Modelling Diffusion Data using a Stretched-Exponential Model : Pitfalls in Estimation Methodology

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Introduction In Diffusion Weighted Imaging (DWI) the dependence of the diffusion rate on the applied magnetic field gradient is known to follow a mono-exponential law in a homogeneous environment. In-vivo samples are known to be heterogeneous, and the IVIM model [1] (intra-voxel incoherent motion model) tackles this by assuming that there are two homogeneous compartments. The statistical properties of this model are such that reliable estimates can only be obtained with relatively noise-free data, e.g. animal models, or in human brain. For many organs such data are difficult to acquire clinically due to effects such as motion, imaging non-linearities, flow effects etc. Recently, the stretched exponential model [2,3] has been proposed as this has can be interpreted as arising from a continuous distribution of diffusion rates within each voxel. The advantage of this model is that its statistical properties are such that reasonable estimates can be obtained from a wider range of clinical data. When the data are noisy it is important to fit the model to the data in an appropriate way, and this work identifies two common pitfalls that lead to sub-optimal estimates. The effects of these pitfalls are demonstrated, and solutions given.

Theory The stretched-exponential model arises from the assumption that the mean-squared displacement of diffusing spins is proportional to t^{α}, where $\alpha<1$ is referred to as sub-diffusion and $\alpha=1$ is standard diffusion. This leads to a model with the form $S = S_0.\exp(-(bD)^{\alpha})$, where S is the acquired signal, S_0 is the native signal intensity, b is the applied diffusion gradient, D is the diffusion constant and α is the heterogeneity index or anomalous exponent. The model equation can be re-arranged to give $\log|\log(S/S_0)| = \alpha\log(b) + \alpha\log(D)$, so the gradient of $\log|\log(S/S_0)|$ vs. $\log(b)$ gives an estimate of α, and the intercept can be used to estimate D. The first pitfall is that although this procedure will produce acceptable estimates for data where the signal to noise ratio (SNR) is very good, for poorer SNRs the estimates will no longer be reliable. This is caused by the double logarithm acting on the observation noise so that the implied noise on the linear fit has neither a normal distribution nor a fixed variance. This is a well known phenomenon, commonly encountered when the transformation is a single logarithm where its effect is relatively small, but in the double logarithm case the results presented below demonstrate that the effect can be surprisingly large. The solution is to use a non-linear fitting routine to estimate the parameters from the original model equation. The second pitfall is that S_0 is often estimated directly as the measurement acquired with $b = 0$, rather than estimating S_0 along with α and D. The problem with the simple approach is that the uncertainty in the estimate of S_0 is larger than if it is estimated with α and D because it is derived from a single data point, and this uncertainty feeds back into the estimates of α and D. In the case when the SNR is poor, this additional uncertainty can be problematic, so it is important to use the data appropriately to extract the most reliable estimates possible.

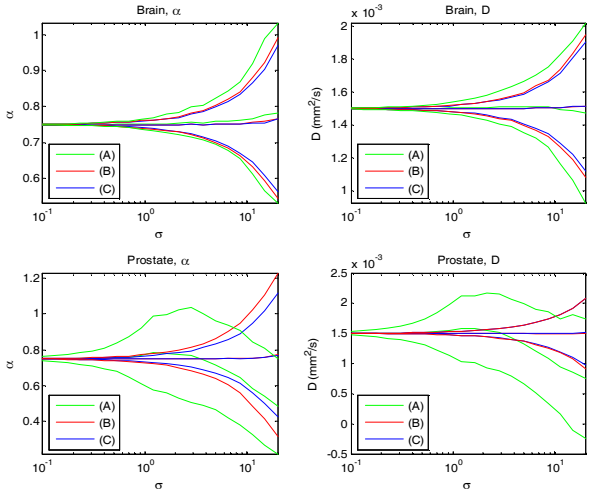

Figure 1: Results of Monte Carlo experiment for three estimation methods as a function of noise standard deviation. The three lines are the mean and ±2 standard deviations in each case.

