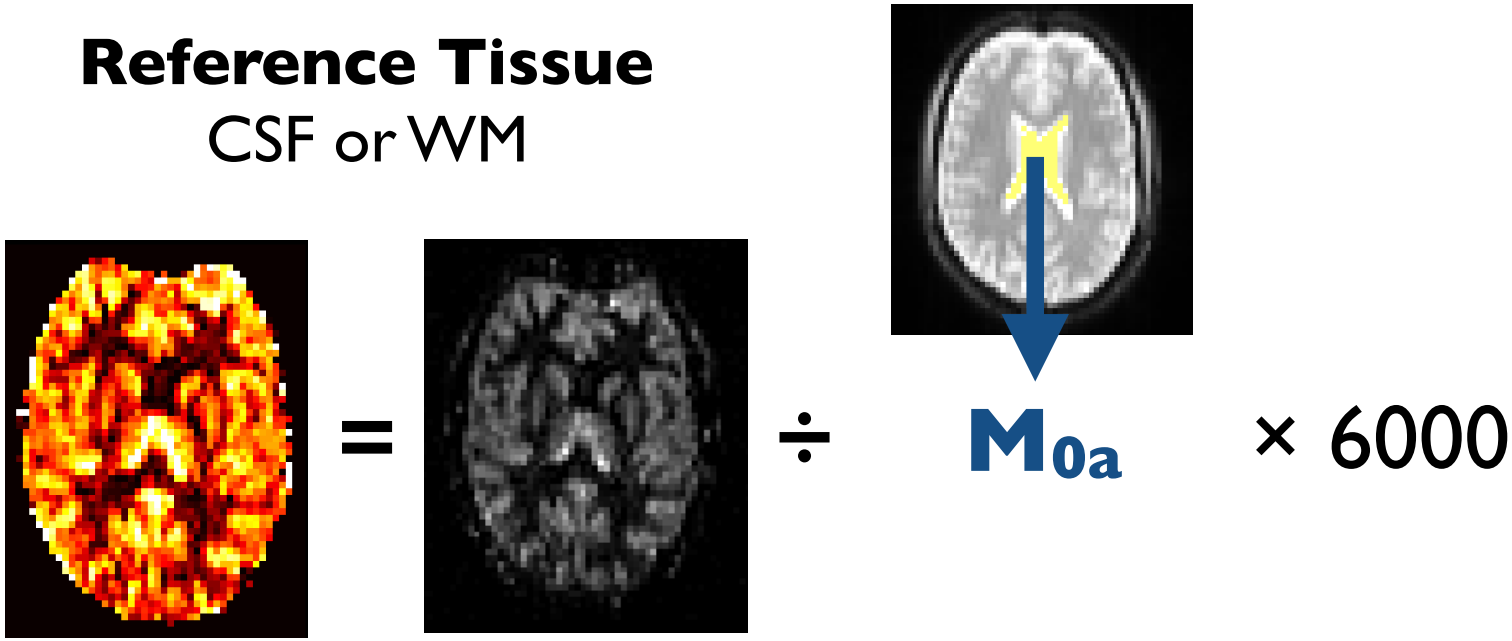

```
oxford_asl ... -c {calibration_image.nii.gz} --tr=[TR]
asl_calib --mode longtr ...
asl_calib --mode satrecov ...
fslmaths {perfusion.nii.gz} -div [M0a] -mul 6000 {perfusion_calib.nii.gz}
```

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 / M_{0a}) × 6000

Reference Tissue
CSF or WM




```
oxford_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'?
  - ➡ 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)

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

```
oxford_asl ... -c {calibration_image.nii.gz} --tr=[TR]
```

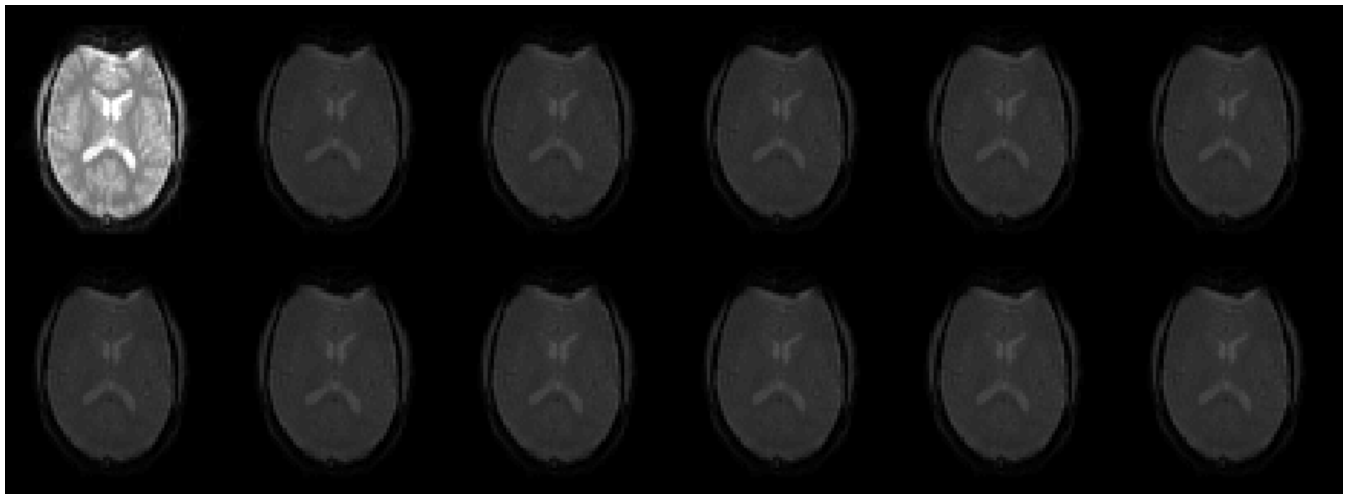
Example

- 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

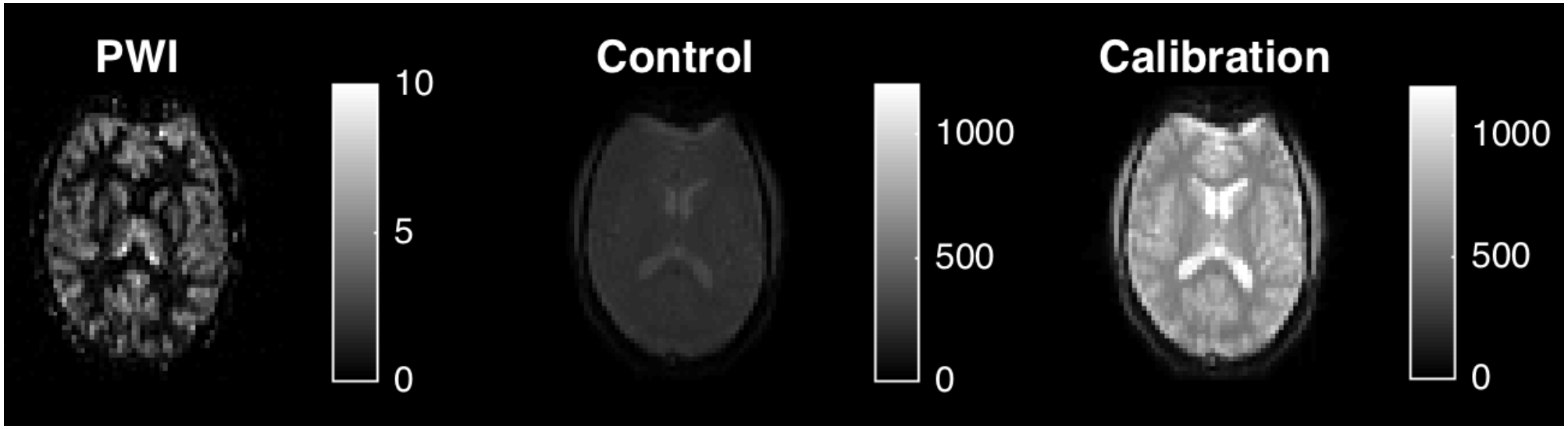
Assume
T1 (blood) : 1.6 s
T1 (tissue) : 1.3 s
ATT : 1.3 s
α : 0.85



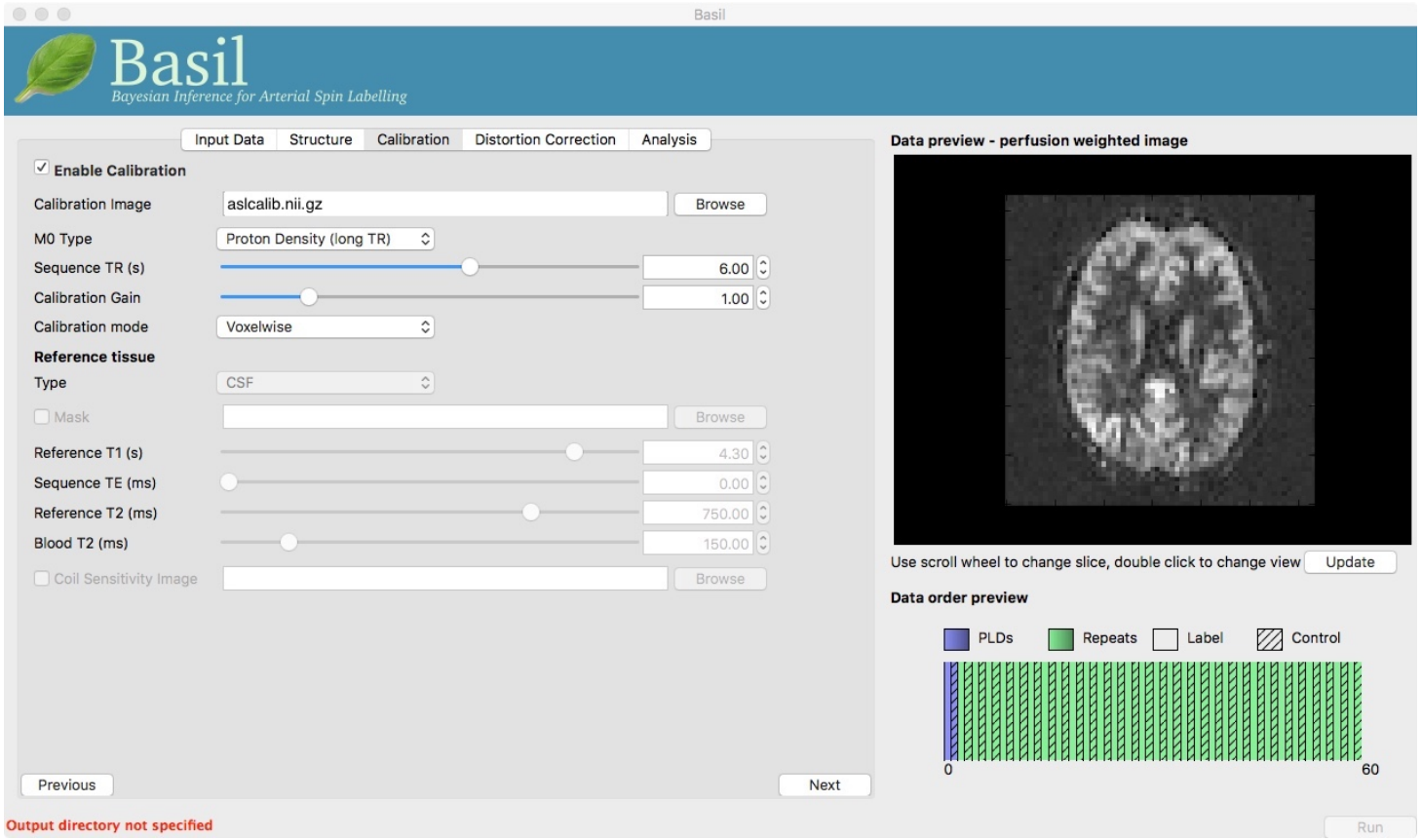
Calibration image

No background-suppression

TR: 4.8 s



Example



Calibration image

TR: 4.8 s

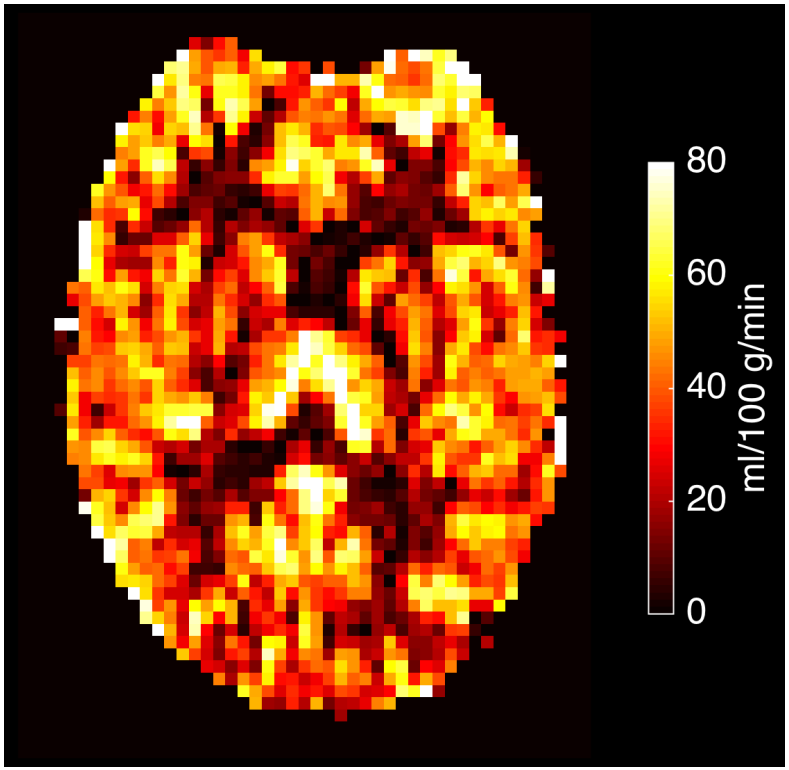
Calibration mode

Voxelwise

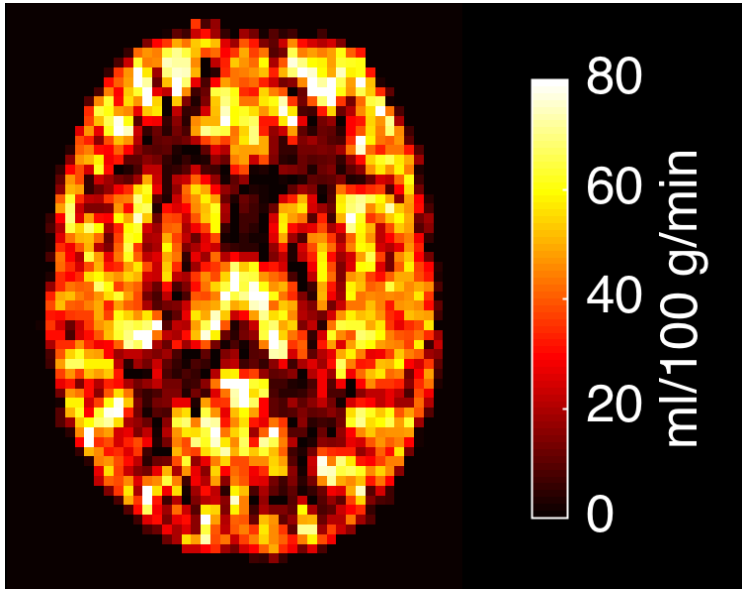
```
# Do the analysis using oxford_asl
>   oxford_asl -i {ASLdata.nii.gz} -o {oxasl} --iaf=tc --casl --tis=3.6 --bolus=1.8 /
      --slicedt=0.0452 --wp --mc –c {calibration_image.nii.gz} --tr=4.8
```

Example

Perfusion (ml/100g/min)

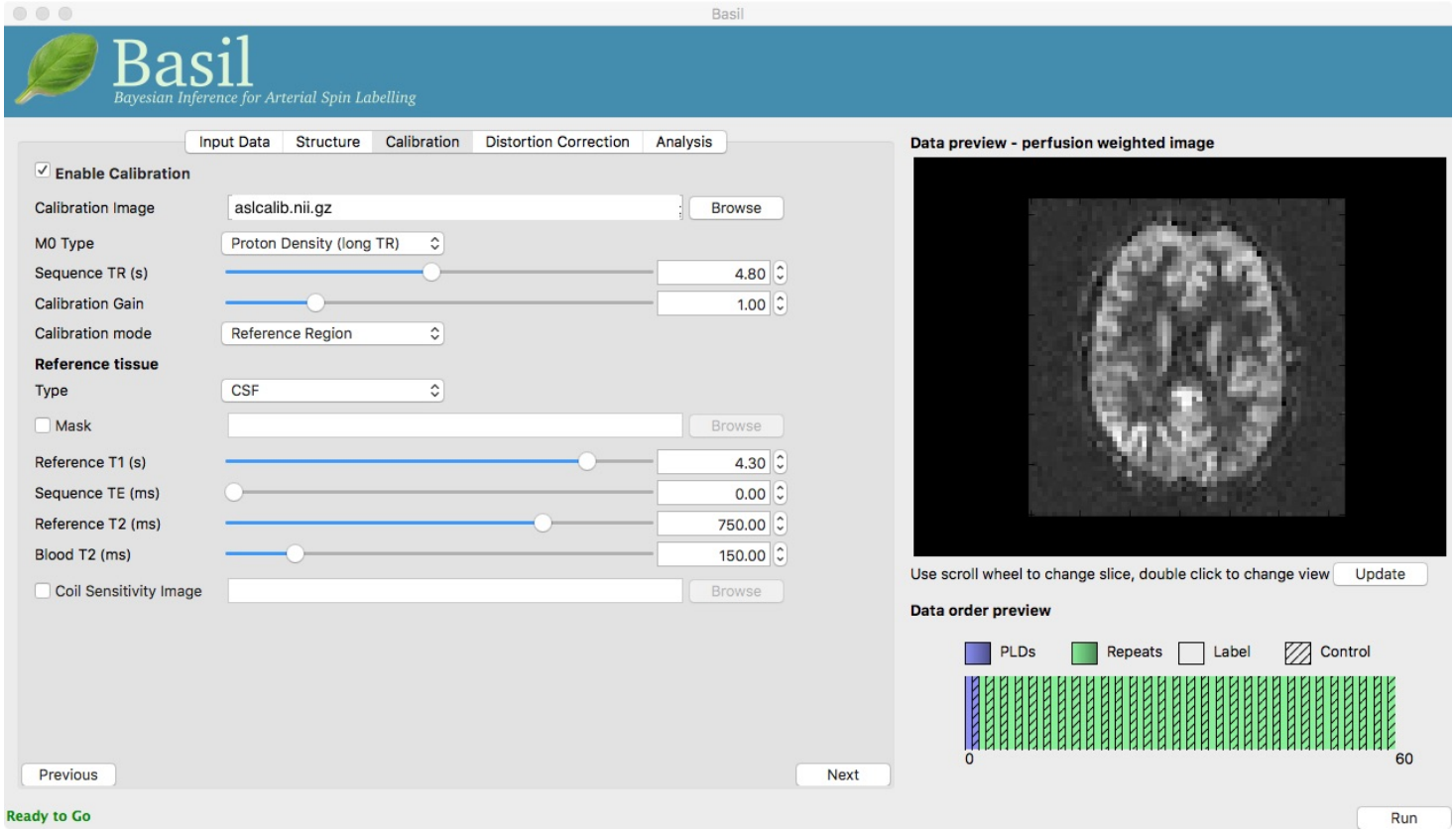


Correct for
'edge effects'
(and distortion)



`oxasl/native_space/perfusion_calib.nii.gz`

Example



Calibration image

TR: 4.8 s

Calibration mode

Reference region

CSF (ventricles)

Calibration mask

(derived automatically from structural image)

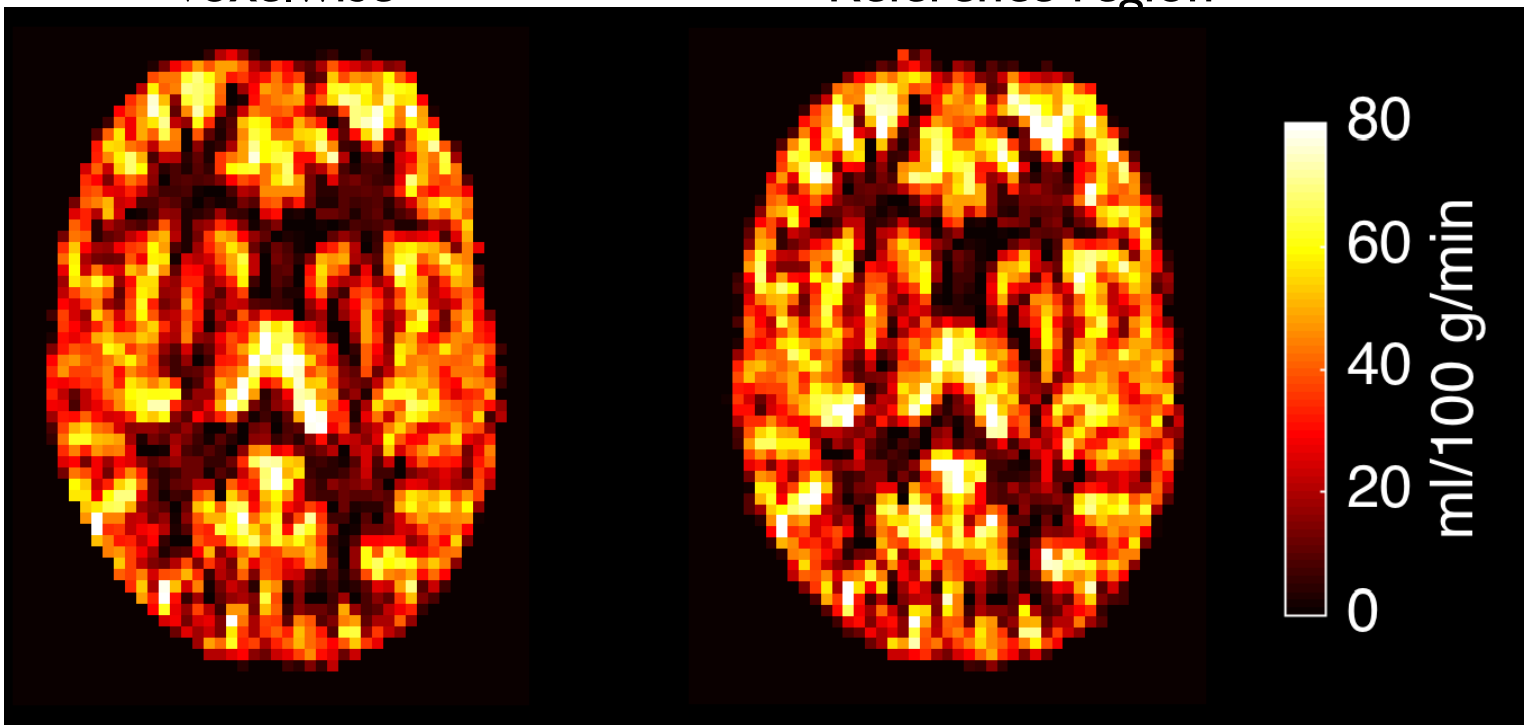
```
# Do the analysis using oxford_asl
>   oxford_asl -i {ASLdata.nii.gz} -o {oxasl} --iaf=tc --casl --tis=3.6 --bolus=1.8 /
      --slicedt=0.0452 --wp --mc –c {calibration_image.nii.gz} --tr=4.8 /
      --fslanat=T1.anat
```

Example

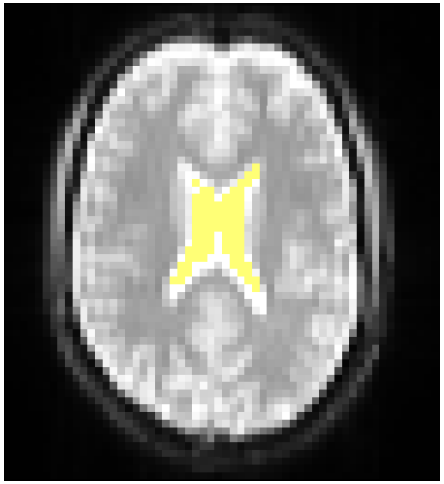
Perfusion (ml/100g/min)

Voxelwise

Reference region



Ventricular mask
(automatically generated)



`oxasl/native_space/perfusion_calib.nii.gz`

Summary

- The ASL 'white paper' quantification formula (pcASL):

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

Subtraction

Kinetic Model Inversion

M0 Calculation (Calibration)

Values:

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

α = 0.85

λ = 0.9 ml/g

Assumptions:

Voxelwise calibration ($M_{0t} = SI_{PD}$)

$T_{1tissue} = T_{1blood}$

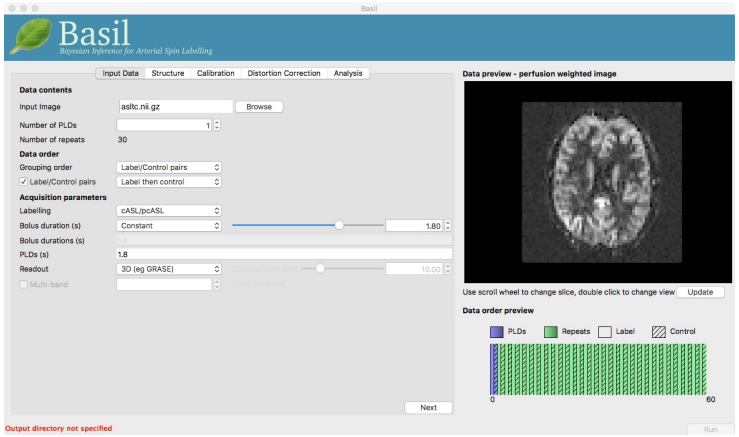
ATT = 0

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

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

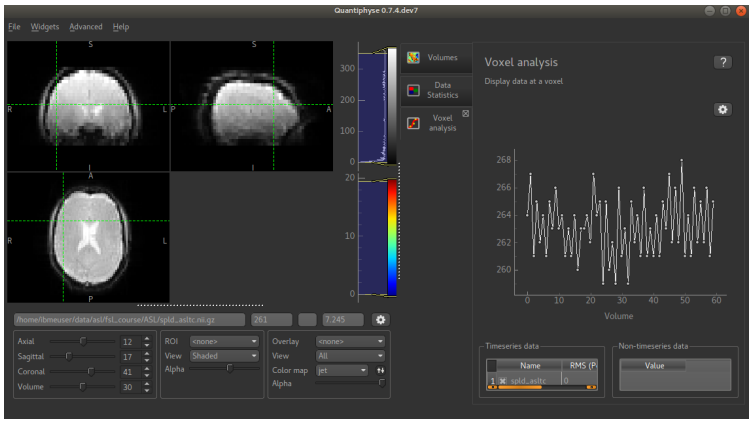
Perfusion quantification using Single PLD pcASL

Oracle VM VirtualBox — ASL practical — password: **asl**



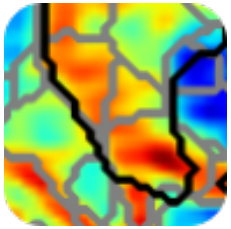
Using BASIL (& FSL):

- ➡ https://oxasl.readthedocs.io/en/latest/practical_gui.html
- ➡ (Data is already loaded on the computer)
- ➡ Open Terminal, type `asl_gui`



Using Quantiphyse

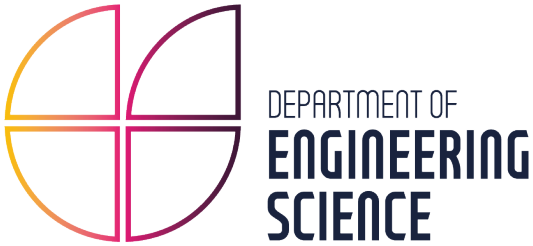
- ➡ https://quantiphyse.readthedocs.io/en/latest/asl/asl_tutorial.html
- ➡ (Data is already loaded on the computer)



Arterial Spin Labelling: Non-invasive measurement of perfusion

Michael A. Chappell
michael.chappell@eng.ox.ac.uk
www.ibme.ox.ac.uk/QuBIc

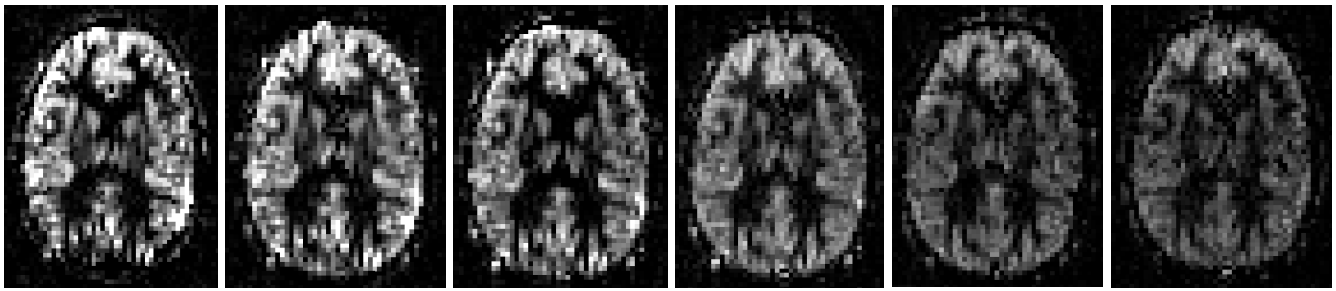
Institute of Biomedical Engineering & Wellcome Centre for Integrative Neuroimaging
University of Oxford.



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

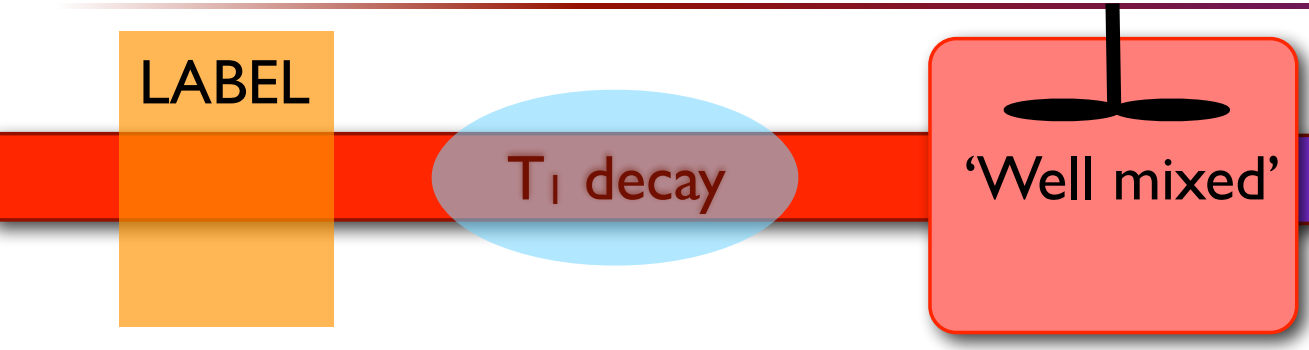
pcASL with
label duration: 1.4 s
post-label delays: 0.25, 0.5, 0.75,1.0, 1.25, 1.5 s



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}
```

