Comparison of the goodness of fit provided by models commonly used to characterise DCE-MRI data

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Introduction

A number of pharmacokinetic models have been formulated to characterise the uptake of contrast agent by tumours in vivo. The most commonly used models in this context include modified Kety [1], extended Kety [1], St. Lawrence and Lee [2] and Griebel [3]. The modified Kety model is parametised by K^{trans} and v_e, which are related to blood flow and permeability and to the fractional volume of the extracellular extravascular space (EES), respectively. The extended form also includes the fractional blood plasma volume, v_p. Conversely, the SLL and Griebel models are parametised directly by flow (F), the permeability-surface area product (PS), extraction (E), mean transit time (MTT), v_e and v_p, thereby offering a more transparent relationship with tissue physiology. However, it is unclear whether the formulation of these more complex models and the inclusion of greater number of fitted parameters is justifiable and whether this increased complexity provides a more accurate description of the data. As an initial evaluation, an optimised method for fitting pharmacokinetic models is used in this study to estimate absolute measures of goodness of fit provided by each of the models using in vivo data from tumours.

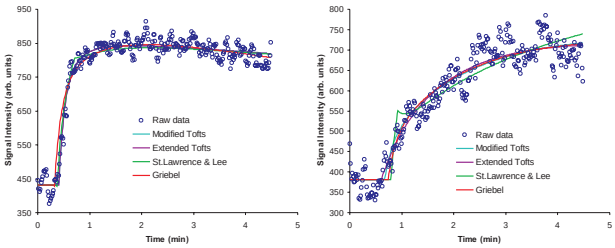

Figure 1: Example fits to signal intensity-time courses using each model.

Materials and Method

MRI Measurement: DCE-MRI data were acquired from 10 patients (5 with rectal cancer, 5 with prostate cancer) using a dual-echo sliding window (DESW) FLASH sequence ($TR/TE_1/TE_2/\alpha$ = 30ms/5ms/30ms/30º for dynamic T1w images; a 5º flip angle was used for reference proton density-weighted images (required for conversion to Gd-DTPA concentration) [4]), with a body phased-array coil. Images were reconstructed with a temporal resolution of 1.1s and total duration 270s; contrast agent (Magnevist, 0.2 mMol/kg body weight) was injected at 5ml/s. Patients received Buscopan (20mg) before scanning to eliminate peristalsis.

Phamacokinetic Modelling: By using the least squares algorithm to fit pharmacokinetic models to signal intensity data (as opposed to Gd-DTPA concentration) and performing the conversion between signal intensity and Gd-DTPA concentration within the optimisation algorithm, the Gaussian distribution of noise within this type of data can be exploited [5]. Using pre-enhancement data to estimate the standard deviation of the noise, the χ^2 goodness of fit was used to discriminate between good and bad fits, in absolute terms. Using this approach, each of the four models was fitted to each pixel within a ROI corresponding either to tumour or prostate and the χ^2 statistic was calculated for each. All of the models require an estimate of the blood plasma concentration, for which a bi-exponential curve from the literature was used [6]. In order to avoid convergence at local minima, ten starting values were used to fit each time course, which were randomly generated within pre-specified limits for each model parameter. For comparative purposes, K^{trans} maps were created for each model; whilst this parameter does not normally feature in the SLL and Griebel models, it was constructed from the relationship $K^{trans} = (1\text{-Hct})EF\rho$, assuming a haematocrit fraction (Hct) of 0.45 and tissue density (ρ) of 1 g ml^{-1}; E and F are extraction and flow, respectively.

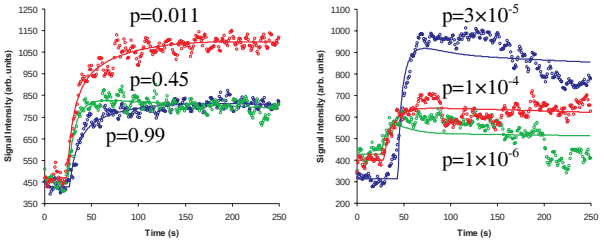

Figure 2: Example fits with (left) p>0.01 and (right) p<0.01.

Statistical Analysis: The probability (p) of measuring a particular χ^2 value for a given number of degrees of freedom can be estimated from standard statistical tables or numerical algorithms. The null hypothesis of the test is that the model does not describe the data; therefore value of $p > 0.01$ implies that the fit to the data is good. For each ROI, the percentage of fits with $p > 0.01$ was calculated. This was repeated for each model in order to compare performance.

Results

Figure 1 shows example fits to two signal intensity time courses from colorectal tumours given by the four models. As can be seen from the left-hand example, all of the models are capable of providing a good fit to the data. Table 1 shows a summary of the goodness of fit analysis of each model. Figure 2 shows examples of fits with $p > 0.01$ and $p < 0.01$.

The modified Kety model was found to provide the greatest number of good fits, closely followed by the extended Kety model. The closeness of these two results was caused by v_p in the extended Kety model tending to negligibly small values (median v_p values ranged from 0.0001 to 0.003), thereby rendering the two models equivalent (apart for a small difference in the number of degress of freedom. Figure 3 shows parametric maps from an example patient, which reveals a close corresponandance between the Kety models and the SLL model. Parameters from the Griebel model are considerably scattered compared with the maps from the other models, implying a potentially large uncertainty in their values.

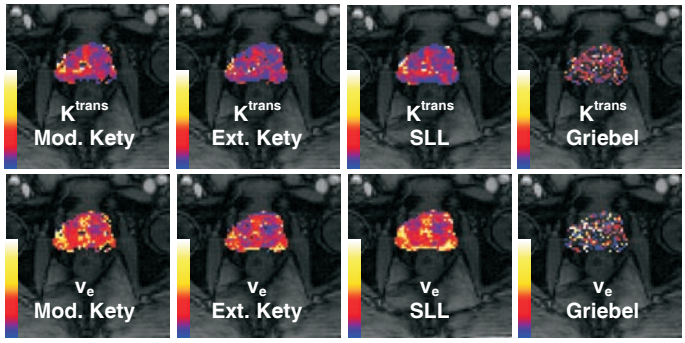

Figure 3: Parametric maps of K^{trans} (top) and v_e (bottom) from each model; (left to right) modified Kety, extended Kety, St. Lawrence & Lee, Griebel.

Discussion and Conclusions

In this study, the goodness of fit provided by four commonly used pharmacokinetic models was compared. Using the χ^2 goodness of fit test with a signficance level $p = 0.01$, the modified Kety model was found to provide the closest characterisation of the data. These results imply that, although more complex, the extended Kety, SLL and Griebel models do not enhance the accuracy of the fit to the data. However, a literature-derived plasma concentration curve was used in this study, which essentially formed a component of each model. Further analysis of these models using measured measured plasma curves would be informative. However, the ability to define an absolute measure of goodness of fit, as described in this study, offers a significant methodological advancement.

	Mod. Kety	Ext. Kety	SLL	Griebel
Av. % of ROI with p>0.01	50.9 ± 28.6	38.8 ± 31.7	21.3 ± 26.0	32.8 ± 23.7

Table 1: Summary of goodness of fit analysis for each model. Uncertainties represent standard deviations.

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