Fitting to signal intensity time course data with intrinsic conversion to Gd-DTPA concentration improves the accuracy and precision of model parameter estimates

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Introduction

The least-squares optimisation algorithm is often used to fit pharmacokinetic models to dynamic contrast-enhanced (DCE) MRI data in order to estimate parameters relating to vascular permeability and flow. Within this analysis, a conversion from raw signal intensity (from magnitude images) to Gd-DTPA concentration is required. The least-squares algorithm assumes normally-distributed noise in the data, yet the distribution of noise following such a conversion is unknown. In this study, the use of the least squares algorithm in fitting Gd-DTPA concentration data is compared with that found by fitting signal intensity data (with a conversion to Gd-DTPA concentration contained within the optimisation routine). Noise in magnitude MRI data is Rician-distributed, which tends to a Gaussian distribution at signal-to-noise ratios (SNR) greater than 2 [1], making this type of data ideal for use in conjunction with the least squares algorithm.

Materials and Method

In Vivo Analysis: In order to evaluate the distribution of noise in Gd-DTPA concentration data, the residuals from a fit by a multi-exponential model to such data in vivo was evaluated and compared with those found from a fit to signal intensity data. Accordance with a Gaussian distribution was evaluated using the Kolmogorov-Smirnov test. Any poor fits to the data were removed from the analysis, based on the χ^2 test (p>0.01).

Simulations: Gd-DTPA concentration-time curves were simulated using the modified Kety model [3] with a range of K^{trans} (the volume transfer constant between blood plasma and extravascular extracellular space (EES)) from 0.01 to 0.50/min and v_e (the fractional volume of EES) from 0.01 to 0.6. A bi-exponential arterial input function was also used [2]. Using the following formula, Gd-DTPA concentration was converted to signal intensity (S) (for a spoiled gradient-echo sequence) [4]:

$$S = \frac{N(1-E_1)\sin\alpha}{1-\cos\alpha E_1}$$

where $E_1 = \exp[T_R(r_1 C_t(t) + R_{10})]$ and α is the flip angle (30 degrees), T_R is the repetition time (30ms), R_{10} is the native longitudinal relaxation rate (1/s), N is related to proton density and scanner gains (set to unity) and r_1 is the contrast agent relaxivity (4.5 /s/mM). Gauss-distributed noise was added to signal intensity-time curves. the variance of the noise was set such that the signal-to-noise ratio was fixed at 30 (typical of that found in dynamic measurements in vivo). For each value of K^{trans} and v_e 1000 Monte Carlo simulations were undertaken, giving the equivalent number of estimates of each parameter. The modified Kety model was fitted to the simulated, noisy data using two approaches (see Fig. 1). In the first (the conventional approach), simulated signal intensity data were converted to Gd-DTPA concentration and then fitted; in the second approach, signal intensity data were fitted, but within the optimisation routine, the *fitted* data were converted from Gd-DTPA concentration to signal intensity. The accuracy and uncertainty of the i^{th} model parameter (a_i and p_i respectively) of model parameter estimates were assessed using: $a_i = <\theta_i - \hat{\theta}_i> / \theta_i$ and $p_i = \sqrt{<\hat{\theta}_i^2> - <\hat{\theta}_i>^2} / \theta_i$, where θ_i is the true (simulated) value of the i^{th} model parameter and $\hat{\theta}_i$ are the estimated values.

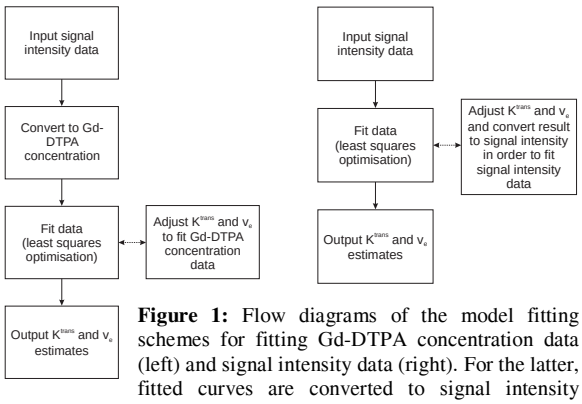

Figure 1: Flow diagrams of the model fitting schemes for fitting Gd-DTPA concentration data (left) and signal intensity data (right). For the latter, fitted curves are converted to signal intensity within the optimisation routine.

