

The importance of the best-fit line through experimental data points

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The look-up table method of T_1 calculation is common in dynamic contrast-enhanced MRI, however the function used to fit the calibration data remains arbitrary. Five different functions were fitted to the same calibration data to produce five look-up tables. These look-up tables were used to calculate the concentration of contrast agent in a dynamic prostate study and model fitted using a standard pharmacokinetic model. The differences in the uptake curves and the values of v_e , K^{trans} and k_{ep} were observed. It was found that the choice of function used to create the look-up table had a significant effect on both the uptake curve and the values of v_e , K^{trans} and k_{ep} . This highlights the necessity of a standard look-up table and the requirement to conduct an accurate calibration experiment over a wide range of T_1 values.

Introduction

The look-up table method of T_1 calibration is a tool for converting signal intensity as seen in a magnetic resonance (MR) image to T_1 , an intrinsic property of the imaged sample that is dependant on the chemical environment surrounding the hydrogen protons in water. Having a knowledge of T_1 is very important in the field of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), a technique commonly used in the detection of tumours and which has shown great potential in monitoring tumour response to treatment [1].

Accurate T_1 measurements are not trivial to perform due to the complicated relationship between signal intensity and T_1 . Many different types of MR imaging sequences exist for obtaining information about T_1 , for example spoiled gradient echo [2, 3, 4] and inversion recovery [5, 6]. The most simple procedure is to perform a prior calibration experiment by imaging a phantom containing a sample of known T_1 values and producing a graph of T_1 against signal intensity S . A line of a known function can then be fit to the data, creating a look-up table relating signal intensity and T_1 .

There has been much discussion about the line used to describe the signal intensity- T_1 relationship, therefore this investigation sets out to produce look-up tables using different lines from the same calibration experiment and observe the effects on subsequent T_1 calculations, contrast agent concentrations and DCE-MRI pharmacokinetic modelling.

Theory

Modelling Tumour Vascularity using DCE-MRI

A tumour without an independent blood supply cannot grow beyond 1-2 mm in diameter [7], and it is angiogenesis, the creation of new capillaries branching from existing vessels [8] that allows a tumour to form the blood supply it needs to grow. This blood supply is different from that of healthy tissue in that the blood vessels are poorly formed and fragile. This leads to breaches in the walls of the capillaries and so blood can perfuse into the surrounding spaces.

Dynamic imaging is a process of repeatedly imaging the same location (<1-5s per image) in a sample and is usually accompanied by the intravenous administration of contrast agent (commonly gadolinium diethylenetriamine pentaacetic acid, Gd-DTPA).

Contrast agents will reduce the T_1 of a sample according to:

$$\frac{1}{T_1} = \frac{1}{T_{10}} + r_1[Gd] \quad (1)$$

Where $1/T_1$ is known as the relaxation rate R^1 , T_{10} is the 'native' T_1 (the T_1 of a sample without contrast agent effects), r^1 is the relaxivity of the contrast agent and $[Gd]$ is the nomenclature for concentration of contrast agent. With knowledge of T_1 , the concentration of contrast agent can be determined. High concentrations of contrast agent will collect in areas of fragile, permeable vasculature common in tumours [8]. These areas will appear brighter in an MR image as lower T_1 , increasing the likelihood of tumour detection for the T_1 weighted ($T_1 W$) sequences used in DCE-MRI.

A quantitative analysis of tumour vasculature can be performed using DCE-MRI. The three main parameters (v_e , K^{trans} and k_{ep}) used to describe the tumour vasculature. v_e is defined as the volume of extravascular, extracellular space (EES, the space in between cells and blood vessels) per unit volume of tissue. K^{trans} is the volume transfer constant between the blood plasma and the EES and k_{ep} is the rate constant between the EES and blood plasma [9]. This is shown in figure 1, where C_p is the concentration of contrast agent in the blood plasma. v_e , K^{trans} and k_{ep} are related by

$$k_{ep} = K^{trans} / v_e \quad (2)$$

These 'pharmacokinetic parameters' can be found using this standard solution:

$$C_t(t) = v_p C_p(t) + K^{trans} \int_0^t C_p(t') e^{-K^{trans}(t-t')/v_e} dt' \quad (3)$$

where $C_t(t)$ is the total concentration of contrast agent in the tissue, v_p is the blood plasma volume per unit volume of tissue.

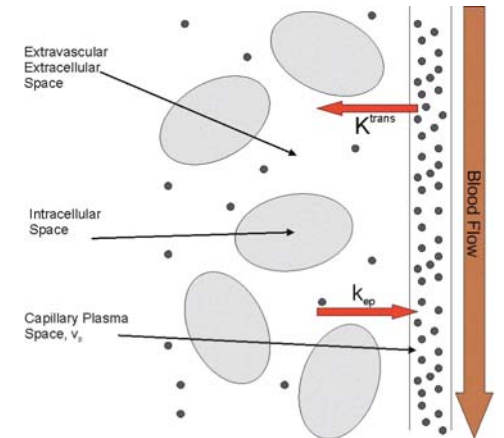


Figure 1: Major compartments and contrast agent transfer

With knowledge of $C_t(t)$, found by converting the T_1 of dynamic images to $[Gd]$ and displayed in the form of a $[Gd]$ against time graph, known as an 'uptake curve', $C_p(t)$, which is assumed using a standard measurement and v_p (this is not always included), the pharmacokinetic parameters can be found.

