Differential Diffusion Imaging (DDI): A novel scheme for resolving small axon diameters by a set of single PGSE experiments.

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Introduction: Q-space imaging relies on single pulse-field gradient spin echo (PGSE) to measure the microstructure of tissue. Water diffusion within axons and myelin (intracellular) can be used to estimate axonal diameter as in ActiveAx or other acquisitions techniques [1,2]. Histological studies from post-mortem human brains have indicated that the axonal diameters range from 0.16μm to 9μm [3]. Due to clinical scanner limitations in gradient strength, accurate estimation of the axon diameter in in-vivo human brain is a challenge [7]. One way to probe restricted diffusion (intracellular) is using frequency domain analysis of the velocity autocorrelation function (VACF) [4]. Under the Gaussian Phase Approximation (GPA), the measured signal attenuation is proportional to a filtered version of the diffusion spectrum $D(\omega)$ of the VACF. This is the basis of several oscillating gradient spin echo (OGSE) based methods, which enable extraction of high frequency or equivalently short time-scale dynamics of the diffusion process. However, several challenges still exist for clinical application of these techniques: For the OGSE-related methods, the diffusion weighting is relatively low (b=300 s/mm^2) due to limited gradient strength, and is confounded by blood perfusion effects. In this work, we present a novel imaging scheme called differential diffusion imaging (DDI), which allows extraction of high frequency (short time scale) information from a set of standard single PGSE acquisitions. Assuming GPA, we present our technique using the frequency domain analysis of [4].

Method: The dephasing spectrum for the PGSE sequence is given by: $|F(\omega)|^2 = \{(\gamma G/\omega^2)\sin(\omega\delta/2)\sin(\omega\Delta/2)\}^2$, where ω is the frequency in radians/s, Δ is the time between gradient pulses, and δ is the length of each gradient pulse. The signal attenuation is given by: $\beta(t) = \int |F(\omega,t)|^2 D(\omega)\, d\omega$, where $D(\omega)$ is the spectrum of the velocity autocorrelation function. As can be seen in Fig 1., a good portion of the attenuation comes from the frequency component at ω=0, i.e. $F(0)$ samples the long-time diffusivity $D(0)$. To perform differential diffusion imaging, at-least 2 standard PGSE acquisitions are required such that $\delta_1 << \delta_2$ and $\Delta_1 << \Delta_2$. Fig 1 shows $|F_1(\omega)|^2$ and $|F_2(\omega)|^2$ for two different set of parameters (δ_1, Δ_1) and (δ_2, Δ_2). Note that, since δ_1 and Δ_1 are small, $|F_1(\omega)|^2$ samples a wide range of frequencies (typically, up to $2\pi/\Delta_1$) albeit at low b-value, whereas for large Δ_2, $|F_2(\omega)|^2$ samples lower frequency components. Thus, from these standard acquisitions, one can obtain the higher frequency components present in one of the acquisitions ($F_1(\omega)$) by subtracting the contribution of lower frequencies from the second acquisition ($F_2(w)$) (See Fig 1). For a standard PGSE sequence, $|F(0)|^2$ can be obtained using L'hopitals rule giving $|F(0)|^2 = \{(3/2)q^2\Delta^2\}$, where $q = \gamma G\delta$, and G is the gradient strength. Setting $\alpha = |F_2(0)|^2/|F_1(0)|^2 = (q_2\Delta_2/\, q_1\Delta_1)^2$ as the scaling factor, we compute the differential signal attenuation as follows: $\beta_d = \alpha\beta_1 - \beta_2 = -\alpha\log(S_1) + \log(S_2)$, where S_1 and S_2 are the signals obtained from the two acquisitions (corresponding to $F_1(\omega)$ and $F_2(\omega)$ respectively). Thus, the contribution of zero and some low frequency components is removed from the **differential signal** $S_d = \exp(-\beta_d)$ and only higher frequency components are retained (see Fig 1).

