Fitting to magnitude diffusion MRI data using a least squares algorithm gives biased ADC values and is less able to characterise necrosis

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Introduction: The apparent diffusion coefficient (ADC) is routinely used in the characterisation of the tumour microenvironment, particularly in drug efficacy studies [1]. A simple exponential relationship is typically assumed between the (magnitude) signal intensity and the b-value (given primarily by the diffusion gradient strengths), with the ADC fitted as the 'rate' constant. Due to its wide availability, the least squares (either linear or non-linear) algorithm is typically used to estimate the ADC value. The least-squares algorithm assumes the noise corrupting the magnitude MR data to be normally-distributed, although it has previously been shown to be Rice-distributed [2]. In this study, a maximum likelihood model is developed that takes the Rice noise distribution into account and compares the resulting ADC values with those derived from fitting with a least-squares algorithm in data derived from orthotopic PC3 prostate tumours.

Materials and Methods: Orthotopic PC3 tumours were propagated in 6 NCr nude mice and allowed to develop for 20 days. They were scanned on a 7T Bruker MicroImaging system using a spin-echo diffusion sequence with 6 b-values (6 to 500 s/mm^2), 3 slices, TR=1s, FOV=3x3cm, slice thickness = 1mm, matrix size=128x128. Data were analysed using software developed in-house in IDL (ITT, Boulder, Colorado). The data were fitted to a function of the form $f(b) = S_0 e^{-ADC.b}$ first using a non-linear least-squares algorithm. S_0 is the signal intensity at b=0 and, along with the ADC, is a fitted parameter. Following this, the data were fitted using an algorithm to minimise the following log likelihood function:

$$L = \sum_{i=1}^{N} \log I_0\left(\frac{f(b_i)M_i}{2\sigma}\right) - \sum_{i=1}^{N}\frac{f(b_i)^2}{2\sigma^2} - \sum_{i=1}^{N}\frac{M_i^2}{2\sigma^2} - N\log(\sigma^2) + \sum_{i=1}^{N}\log(M_i)$$

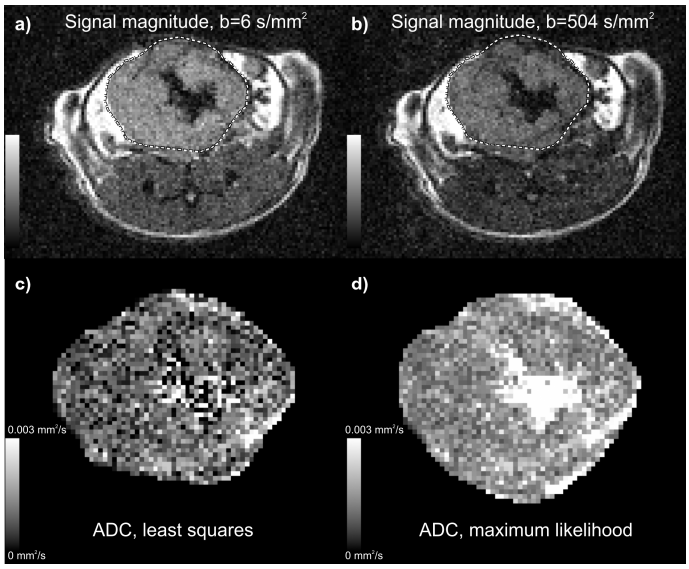

Figure 1: (a and b) Signal magnitude and (c and d) example ADC maps from the same tumour. ADC maps were estimated using the least-squares algorithm (left) and the maximum likelihood algorithm (right).

