Stimulated Echo Diffusion Tensor Imaging with Varying Diffusion Times as a Probe of Breast Tissue

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Introduction: Diffusion tensor imaging (DTI) is a powerful MRI technique sensitive to the extent and directionality of microscopic random water diffusion[1]. Conventional DTI protocols commonly use a pulsed-gradient spin-echo (PGSE) sequence that employs two diffusion sensitizing gradients spaced by the diffusion time to characterize the water diffusion process. Therefore, for tissues with a short T2 relaxation time, the range of feasible diffusion times is strictly limited to avoid the loss of transverse magnetization. Stimulated echo acquisition mode (STEAM) presents an advantage when longer diffusion times are needed[2], in particular for tissues where T1 is much longer than T2, as it is in the case of breast tissue[3]. In our study, we aim to characterize the length scales of healthy fibroglandular tissue (FGT) using a STEAM DTI acquisition with variable diffusion times.

Methods: Two healthy volunteers (age: 25,28) were imaged in a 3T Siemens Biograph scanner using a 4-channel breast coil. The protocol collected bilateral axial images using a prototype STEAM-DTI sequence with an echo-planar imaging (EPI) readout and SPAIR fat suppression (TR/TE: 11500/45 ms, matrix: 192x132x10, resolution: 2.1x2.1x5 mm, 6 directions, 3 averages, GRAPPA parallel imaging factor 2) with anterior-posterior (AP) phase encoding direction using two different b-values (0 and 500 s/mm^2). The acquisition was repeated using 6 different diffusion times (t_D: 68.5, 102.5, 172.5, 322.5, 622.5 and 902.5 ms) by varying the mixing time. The time for each acquisition at each diffusion time was 5 minutes. An additional b=0 s/mm^2 image with reversed phase encoding (PA) was collected for each diffusion time to correct for field inhomogeneity induced distortion. Images were corrected for eddy current induced distortion using an affine registration with normalized mutual information metric[4], and for inhomogeneous static field induced distortion as described in a previous study[5]. Both breasts were fully segmented in two slices per case and low signal intensity voxels were filtered out to maximize the signal to noise ratio (SNR) within the region of interest (ROI). Due to the high contribution to diffusion of the imaging gradients when using a STEAM sequence, a tensor fitting using the full b-matrix which accounted for all imaging and diffusion gradients was performed. Parametric maps of mean diffusivity (MD), fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD) were derived from the diffusion eigenvalues (λ_1, λ_2 and λ_3) with AD = λ_1 and RD = (λ_2+λ_3)/2. Surface-to-volume ratio (SVR) and consequently a structure diameter estimation based on the RD evolution with respect to the diffusion times were calculated using the Mitra early time limit model[6] $D(t) = D_0\left[1 - SVR\frac{4\sqrt{D_0 t}}{3\sqrt{\pi}}\right]$. To ensure quantitative accuracy, SNR was calculated for each diffusion time by evaluating the noise within the same ROIs prescribed for analysis using the difference images obtained from the three averages in a similar fashion as the one described for two averages in a previous study[7]. Finally, to validate our analysis, an isotropic gel phantom[8] was employed to confirm the diffusion time independence in an isotropic environment.

Results: AD, RD, MD and FA maps at the shorter and longest diffusion time for one healthy volunteer case is shown in Fig. 1. Fig. 2 presents the evolution of the AD and RD with the square root of the diffusion time together with a constant and linear regression fit respectively (as in the Mitra early time limit), for the same case shown in Fig. 1. SVRs found in healthy tissue using the RD median value of each ROI were 5.4 and 4.0 mm^{-1} for the first and second case respectively, translating to diameters of 0.37 and 0.50 mm. The mean SNR value for the b=0 s/mm^2 images through the different diffusion times for the first case was 17.1±3.8 with range [22.9;12.1], and 20.5±9.7, with range [35.3;11.8] for the second case. For both cases, the median values and interquartile ranges of each parameter at the shortest and longest diffusion time are reported in Table 1. For the isotropic phantom, the AD and RD mean and standard deviation through the diffusion time range were 2.00±0.05 and 1.80±0.03 µm^2/ms respectively.

