UCSF ASL Perfusion Processing Methods

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November 6, 2012

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Overview

The Center for Imaging of Neurodegenerative Diseases (CIND) processing pipeline for Arterial Spin Label (ASL) imaging, prepares perfusion-weighted images (PWI) and computes a quantitative map of cerebral blood flow (CBF) and a regional analysis. The quantification of CBF and correspondence to high-resolution anatomical MRI data, is achieved by implementing multiple tools from the public domain such as, SPM8 [1], EPI nonlinear geometric distortion correction [2], various FSL tools [3], FreeSurfer [4], Insight Toolkit (ITK) [5] and in house MATLAB scripts.

In brief, the pipeline performs 1) motion correction of the individual ASL frames, 2) computation of the PWI by subtracting the mean of tagged from untagged ASL data sets, 3) alignment of ASL and structural MRI data, 4) geometric distortion correction, 5) partial volume correction, 6) and CBF quantification in physical units by normalizing ASL to an estimated blood water density signal.

The outputs include the PWI and a CBF image, both corrected for EPI distortion in two representations: a) in native perfusion MRI space and b) in the subject-specific space of the corresponding structural MRI data. Each output offers users a variety of options for further processing and analysis of the data, such as subject-specific analysis using anatomical regions of interest or group-specific analysis, such as parametric mapping.In addition, summary measures of CBF within anatomically defined brain regions are provided separately.

Brief Description of ASL

The concept of ASL provides a means of measuring cerebral blood flow (CBF) completely noninvasive by exploiting the endogenous spins of arterial water as a proxy for blood flow. Labeling (or tagging) is achieved by selectively inverting the magnetization of the arterial spins using MRI principles. After a short delay, allowing the arterial spins to reach the brain, conventional MRI methods are used to map the spatial distribution of the ASL signal. The signal to noise ratio of ASL signal is inherently low due to intense background signal from tissue water. Therefore, the ADNI-2 ASL acquisition protocol requires a set of 52 pairs of repeated tagged and untagged image frames which are then averaged to increase the SNR.

Many variants of ASL have been developed over the years, such as continuous, pulsed, and velocity selective labeling. Here, we describe a pipeline to process a version of pulsed ASL method referred to as "QUIPSS II with thin-slice TI1 periodic saturation" or "Q2TIPS" [6], augmented by conventional echo-planar imaging (EPI), which has been used in ADNI-2. In Q2TIPS, arterial spins are labeled within a thick ($\approx 10\ cm$) inversion slab, placed proximal to the imaging slices, as shown in the figure below. The critical timing parameters of Q2TIPS for quantifying flow are the ASL bolus duration and the transit delay from the time of inversion to the time of EPI mapping.
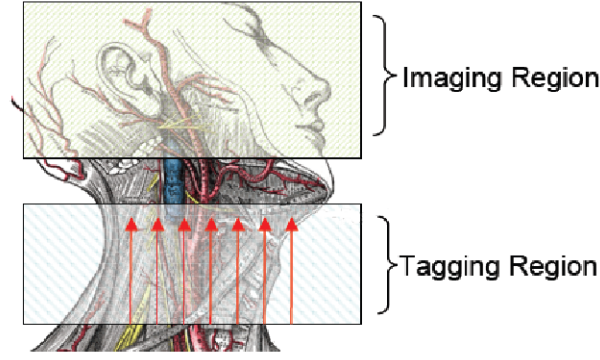
Diagram of ASL regions
http://www.birncommunity.org/wp-content/uploads/2009/08/4077_Rasmussen.pdf

ASL-MRI Pre-Processing Steps

1. Motion Correction: The ASL image series is converted from DICOM to NiFTI format. Each frame is aligned to the first frame to correct for head motion, by a rigid body transformation and least squares fitting, using SPM8.

