Basics of Quantification of ASL

Matthias van Osch

Contents

• Thoughts about quantification
• Some quantification models
  • Bloch equations
  • Buxton model
• Parameters that need to be estimated
  • Labeling efficiency
  • $M_0$
  • Bolus arrival time
  • Bolus width
  • $T_1$ of arterial blood/tissue
  • $T_2$ of label
• Or use phase contrast MRA to calibrate CBF

Two kinds of quantification

• Multiplication factors to scale to absolute perfusion (ml/100ml/min) that are constant for the whole image
• Factors that differ within the ASL-image and therefore will change relative perfusion
  • Transit time differences
  • Labeling efficiency for different arteries
  • Etc
Do we need absolute quantification?

- For many studies global scaling factors are not essential
- Scaling of ASL-images with respect to whole brain average
- How does disease affect blood flow distribution
- Relative perfusion of tumor compared to normal appearing GMWM
- Comparison with contralateral hemisphere
- Correction for regional differences is often more important
- Absolute quantification is essential for “whole brain” diseases, like large vessel occlusive disease, neurodegenerative disease, sickle cell disease, etc
- Especially important when comparing patients to controls (differences in $T_1$, labeling efficiency, or brain perfusion?)

Arterial spin labeling

1) Label blood magnetically (inversion)
2) Wait 1-2 seconds for label to arrive in brain tissue
3) Acquire images of the brain

Half-time of tracer

The labeled spins decay with the longitudinal relaxation time $T_1$ ($T_1,\text{blood} = 1650 \text{ ms @ 3Tesla}$)
**Arrival-time of label**

- Transport time to imaging slice is approximately 1 sec
- Probably takes another 1-1.5 s to reach capillary bed

**Arrival-time of label vs decay of tracer**

Wait long for arrival of spins in microvasculature
Image as quickly possible due to loss of label

**Loss of label: longitudinal relaxation**

The labeled spins decay with the longitudinal relaxation time $T_1$ ($T_{1,\text{blood}} \approx 1650 \text{ ms @ 3Tesla}$)
Principle of arterial spin labeling

- ASL is based on tracer kinetics to measure blood flow, similar to the nitrous oxide method, perfusion CT and DSC-MRI
- Use blood as a tracer by inverting its longitudinal relaxation: NO CONTRAST AGENT
- Half-time of tracer governed by the longitudinal relaxation time
- Freely diffusing tracer: accumulation of tracer reflects blood flow

Quantification models I: Bloch

\[
\frac{dM_1(t)}{dt} = \frac{M_0^B(t) - M_2(t)}{T_{1\text{, tissue}}} + \frac{f(M_0(t) - M_2(t))}{T_{1\text{, tissue}}} \\
\text{Inflow of label} \quad \text{Outflow of label} \\
\text{Correction for differences in water content} \\
\text{Under assumption of well mixed compartment}
\]

Solution steady state: \[ f = \frac{\lambda}{T_{1\text{, app}}} \left( 1 - \frac{M_{\text{label}}}{M_{\text{control}}} \right) \]

Quantification models II: Buxton

A General Kinetic Model for Quantitative Perfusion Imaging with Arterial Spin Labeling

Richard H. Buxton, Lawrence L. Frank, Eri C. Wong, Bethine Stewart, Steven Wiesmann, Robert R. Klatzo

Recently, several implementations of arterial spin labeling (ASL) have been developed to produce MR images without the need for an intravenous contrast agent. Quantitative perfusion images are obtained by measuring the changes in signal intensity as a function of time. In this paper, a general kinetic model for ASL is presented. The model incorporates the effects of the inflow and outflow of labeled water, the effects of the longitudinal relaxation time, and the effects of magnetization transfer. The model is solved numerically to predict the time course of the signal intensity. The model is applied to a clinical dataset to demonstrate the accuracy of the model in predicting the signal intensity. The results show that the model accurately predicts the signal intensity and that the model is robust to variations in the input parameters. The model provides a useful tool for quantifying perfusion in the brain and other organs.
Formulation of ASL signal as a convolution

\[ \Delta M = \frac{2\pi M_0\text{blood}}{\rho} \int_0^t r(t') \cdot m(t - t') \, dt' \]