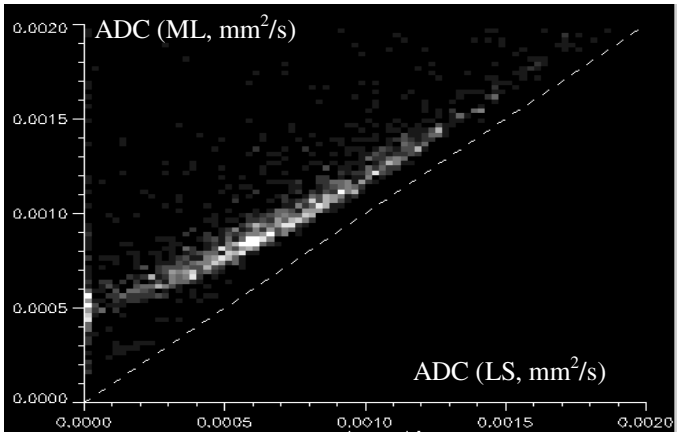

Figure 2: A 2-dimensional histogram of ADC values taken from an example tumour. The horizontal axis displays ADC estimates from the least-squares (LS) algorithm and the vertical axis shows estimates from the maximum likelihood (ML) algorithm.

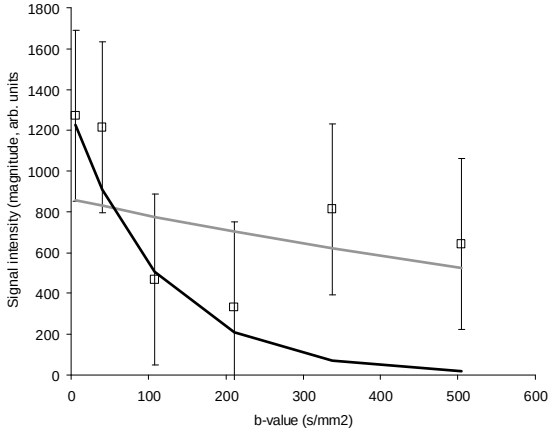

Figure 3: Example fits to a single pixel with relatively low signal-to-noise, given by the least-squares and maximum likelihood algorithms (grey and black, respectively). Note that the least-squares fit attempts to fit the data symmetrically, whilst the maximum likelihood algorithm ignores data points with negligible signal, resulting in an unbiased ADC estimate.

where I_0 is the modified Bessel function of the zeroth kind, M is the magnitude data value, σ is the standard deviation of the Rice noise and N is the number of magnitude data points. At high signal-to-noise ratios, the likelihood function reduces to that for normally-distributed noise [2]. σ was estimated by fitting a Rayleigh distribution to a histogram of magnitude values from a region of background noise [2]. For all optimisations, log(ADC) and log(S_0) were estimated in order to constrain ADC and S_0 to be positive.

Results and Discussion: Figure 1 shows two example tumour ADC maps fitted using the least-squares and maximum likelihood methods. Of particular interest is the bright region in the centre of the tumour which is typically associated with necrosis. All tumours in this study displayed this feature, but only when fitted using the maximum likelihood method. A two-dimensional histogram is featured in Figure 2, which shows the ADC estimates derived from the least-squares algorithm are consistently smaller than those from the maximum likelihood algorithm. Across the group this average deviation was 23.4±12%, but was greater at lower ADC values. Figure 3 shows example fits to magnitude data, which illustrates how the least-squares algorithm biases the ADC values; pixels in which the signal intensity has become comparable with the noise (such as at larger b-values) do not have equivalent noise distributions to those with higher signal intensity. However, the least-squares algorithm still attempts to fit the data symmetrically, resulting in an under-estimate of the ADC. A similar effect occurs in regions of necrosis (which typically has lower signal intensity than viable tumour tissue).

Conclusion: The least-squares algorithm biases estimates of tumour ADC compared with estimates from a maximum likelihood model which accounts for Rice-distributed noise. This effect is particularly pronounced in tissues with large b-values or with low initial signal intensity (such as regions of necrosis) and, in this study, resulted in an average deviation of 23.4 ± 12 %. It is recommended that the maximum likelihood method is used in preference to the least-squares approach. However, it should be noted that in systems with multiple receiver channels, the noise distribution can be more complex than in a single receiver system, as presented here.

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References: [1] Moffatt B.A., MAGMA 17;249-259 (2004) [2] Sijbers J., Magn Reson Imaging.16(1):87-90 (1998)