The influence of model used to fit DW-MRI data on Apparent Diffusion Coefficient estimates and their reproducibility in normal tissues

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Introduction: There is an increasing interest in use of Diffusion Weighted MRI (DW-MRI) in clinical trials as a potential biomarker for early therapy response. The choice of b values and model used for fitting data acquired potentially affects the quantified ADC values and their reproducibility. The literature suggests that assumption of a simple exponential relationship between signal attenuation and b value for ADC calculation may be too simplistic[1,2] and that using more complicated mathematical models which account for the non-monoexponential behaviour of the diffusion signal attenuation in tissues results in a better data fitting[3,4] and potentially less variable ADC estimates. Approaches which have been used to model the nonlinear decay of DWI signal intensity when more than 2 b-values are acquired, include Intravoxel Incoherent Motion (IVIM)[5], stretched-exponential fitting, which describes diffusion-related signal intensity decay as a continuous distribution of sources decaying at different rates[6], diffusion kurtosis which takes into account the extent to which the diffusion of the water molecules deviates from a Gaussian distribution[7] and a gaussian model[8] which accounts for within-voxel heterogeneity. The purpose of this study was to evaluate the influence of the mathematical model used to fit the DW-MRI data on the ADC values and their reproducibility. The goodness of fit for each model was also assessed.

Methods: 10 healthy volunteers were scanned twice, 1-7 days apart, on 1.5T Avanto (Siemens, Erlangen, Germany). The DW-MRI measurements were acquired with a free-breathing, multiple-averaging technique, using single-shot echo-planar MR imaging (TR/TE 3500/69ms, 5mm thickness, 340-mm FOV, 128 × 104 matrix, images interpolated to a 256×208 matrix, 7 b-Values of 0, 50,100, 300, 600, 900 and 1050 s/mm2 in three orthogonal directions). An experienced radiologist drew regions of interest (ROI) within the right lobe of the liver, spleen, psoas muscle and renal cortex on the 20 studies. The ROIs were visually matched between the two visits for same volunteer and also visually matched as closely as possible between subjects. Same size ROI (200pixels) was used throughout and care was taken to avoid vessels, artefact and renal calyceal system. Data were analysed using Adept (in house DWI analysis platform). Median ADC values were calculated for each organ using all 7 b values. The ADC was calculated using 7 methods: monoexponential fitting using linear regression (L), Levenberg–Marquardt (LM) algorithms, IVIM and stretched exponential (S) using LM and and Markov Chain Monte-Carlo (MCMC) as solvers and Kurtosis (K) and Gaussian (G) mathematical models using LM as solver algorithm. Bland–Altman analysis was performed to test reproducibility. Model comparison was tested using Bayesian (BIC) and corrected Akaike (AICc) information criteria[9], which are affected by the data goodness of fit and include terms to penalised over-complex models – increasingly negative values indicate the preferred model.

Median ADC Reproducibility		*Mono-exponential*		*Non-Monoexponential*				
		Linear	LM	IVIM_LM	IVIM_MCMC	K	S_LM	S_MCMC
Liver	wCV	0.03	0.04	0.06	0.05	0.08	0.08	0.08
	r as %	9.21	11.09	17.78	15.10	22.64	21.83	22.11
Spleen	wCV	0.05	0.05	0.11	0.05	0.08	0.06	0.06
	r as %	14.52	13.80	29.58	14.63	21.91	16.79	17.09
Kidney	wCV	0.02	0.05	0.03	0.03	0.11	0.09	0.09
	r as %	5.53	14.65	8.40	9.22	31.34	25.93	24.80
Muscle	wCV	0.04	0.04	0.06	0.05	0.07	0.05	0.04
	r as %	11.61	12.14	17.09	12.95	18.97	13.32	11.40

Table 1. The reproducibility coefficient r% and wCV (within subject coefficient of variation) using Bland Altman analysis

Mean Corrected Residuals		*Mono-exponential*		*Non-Monoexponential*				
		Linear	LM	IVIM_LM	IVIM_MCMC	K	S_LM	S_MCMC
Liver	AICc	-5.03	-3.73	6.36	5.98	-0.49	4.51	-1.73
	BIC	-5.14	-3.83	6.14	5.76	-0.65	4.34	-1.89
Spleen	AICc	-4.78	-3.90	3.24	2.81	0.00	0.85	-1.90
	BIC	-4.89	-4.01	3.02	2.60	-0.15	0.69	-2.06
Kidney	AICc	-10.56	-7.91	2.27	1.99	-2.28	1.21	-5.91
	BIC	-10.66	-8.02	2.06	1.78	-2.44	1.05	-6.07
Muscle	AICc	-1.09	-0.07	6.48	5.86	3.24	4.68	1.93
	BIC	-1.20	-0.18	6.27	5.64	3.08	4.52	1.77

Table2 . Mean corrected residuals

Results: The distribution of the ADC values using different models followed a similar pattern across the organs with the highest values being obtained using the kurtosis model and the lowest values using the IVIM model. The Gaussian model was able to fit only the data obtained from the kidneys. The best reproducibility was obtained using a monoexponential model with a linear regression solver (table 1), which also had the smallest corrected residuals (table 2). For the IVIM model, using MCMC as a solver resulted in an improved reproducibility and less residuals.

Discussion and Conclusion: Using a more complicated model did not result in a better reproducibility or in a better fitting of the data obtained from normal organs with the described combination of b values. It may be that the more complicated models require a larger number of low b values to characterise the initial, perfusion dependent part of the DW-MRI signal intensity decay curve. Larger studies are needed to explore the value of more complicated models in tumour response assessment. Until then, we envisage that for the purpose of clinical trials a monoexponential model using linear regression will provide best available reproducibility and fitting of the data.

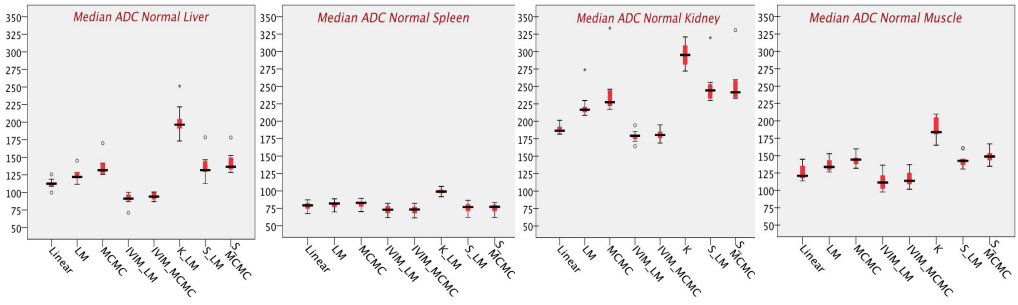

Figure 1. Distribution of median ADC values
The linear and LM refer to the algorithm used for monoexponential fitting of the data; the IVIM has been fitted using LM and MCMC as solvers; K –kurtosis model, S- Stretched exponential; the Y axis represents the median ADC (10^{-5}mm^2/s)

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