Kinetic Model Inversion



Parameters:

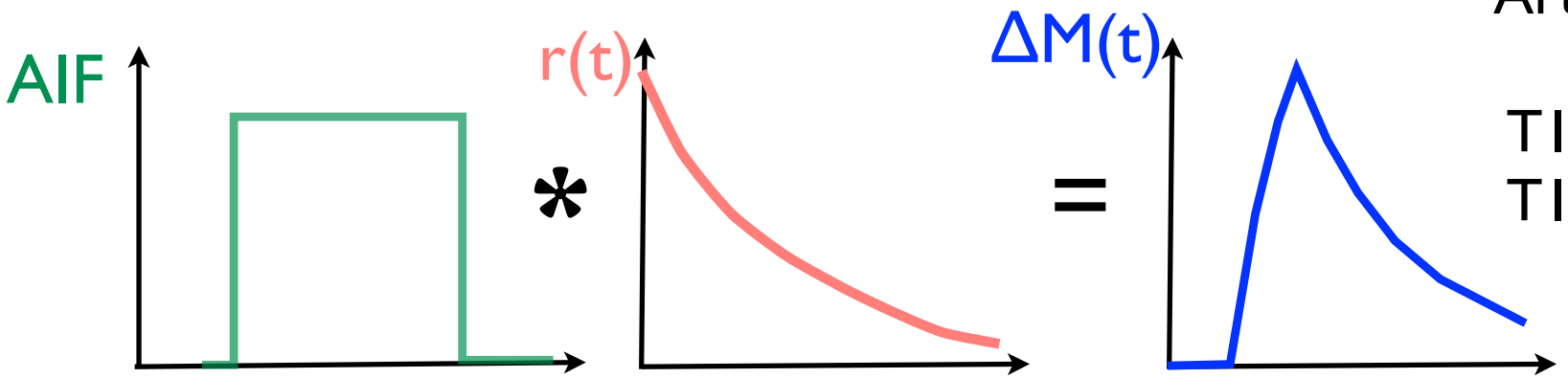
Perfusion - F

Arterial Transit Time

Label duration

T1 decay (in blood)

T1 decay (in tissue)



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

Kinetic Model Inversion

Parameters:

Perfusion - F

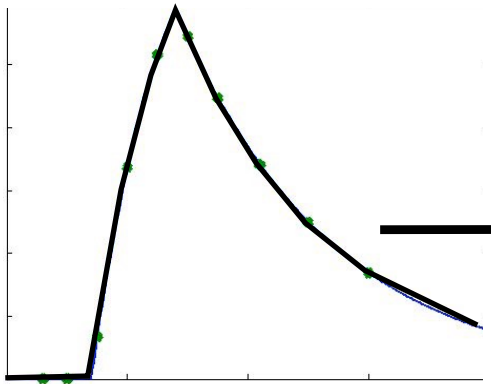
Arterial Transit Time

Label duration

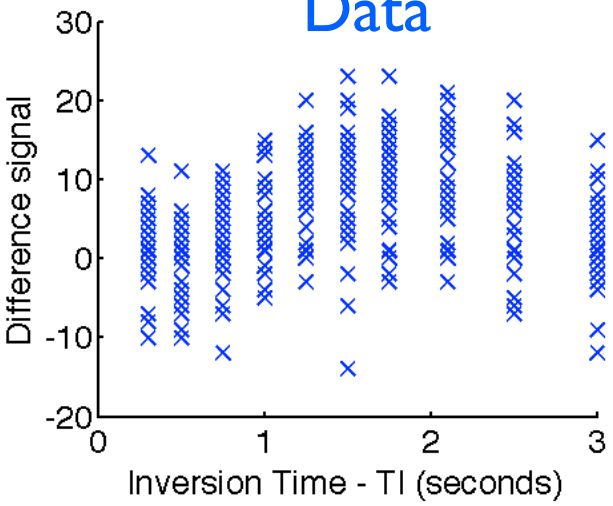
$T_{1tissue}$

T_{1blood}

Model



white noise



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

but limited to a sensible range

- 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

Doesn't T_1 vary a bit?

  - ➡ 1.65 at 3T **- fixed**

Kinetic Model Inversion

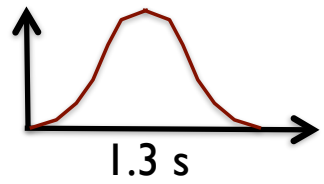
Priors:

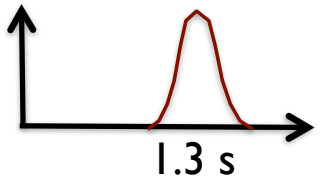
Perfusion

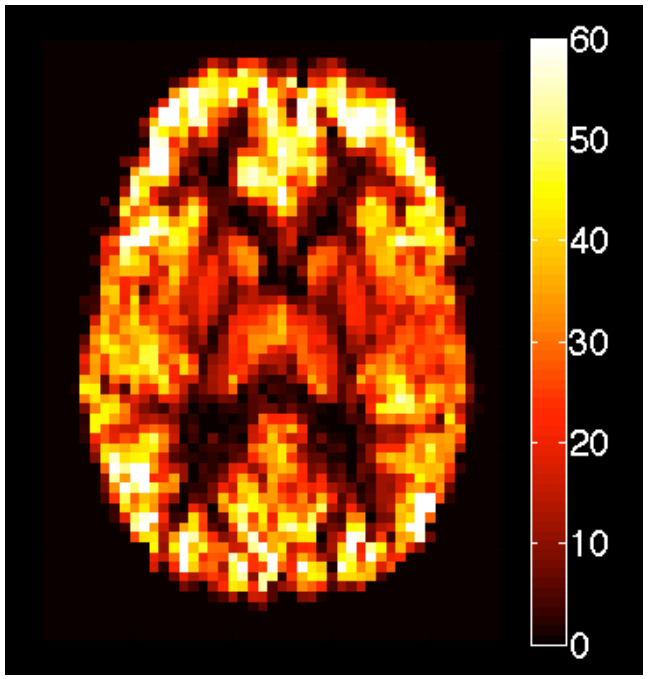
Arterial Transit Time

TI

Spatial

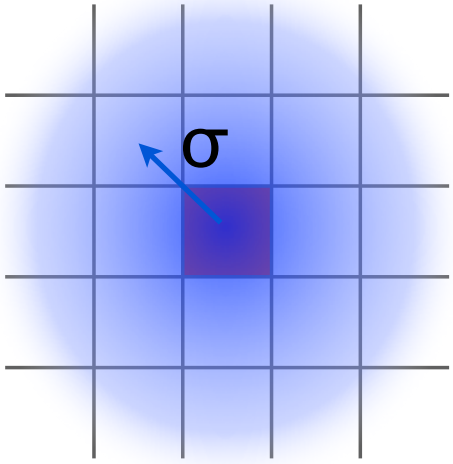






Spatial prior:

Prior distribution for perfusion in voxel defined over its neighbours

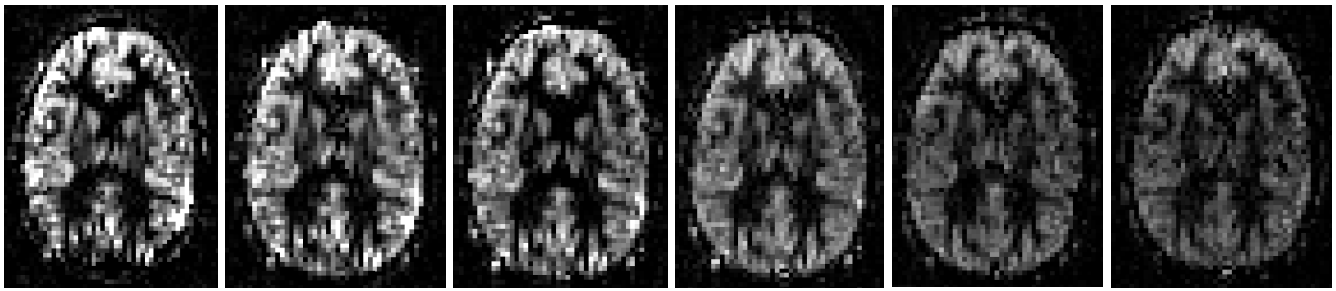


σ - spatial scale of prior (determined from the data)

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.