2. PWI Computations: The ASL images are arranged in groups of tagged and untagged scans and the mean of each group is computed and saved as an image. Then the difference of the mean-tagged and mean-untagged images ($mean_{tagged} - mean_{untagged}$) is taken to obtain a PWI. In addition, the very first untagged ASL image, which provides a fully relaxed MRI signal, is used as a reference of water density and termed M_0. The reference image is primarily used to calibrate the ASL signal for computations of the CBF and also as an intermediate frame to estimate the transformation to co-register between images from the ASL MRI and structural MRI. In this capacity, the M_0 is used as the blood-water-density proxy, M_{blood}, see below.

3. Intensity Scaling: The PWI image as well as the M_0 image, are intensity scaled. The PWI is scaled to account for signal decay during acquisition and also to provide intensities in meaningful physical units. The M_0 is scaled to become M_{blood}, that is, water to blood density.

Description of PWI Scaling: PWI intensities are corrected for the longitudinal relaxation of the spin tracers during data acquisition, including time lags between consecutive image slices, as well as for incomplete labeling. Assuming an ascending slice order at acquisition with $n = 1$ indicating the first slice, the intensity correction for the nth slice is:

$$PWI_{lag-corr} = \frac{PWI_{raw}}{2\alpha TI_1} \; e^{[R_{1a}(TI_2+(n-1)\;\tau)]}, \tag{1}$$

where α is the tagging efficiency, R_{1a} is the longitudinal relaxation rate of blood, TI_1 is the inversion time of arterial spins and TI_2, is the total transit time of the spins, n is the nth slice, and τ is the time lag between slices.Specific intensity correction parameters used in our implementation are reported in Table 1. R1a is a

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biological parameter whereas TI1, TI2, and τ are specific to ADNI-2 acquisition protocol. The resultant image in the native ASL image space is provided in units of blood flow.

Intensity Scaling of M_0: The control (M_0) image is scaled to estimate a map of the blood magnetization, M_{blood} by correcting for the lower density of tissue water relative to arterial blood water, λ , and for the different relaxation characteristics of tissue and arterial blood water,as follows:

$$M_{blood} = \frac{M_0}{\lambda} e^{(R^*_{2tissue} - R^*_{2blood})TE} \ , \tag{2}$$

where λ is the blood/water ratio in tissue, R^* are the two relaxation rates and TE is the blood relaxation time. See table 1 for the parameter values.

Table 1

$Parameter$	Values
α	0.95
λ	0.90
τ	22.5 ms
TE	12 ms or 13 ms protocol specific
$TI1$	700 (ms)
$TI2$	1900 (ms)
$R1a$	1/1684 (kHz) [8]
$R*_{2tissue}$	1/44 ms [9]
$R*_{2blood}$	1/43 ms [10]

Computing A CBF in ASL Space: A CBF map in the ASL space, can be formed with the M_{blood} and the $PWI_{lag-corr}$, using,

$$CBF_{ASL} = \frac{PWI_{lag-corr}}{M_{blood}} \ . \tag{3}$$

Structural-to-ASL coregistration and nonlinear geometric distortion correction

EPI-based perfusion images suffer from nonlinear geometric distortion due to magnetic susceptibility variations whereas structural MR images are less susceptible to geometric distortions. This is a key challenge in achieving an accurate anatomical match between data from ASL-MRI and structural MRIs. We use a variational image-based approach to correct for these EPI-induced nonlinear geometric distortions in ASL-MRIs.

The geometric distortion correction step is performed in the PWI native space. Instead of using the $T2^*$ image, we use a simulated T2 weighted image, made from the $T1$ in the acquisition series. The T2 simulation process is briefly described in the appendix.

The processing steps for nonlinear geometric distortion correction areas follows:

- $SimT2$ image is masked leaving a layer of sulcal CSF around the brain.

- M_{blood} is skull stripped with BET [7] and coregistered to the masked T2 using the normalized mutual information metric with 9 degrees of freedom.

- Masked $SimT2$ is down sampled to the M_{blood} space and named, $T2_{rPWI}$.

- Distortion correction performed on the M_{blood} using the $T2_{rPWI}$ and the correction field applied to the PWI.