- **Labeling efficiency**
- **Delivery function**
  Normalized arterial concentration of magnetization at voxel
- **Residue function**
  Fraction of tagged spins arrived at \( t' \) and still present at \( t \)
- **Relaxation function**
  Relaxation between \( t' \) and \( t \)

**Factor 2:** most ASL-techniques employ inversion to create maximal signal difference (except e.g. velocity selective ASL)

\[ \alpha = \text{Labeling efficiency} = \frac{M_{\text{blood,control}}(t) - M_{\text{blood,tagged}}(t)}{2M_{\text{blood}}} \]

- Check inversion efficiency and profile in phantoms
- Redo these experiments in vivo, because \( B_1 \)-distribution is different in vivo than in phantoms
- Acquire images at different delay times (inversion recovery)
Remember: switch off pre-saturation pulses and post-labeling saturation.

Labeling efficiency of PASL can be very close to 100% for PASL, but also check control condition.
Labeling efficiency of CASL and pCASL

More difficult to measure, because inversion is achieved by flow-driven (pseudo-)adiabatic inversion

Labeling efficiency therefore frequently determined by means of simulation of Bloch equations

Which you will be doing this afternoon...

Quantification of ASL

\[ \Delta M = 2 M_0 \text{Blood} \int_0^t c(t') - r(t - t') \cdot m(t - t') \, dt' \]

- \( M_0 \) is the equilibrium signal (TR=\infty, TE=0) in a voxel containing 100\% arterial blood
  - Is therefore proportional to voxel volume
  - Take care of scaling between scans on your scanner (\( M_0 \) vs ASL)

- Measure \( M_0 \) with PD-weighted sequence in vein
- Use reference ROI (WM or CSF)
- Use separate \( M_0 \) scan

Separate \( M_0 \)-scan

- PD-weighted sequence with similar readout as ASL
- Correct for differences in water content of tissue and blood \((\lambda_{GM} = 0.82, \lambda_{WM} = 0.98)\)
- Perform voxel-wise correction (=division)
- Also possible to use control image (be aware of T1-effects and should not be combined with background suppression!)

Separate M₀-scan

- Automatically correction for regional differences in T₂(*)
- Assuming that T₂(*) of ASL signal equals T₂(*) of PD-signal (tissue dominated)

Quantification of ASL

Errors in single echo ASL when assuming uniform T2*

<table>
<thead>
<tr>
<th>Region</th>
<th>Slice Thickness</th>
<th>difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>frontal sinus</td>
<td>5mm</td>
<td>8mm</td>
<td>0.002</td>
</tr>
<tr>
<td>nasal cavity</td>
<td>47</td>
<td>50</td>
<td>0.004</td>
</tr>
<tr>
<td>paranasal sinus</td>
<td>24</td>
<td>34</td>
<td>0.567</td>
</tr>
<tr>
<td>grey matter</td>
<td>1</td>
<td>1</td>
<td>1.000</td>
</tr>
<tr>
<td>white matter</td>
<td>-7</td>
<td>-7</td>
<td>0.862</td>
</tr>
</tbody>
</table>

- Table shows relative error in S₀ calculation from single echo approach assuming a uniform T₂* = 50 msec as compared to dual echo approach. Errors can amount to more than 50%.
- In areas close to air containing cavities the error is significantly reduced with smaller slice thickness.
- Relative error in grey and white matter at a higher level is not significant.