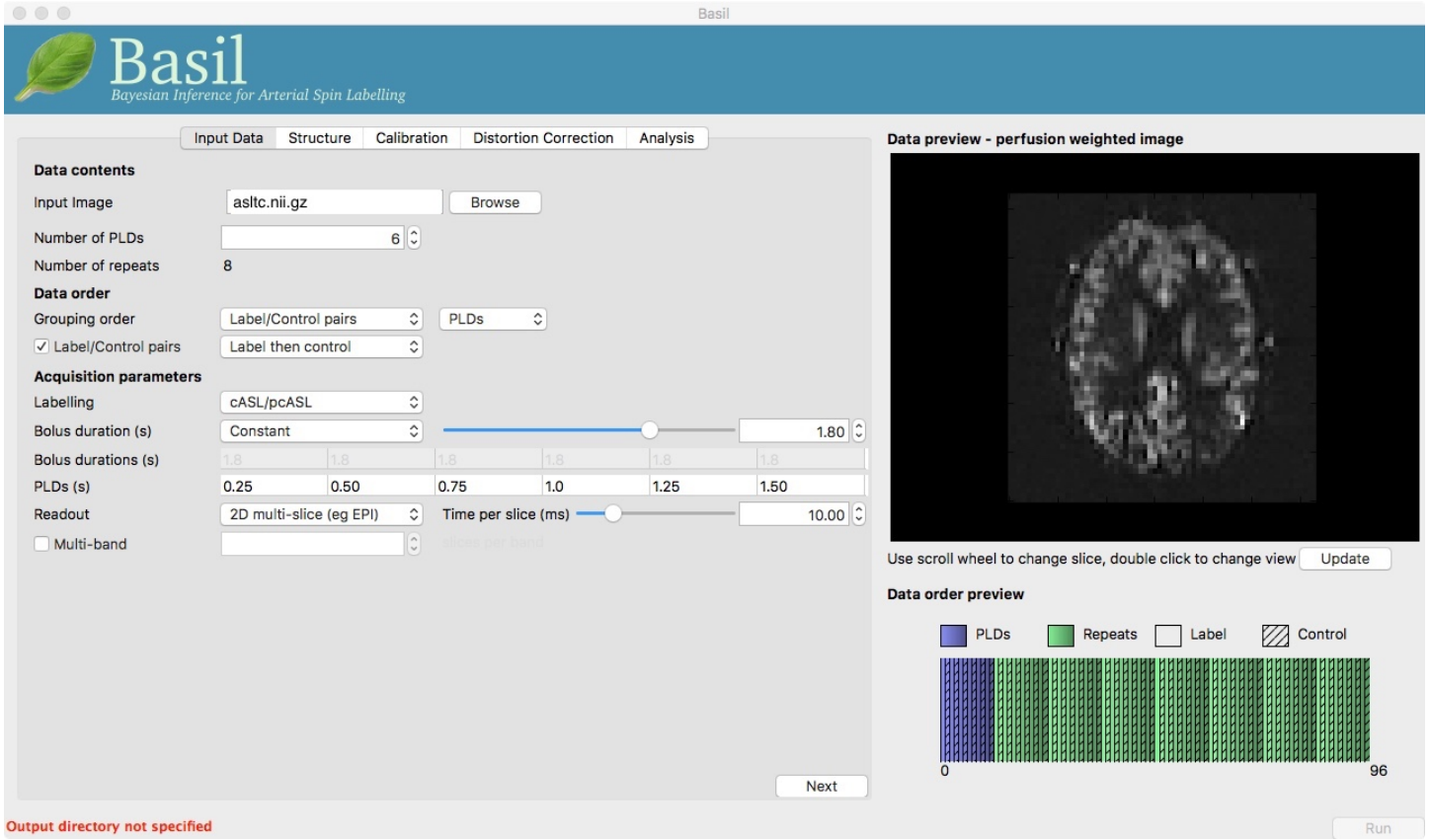
pcASL with
labeling duration: 1.4 s
post-label delays: 0.25, 0.5, 0.75,1.0, 1.25, 1.5 s



TI: 1.65 1.9 2.15 2.4 2.65 2.9

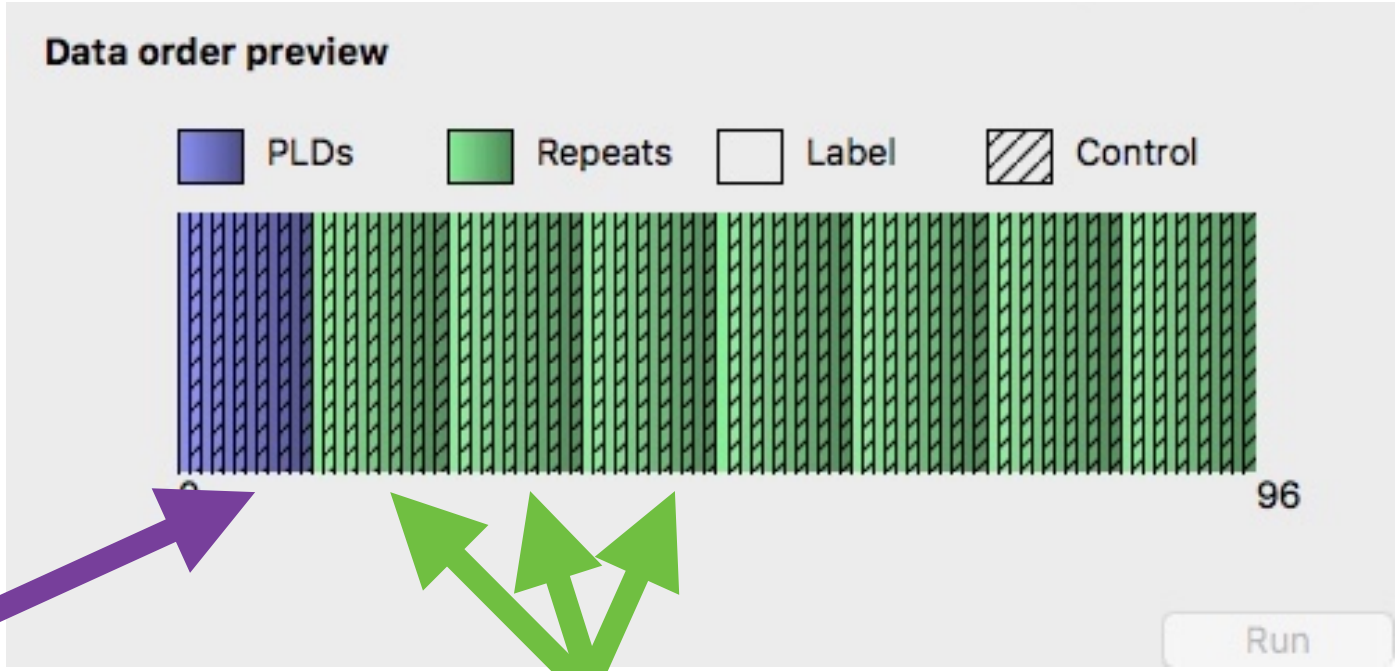
```
# Label control subtraction for each PLD individually
>  asl_file --data={ASLdata.nii.gz} --ntis=6 --iaf=tc --ibf=rpt --diff --split \
    --mean={asldiffdata_mean_at_each_PLD.nii.gz}
```

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
```



One (full) set of PLDs

Another (repeated) set of PLDs

```
>   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

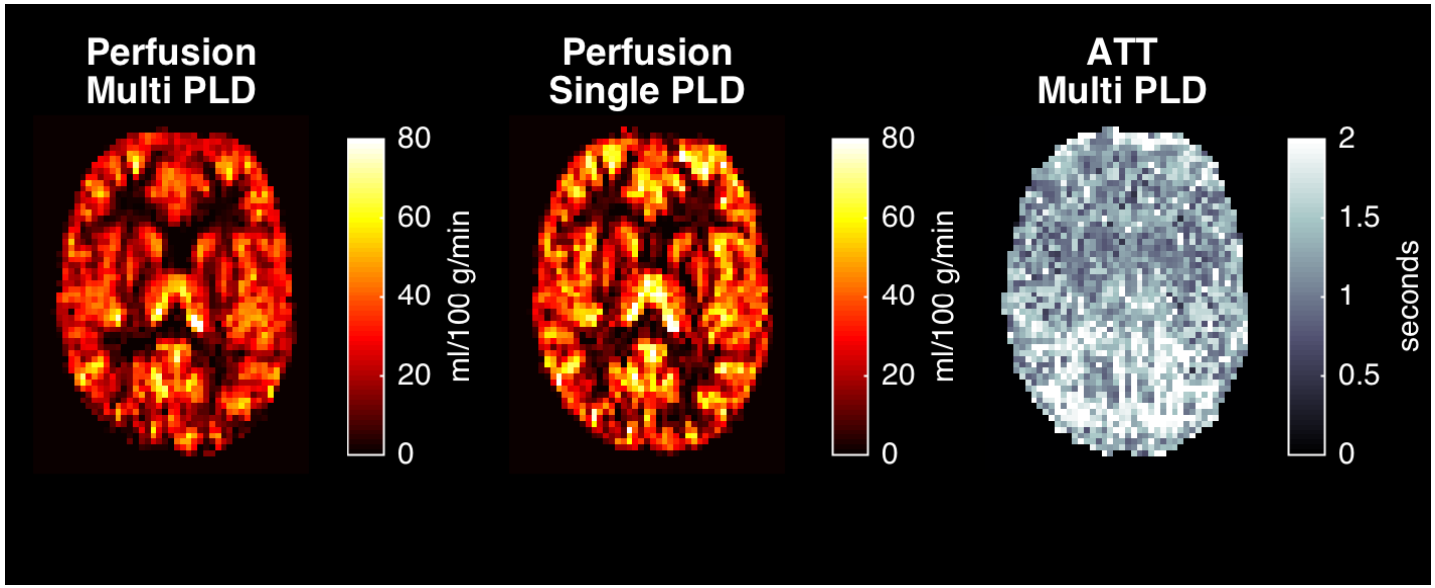
  post-label delay: 1.8 s

  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

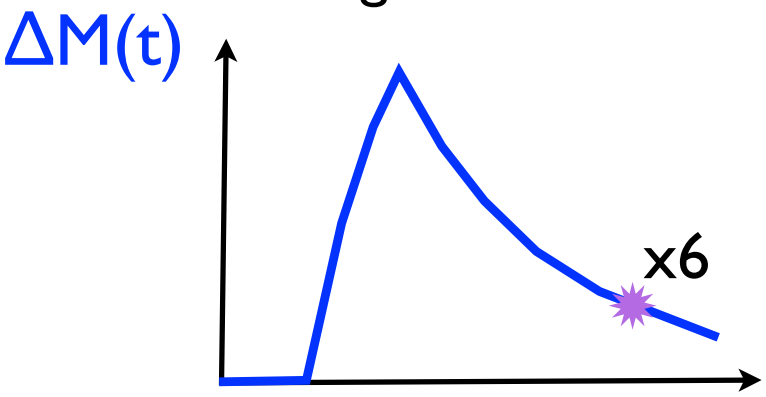



```
oxasl/native_space/perfusion_calib.nii.gz
oxasl/native_space/arrival.nii.gz
```

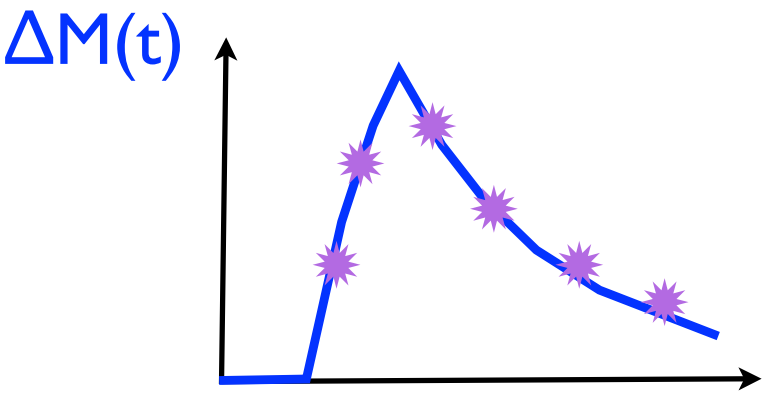
Single- vs. Multi-PLD

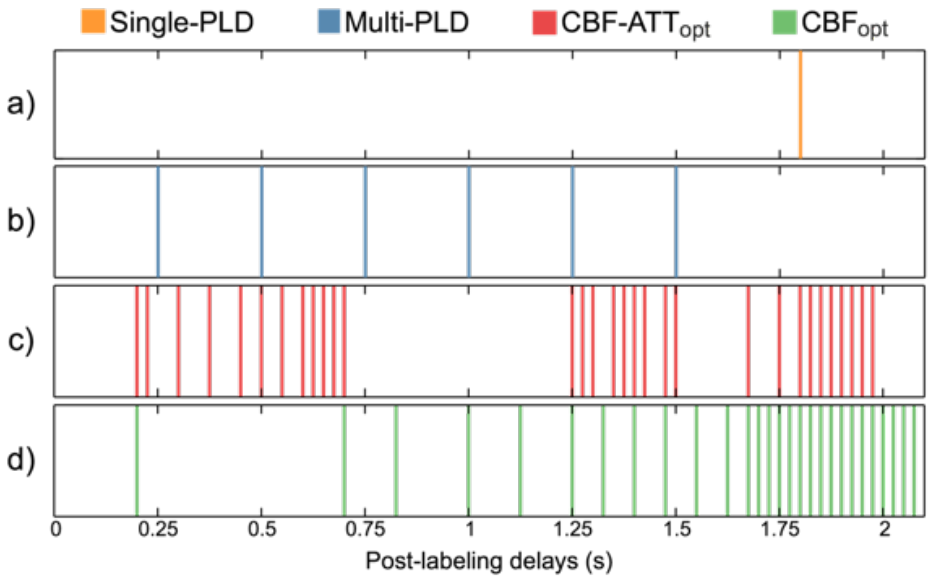
- Which is better in a **fixed** scan duration?

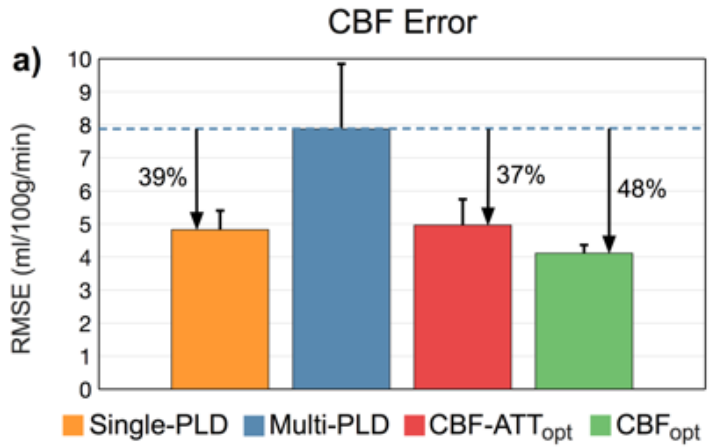
Single-PLD



Multi-PLD







Woods et al. MRM 2018 in press

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:
  - ➡ Motion, Distortion & Artefacts
  - ➡ Cerebrovascular Reactivity/Reserve
  - ➡ Macro Vascular Contamination
  - ➡ Partial Volume Effects

Preparing for Group Analysis

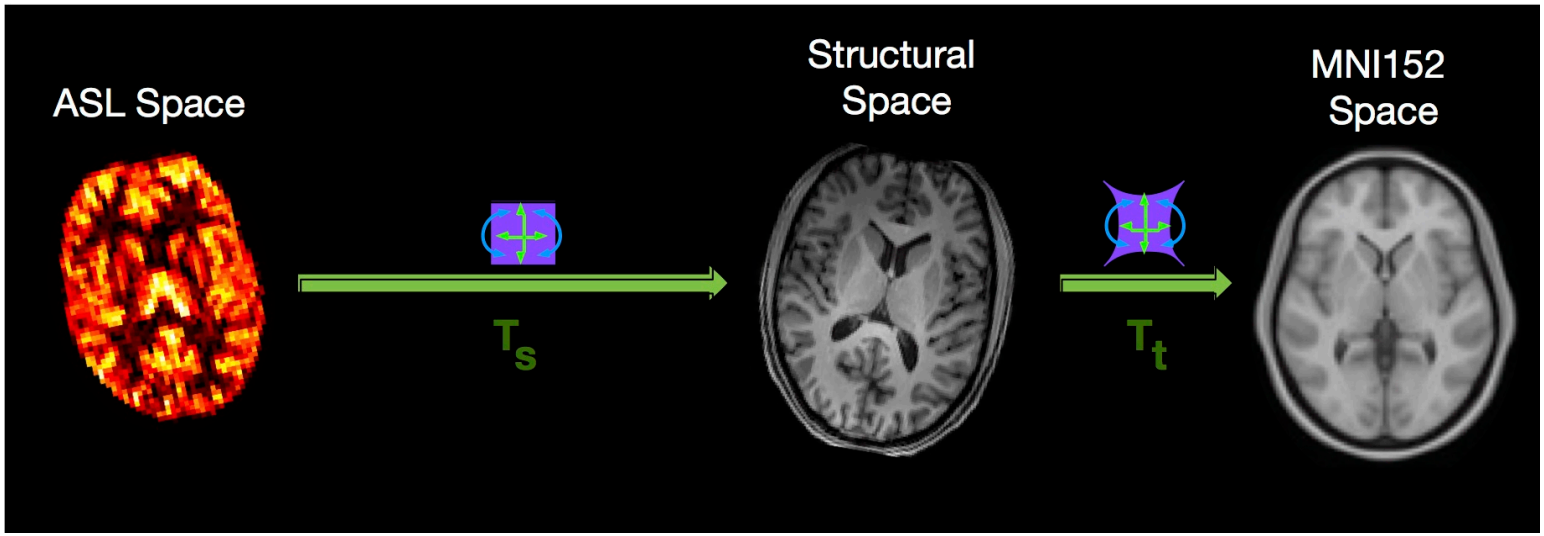
- Group analysis and quantitative comparisons between individuals requires consistent representation

