Assessing exchange between multiple compartments using multi-directional double wave diffusion sequences

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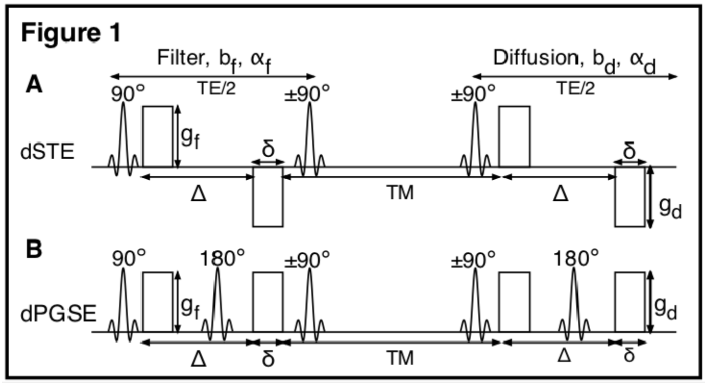
The Apparent Exchange Rate (AXR) has recently been suggested as a model free measure of water exchange between microstructural compartments using a double wave pulsed gradient spin echo (dPGSE) sequence [1][2]. The AXR value has been assumed to be independent upon measurement direction [3] but could potentially be affected by the local anisotropy of microscopic subspaces. In this study we evaluate the AXR measure in different directions in cortical gray matter (GM) of a fixed monkey brain. GM has a high cell density but is also characterized by anisotropic structures [4]. Furthermore we propose a novel pulse sequence for these experiments sharing some resemblance to a regular stimulated echo sequence, which utilizes a simpler design than the twice refocused dPGSE sequences used in previous studies. Our results demonstrate that AXR is indeed not a rotationally independent measure. This could be explained by variations in exchange rates between multiple sub compartments affected differently by measurement direction. We suggest that this rotationally dependent measure potentially could render more detailed information about water exchange in complex tissue.

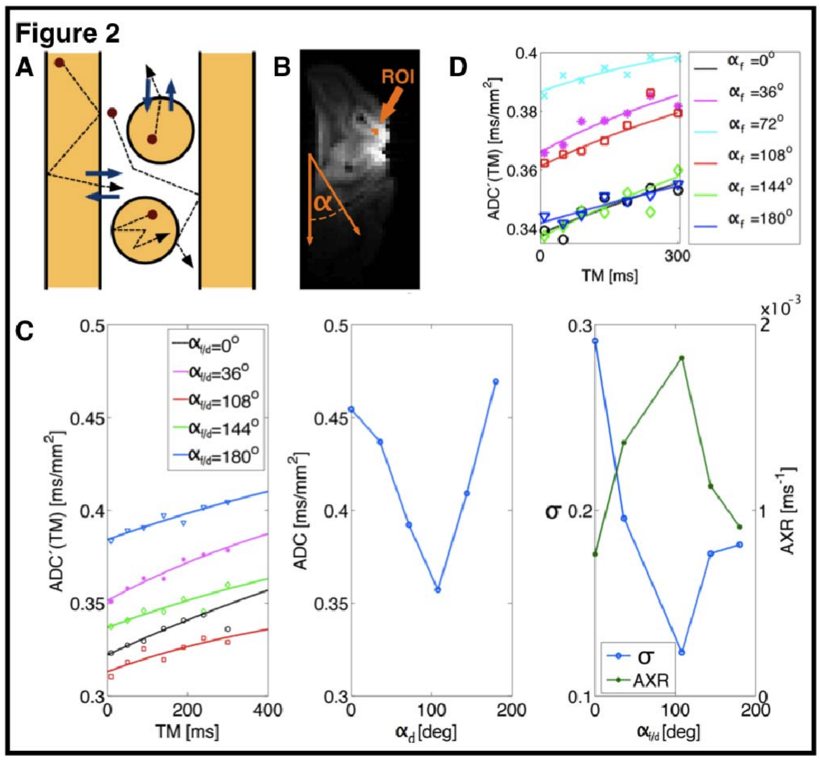


Method:

The novel double bipolar stimulated echo (dSTE) sequence used for data acquisition can be seen in figure 1A) along with the dPGSE sequence, figure 1B). The dPGSE sequence offers in theory the possibility to overcome the loss of half the signal seen in stimulated echo sequences but B_1-ihomogeneties prevent the echo stored between the 2nd and 3rd 90° RF pulses to be perfectly recreated. Hence we propose a simpler and more robust design where the two 180° RF pulses are omitted resulting in a simpler signal pathway and also slightly higher SNR. The filter gradients selectively attenuate the fast diffusion signal components whereas the diffusion gradients encode with regular diffusion sensitivity. b_f and b_d denote the diffusion weighting from the filter and diffusion pair of gradients respectively. To estimate the AXR b_f was kept fixed and b_d varied between two different values yielding a regular ADC with $b_f \approx 0$ and the mixing time(TM) at minimum(9ms) and ADC'(TM) with varying TM times. The AXR values can then be calculated as

$$S(b) = S(0) \cdot e^{-ADC \cdot b},\ S(b_d, TM) = S_f(0, TM) \cdot e^{-ADC'(TM) \cdot b_d},\ ADC'(TM) = ADC(1 - \sigma \cdot e^{-AXR \cdot TM}) \quad (1)$$

where σ is the filter efficiency expressing the selectivity of b_f, S and S_f are the signal intensity and filtered signal intensity respectively [1]. We hypothesize a simple multi-compartment system in GM, illustrated in figure 2A), consisting of spherical cell bodies and piecewise cylindrical axons and dendrites forming an anisotropic compartment. Multiple compartments are believed to be involved in exchange processes. Figure 2A) illustrates that anisotropic compartments are expected to be affected differently according to the measurement direction i.e. along or parallel to the main fiber direction. Furthermore equation (1) implicitly assumes that all compartments are in exchange since $lim_{TM \to \infty} ADC'(TM) = ADC$ which might not be true, for an example due to myelination. ***Animal:*** A perfusion fixed 32-month Vervet monkey brain was cut into smaller blocks. Here we used a block of tissue from the frontal region of the cortex. Procedures for handling experimental animals followed guidelines approved by relevant authorities. ***Imaging:*** The tissue block of monkey brain, prepared as in [4], was scanned in an experimental 4.7 T Varian Imaging System using a 19 mm diameter surface coil. For the dSTE sequence outlined in figure 1A) we used the following parameters: TE=38ms, TR=2500ms, 6 slices, voxel size of 0.75x0.75x1.5mm^3 and 6 repetitions that ensured SNR ~100. b_f was 1582s/mm^2 and b_d = 1316 s/mm^2, both using Δ = 10ms. In one experiment, both the filter- and diffusion blocks were rotated in the image plane with $\alpha_{f/d}$ = [0, 36, 72, 108, 144, 180] degrees. In a second experiment the orientation of the filter-block was rotated α_f = [0, 36, 72, 108, 144, 180] degrees whereas the diffusion-block was fixed α_d = 144 degree. For each rotational combination TM was varied in seven steps from 9 to 300 ms. ***Voxel-wise fitting*:** For each rotation, the data in the two experiments ADC(α) and ADC'(TM,α) were calculated from which AXR and σ were obtained by fitting with a Trust region dogleg algorithm implemented in MATLAB. Fits with R^2 <0.7 were discarded from the analysis. *ROI placement:* Voxels placed in the outer rim of cortical grey matter (GM) (top layers) were studied as shown in figure 2B).



Results and Discussion

The effect of keeping the filter and diffusion blocks in parallel but at different angle relative to the cortex is shown in figure 2C) The AXR values ranged from 0.75 to 1.51 s^{-1} and σ from 0.19 to 0.29 dependent on measurement direction α. Low ADC generally corresponds to high AXR and low filter efficiency σ. Regarding the σ value this seems reasonable since the filter should attenuate fast diffusing signal components. We propose that the composition and anisotropy of microscopic compartments with different exchange properties might explain the difference in AXR. We note that the ADC'(TM, α) for $\alpha_{f/d}$ = 0 degree deviates from the overall pattern and the $\alpha_{f/d}$ = 180 degree measurement. Since the ADC (α) value for α_d = 0 follows the overall pattern this will cause artificially high AXR values for this direction as seen in figure 2C).

The effect of keeping the diffusion block fixed but changing the filter block direction independently is shown in figure 2D). Clearly the rotation of the filter affects the ADC'(TM) values which could be due to changes in filter weighting of multiple water pools with different exchange properties. Although related to the AXR value another model is probably needed to incorporate the effects of independently rotating the filter and diffusion blocks.

Conclusion: This study demonstrates that the AXR value is not a rotationally independent measure and that different measurement directions could reveal more information about the underlying microstructure than a geometrically averaged value. Further studies are however needed to connect these findings with the exchange properties of the underlying sub-compartments.

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References: [1] Lasič et. al. 2011 MRM, [2] Åslund et. al. 2009 JMR, [3] Nilsson et. al 2010 ISMRM, [4] Dyrby 2011 HBM