Methods A Monte Carlo simulation was carried out to assess the properties of three estimators at a range of SNRs and for two different b-value regimes. The three estimators were: (A) Linear regression on $\log|\log(S/S_0)|$ vs. $\log(b)$, to estimate α and D, (B) Non-linear regression on S/S_0 vs. b, to estimate α and D, (C) Non-linear regression on S vs. b, to estimate α, D and S_0. The two b-value regimes were 20 logarithmically spaced values in the range 50 - 5000 s/mm^2, and 10 logarithmically spaced values in the range 1 - 800 s/mm^2, both regimes include an acquisition with $b = 0$. These reflect parameters typically used in brain and prostate respectively. The model parameters were set to $\alpha = 0.75$, $D = 1.5\text{x}10^{-3}$ mm^2/s and $S_0 = 300$. Simulated data were generated using the stretched-exponential model and Gaussian noise was added with a standard deviation in the range $\sigma = 0.1$ to 20. For each parameter configuration 1000 data sets were generated with independent noise, and the three methods used to obtain estimates of α and D. From this the mean and standard deviation of each estimator can be estimated as a function of the noise standard deviation and the two b-value regimes.

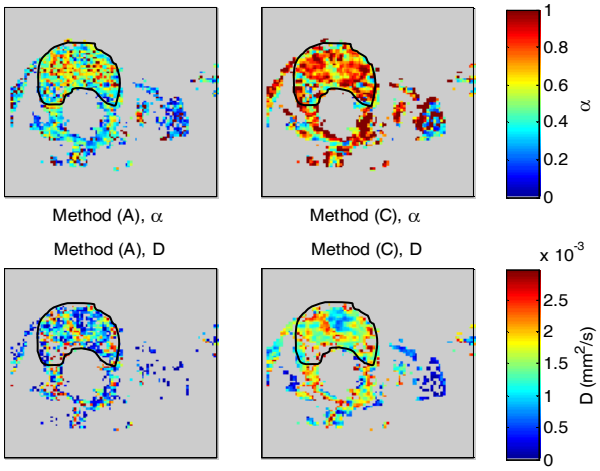

Figure 2: Parameter maps from DWI prostate data using methods (A) and (C).

Results Figure 1 shows results from the Monte Carlo experiment. The top row shows results using the b-value regime for brain, where it is evident that method (A) has a slight bias that increases as the noise increase. The standard deviation of method (A) is noticeably larger than method (C), with proportional increases in the range 25-65% for α, and 40-100% for D. Methods (B) and (C) have very similar properties in this regime, but the standard deviation of method (B) is larger by 6-13% for both α and D. In this regime the differences are relatively small with respect to the overall uncertainties. The bottom row shows results of the b-value regime for prostate where the differences between the three methods are more apparent. Method (A) has considerable bias that has a peculiar relationship with increasing noise level, and this is coupled with a plateau in the standard deviation of the estimator at around $\sigma = 2$. Methods (B) and (C) have a more predictable behaviour, but it is clear that the standard deviation of method (B) is larger than method (C) for α, where the proportional increase is in the range 32-48%, though this is only 0-5% for D. Figure 2 shows parameter maps from in-vivo data taken from a prostate (highlighted). The estimates using method (A) show a pronounced increase in variability over method (C). The noise standard deviation was estimated from the data to be in the range $\sigma = 2$ to $\sigma = 20$, which means these data are similar to those giving the right-hand portion of the simulation results in the bottom panels in figure 1. The simulation predicts that for this range of σ, method (A) will have a downward bias for both α and D, which is observed in the estimates in figure 2.

Conclusions These simulations demonstrate that for two common b-value regimes, estimates using non-linear regression have reduced variability and bias over using linear fitting on a transformed model equation. Moreover, a reduction in variability is also seen when S_0 is estimated from all the data, and this is more pronounced in the b-value regime designed to simulation prostate acquisitions. These effects have also been demonstrated with in-vivo data from a prostate, and so we recommend that method (C) is to be preferred as it has more stable statistical properties.

References [1] Clarke & Le Bihan, Mag. Res. Med. (2000) 44:852-859. [2] Bennett et. al, Mag. Res. Med. (2006) 56:235-239. [3] Hall et. al. Proc. ISMRM 2006, 1023.

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