- **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

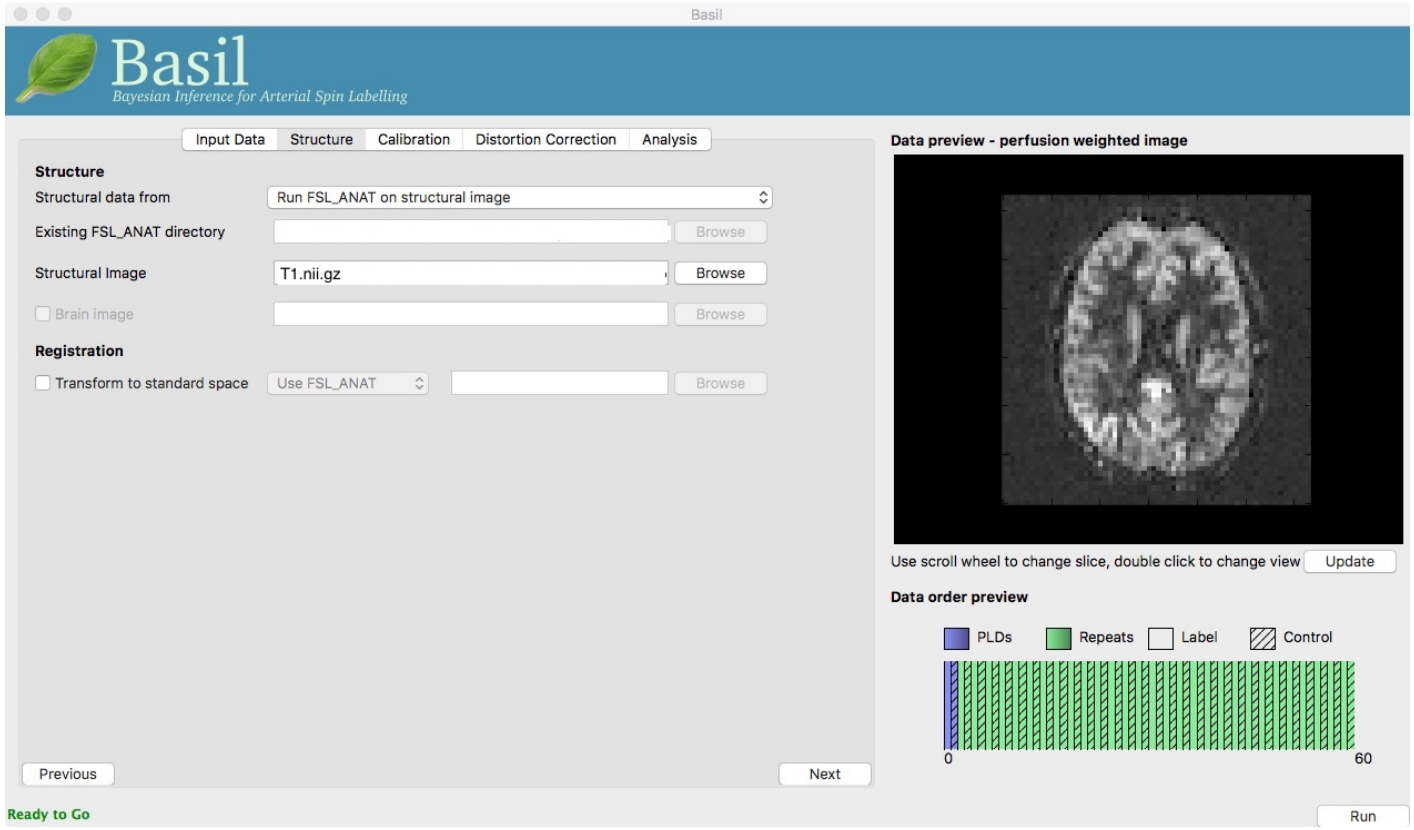
- Registration to 'standard' space
  - ➡ ASL → Structural
    linear - 6 DOF
  - ➡ Structural → Standard
    linear - 12 DOF
    non-linear




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

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

Example



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
```

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.
  - ➡ Removes inter subject variability in 'global' perfusion.
- Cons:
  - ➡ Relies on a consistent reference.
  - ➡ Loose information on 'global' perfusion changes.

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

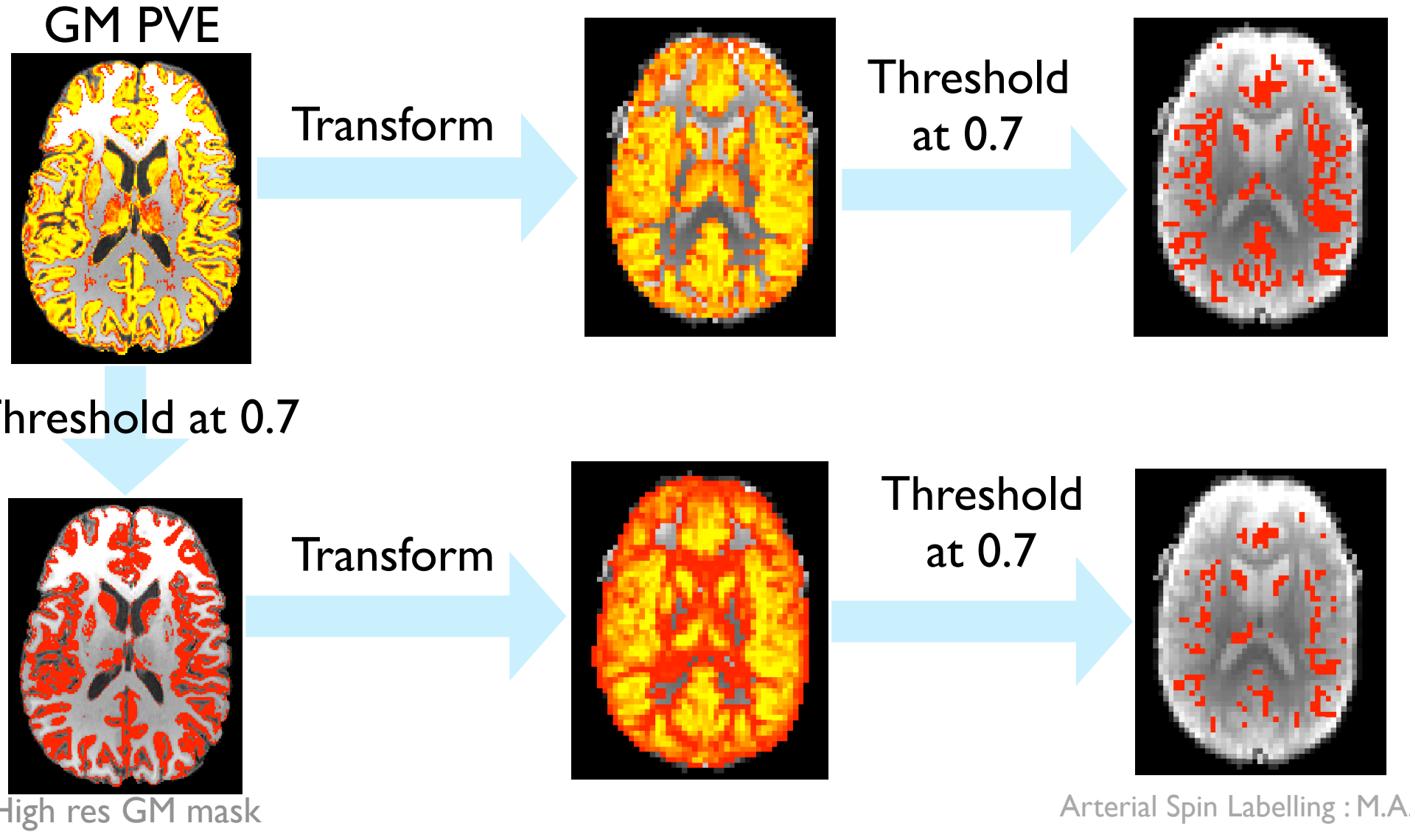
    Interpolation occurs on perfusion values, ROI untouched.

- 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



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.

Arterial Transit 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

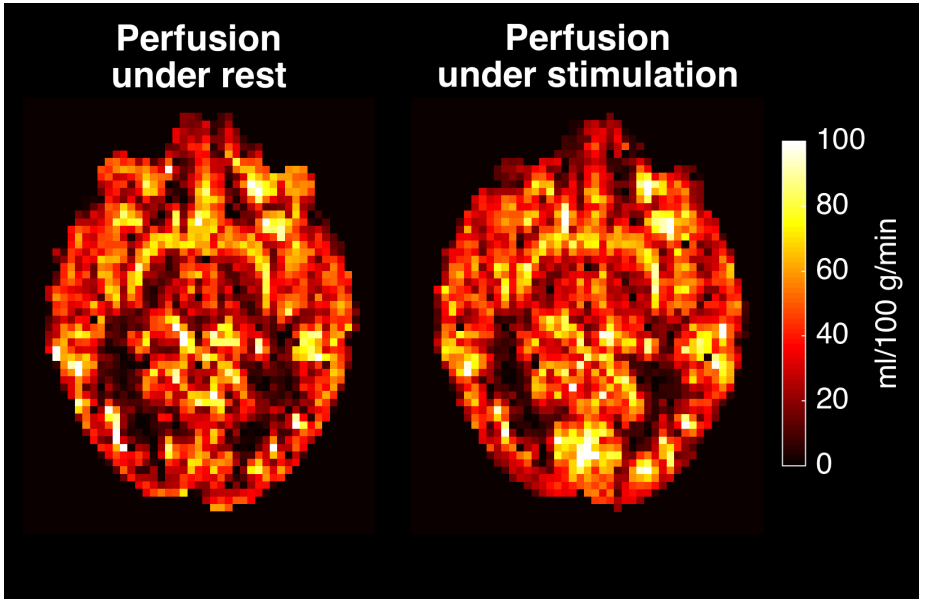
- What I have...
  - ➡ ASL perfusion in multiple sessions/subjects
  - ➡ Structural images
- What I want...
  - ➡ Perfusion change/ difference

    (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
```

EXAMPLE

- Data:

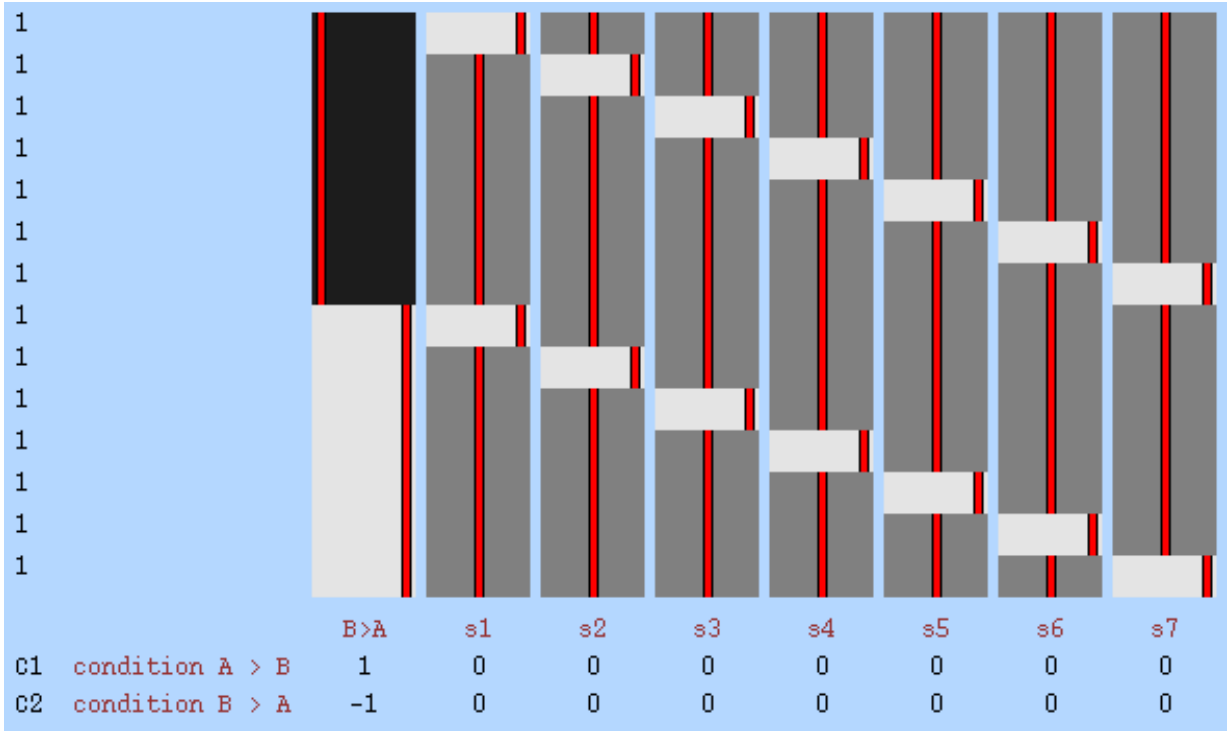
  pcASL, Multi-PLD

  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
```

EXAMPLE

- Data:

pcASL, Multi-PLD

label duration: 1.4 s

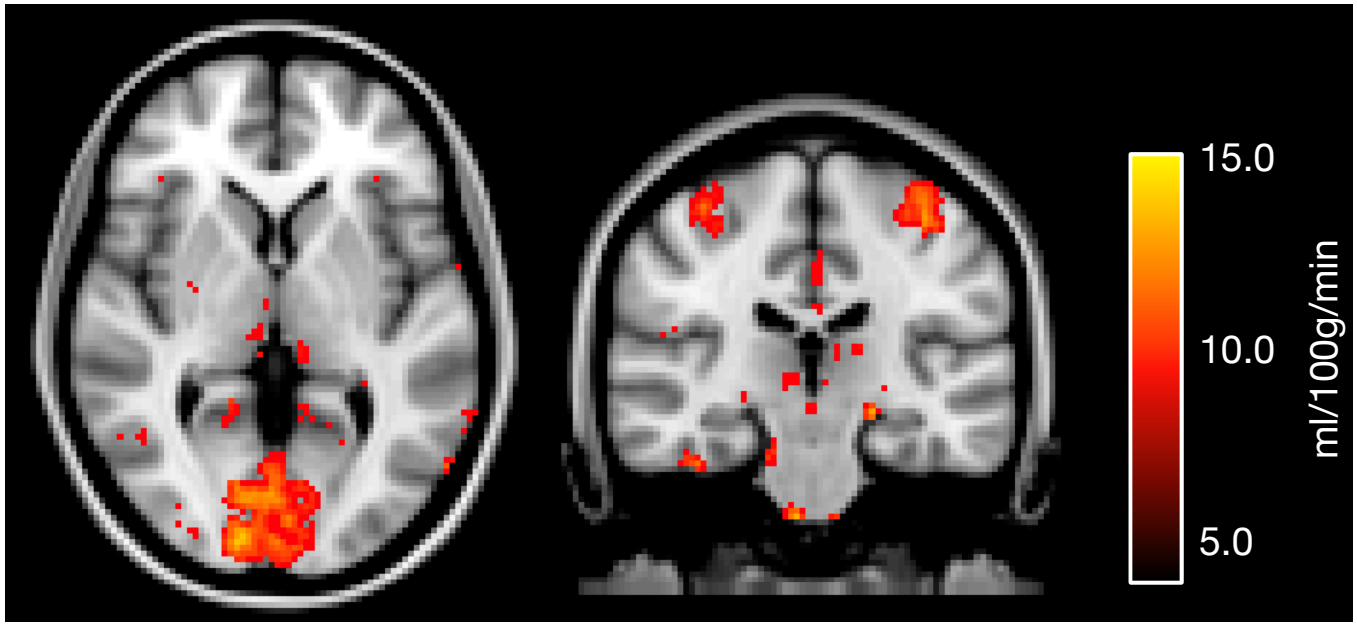
PLDs: 0.25, 0.5, 0.75, 1.0, 1.25, 1.5 s

8 individuals

task - finger tapping and visual stimulation

- Paired t-test

Perfusion change (effect size)



Example

- Data:

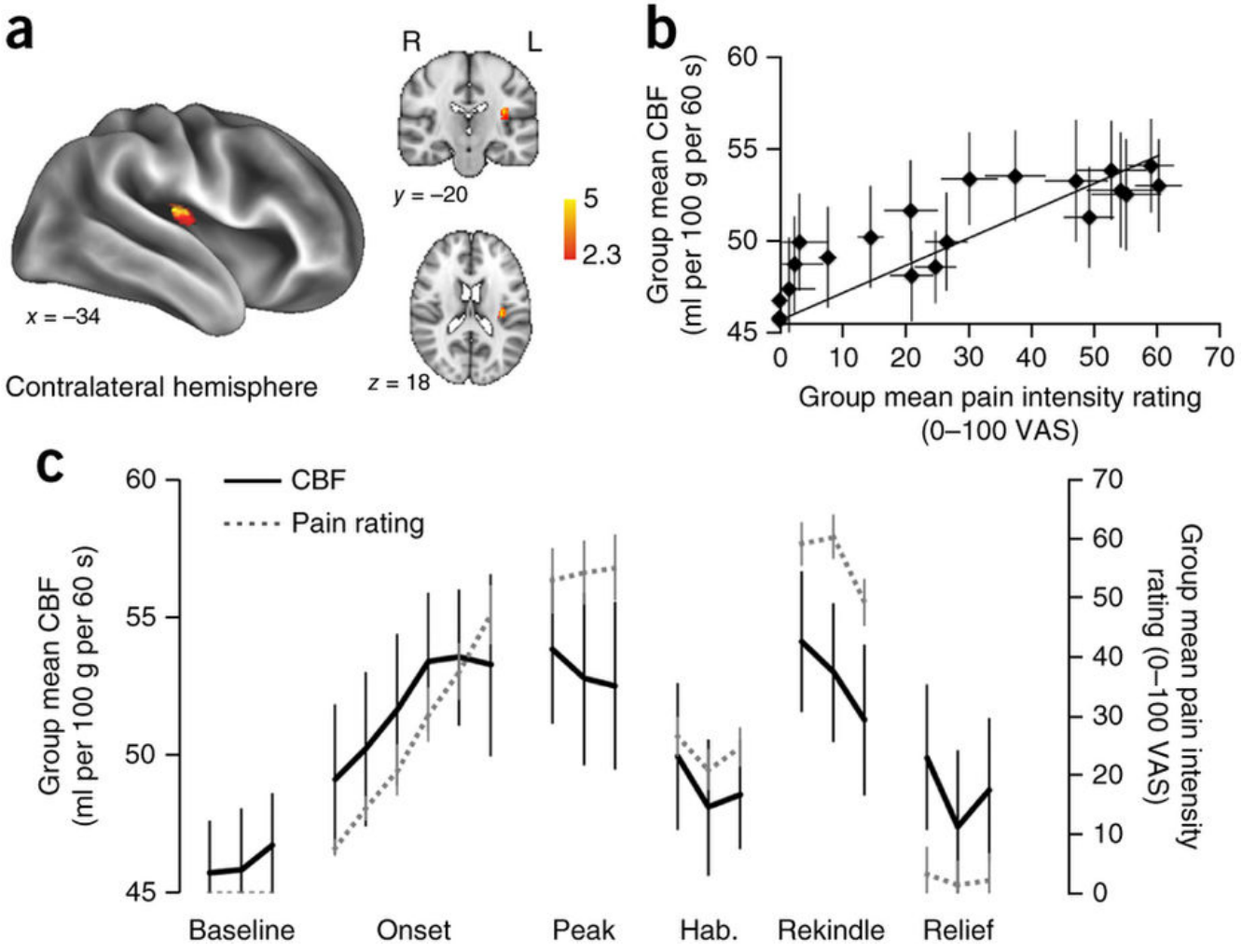
  pcASL, Multi-PLD

  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

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- Keep it simple!
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- Quantitative perfusion:
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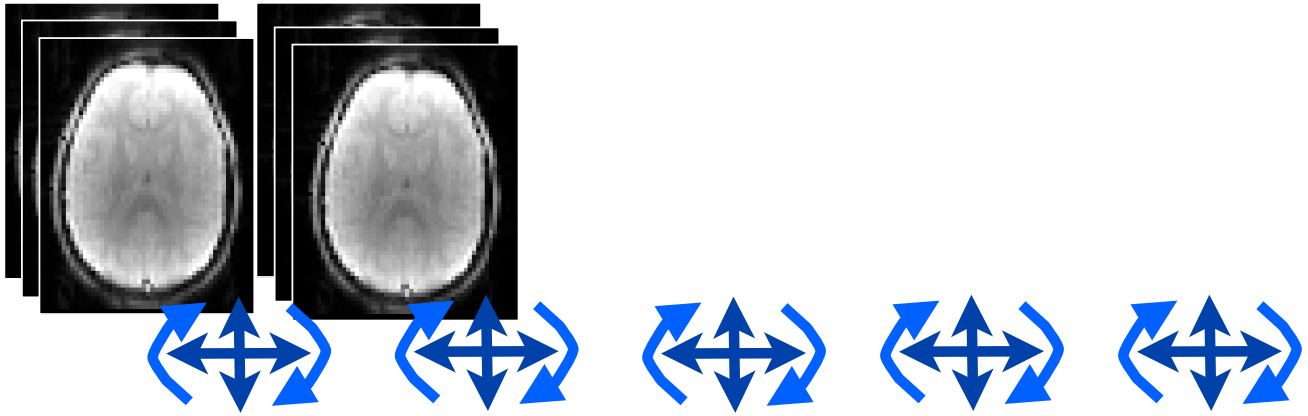
  - ➡ Calibration: Measuring arterial blood magnetization.
- Preparing for group analysis.
- Advanced quantification:
  - ➡ Motion, Distortion & Artefacts
  - ➡ Cerebrovascular Reactivity/Reserve
  - ➡ Macro Vascular Contamination
  - ➡ Partial Volume Effects

Advanced: Motion Correction

- 'Standard' motion correction
  - ➡ cf fMRI BOLD etc
  - ➡ 6 DOF between volume registration



- Might interpret label-control as motion
  - ➡ Separate label and control correction
- Challenging with 'aggressive' background suppression