Simulations: We performed PGSE simulations using the formulation given in [4] for restricted diffusion (S_r) in a cylinder. Due to membrane permeability, exchange effects were incorporated by adding a constant diffusivity of 0.0005 mm^2/s to $D(\omega)$ as a weighted combination [8]. The signal was generated according to $S = f_h S_h + (1-f_h)S_r$, where f_h is the hindered diffusion fraction and S_h and S_r are signals due to hindered and restricted compartments. Further, we assumed a linear dependence of the frequency on the signal attenuation in the hindered compartment, which is a valid assumption in low frequency regimes [5], i.e., $S_h(\omega) = \exp(-b(D_h + C_h\,\omega))$, where C_h is the slope set to 0.1μm^2 and D_h=0.5μm^2/ms [6]. We set: f_h= 0.2, G_1=100mT/m, (δ_1, Δ_1) = (8,13) ms, and G_2=25.82mT/m, (δ_2, Δ_2) = (45,50) ms, leading to b-values of b_1=480 s/mm^2 and b_2=3380s/mm^2 respectively. The first acquisition samples frequencies up to 60 Hz, whereas the second one samples frequencies up to 20 Hz (Fig 1). We simulated the signal [4] for various cylinder radii (1 to 15 μm) with gradient direction orthogonal to the cylinder axis and obtained the signal attenuation from standard acquisition (S_1, S_2, Fig 2, left) as well as using the proposed DDI method (S_d). The signal change in S_1 and S_2 for small cylindrical radii (up to 5μm) is very minimal, making the estimation less sensitive to the smaller axons. On the other hand, the proposed DDI based technique gives a sharp change in signal for small radii, with the signal being almost zero beyond a cylinder of radius 5μm (Fig 2). For the particular set of parameters described above, the effective b-value (computed as the area under the curve in Fig 1(right)) is 11382 s/mm^2. This is due to the appropriate scaling of the frequency response (by a factor of α) described earlier (Fig. 1-right). The proposed technique is not limited to the above parameter settings, and lower gradient strengths (G=80mT/m or lower) can also be used to obtain similar results albeit with different attenuation of the signal. Further, acquisition schemes such as the ones used in ActiveAx can also be used within the proposed framework. Future work entails monte-carlo simulations, analysis of the sensitivity in the presence of noise, consideration of the limited slew rate (for gradient rise time) and model fitting procedures to analyze the signal. **Conclusion:** We proposed a novel diffusion imaging scheme called Differential Diffusion Imaging (DDI), which uses a differential of two or more standard single PGSE sequences to boost the sensitivity to restricted diffusion by isolating high frequency components of D(w). The DDI scheme might potentially allow resolving smaller axon diameters compared to the standard single PGSE sequences.

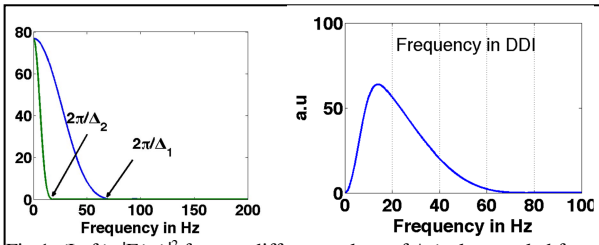

Fig 1. (Left): $|F(w)|^2$ for two different values of Δ (values scaled for comparative visualization), (Right): The effective frequency response $|F_d(w)|^2$ in DDI.

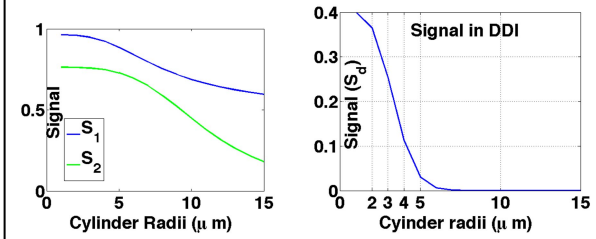

Fig 2. (Left): Signal decay with cylinder radii for PGSE parameters described before. (Right): The signal for the proposed DDI method. Note the sharp change in signal (slope) for very small cylinder radii.

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