Partial Volume Correction

We are interested in the blood flow of gray matter tissue (GM), which is bounded by cerebrospinal fluid (CSF) and white matter (WM) tissues. To correct for variations in both $PWI_{lag-corr}$ and M_{blood} due to variable coverage of GM, WM and CSF at each voxel, both images are corrected for the tissue partial volume effects before computation of a CBF map.

Both $PWI_{lag-corr}$ and M_{blood} maps are first upsampled to the T1-weighted MR image space using trilinear interpolation and inverse affine transformation estimated to coregister simulated T2 to masked M_{blood}.

The $PWI_{lag-corr}$ intensities are adjusted voxel wise, according to GM and WM tissue density distributions estimated using 4 tissue segmentation provided by SPM8, and assuming a constant ratio between GM and WM matter perfusion. The intensities are corrected according to,

$$PWI_{gm} = (PWI_{rT1}) \left[\frac{GM}{GM + 0.4WM} \cdot \right] \tag{4}$$

Here, PWI_{rT1} is the $PWI_{lag-corr}$ resliced to T1 image space. βGM and βWM are the volume fractions of gray matter and white matter respectively.

In this partial volume model of PWI_{rT1}, we assume that signal at each voxel is a weighted linear combination of perfusion from GM and WM, with the weighting coefficients expressing perfusion in terms of the corresponding tissue densities (i.e., β_i for $i = GM_i$, WM_i) and the ratio of GM to WM perfusion is spatially constant at 2.5 value (Kanetaka et al., 2004) [11].

A similar PVC is performed for the M_{blood}. In contrast to PWI, however, partial volume correction for the tissue water reference image needs to include CSF. Partial volume correction of the M_{blood} is computed according to,

$$M_{blood-PVC} = (M_{rT1-blood}) \left[\gamma GM \left(\gamma^{-1}GM + \gamma_1^{-1}WM + \gamma_2^{-1}CSF \right) \right] + \kappa \ . \tag{5}$$

The ratios of tissues to water are,

$$\gamma = \frac{GM}{H_2O} = 0.78 \ , \ \gamma_1 = \frac{WM}{H_2O} = 0.65 \ , \ \gamma_2 = \frac{CSF}{H_2O} = 0.97 \ ,$$

and

$$\kappa = \frac{1 - \sum (GM + WM + CSF)}{1 \times 10^{100}} \ .$$

The κ parameter is used to regularize the CBF computation (see next section),in the limits where the voxels are entirely made up of gray matter in the CBF (numerator) image, or CSF.

Computation of CBF in T1 Space

The PWI_{PVC}, is normalized by the $M_{blood-PVC}$ to express the ASL signal in physical units of arterial water density $\left(\frac{ml}{100g\ 60s}\right)$, yielding CBF according to

$$CBF = \frac{PWI_{PVC}}{M_{blood-PVC}}\ .\tag{6}$$

The M_{blood} in the denominator, is spatially smoothed using a 3D isotropic Gaussian smoothing kernel, whose FWHM is the largest voxel dimension in millimeters, of the native ASL MR image. The normalization also eliminates spatial B1-inhomogeneity by definition, since both maps are subject to the same B1-inhomogeneity distribution.

The CBF image is also threshold-ed for high intensity outliers by finding the intensity, C, that corresponds to 1% of mean CBF signal. The global mean CBF is computed as the center of a the mode in a histogram of the normalized output. CBF intensities are then truncated such that intensities greater than are set to $C + \epsilon_r$, where ϵ_r is a random number between zero and one.

The CBF data type is initially double precision floating point numbers. The final output CBF is saved with a data type of INT32. To preserve the data through this change of data type, the values are scaled up by 1×10^4. Therefore, all values read from a viewer must be divided by 1×10^4 to obtain CBF in units of $ml/100mg/min$.

$$CBF = \frac{voxel\ intensity}{1 \times 10^4}\tag{7}$$

Free Surfer ROI Statistics

In addition to the CBF image, ROI statistics from anatomical regions of interest are also computed, from the CBF image in T1 space. FreeSurfer is used to segment sub-cortical structures and parcellate the cortical surface into regions of interest (ROI). Because the ASL-MRI acquisition might have partial brain coverage (e.g., possible temporal and occipital cut-offs), FreeSurfer ROIs are truncated with a non-zero CBF brain mask. An Insight-Toolkit (ITK) based in house C++ program is then employed to compute the quantities listed below. The output is a space delimited text file named 'ROIperfusion.log' and contains only regions with a non-zero count of voxels in the ROI.