Quantification of ASL

Separate M₀-scan

- Automatically correction for regional differences in T₂(*)
- Assuming that T₂(*) of ASL signal equals T₂(*) of PD-signal (tissue dominated)
- Also correction for B₁-inhomogeneities and other scaling factors is achieved (i.e. parallel imaging)

Quantification of ASL
Correcting B₁-inhomogeneities

Error in CBF as a function of readout flipangle

ASL @ 7T

B₁ map

With correction for B₁

ASL @ 7T

B₁ map

Without correction for B₁
Separate M₀-scan

- Automatically correction for regional differences in T₂(*)
- Assuming that T₂(*) of ASL signal equals T₂(*) of PD-signal (tissue dominated)
- Also correction for B₁-inhomogeneities and other scaling factors is achieved (i.e. parallel imaging)
- Without correcting for voxel-wise differences in lambda, some errors are made

| TABLE 1: Partition coefficients for whole brain (T₂), grey matter (T₂)ₚ and white matter (T₂)ₚₚ |
|---|---|---|
| | sub | mF | mH |
| L₀ | 0.96 | 0.96 | 0.95 |
| L₁ | 1.02 | 1.02 | 1.00 |
| L₂ | 0.97 | 0.92 | 0.96 |


Choice of TR

- TR = 2000 ms
- TR = 10000 ms

M₀ in CSF

- Same readout as ASL
- Inversion pulse of background suppression
- Perform fit
Quantification of ASL

### 11 M$_0$ in CSF

$$M_{0,\text{blood}} = M_{0,\text{CSF}} \frac{\lambda_{\text{blood}}}{\lambda_{\text{CSF}}} e^{\frac{\Delta T}{T_{\text{CSF}}}} \approx 0.87 \cdot M_{0,\text{CSF}} \cdot e^{\frac{\Delta T}{T_{\text{CSF}}}}$$

Quantification of M$_0$.

### 11 Comparison of M$_0$-methods

- pCASL
- FAIR

**ROI in CSF**
- Voxelwise

**ROI in WM**
- Voxelwise

**ROI in activity correction for $\lambda_{CSF}$ and $\lambda_{CSF}$**
- Control

Image courtesy: Chen, Wang, Detre, ISMRM 2011, abstract nr 300

Quantification of M$_0$.

### 11 Quantification models II: Buxton

**Delivery function**
- Normalized arterial concentration of magnetization at voxel

$$\Delta M = 2aM_{0,\text{blood}} \int_0^\infty e^{-\frac{\Delta T}{T_{\text{CSF}}}} \cdot \tau(t-t') \cdot m(t-t') \, dt'$$

Quantification of ASL.
Perfusion and permeability

- Later arrival
- More relaxation of label

PASL

Input function for PASL

- Early arrival
- Little relaxation of label
- Later arrival
- More relaxation of label

Transit delay

Bolus width

Quantification of ASL

Input function in PASL

For PASL a large part of the vasculature is labeled. The amount of labeled spins is dependent on the volume of the arteries in the labeling plane (e.g. curved vessels, collateral pathways, etc).

Will be different for different vessels (especially anterior vs posterior)

Bolus width (τ)

- Determined by width of labeling slab
- Or by extent of RF-coil
- Or is set by QUIPSS-time (temporal cut-off of the bolus)
- Can be measured by fitting multi-TI data

Trailing edge

**Choice of QUIPSS time (ms, TI = 2400 ms)**

![Image of brain scans with various QUIPSS times](image)

**Input function for PASL and CASL**

- **PASL**
- **(p)CASL**

![Image of input functions for PASL and CASL](image)

\[ c(t) = \begin{cases} 
0 & t < \Delta t \\
\Delta t < t < \Delta t + \tau \\
0 & t > \Delta t + \tau 
\end{cases} \]

\[ c(t) = \begin{cases} 
0 & t < \Delta t \\
\Delta t < t < \Delta t + \tau \\
0 & t > \Delta t + \tau 
\end{cases} \]
How to determine $\Delta t$?

