# A novel efficient denoising method for ASL data: Assessment using voxel-wise network analysis

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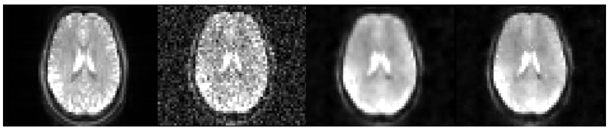
**Introduction:** The properties of small-world networks have been shown by Watts and Strogatz to have topologies intermediate between regular and random [1]; these models of complex networks with small-world properties show enhanced signal-propagation speed, computational power, and synchronizability. It has become commonly accepted that the human brain is a biological small-world network. The complex-network theory can provide measures as diagnostic markers to quantify differences between control and patient groups, such as Alzeimer's disease, schizophrenia, epilepsy and stroke. Although BOLD fMRI is the most common method for mapping functional connectivity, arterial spin labeling (ASL) is a technique to measure cerebral blood flow (CBF) [2], and thus can be used as an fMRI method that provides a more direct quantitative correlate of neural activity in comparison to BOLD. However, given its intrinsic low SNR, the reliability of detecting networks, and thus that of measuring network metrics, is compromised. Therefore, denoising methods for ASL data [3,4] could play an important role. Since non-local means (NLM) denoising methods have been shown to be more efficient than its peers in removing noise while retaining true details [5], we aim to develop a more efficient method for denoising ASL data for functional connectivity analysis based on NLM. Given that the filtering parameters are not optimal across all frequency bands, a multi-resolution framework, combining NLM with discrete wavelet transform (DWT), has been proposed to adaptively denoise images [6]. However, compared to complex wavelet transform (CWT), DWT has the following disadvantages: oscillations, shift variance, aliasing and lack of directionality [7, 8]. To enhance the reliability of measuring network metrics using ASL, we propose a method of combining NLM and dual-tree CWT (DT-CWT) to remove noise and preserve the true ASL signal more efficiently.

**Methods:** With the NLM filter, the denoised intensity $D(I)(x_i)$ of voxel $x_i$ is a weighted-average of voxels intensities $I(x_i)$ within the search volume $Vi$ of size $(2M+1)^3$ : $D(I)(x_i)= \Sigma w(x_i,x_j)I(x_j)$, where $w(x_i,x_j)$ is the weighted-value, defined as: $w(x_i,x_j)=\exp(-\|I(N_i)-I(N_j)\|_2^2/h^2)/Z_i$, where $Z_i$ is a normalization constant and $h$ is a smoothing parameter [5]. For block-wise (BW) NLM, the parameter $\alpha$ determines the block-size and, therefore, the degree to which the image is denoised and smoothed. In this study, two $\alpha$ values ($\alpha$=3 and 5) were used to produce images with image feature preserved (*I1*) and noise components removed (*I2*), respectively. Based on the observation that, in the frequency domain, low frequency information represents the main contrast and features of the image, and the high frequencies represent finer details and noise, the proposed method was implemented as follows: (1) Producing images *I1* and *I2* using BW-NLM; (2) Applying DT-CWT to *I1* and *I2* to decompose the images; (3) Mixing the frequency sub-bands of *I1* and the frequency sub-bands of *I2* using Bayes shrinkage algorithm, but retaining the lowest frequency sub-band of *I1*; (4) Applying inverse DT-CWT. To demonstrate the superiority of the proposed method over the BW-NLM combined with DWT, and to determine optimal parameter *M*, simulations were conducted as follows. ***Simulation***: Simulated data were generated based on one acquired ASL calibration image ($M_0$), due to its high SNR, with 8 different levels of (Rician) noise added. In addition, 4 different values of *M* (=2,3,4,5) were compared to determine the optimal value: peak signal-to-noise ratio (PSNR=20log$_{10}$(MAXi/RMSE), where MAXi is the maximum possible voxel value and RMSE is the root mean square error estimated between the true and the denoised images), was employed to evaluate the denoising results; the *M* with highest PSNR was chosen for analyzing in vivo data. ***In vivo data:*** 2 healthy subjects were scanned on a 3T Siemens Trio scanner with a whole-brain 3D-GRASE pCASL sequence [9] with the following parameters: TR/TE =3750/56ms, resolution=4x4x6mm$^3$, 20 slices, matrix size =64x51, post-labeling delay (PLD)=600ms, with labeling duration = 1284ms. Background suppression (BS) was achieved using inversion-times of 1913ms and 523ms, 60 pairs of ASL images. In addition, anatomical and calibration images were acquired for registration. ***Image Analysis:*** The proposed denoising method was applied to ASL perfusion images, followed by de-trending and band-pass filtering. To remove intravascular contributions, independent component analysis was performed using FSL MELODIC software. The pre-processed ASL perfusion images (masked by a gray matter mask) were employed as inputs to obtain a voxel-wise connectivity matrix with a threshold of *R*=0.6 (Pearson correlation coefficient); the degree of each voxel (the sum of the correlation coefficients of all connections to the voxel) was then calculated. The degree distribution was then fitted by using an exponentially truncated power law model ($c*x^{-a}e^{-x/b}$) [10]. Voxels with degrees larger than a threshold (mean+std across the gray matter) were considered as hub voxels [11]. All procedures were also applied to ASL data without denoising and data denoised with DWT, for comparison. Note that all these analyses were conducted at individual-level.