- number of voxels in the ROI
- minimum
- maximum
- mean
- median
- standard deviation

CBF Output Quality Control (QC) Criteria and Steps

1. Image Quality QC

   (a) Raw Data QC: Pass/Fail

      i. This is the only level where we are making a judgment based on the image quality.

   ii. All data is run regardless of QC

2. Processing QC: Registration check to determine the success of the processing pypeline

   (a) Registration QC: The output image check and the only category that determines exclusion from uploads.

      i. This QC is performed by overlaying the Final_Mblood file ("SubjectCode_Mblood-EpiCorr-rT1-PVC-Smoothed.nii") onto the raw T1 ("SubjectCode _T1.nii").

      ii. Pass: Mblood overlays completely onto T1. Verified by checking brain edges and, if possible, Vents.

      iii. Follow-up: Anything strange; brain edges not aligned, Ventricles off, or perhaps a 3D lateral shift

      iv. Note: We are not doing a QC on the quality of the MBlood image. So any signal loss in the extremities like inferior temps or medialorbitofrontal does not affect the rating. We are checking for a successful registration only.

   (b) There is no rating of Fail in the processing QCs because at the moment we are attempting to resolve all issues that require follow-up.

Mblood-EpiCorr-rT1-PVC-Smoothed.nii
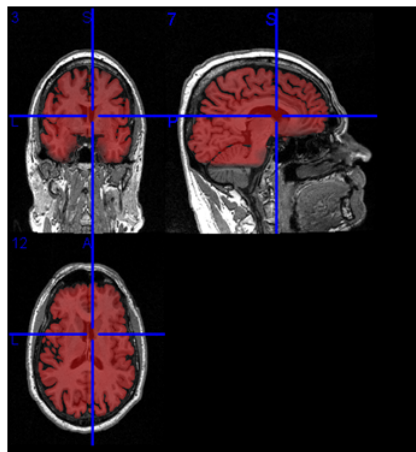
QC Registration *Pass*   QC Registration *Follow Up*
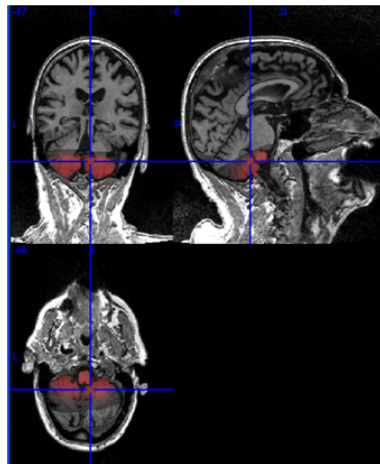
Limitations

1. *DEFORMATION FIELD*: The method of variational matching for the distortion correction in ASL does not account for intensity variations due to pixel aliasing. Thus, ASL values from regions with prominent susceptibility distortions should be interpreted with caution.

2. *INTENSITY SCALING*: The current implementation of intensity scaling of PWI and M_0 maps does not account for regional and subject-specific variations in the signal relaxation rates. Moreover, the scaling of PWI does not account for regional and subject-specific variations in transit delays of the ASL bolus. Therefore, a bias in scaling is introduced to the extent that signal relaxation rates and transit delays vary across regions and subjects.

3. *PARTIAL VOLUME CORRECTION*: The current implementation of partial volume correction does not account for regional variations in the ratio of gray matter to white matter perfusion nor is the ratio value driven by the data. Therefore, a bias in gray matter perfusion is introduced to the extent that the ratio varies across regions and subjects.