```
oxford_asl ... --mc
mcflirt ...
```

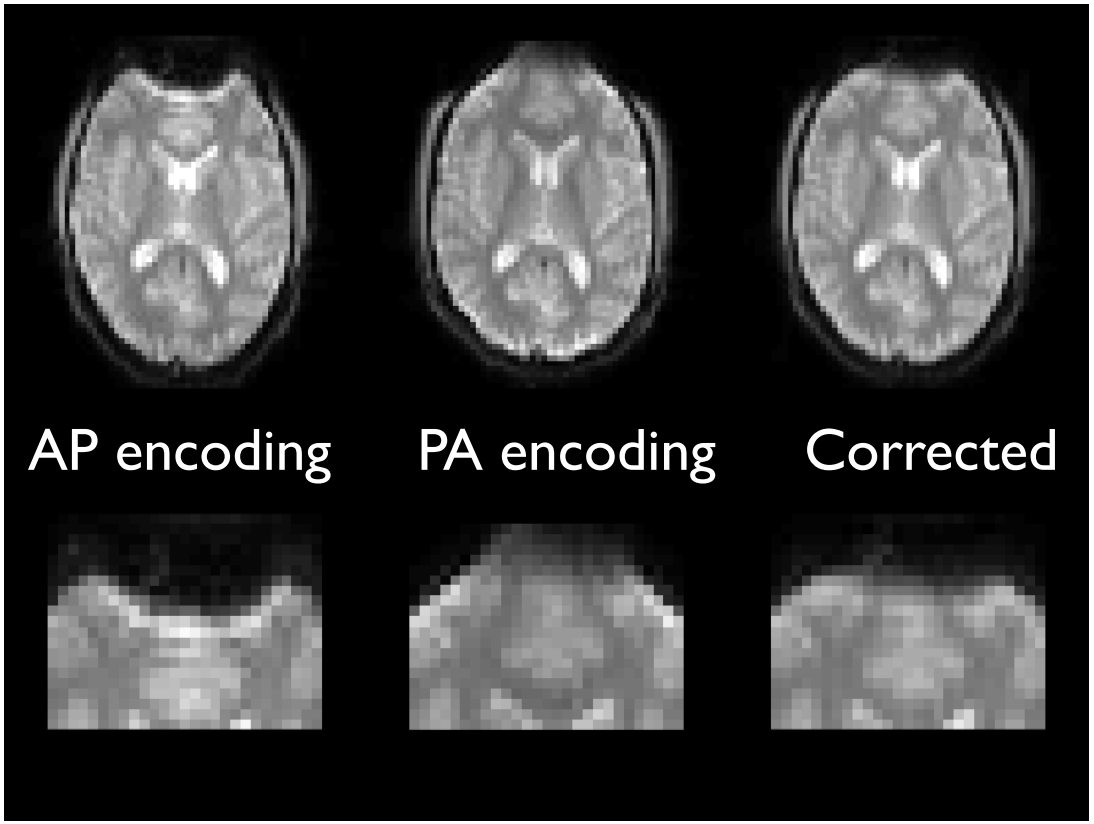
Advanced: Artefact Suppression

- Subtraction artefacts arise during label-control subtraction
  - ➡ Gross subject (head) motion
  - ➡ 'Physiological' motion/changes
  - ➡ Scanner instability
  - ➡ Mismatched background signal intensity

- Remove using:
  - ➡ Data scrubbing - manually by inspection, or automatically based on 'quality' metric.
  - ➡ ENABLE - identifies volumes that should be retained based on statistical measures.
  - ➡ ICA-FIX - Independent Component Analysis to identify 'components' and manual or automated (FIX) removal.

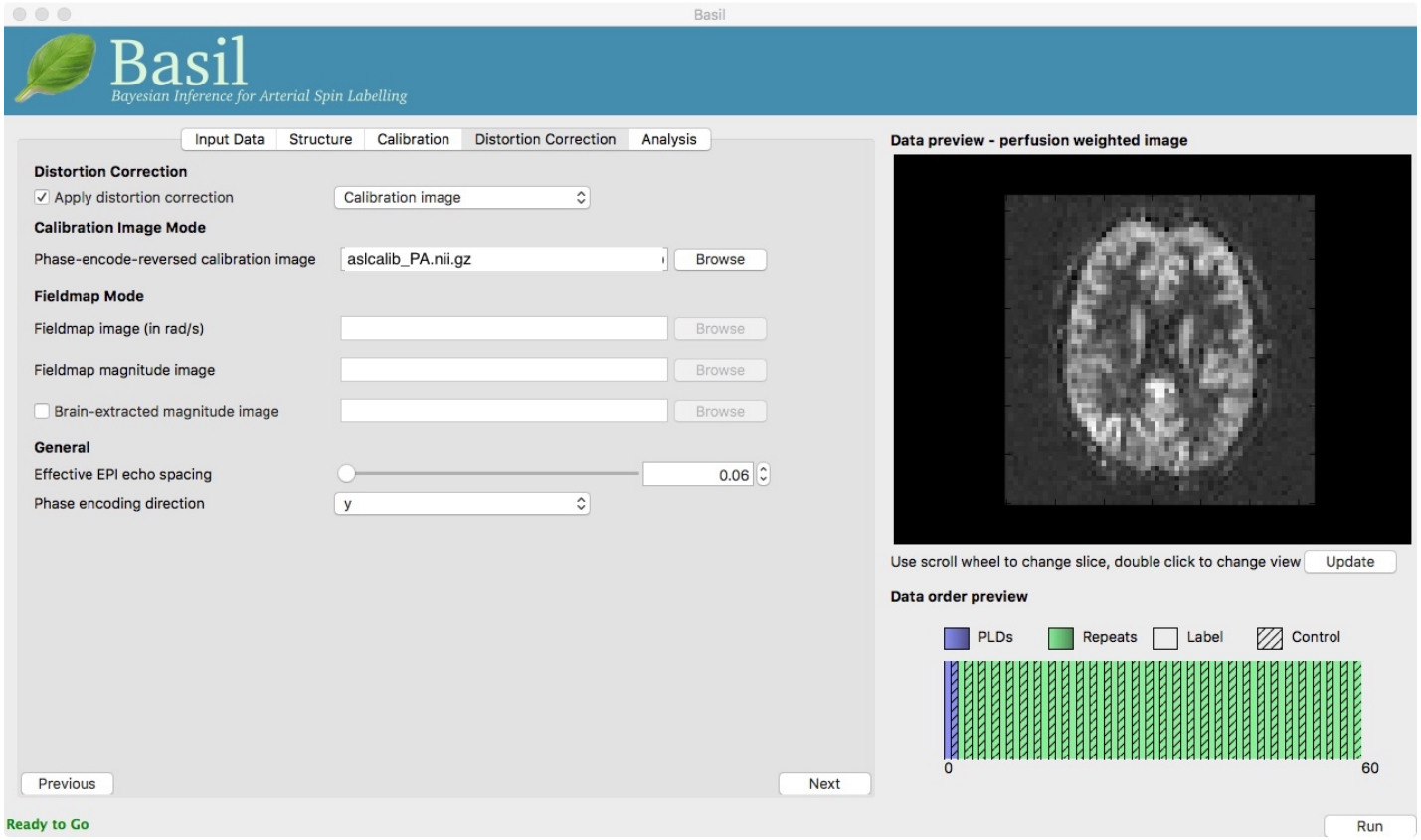
Advanced: Distortion Correction

- 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