Multi TI PASL

Average arterial transit map (284 subjects)

Courtesy: Petersen, Mouridsen, Golay. The QUASAR reproducibility study; NeuroImage Volume 49, Pages 104-113

Input function for PASL and CASL

$e(t) = \begin{cases} 
0 & t < \Delta t \\
\Delta t < t < \Delta t + \tau \\
0 & t > \Delta t + \tau 
\end{cases}$

Input function for PASL and CASL

$e(t) = \begin{cases} 
0 & t \leq \Delta t \\
\Delta t < t < \Delta t + \tau \\
0 & t \geq \Delta t + \tau 
\end{cases}$

$T_1, \text{blood}$

4.7 Tesla

3.0 Tesla


Lu et al., Magn Reson Med. 2004, p 679-82

Frequently, the value is taken from literature experiments in bovine blood

4.7 Tesla
A method for rapid in vivo measurement of blood $T_1$

Marta Varela*, Joseph V. Hajnal**, Esben T. Petersen*, Xavier Golye*, Nazakat Meekchant* and David J. Larkman*

We present a technique to measure the longitudinal relaxation time constant of various brain $T_1$-value sites in a few seconds. The 1H magnet is an axial 1.5 Tesla whole-body scanner and is positioned by a patient. The $T_1$-relaxation time constant of blood is measured by exciting a single slice in the head region, with a small water-free region being confirmed from three overlapping slices, and the blood-$T_1$ measured on a single inversion recovery echo planar imaging (EPI) sequence. The image was acquired in a single slice with the measured method, allowing the calculation of the blood-$T_1$ and the hematocrit was established in 12 volunteers. Copyright © 2014.}

Quantification of $T_1$, blood


**Quantification of $T_1$**

$T_1$, blood measurements

Zhang, Petersen, Olbing, De Vos, Wells, Timmers, Hendrikse, van Osch, Mega Brain Map 2012
Quantification models II: Buxton

\[ \Delta M = 2aM_{0\text{blood}} \int_0^t \frac{c(t')}{\lambda} \left[ \frac{1}{1 + e^{-\frac{t-t'}{T_1}}} - m(t-t') \right] dt' \]

Assumption of well-mixed compartment

Relaxation function

\[ r(t) = \exp\left(-\frac{t}{\lambda}\right) \]

Which T1? T1 of blood or of tissue?

Where is my label? Does it exchange immediately?

Exchange of label?

Monitor T2 changes as a function of delay time

Determination of Spin Compartment in Arterial Spin Labeling MRI

Polying Liu, Beom Oh, and Hanhong Lin
Two compartment model

Improved Accuracy of Human Cerebral Blood Perfusion Measurements Using Art for Capillary Water Pro

Conclusion: $T_{1,bl}$ is best candidate, especially since moment of exchange is often unknown.

Quantification of ASL

Quantification models II: Buxton

$\Delta M = 2 \alpha M_0 \text{blood} \left( e(t) - e(t - t') \right) dt'$

$\alpha \approx 1$ PASL

$\alpha \approx 0.65$ CASL

$\alpha \approx 0.82$ pCASL

Quantification of ASL

Buxton model: putting everything together

Quantification of ASL
Buxton model results

Influence of width of input function

Buxton fit to multi-TI data
Post-processing of (multi-TI) PASL

- QUASAR: deconvolution with input function
- Voxel-wise or ROI-wise fitting of Buxton model
- Fixation of parameters (especially, \(\tau\) by means of QUIPSS)
- See Esben’s presentation of tomorrow


What is recommended?