OUTPUT SUMMARY

EPI Corrected ASL Space

Theoretical Name		*Filename*
$PWI_{scaled-epi-corr}$	....	`ScaledPWI-aACPC-EpiCorr.nii`
$M_{blood-EpiCorr}$	....	`Mblood-EpiCorr.nii`

T1 Space

$PWI_{scaled-EpiCorr-rT1}$	....	`ScaledPWI-aACPC-EpiCorr-rT1.nii`
$M_{blood-EpiCorr-rT1}$	....	`Mblood-EpiCorr-rT1.nii`
GM segmentation image	....	`T1-GmMask.nii`
WM segmentation image	....	`T1-WmMask.nii`
CSF segmentation image	....	`T1-CsfMask.nii`
$PWI_{scaled-EpiCorr-rT1-pvc}$	....	`ScaledPWI-aACPC-EpiCorr-rT1-PVC.nii`
$M_{blood-EpiCorr-rT1-pvc}$	....	`Mblood-EpiCorr-rT1-PVC.nii`
CBF	....	`ScaledPWI-aACPC-EpiCorr-rT1-PVC-Norm.nii`

FreeSurfer ROI Statistics

First order statistics per ROI	....	`ROIperfusion.log`

Processing Steps Flow Diagram

Mean of Tagged ASL
(not an output)

Mean of Untagged ASL
(not an output)

M0, tissue water proxy
(not an output)

(1.3)

Mblood
(not an output)

(1.1,2)

Raw PWI
(not an output)

Inputs to EPI Dist. Corr.

T2 down sampled to
ASL space and masked.

M blood skull stripped
and sent to EPI distortion
correction

blood after skull stripping and EPI distortion correction

ScaledPWI.nii

Time lag and
flow unit scaled
PWI

(1.3)

(2)

EPI
Correction
Output

Mblood_EpiCorr.nii

(not an output)

(not an output)

ScaledPWI_EpiCorr.nii

EPI
Correction
Output

Mblood Coregistered
and resliced to T1

(3)

Mblood_EpiCorr-rT1.nii

PWI EPI
distortion
corrected

PWI EpiCorr resliced to T1 space

PWI EPI Corr iin T1 space

Mblood in T1 space after PVC

M blood in T1 after smoothing
with Gaussian kernel.

(3)

(3)

(4)

(4, equation 5)

The final CBF image is the quotient of
the PWIScaled-EpiCorr-rT1-PVC.nii and
the Mblood-EpiCorr-rT1-PVC-Smoothed.nii

PWIScaled-EpiCorr-rT1-PVC-Norm.nii

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Appendix: Simulated T2-weighted MRI

A framework to simulate subject-specific T2-weighted MR images was engineered by Dr Duygu Tosun-Turgut. The framework is based on the work by Benoit-Cattin et al.[12] To mimic clinical neuroimaging practice, we chose the following 2D Turbo Spin Echo (TSE) sequence parameters for simulated T2-MRI.

Parameter	Value
TR	$3210 \ ms$
TE	$101 \ ms$
slice thickness	$3 \ mm$
resolution	$1 \times 1 \ mm$
flip angle	$150°$
bandwidth	185 Hz
GRAPPA	2

T2-MRI simulation steps are as follows:

In brief, the steps to make a simulated T2 are:

- Create a binary brain tissue mask from FreeSurfer 'aparc+aseg' anatomical annotation.

- Apply a morphological closing operator followed by a morphological dilation to eliminate holes in brain mask and to include sulcal CSF.

- Apply resulting brain mask to T1-MRI, yielding skull-stripped T1 image.

- Downsample skull-stripped T1 image to $1 \times 1 \times 3 \ mm^3$ image resolution to mimic clinical neuro imaging practice.

- Apply a fuzzy c-means clustering algorithm to estimate GM,WM, and CSF tissue density at each image voxel in downsampled skull-stripped T1 image space

- Based on selected acquisition parameters and tissue density estimates, simulate a T2-MRI.

Each 2D axial slice is simulated separately and finally merged back to form a simulated 3D T2-MRI.

Data Set Information

UCSF ASL FS   Uploaded on November 1st, 2012

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