```
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]
```

Example



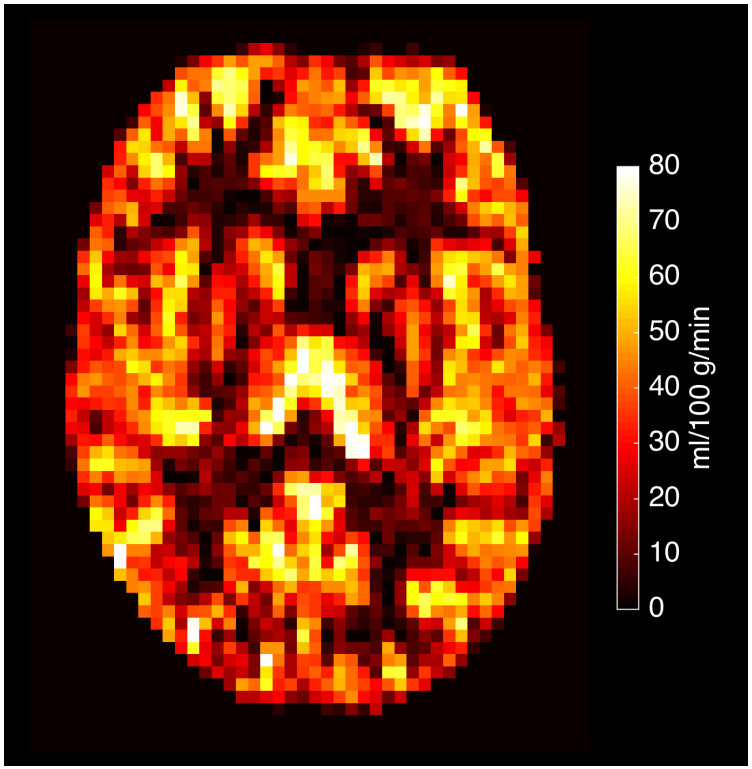
pcASL with
labeling duration: 1.8 s
post-label delay: 1.8 s
2D readout
45.2 ms per slice

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)

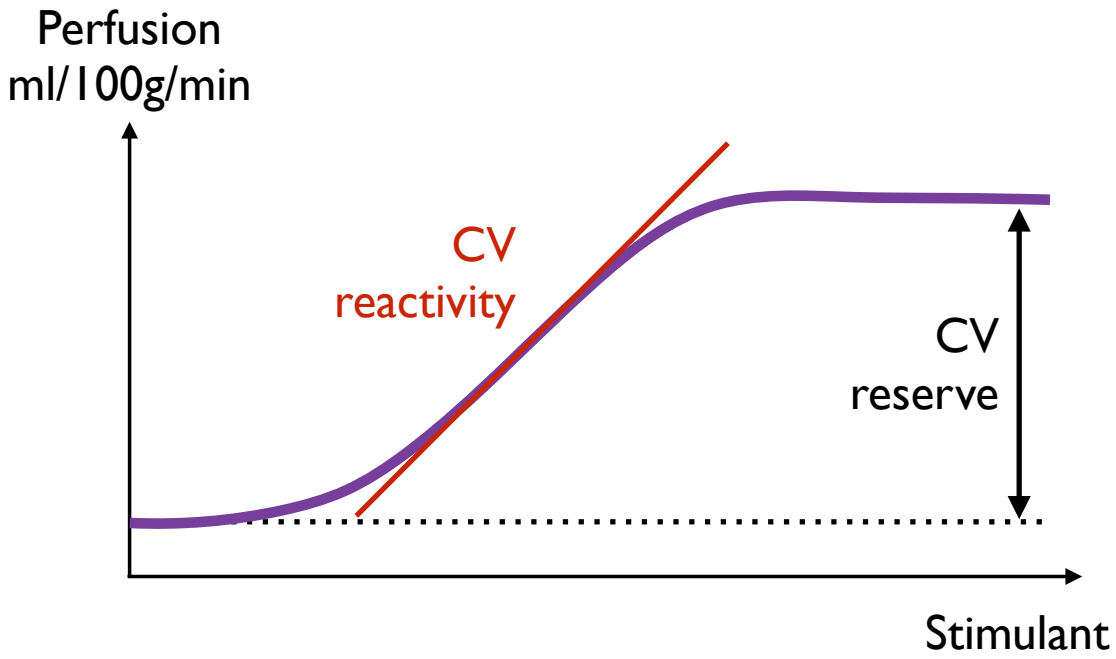


`oxasl/native_space/perfusion_calib.nii.gz`

Advanced: CVR

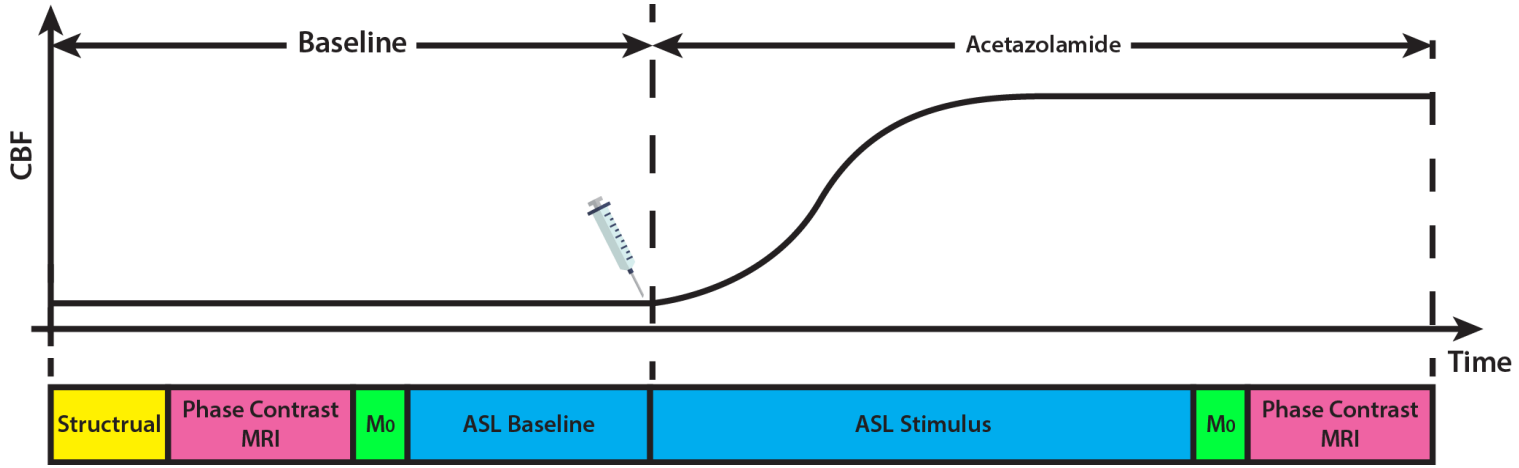
- A 'task-based' experiment where the aim is to examine a physiological rather than 'functional' process.
- Cerebrovascular Reserve
  - ➡ Maximal induced change in perfusion (%)
  - ➡ Drug induced, e.g., acetazolamide.
- Cerebrovascular Reactivity
  - ➡ Change in perfusion with applied stimulus
  - ➡ *cf* BOLD CVR measurement
  - ➡ Drug induced, e.g., caffeine (% per mg/Kg)
  - ➡ Gas challenge, e.g., CO_2 (% per mmHg)

$$CVR = \frac{CBF_{stimulus} - CBF_{baseline}}{CBF_{baseline}} \times 100\%$$



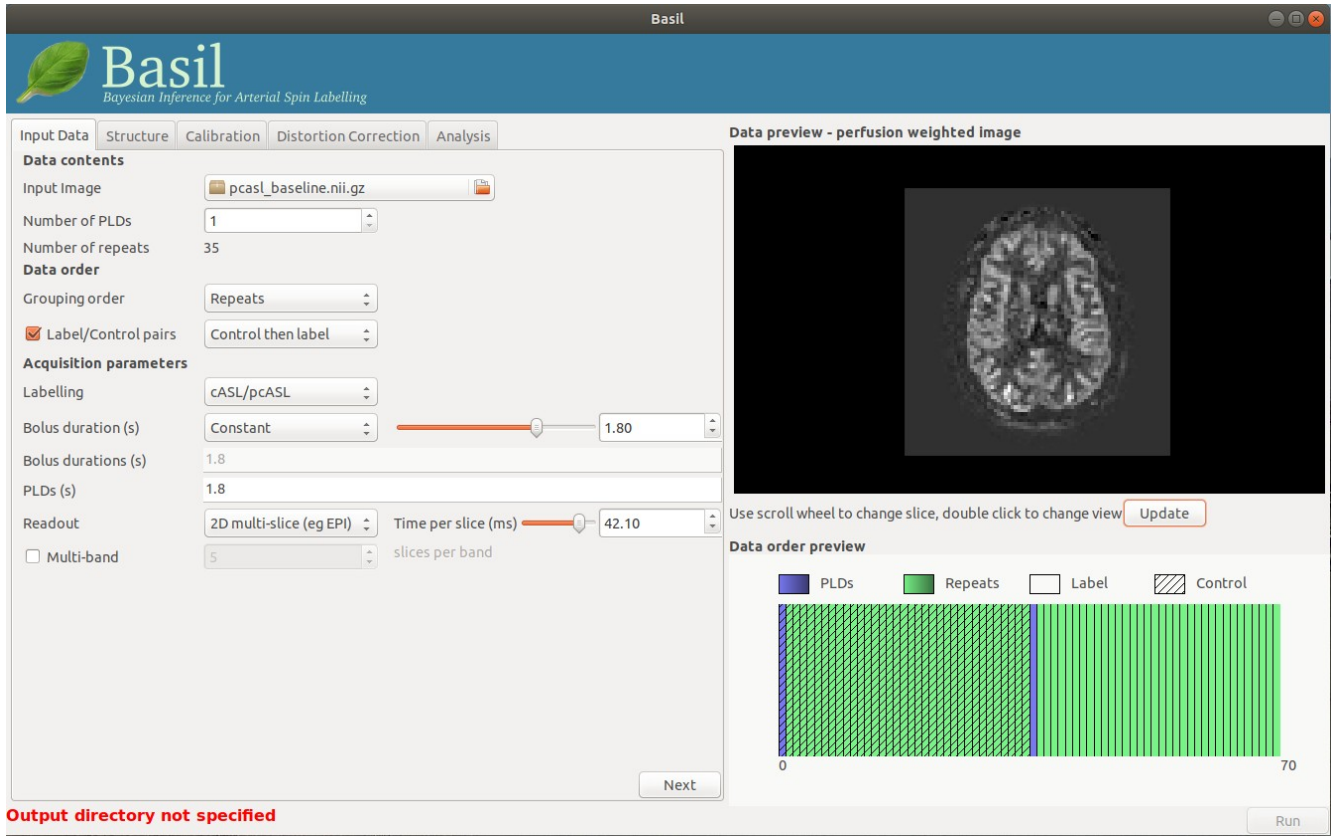
Example

- Cerebrovascular Reserve Study
  - ➡ Acetazolamide as stimulant
  - ➡ pcASL data acquired before, (during), and after stimulant.



Václavů L, Meynart BN, Mutsaerts HJ, et al.
Hemodynamic provocation with acetazolamide shows impaired cerebrovascular reserve in adults with sickle cell disease.
Haematologica. 2019;104:690–699.

Example



Baseline Perfusion

pcASL with

labeling duration: 1.8 s

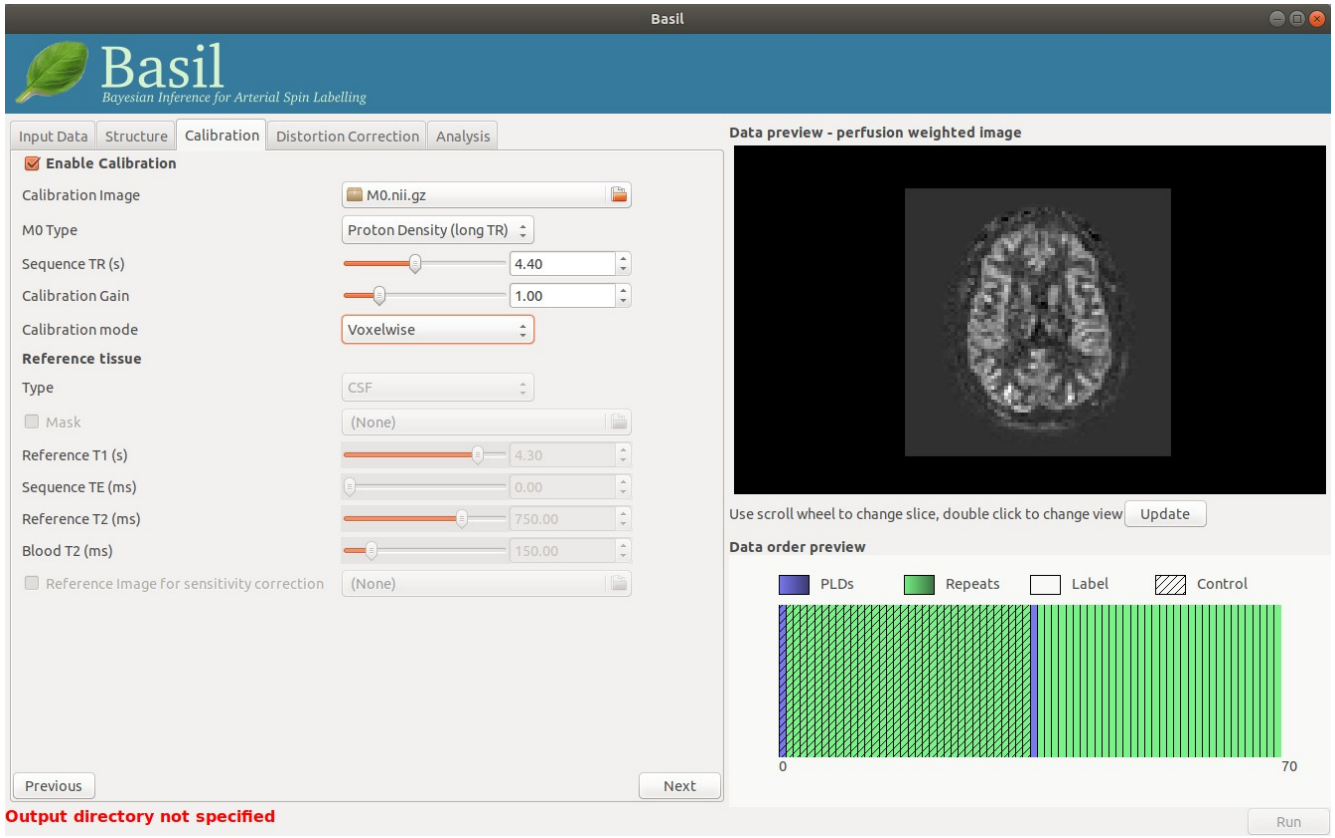
post-label delay: 1.8 s

35 repeats

2D readout

42.1 ms per slice

Example



Baseline Perfusion

pcASL with

labeling duration: 1.8 s

post-label delay: 1.8 s

35 repeats

2D readout

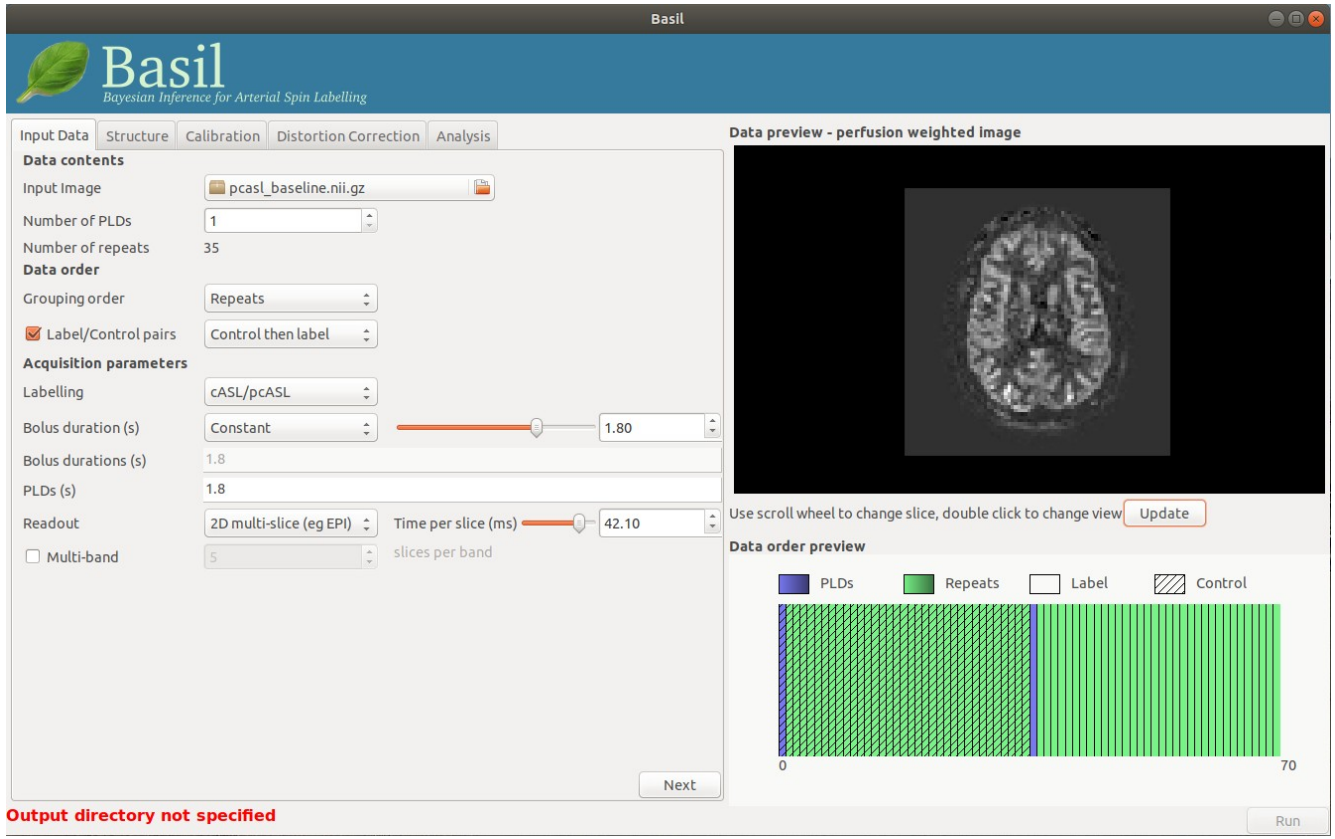
42.1 ms per slice

Calibration images

TR: 4.4 s

Voxelwise

Example



Stimulated Perfusion

pcASL with

- labeling duration: 1.8 s
- post-label delay: 1.8 s
- 35 repeats

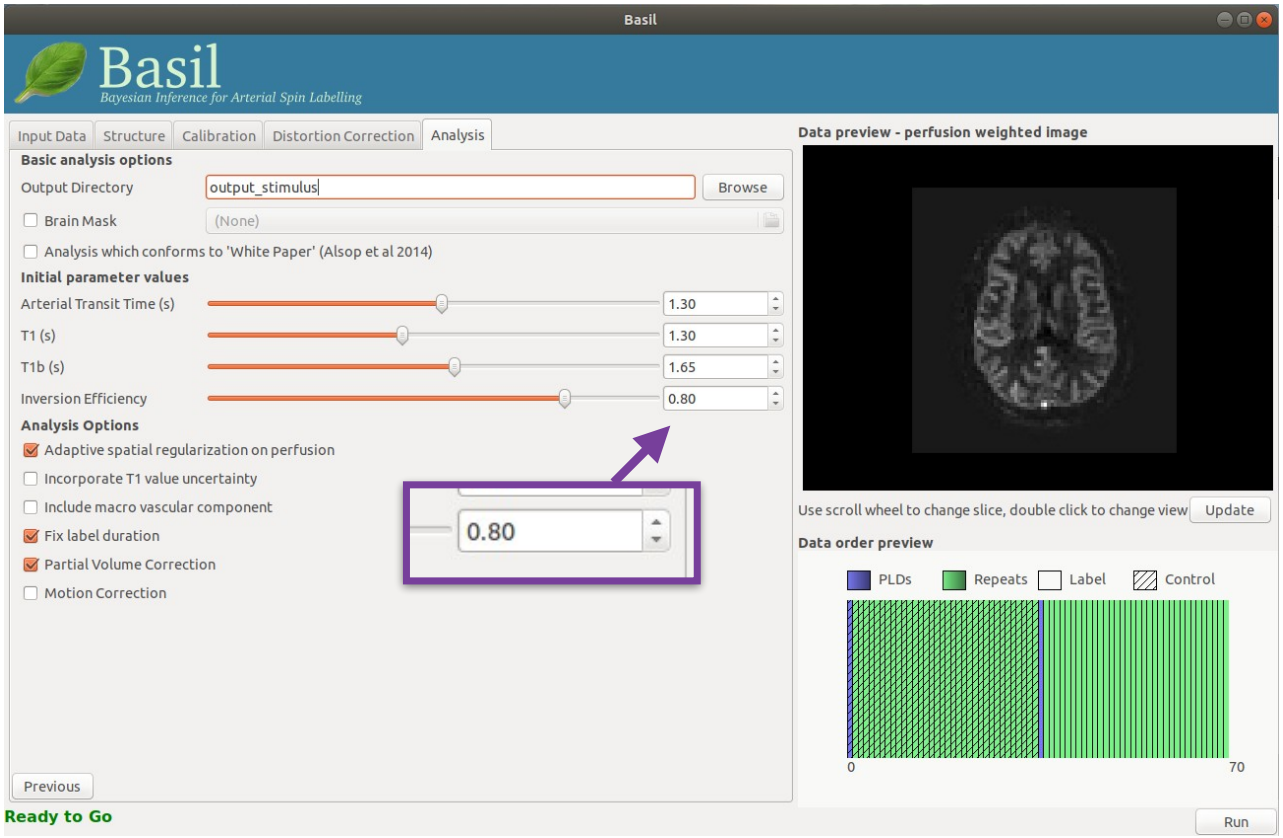
2D readout

- 42.1 ms per slice

Calibration images

- TR: 4.4 s
- Voxelwise

Example



Stimulated Perfusion

pcASL with

labeling duration: 1.8 s

post-label delay: 1.8 s

35 repeats

2D readout

42.1 ms per slice

Calibration images

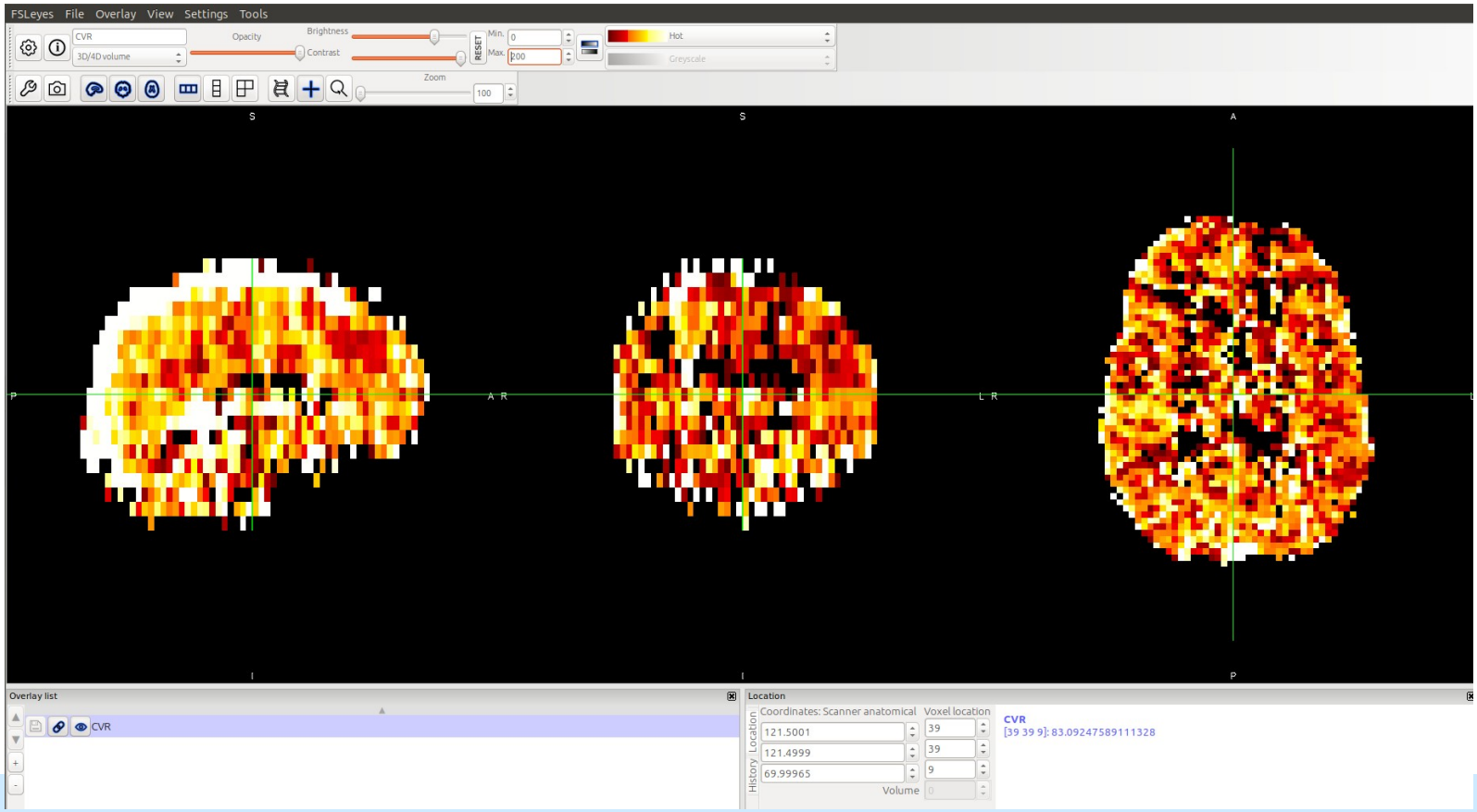
TR: 4.4 s

Voxelwise

Inversion Efficiency

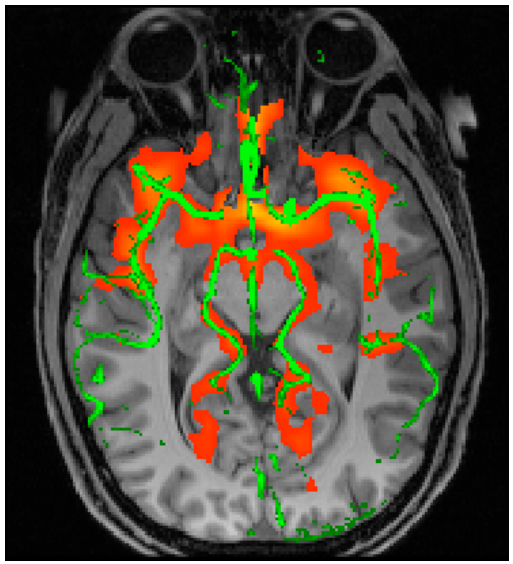
0.8 (calculated)

Example

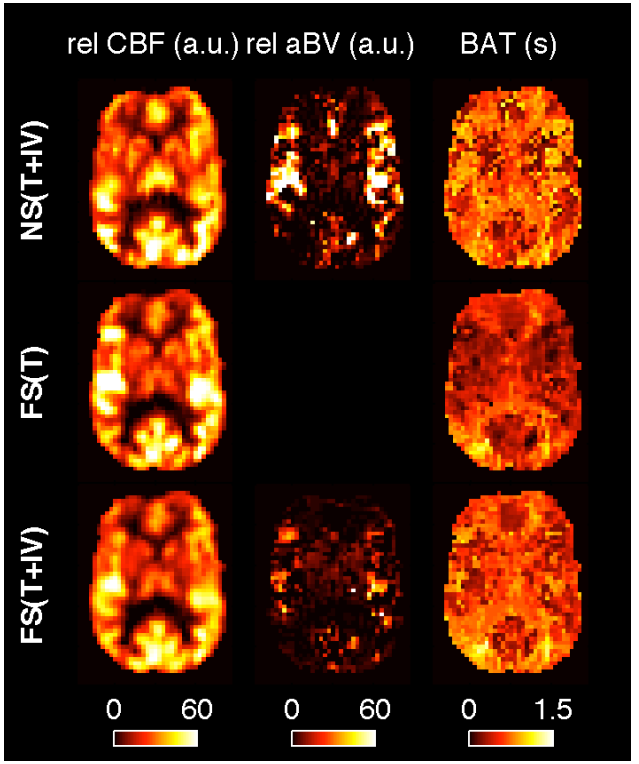

FSLeyes File Overlay View Settings Tools
CVR
3D/4D volume
Opacity
Brightness
Contrast
RESET
Min. 0
Max. 200
Hot
Greyscale
Zoom
100
S
S
A
P
A R
L R
I
I
P
Overlay list
CVR
Location
Coordinates: Scanner anatomical
Voxel location
121.5001
121.4999
69.99965
39
39
9
Volume
History
Location
CVR
[39 39 9]: 83.09247589111328

Advanced: Macro Vascular Contamination

- Early PLDs may contain label still within larger arteries.
  - ➡ perfusion overestimation
- Use long PLD(s)
- Use flow suppressing gradients
- Include in model - multi-PLD 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.

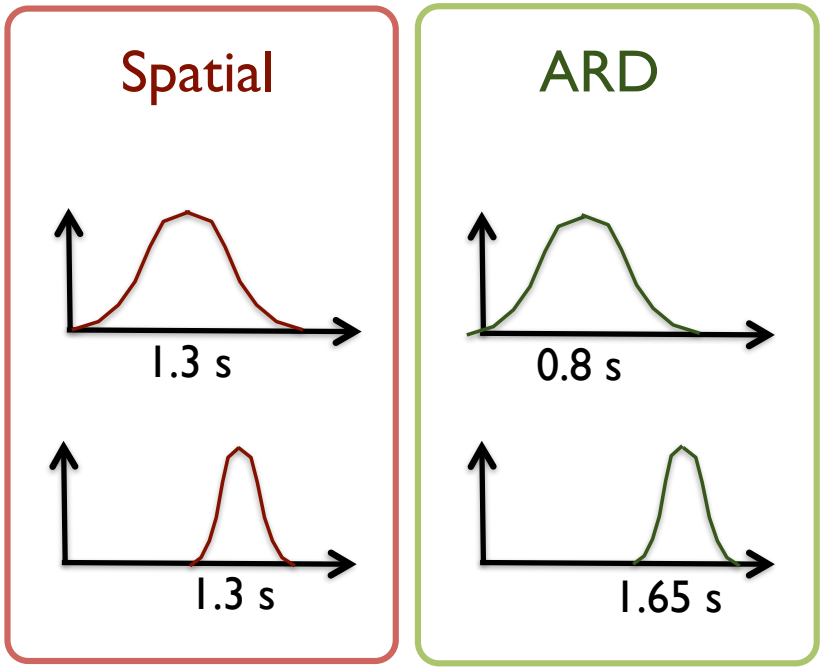
Advanced: Macro Vascular Contamination

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

Perfusion/ aBV

Arterial Transit Time

TI

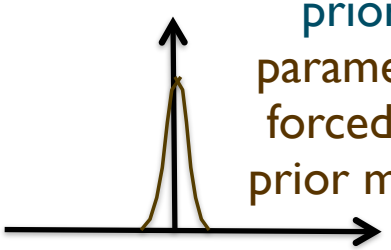


ARD prior: $\sim N(0,v)$

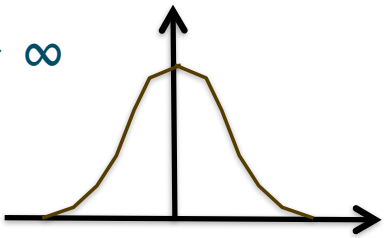
v determines the **relevance** of the prior. v is determined from the data.

$v \rightarrow 0$

Restrictive prior: parameter forced to prior mean



$v \rightarrow \infty$

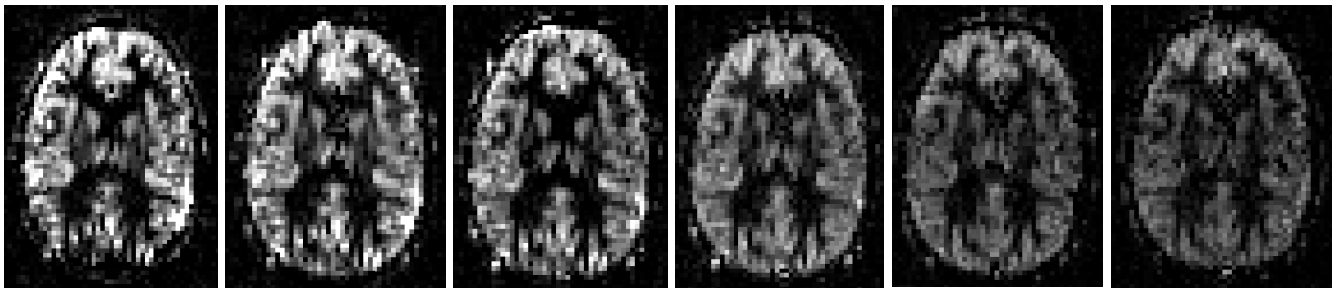


Liberal prior: parameter free to be estimated from data

EXAMPLE

- 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

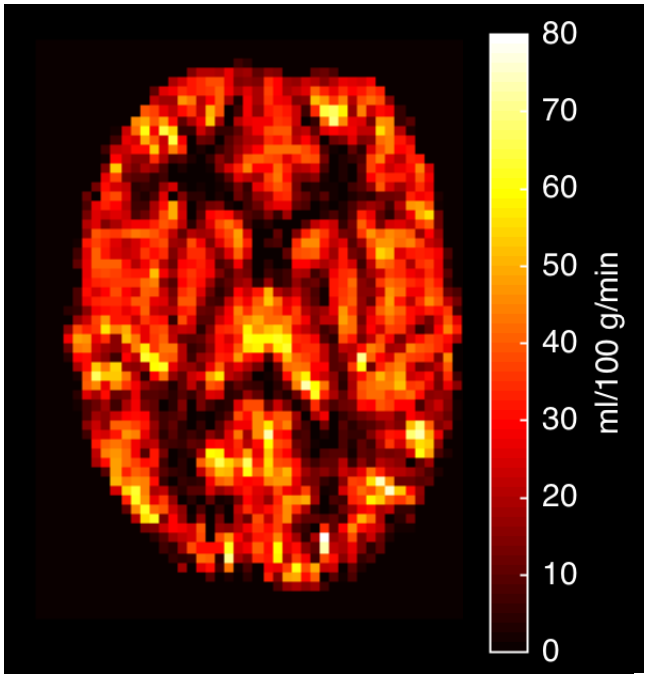


TI: 1.65 1.9 2.15 2.4 2.65 2.9