Discussion: Our results demonstrate that for healthy FGT the axial diffusivity remains practically unchanged while there is a linear decrease of the radial diffusivity with the square root of the diffusion time (Fig. 2). This is consistent with the expected behavior of water diffusion confined in an anisotropic structure and could be potentially caused by the presence of lactiferous ducts. While water molecules do not experience a noticeable restriction through the main direction of diffusion, the presence of walls in the radial trajectories decrease the observed radial diffusivity with increasing diffusion times. Few studies have explored the size of the milk ducts in the non-lactating breast. Taneri et al[9] reported a mean diameter of 0.57 mm in their series of 226 nipples and Rusby et al[10] reported a diameter of 0.7 mm at 3mm beneath the nipple. The length scales obtained in our study are in the same order of magnitude of these previous reports. Our workflow of analysis has taken into account the known limitations of DWI and has been set to mitigate possible drawbacks form eddy currents and inhomogeneous static field induced distortion. In addition, SNR was explicitly calculated to ensure an accurate DTI reconstruction.

Conclusion: This work presents the first attempt to calculate breast tissue length scales in vivo at the clinical level using MRI. The use of variable diffusion times may provide an in vivo non-invasive tool to probe diffusion lengths in breast tissue and breast pathology opening new possibilities for tissue and lesion structural characterization.

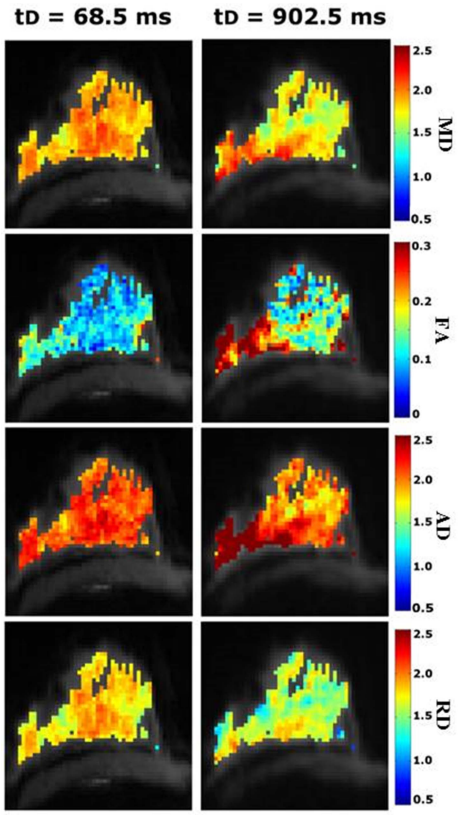

Fig.1: Mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD) in µm^2/ms, and fractional anisotropy (FA) parametric maps at the shortest and longest diffusion time for the same case.

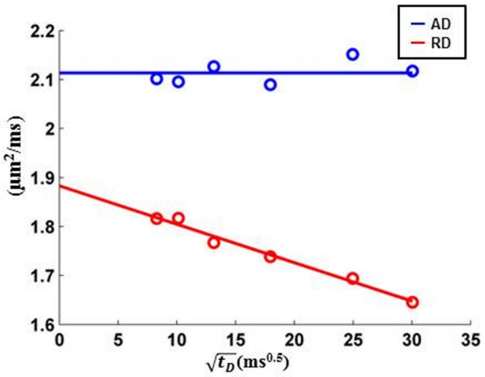

Fig. 2: Scatter plot and linear regression of the radial diffusivity (RD), and scatter plot and fitting to constant of the axial diffusivity (AD) plotted as a function of the square root of the diffusion times (t_D) for one case. Median values of the full ROI were employed.

References: [1] Basser PJ, et al. Biophys J 1994. [2] Merboldt KD, et al. Magn Reson Med 1991. [3] Rakow-Penner R, et al. J Magn Reson Imaging 2010. [4] Zitova B, et al. Image Vis Comput 2003. [5] Teruel JR, et al. Magn Reson Med 2014. [6] Sen PN. Concepts Magn Reson Part A 2004. [7] Dietrich O, et al. J Magn Reson Imaging 2007. [8] Lavdas I, et al. J Magn Reson Imaging 2013. [9] Taneri F, et al. Eur Surg Res 2006. [10] Rusby JE, et al. Breast Cancer Res Treat 2006.

Table 1	t_D = 68.5 ms				t_D = 902.5 ms			
	MD	FA	AD	RD	MD	FA	AD	RD
Healthy FGT (Case 1)	1.54 [0.40]	0.17 [0.10]	1.78 [0.51]	1.42 [0.38]	1.44 [0.37]	0.22 [0.13]	1.81 [0.42]	1.28 [0.38]
Healthy FGT (Case 2)	1.92 [0.18]	0.10 [0.05]	2.10 [0.19]	1.82 [0.19]	1.82 [0.25]	0.17 [0.13]	2.12 [0.38]	1.65 [0.25]

Values expressed in median [interquartile range] for the full ROI. MD (Mean diffusivity), AD (Axial diffusivity) and RD (Radial diffusivity) in µm^2/ms. FA (Fractional anisotropy).