Results

In Vivo Analysis: Figure 2 shows the distribution of residuals from a fit to signal intensity data and to Gd-DTPA concentration data in an example patient. Residuals from fits to Gd-DTPA concentration data were not Gaussian distributed (p>0.05), whilst those associated with the fit to signal intensity data were Gaussian distributed (p<0.05).

Simulations: Figure 3 shows the ratio of the accuracy of K^{trans} given by the fits to Gd-DTPA concentration and that given by the fits to signal intensity data. Whilst there is a complex relationship between the accuracies given by the two approaches, this graph shows that parameter accuracy is consistently poorer when Gd-DTPA concentration data is fitted, compared to that when signal intensity data is used (denoted by the ratio of the two quantities being consistently greater than 1). The same graph for K^{trans} uncertainty is also shown in Fig. 3, which shows that uncertainty from the two approaches is comparable, other than when the true v_e is small. The same effect was found in the accuracy and uncertainty of v_e estimates.

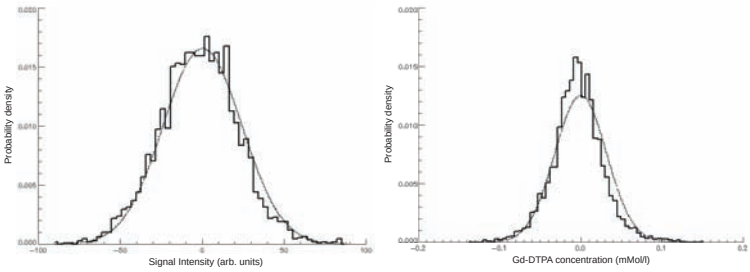

Figure 2: Noise distributions measured in vivo from (left) signal intensity data and (right) Gd-DTPA concentration data. Dashed lines show Gaussian distribution based on the mean and variance of both distributions; only the signal intensity distribution is signficantly Gaussian-distributed.

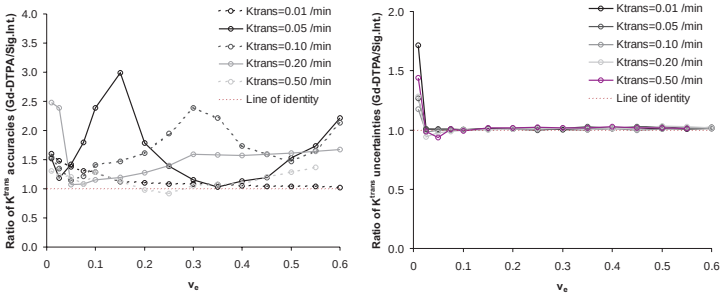

Figure 3: (left) The ratio of K^{trans} accuracy given by fits to simulated Gd-DTPA concentration-time data to the accuracy given by fits to signal intensity data. (right) The same, but for K^{trans} uncertainty.

Discussion and Conclusions

In this study it was argued that, as magnitude MRI data with a sufficient SNR has Gauss-distributed noise, it is of benefit to utilise this in the least squares algorithm. Measurements of noise distributions in vivo revealed that the non-linear conversion from signal intensity to Gd-DTPA concentration Measurements of noise distributions in DCE-MRI signal intensity and Gd-DTPA concentration data revealed that the conversion to Gd-DTPA concentration destroyed the Gaussian distribution of the noise. By incorporating the relationship between signal intensity and Gd-DTPA concentration into the optimisation routine, it was shown using simulations that the accuracy and uncertainty of parameter estimates can be improved by up to 3%. Furthermore, by estimating the standard deviation of the noise, metrics such as the χ^2 goodness of fit can be utilised, in addition to parameter uncertainty estimates based on the χ^2 Hessian matrix. It is therefore recommended that this approach should be used in preference to fits to Gd-DTPA concentration data.

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References: [1] Gudbjartsson H. et al, *Magn Reson Med* 34(6):1995;910-4, [2] Walker-Samuel S. et al, *Phys Med Biol,* 51(14):2006; 3593-602, [3] Tofts P. et al, *Magn Reson Med,* 17(2):1991; 357-67, [4] Haake E.M. et al, Wiley-Liss, Chichester, 1999.