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

Writing Group (in alphabetical order):
- David Arleo
- John Derie
- Xavier Galay
- Matthias Gautier
- Jeroen Hendriks
- Luis Hernandez Garcia
- Hanzhang Lu
- Nest MacIntosh
- Laura Partners
- Masion Smits
- Matthias van Osch
- Dennis Li Wang
- Eric Wong
- Greg Zelleschuk

White paper recommendation

Quantification of CBF

One of the most attractive features of ASL is its ability to quantify perfusion, an important indicator of tissue health as well as neuronal activity. For quantification of CBF from single PTLI/ASL data a relatively basic model is proposed. The major assumptions of this model are:

1. The entire labeled bolus is delivered to the target tissue. This is the case when PTLI=ATT for PCASL, or (T1-TH)- ATT for QUIPSS II PASL.
2. Labeled blood water is well mixed with tissue before outflow occurs. Because the tissue water pool is much larger than the blood water pool, and water exchange between blood and tissue is rapid, this is generally a valid assumption.
3. The relaxation of the labeled spins is governed by blood T1. While this assumption is not likely to be strictly true, the errors introduced by this assumption, which are related to the differences in T1 between blood and tissue, are typically relatively small.
**White paper recommendation**

Under these assumptions CBF in each voxel can be calculated for PCASL using (41):

\[
CBF = \frac{6000 \cdot \lambda \cdot (S_{control} - S_{labes}) \cdot e^{-\frac{T_{PD} \cdot T_{blood}}{2}}} {PLD \cdot 2 \cdot \alpha \cdot T_{blood} \cdot T_{PD} \cdot (1 - e^{-\frac{T_{labes}}{T_{blood}}})} \quad [\text{ml}/100 \text{ g/min}]
\]

where \( \lambda \) is the blood/blood partition coefficient in ml/g. \( S_{control} \) and \( S_{labes} \) are the time-averaged signal intensities in the control and labes images respectively. \( T_{labes} \) is the label duration, \( T_{PD} \) and \( T_{blood} \) are as defined above. The factor of 6000 converts the units from ml/g/min, which is customary in the physiological literature. See Table 3 for a summary of parameters for use in CBF quantification. Since Ti PASL without the QUIPSS II modification cannot be reliably converted into CBF.

---

**Table 3 of white paper**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \lambda ) (blood-brain partition coefficient)</td>
<td>0.9 ml/g (1)</td>
</tr>
<tr>
<td>( T_{1, \text{blood}} ) at 3.0 Tesla</td>
<td>1650 ms (2)</td>
</tr>
<tr>
<td>( T_{1, \text{blood}} ) at 1.5 Tesla</td>
<td>1350 ms (3)</td>
</tr>
<tr>
<td>( \alpha ) (labeling efficiency) for PCASL</td>
<td>0.85 (4)</td>
</tr>
<tr>
<td>( \alpha ) (labeling efficiency) for PASL</td>
<td>0.98 (5)</td>
</tr>
</tbody>
</table>

Recommendation

CBF = \( \frac{6000 \times (\text{control} - \text{sham}) \times e^{r_{t_{\text{blood}}}}}{T_{1 \text{blood}} (1 - e^{r_{t_{\text{blood}}}})} \) [ml/100 g/min]

Conversion to ml/100ml/min \( \Delta M \) (ASL-signal)

ASL is based on inversion

Labeling efficiency \( M_0 \): proton density scan corrected for difference in proton content between water and tissue

Quantification of ASL

Amount of label

\[ \int_0^T e^{-\frac{t}{T_{1 \text{blood}}}} dt = -T_{1 \text{blood}} \left[ e^{-\frac{T}{T_{1 \text{blood}}}} \right]_0 = -T_{1 \text{blood}} \left( 1 - e^{-\frac{T}{T_{1 \text{blood}}}} \right) \]

\( T_1 \)-decay during delay time

Recommended labeling

PLD

Imaging

Quantification of ASL
Quantification too difficult? Use PC-MRI!

Measure blood flow in the internal carotid arteries and calibrate perfusion maps based on a tissue segmentation of a 3D-T1 scan.


Is this all about quantification?

No!! Think about:

• Dispersion of the bolus of labeled spins
• Dependency on cardiac cycle
• Motion artifacts
• Scanner problems (spikes, drift, instabilities)
• Intersubject differences
• Etc, etc, etc

• More research needed!

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