Producing a Look-up Table

The calibration experiment requires a phantom of various known T_1 values to be imaged both $T_1 W$ and proton density weighted (PdW) at nutation angles of θ_1 and θ_2 respectively. The ratio (r) of the two images ($T_1 W$ /PdW) is then taken. By doing this the dependance of the signal intensity on any receiver gains or scale factors is removed. The known T_1 values of the phantom are then plotted against the corresponding ratio value. A best-fit line is fitted to the data. Quite often, this line is of the form of a single or

bi-exponential decay, although other types are also used. With knowledge of the fitted parameters of the function used, T_1 can be calculated for any value of r acquired using an identical sequence and values of θ_1 and θ_2 .

Each look-up table is unique for the sequence parameters used in the calibration experiment. Any T_1 calculations using a different sequence, or if the sequence parameters such as θ_1 or θ_2 will require a repeat in the calibration experiment.

Methods

Calibration Experiment

Calibration experiment was performed on a 1.5T Siemens Vision system (Siemens, Erlangen, Germany) transversely imaging a Eurospin test object (Diagnostic Sonar, Edinburgh) containing 11 gels of T_1 from 211-992ms. RF pulse was transmitted using the in-built body coil and received using a phased array surface coil. Imaging sequence used was a spoiled gradient echo 2D dual echo FLASH sequence with a sliding window K-Space acquisition [10]. All receiver gains and scaling factors were kept constant for every image acquired. A PdW image at a 5° flip angle and a T_1 W image at a 30° flip angle (figure 2) were acquired. Sequence and sequence parameters were as used in previous DCE-MRI studies. Look-up tables were created as in the theory, and five lines of the form of equations 4-8 were fitted to the graph to produce 5 separate look-up tables as shown in figure 3

$$y = Ae^{Bx} \quad (4)$$

$$y = Ae^{Bx} + Ce^{Dx} \quad (5)$$

$$y = A + B/x \quad (6)$$

$$y = A \ln Bx \quad (7)$$

$$y = Ax + B \quad (8)$$

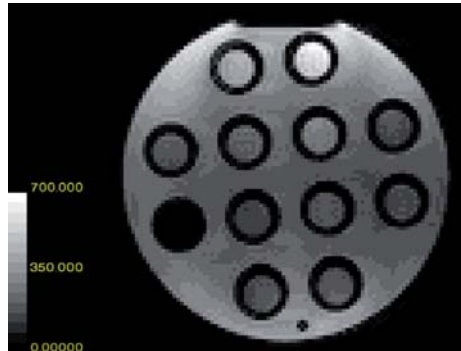


Figure 2: Phantom image acquired at a 30° flip angle

Application of the T_1 Values to DCE-MRI

The five look-up tables created were used to calculate T_1 of a dynamic prostate study, which in turn was converted to [Gd] using equation 1. Figure 4 shows a graph of the average [Gd] over the whole prostate against image number, $C_1(t)$.

Pharmacokinetic parameters were derived from the Tofts and Kermode model [11], a variation of equation 3. This was achieved using a least squares fitting algorithm in IDL (RSI Ltd) to find the optimum values of K^{trans} , v_e and k_{ep} . The parameters calculated from each curve are compared in table 1.

Table 1: Values of the pharmacokinetic parameters

Look-up table	K^{trans}	v_e	k_{ep}	Fit
Single Exp	0.120	0.274	0.434	78%
Bi Exp	0.118	0.273	0.492	76%
Inverse	0.115	0.261	0.416	80%
Logarithmic	0.102	0.243	0.420	69%
Linear	0.0753	0.203	0.430	64%
Difference	0.045	0.071	0.076	

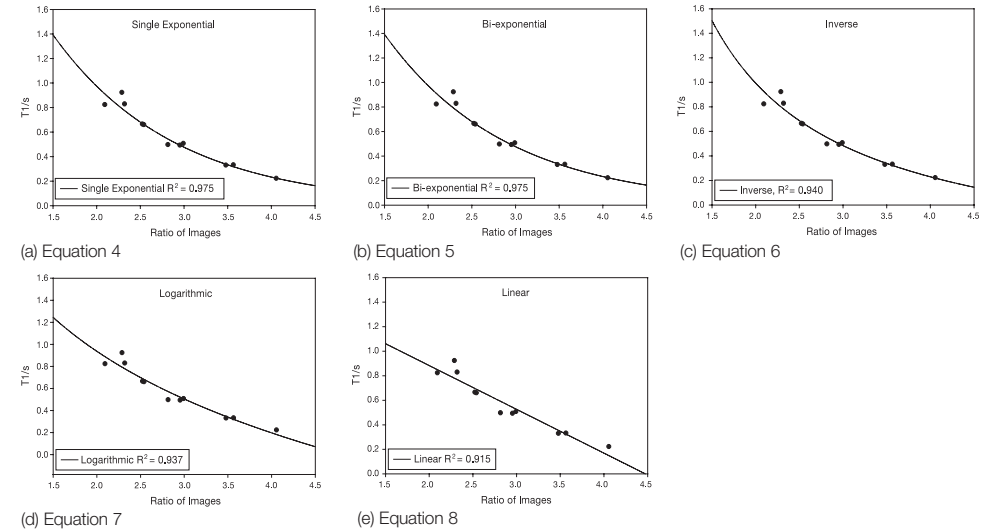


Figure 3: Functions fit to the signal ratio data obtained from the dual echo 2D FLASH sequence