(a) Original (b) Noisy (c) DWT (d) DT-CWT

Fig. 1 Simulation: (a) gold standard; (b) 5% of Rician noises were added; (c) DWT; (d) DT-CWT.

(a) Noisy (b) DT-CWT

Fig. 2 In vivo (a) before and (b) after denoising with the proposed method.

**Results:** The simulation results consistently show that *M*=3 yields the highest PSNR (data not shown); this value is therefore used for the in vivo data. Table 1 shows that the proposed method yields better PSNR compared to DWT method (see also examples in Fig. 1; *note also reduced blurring in 1(d) vs. that in 1(c)*). Fig. 2 shows that the proposed method greatly improves the ASL image quality by denoising. Fig. 3 shows a consistent broader degree distribution after denoising with DT-CWT than that without denoising (left) and that with DWT (right). Fig. 4 shows hub voxels (*R*=0.6) extracted without denoising (left) and with DWT (middle) and DT-CWT (right). These results show increased sensitivity to detect connectivity and hub voxels by using the proposed method; this suggests that the loss of hubs caused by noise can be compensated by applying the proposed denoising method. The $R^2$ of degree distribution fitting without denoising, with DWT, and with DT-CWT are as follows: subject 1: 0.9562, 0.9747 and 0.9824; subject 2: 0.9844, 0.994 and 0.995; these results demonstrate that the data, after denoising with the proposed method, can be better characterized by the exponentially truncated power law model than the original data.

Table 1 Simulations with 8 different levels of Rician noises.

| Rician noise level | DWT (PSNR) | DT-CWT (PSNR) |
|---|---|---|
| 0.125% (SNR=41) | 41.67 db | 42.73 db |
| 0.25% (SNR=40) | 36.04 db | 36.40 db |
| 0.5% (SNR=35) | 34.17 db | 34.41 db |
| 1% (SNR=22) | 31.85 db | 31.97 db |
| 2% (SNR=12) | 27.59 db | 27.62 db |
| 3% (SNR=8) | 24.40 db | 24.45 db |
| 4% (SNR=6) | 21.92 db | 21.98 db |
| 5% (SNR=5) | 19.98 db | 20.04 db |

**Discussion:** The SNR of fMRI images is critical for functional connectivity studies. Although ASL has some advantages over BOLD fMRI, the reliability for detecting networks may be compromised due to its intrinsic low SNR. In this study, we proposed a denoising method combining BW-NLM and DT-CWT to enhance the SNR of ASL images. Simulations show that the proposed method was superior to DWT. The validity of the proposed method has been further confirmed by the more robust detection of functional connectivity from in vivo data. Overall, the proposed method can enhance the SNR of ASL data significantly and thus enable more reliable network detection. We note that this is a general method, which should benefit other ASL applications, as well as a broad range of image analyses.

**References:** [1] Watts DJ et al., Nature 1998; 393: 440-2; [2] Detre JA et al., MRM 1992; 23: 37-45; [3] Bibic A et al., MAGMA 2010; 23(3): 125-37; [4] Wells JA et al., MRM 2010; 64: 715-24; [5] Buades A et al., CVPR 2005; 2: 60-5;; [6] Coupe P et al., Int J of Biomedical and Imaging 2008; [7] Kingsbury N, Phil. Trans. Royal Society London 1999; [8] Selesnick IW et al., IEEE signal processing magazine 2005; 22 (6): 123-151; [9] Liang X. et al., Int J of Imag and Syst Tech 2012; 22(1): 37-43. [10] Achard et al., The Journal of Neuroscience 2006; 26(1): 63-72; [11] van de Heuvel et al., The Journal of Neuroscience 2011; 31(44): 15775-86.

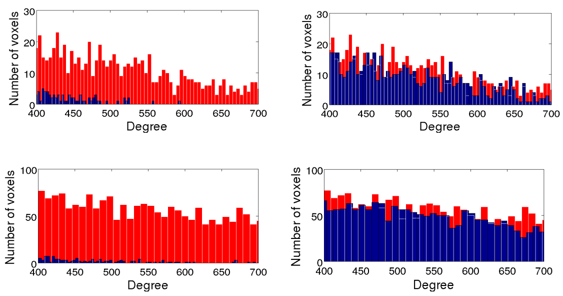



Fig.3 Degree distribution comparisons: left: DT-CWT (red) vs. without denoising (blue), right: DT-CWT (red) vs. DWT (blue) for subject 1 (top) and 2 (bottom). Note that only degrees within the range of 400-700 are plotted to show the disparity of the degree distributions.

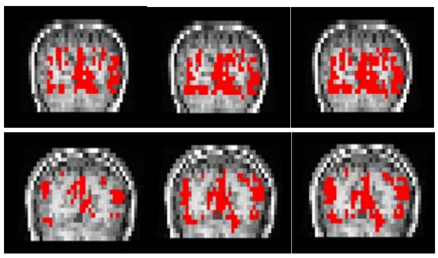


Fig.4 Hub-voxels extracted without denoising (left), denoised with DWT (middle) and DT-CWT (right) overlaid on anatomical image for subject 1 (top) and subject 2 (bottom). The proposed method provides the most sensitivity in connectivity detection (more extensive and coherent hub-voxels).