```
> 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
```

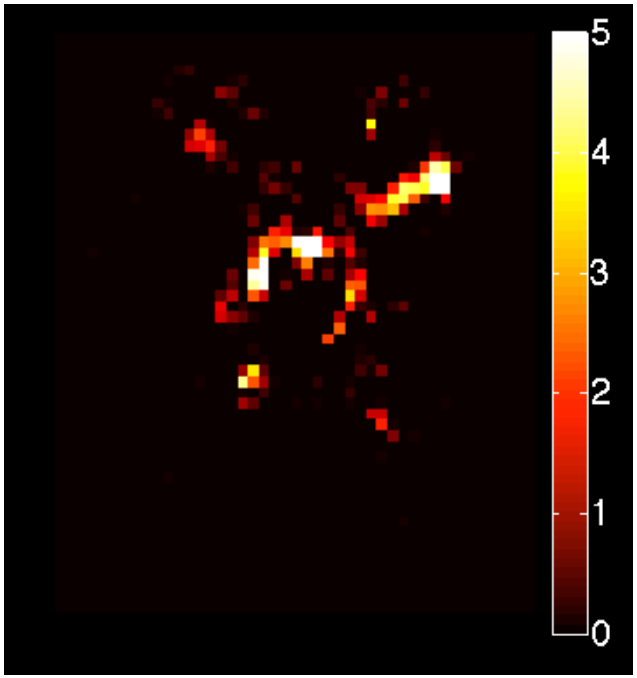
Example

Perfusion ml/100g/min



middle slice

Arterial cerebral blood volume % (ml/ml * 100)



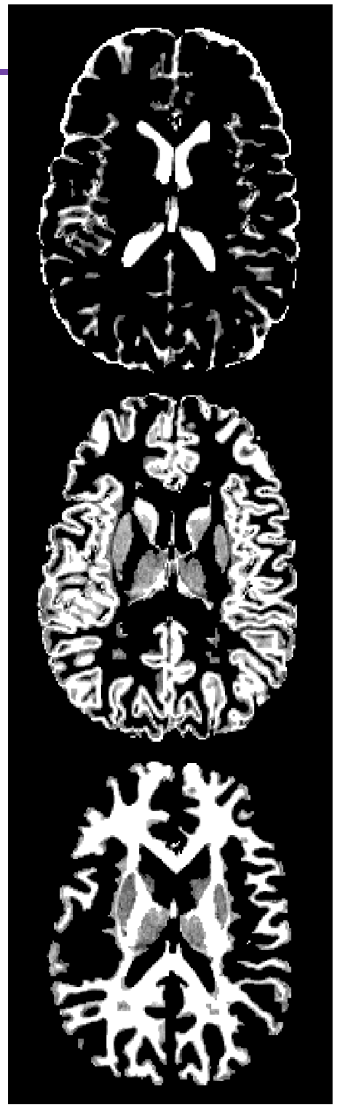
lower slice ~ Circle of Willis

```
oxasl/native_space/perfusion_calib.nii.gz
oxasl/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.

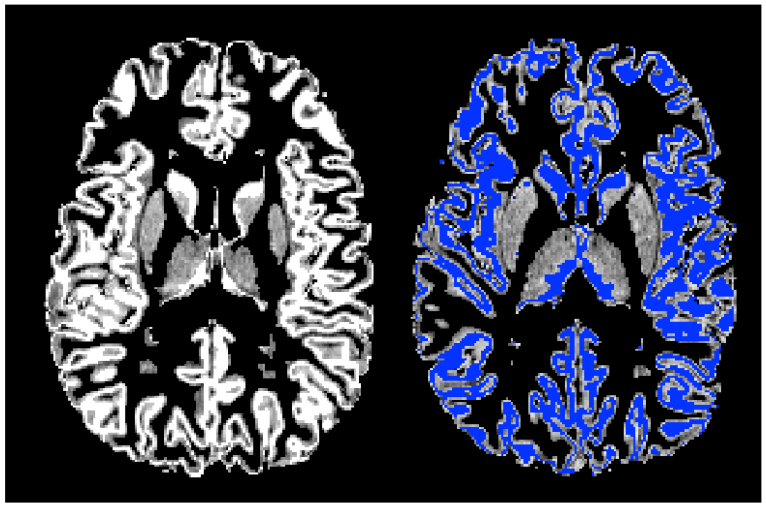


Advanced: Partial Volume Correction

- 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

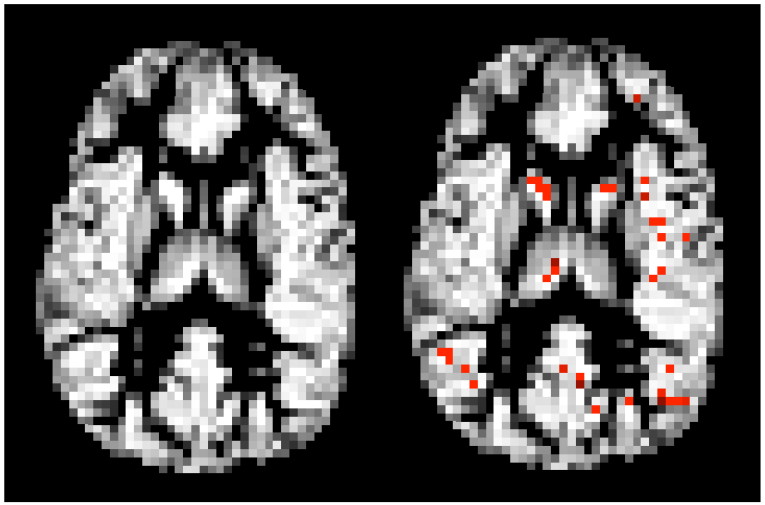
Structural resolution

Partial Volume Estimate | Threshold at 90%



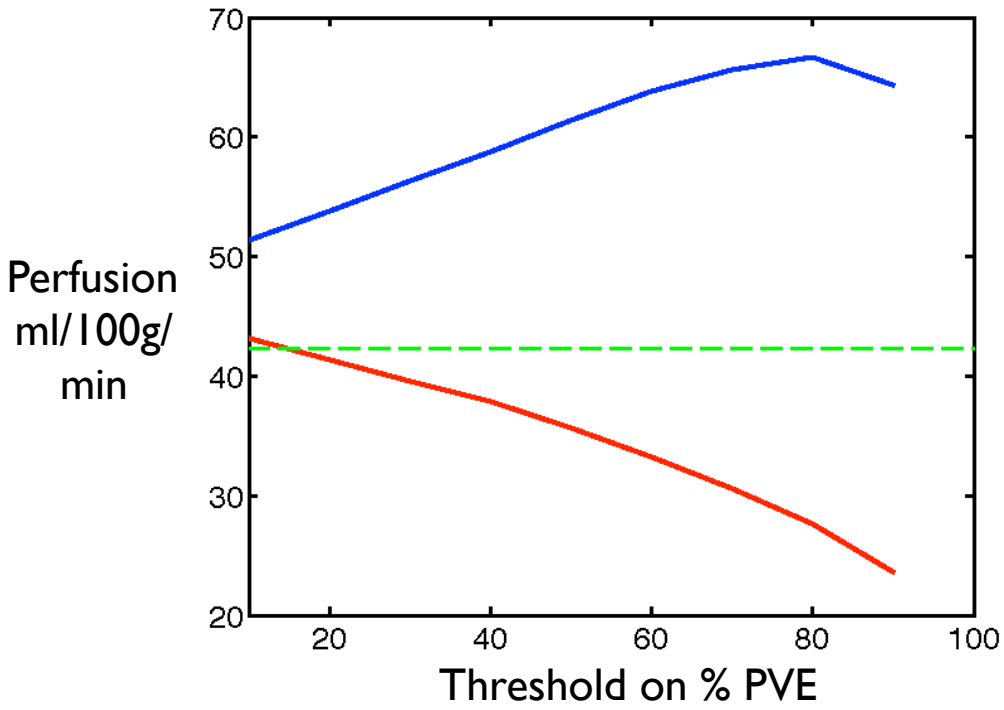
ASL resolution

Partial Volume Estimate | Threshold at 90%

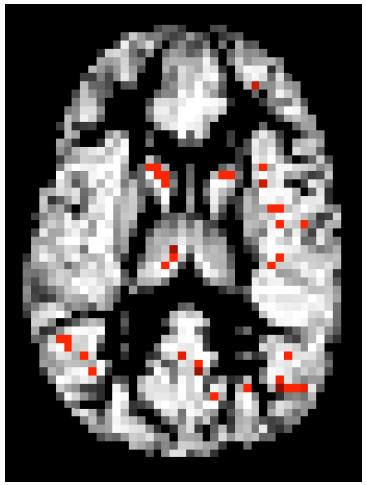


Advanced: Partial Volume Correction

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



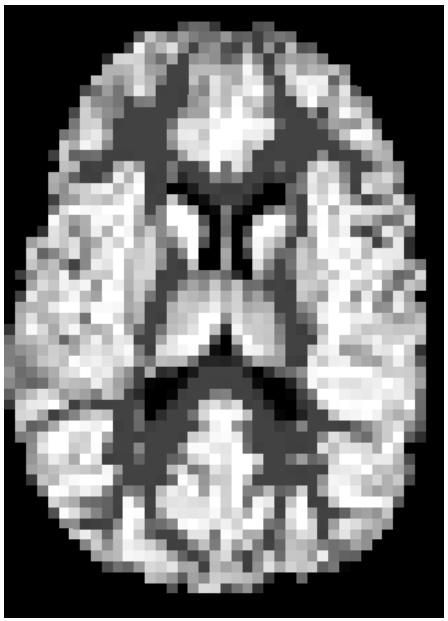
GM mask threshold at 90%



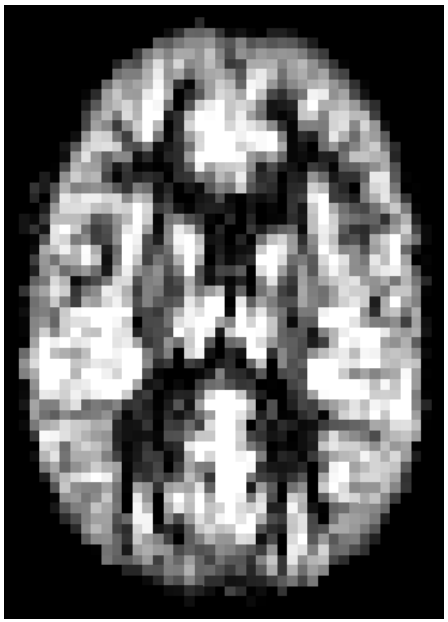
```
oxford_asl ... --report
```

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?