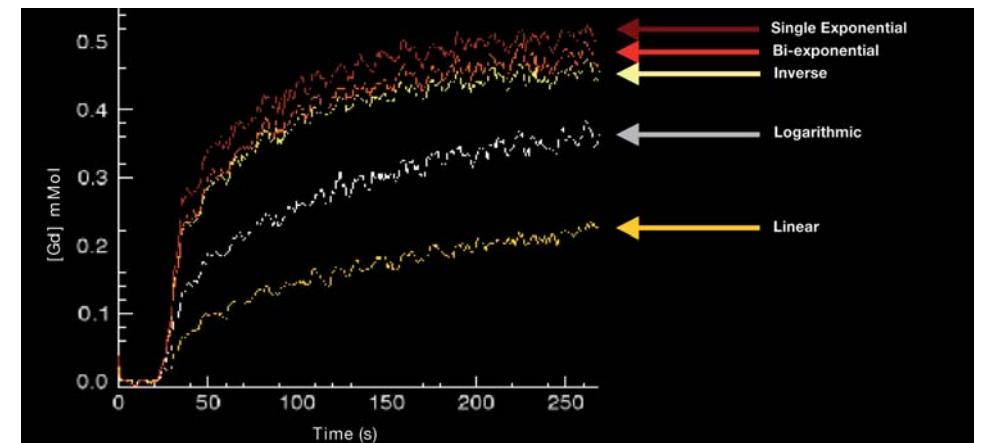


Figure 4: Uptake curves as calculated from the five different look-up tables

Results

Effect of T_1 on Uptake Curves

The calculated uptake curves are shown in figure 4. It can be seen that there is a large effect on the maximum calculated [Gd] depending on the look-up table used. There is a 60% difference between the maximum [Gd] calculated from the single exponential and the linear look-up table.

The general shape of the curve, however, does not change but differences in the noise of the curves can be observed. The differences in the uptake curves expand with increasing [Gd] or decreasing T_1 , and occur due to the ability of the look-up table to describe the ratio data at low T_1 values, which will be dependant on the function used. In this situation, some functions will describe the data with more accuracy, but in the mid-range T_1 values without contrast agent administration all the look-up tables describe the data with equal accuracy.

Effect of T_1 on Pharmacokinetic Modeling

A standard model was fit to the uptake curves on a pixel by pixel basis within a region of interest (ROI) around the prostate. The average values of K^{trans} , v_e and K_{ep} that best fitted the uptakes curves and the percentage of curves that the model fitted are shown in table 1. It can be seen that there is a dependence between the maximum calculated [Gd] and K^{trans} and v_e , and that variations in K_{ep} are also observable. The variations in K^{trans} are large and the difference between the maximum and minimum value accounts for 38%-60% of the individual values.

The low value of K^{trans} as calculated from the linear look-up table is unphysiological and would not be an expected value to find in a tumour, suggesting that using a linear look-up table is inadequate in the calculation of T_1 in DCE-MRI.

Discussion

This investigation highlights the importance of the choice of calibration curve when using look-up tables. All of the functions fitted to the calibration data had an R^2 value greater than 0.9. However, the difference in the uptake curves of figure 4 is significant, and the pharmacokinetic parameters of table 1 were not physiologically likely if certain look-up tables were used.

This raises the question of what is the right look-up table to use in this situation. The theoretical dependence on the ratio between two images and T_1 is complicated and so none of the curves precisely describe the ratio data as a function of T_1 . Based on the comparison between the five look-up tables investigated, the single and bi-exponential and the inverse functions produced similar and values of the pharmacokinetic parameters that are more physiological. The bi-exponential function does have the disadvantage of two extra parameters to describe the ratio data and as a result there are many values of A, B, C and D (equation 5) to describe the same data, making reproducibility experiments challenging.

There is a need in the field of DCE-MRI for a standard look-up table, as work has been published using a variety of look-up tables making results in DCE-MRI incomparable. It can be recommended from this investigation that a linear (equation 8) or logarithmic (equation 7) look-up tables should not be used because of the questionability over the accuracy of the description of the ratio data. Single exponential (equation 4) or an inverse (equation 6) look-up tables produce more physiologically accurate pharmacokinetic parameters. Importantly, there is also a need to perform accurate calibration experiments over a large range of T_1 values to ensure an accurate fit to the ratio data.

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