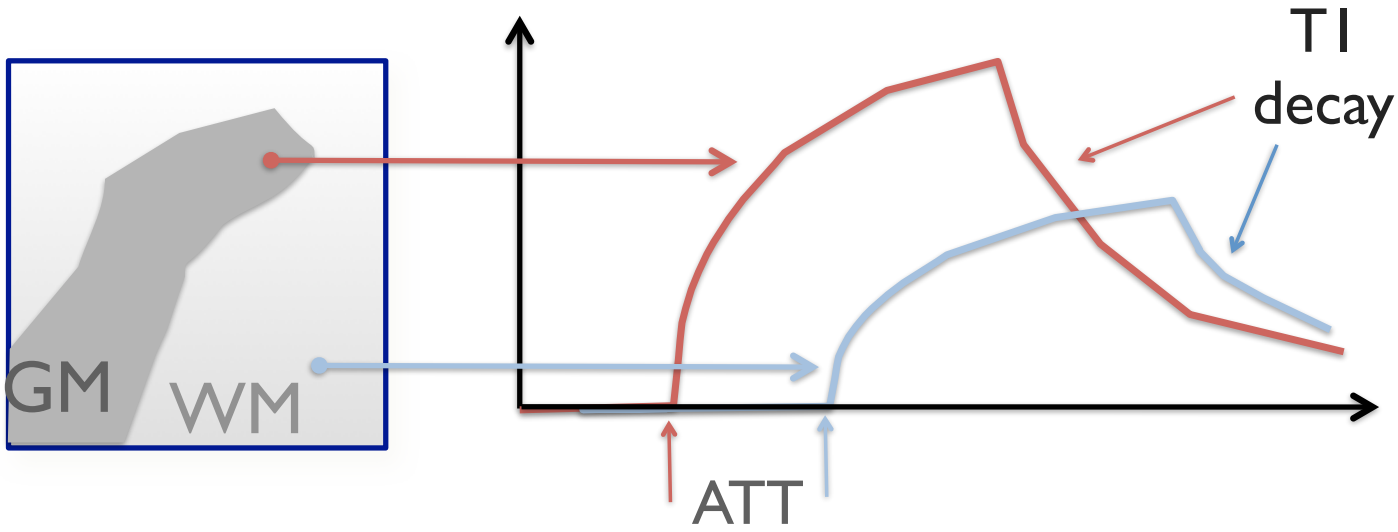
$60 * PVE_{GM} + 10 * PVE_{WM}$

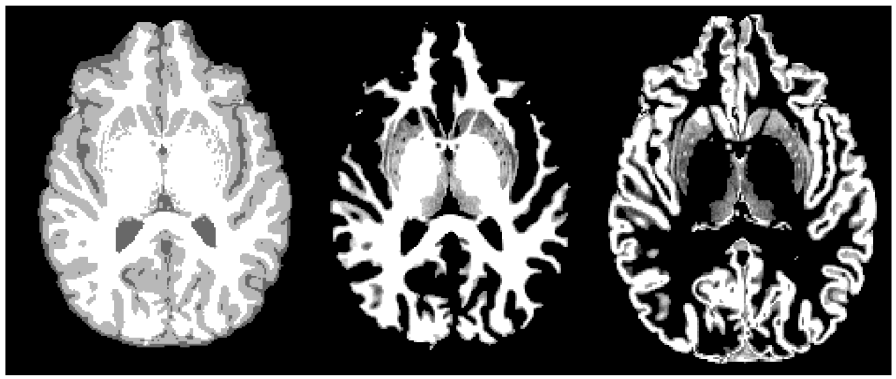


Estimated perfusion from ASL

Advanced: Partial Volume Correction

- Partial volume correction exploiting kinetic data:





➡ Perfusion: GM > WM

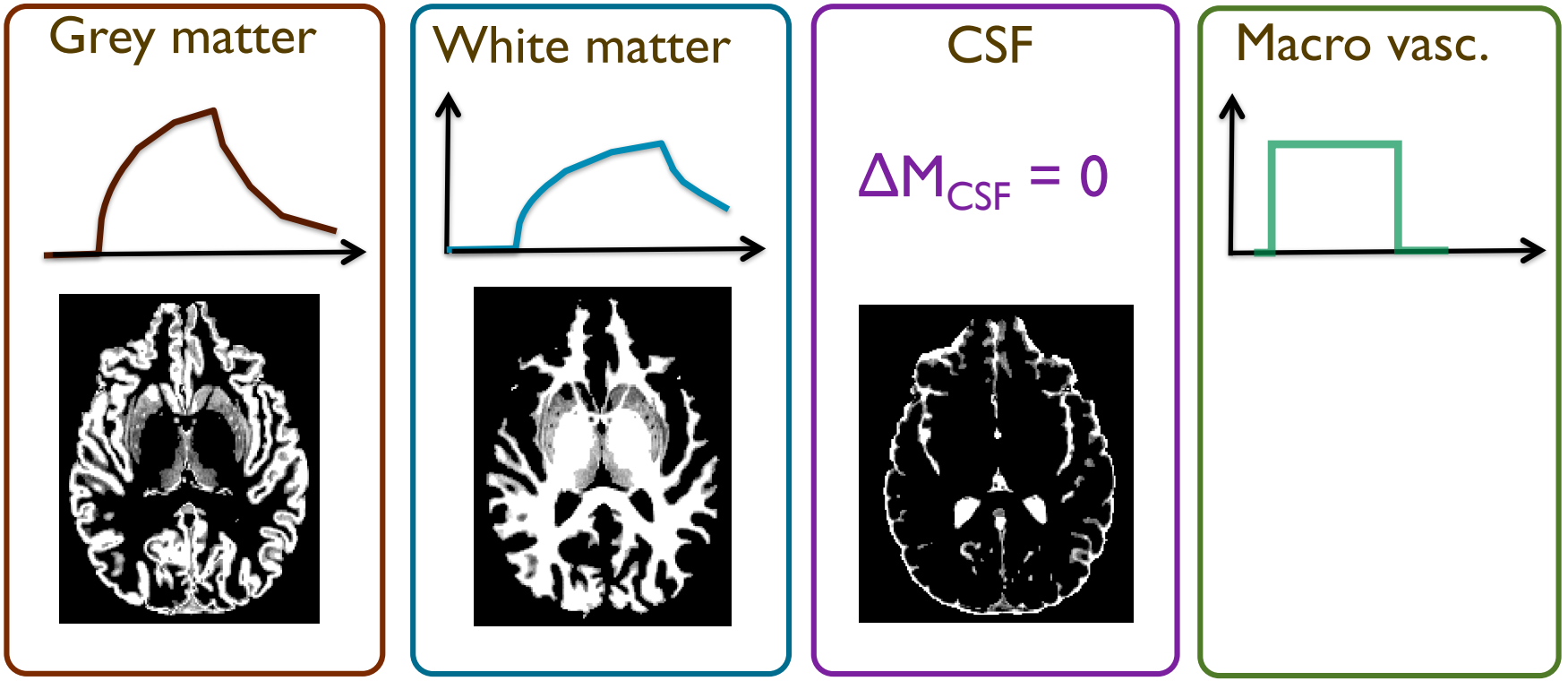
➡ ATT: WM > GM

➡ T1: WM < GM

Advanced: Partial Volume Correction

- Multi-component model:

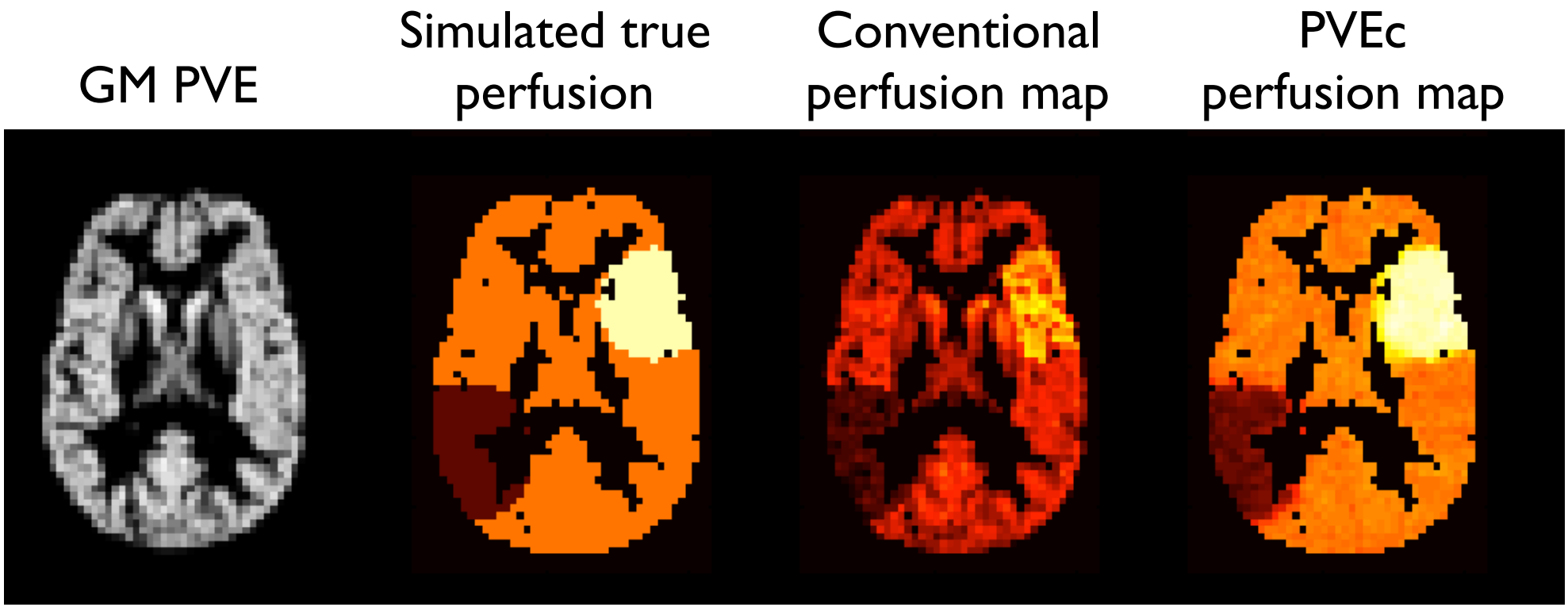
$$\Delta M(t) = PV_{GM}\Delta M_{GM}(t) + PV_{WM}\Delta M_{WM}(t) + PV_{CSF}\Delta M_{CSF}(t) + aBV\ \Delta M_{MV}(t)$$



- Spatial priors on CBF for GM and WM

Advanced: Partial Volume Correction

- Example from simulated data

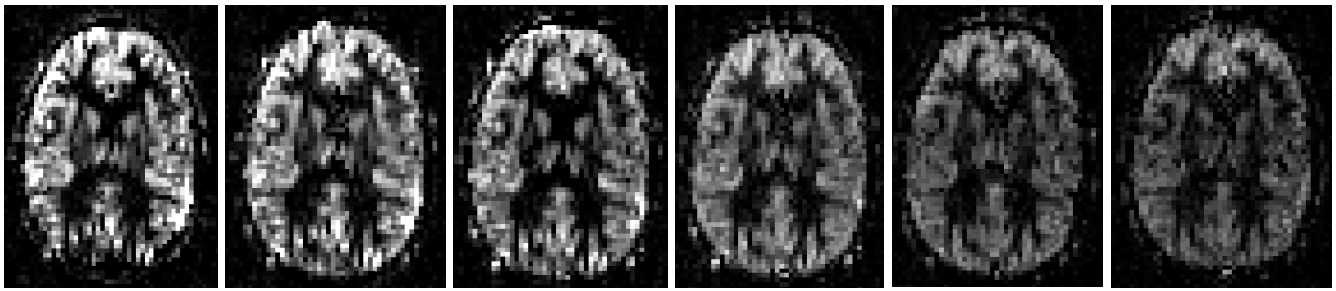


Chappell et al., MRM 65(4), 2011.

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



TI: 1.65 1.9 2.15 2.4 2.65 2.9

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

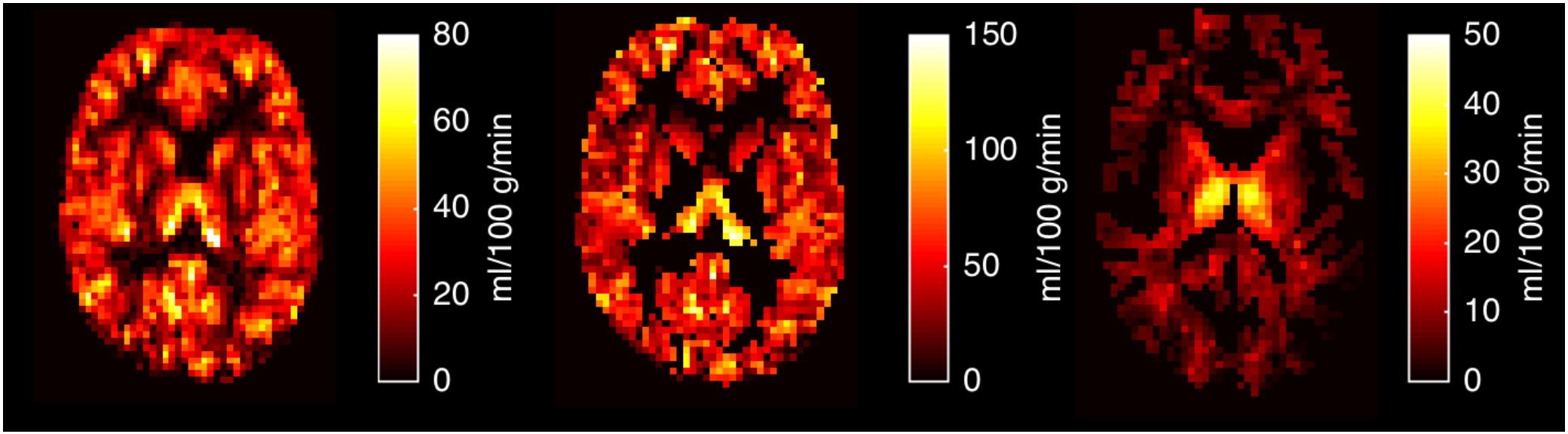
```
> oxford_asl -i {ASLdata.nii.gz} -o {oxasl} –iaf=tc --ibf=rpt  --casl \
      --tis=1.65,1.9,2.15,2.4,2.65,2.9 –bolus=1.4 --slicedt=0.0452 \
      --fixbolus --mc --pvcorr --fslanat=T1.anat \
      -c {calibration_image.nii.gz} --tr=4.8
```

EXAMPLE

Perfusion (uncorrected) ml/100g/min

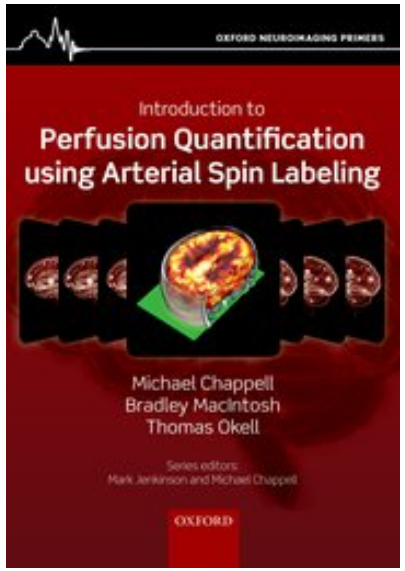
Grey matter perfusion ml/100g/min

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
```

Need to know more...



Oxford Neuroimaging Primers:

Introduction to Perfusion Quantification using Arterial Spin Labelling

- ➡ Cover material in this lecture and more.
- ➡ http://www.neuroimagingprimers.org

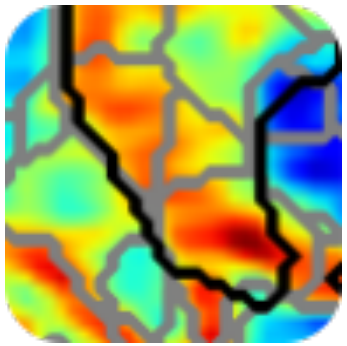
  Examples using BASIL (extended from the course)

FSL: The FMRIB Software Library

- ➡ BASIL: www.fmrib.ox.ac.uk/fsl/basil

  User guide & tutorials for FSL v6.0+

  Follow the link for the 'pre-release' and updated user guide/tutorials

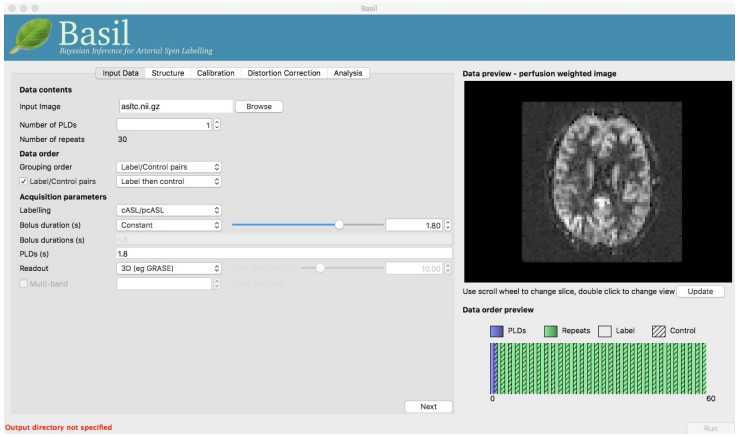


Quantiphyse

- ➡ www.quantiphyse.org

  User guide & tutorials for ASL perfusion quantification

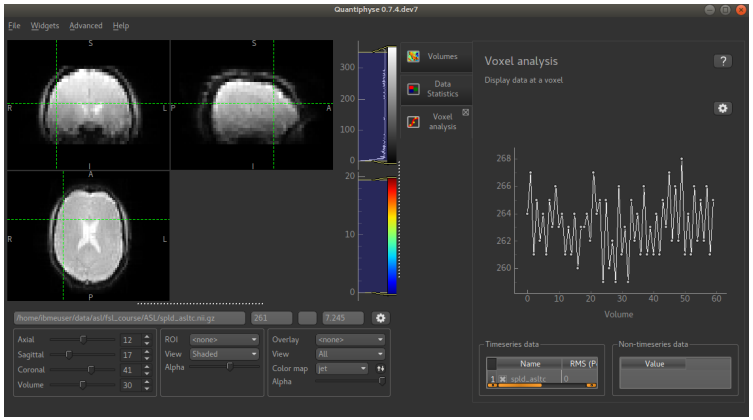
Practical Part II



Using BASIL (& FSL):

➡ https://oxasl.readthedocs.io/en/latest/practical_gui.html

➡ (Data is already loaded on the computer)



Using Quantiphyse

➡ https://quantiphyse.readthedocs.io/en/latest/asl_tutorial.html

Tumour ASL data (data password: **asl5327**)

➡ https://quantiphyse.readthedocs.io/en/latest/imago_tutorial.html

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  - Martin Craig
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