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A general model to calculate the spin-lattice (T_1) relaxation time of blood, accounting for haematocrit, oxygen saturation and magnetic field strength

Patrick W Hales[1], Fenella J Kirkham[2] and Christopher A Clark[1]

Abstract

Many MRI techniques require prior knowledge of the T1-relaxation time of blood (T_{1bl}). An assumed/fixed value is often used; however, T_{1bl} is sensitive to magnetic field (B_0), haematocrit (*Hct*), and oxygen saturation (*Y*). We aimed to combine data from previous *in vitro* measurements into a mathematical model, to estimate T_{1bl} as a function of B_0, *Hct*, and *Y*. The model was shown to predict T_{1bl} from *in vivo* studies with a good accuracy (±87 ms). This model allows for improved estimation of T_{1bl} between 1.5–7.0 T while accounting for variations in *Hct* and *Y*, leading to improved accuracy of MRI-derived perfusion measurements.

Keywords

ASL, cerebral blood flow measurement, MRI, perfusion weighted MRI, mathematical modelling

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Introduction

The spin-lattice relaxation time of blood (T_{1bl}) plays a critical role in a range of MRI applications. In particular, the accuracy of blood flow measurements made using arterial spin labelling (ASL)[1] depends directly on accurate knowledge of T_{1bl} in a given subject. Black blood angiography, vascular space occupancy imaging, dynamic contrast-enhanced magnetic resonance imaging, cardiac MRI applications, and MR-based temperature monitoring also rely on accurate estimation of this parameter.

A number of factors influence spin-lattice relaxation time (T_1). T_1 increases with Larmor frequency, and therefore magnetic field strength (B_0), which in single phase homogeneous substances can be described using the Bloembergen-Purcell-Pound theory.[2] In human tissues and blood, the relationship is more complex, as macromolecules such as proteins provide relaxation pathways which speed up T_1 relaxation. One such protein is haemoglobin, which is an oxygen transport protein that resides in erythrocytes (red blood cells), and hence haematocrit (*Hct*), which describes the volume fraction of erythrocytes in whole blood, will influence T_{1bl}. Proteins residing in blood plasma, such as albumin and globulin, will similarly effect T_{1bl}. In addition, paramagnetic materials provide a further T_1 relaxation pathway, and, as deoxyhaemoglobin is weakly paramagnetic, the oxygen saturation fraction of blood (Y) will also influence T_1 relaxation. Lastly, the T_1 relaxation time is temperature-dependent, with longer relaxation times found at higher temperatures.

In general, an assumed value of T_{1bl} will be used in the MRI techniques described above, particularly in the clinic, where technical and scan time constraints prevent measurement of T_{1bl} on a patient-by-patient basis. Although many previous studies have determined values of T_{1bl} empirically (see Table 1), these have generally been performed under differing physiological/experimental conditions (magnetic field

[1]Developmental Imaging and Biophysics Section, Institute of Child Health, University College London, London, UK
[2]Clinical Neurosciences Section, Institute of Child Health, University College London, London, UK

Corresponding author:
Patrick Hales, Developmental Imaging and Biophysics Section, University College London Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK.
Email: p.hales@ucl.ac.uk

Table 1. Sources of literature values of R_{1bl}.

Ref.	B_0 (T)	No. data points	Blood source	Age range (years)	Gender	Hct	Y
Stefanovic and Pike[6]	1.5	8	Human (22°C)	–	–	Measured (0.51 ± 0.004)	Measured (0.42–0.93)
Lu et al.[5]	3.0	9	Bovine (37°C)	–	–	Measured (0.38–0.46)	Measured (0.69–0.99)
Rane and Gore[7]	7.0	10	Human (37°C)	–	–	Measured (0–1)	Measured (0.66–0.97)
Grgac et al.[3]	7.0	13	Bovine (37°C)	–	–	Measured (0–1)	Measured (0.4–1.0)
Dobre et al.[8]	4.7,7.0	2	Bovine (37°C)	–	–	Measured (0.43)	Measured (0.79–0.81)
Zhang et al.[4]	1.5, 3.0, 7.0	18	Human in vivo	24–38	M, F	Estimated	Estimated (venous)
Wu et al.[9]	3.0	8	Human in vivo	7–39	M, F	Estimated	Estimated (venous)
Varela et al.[10]	3.0	19	Human in vivo	0.4–37	M, F	Measured	Estimated (venous)
De Vis et al.[11]	3.0	3	Human in vivo	0.05–0.24	M,F	Measured	Estimated (venous)

Note: The range of *Hct* and *Y* are shown if these parameters were measured, if not estimated values were used, adjusted for the age and gender of the subject (for *Hct*), and whether the blood was arterial or venous (for *Y*).

strength, blood oxygenation, haematocrit, etc.), often without direct measurement of all the influencing factors. The aim of this study was to bring together the results of previous studies into a general mathematical model for predicting T_{1bl}, as a function of B_0, Hct, and Y. This will provide estimates of T_{1bl} values in arterial and venous blood, over the range of magnetic field strengths used in clinical practice (1.5–7.0 T). This should lead to subsequent improvements in the accuracy of ASL-derived blood flow measurements, particularly in pathologies where the constitution of the blood is known to be outside the normal range.

Materials and methods

Theory

A two-compartment blood model, consisting of erythrocytes and plasma in fast exchange, was previously described in Grgac et al.[3] In this model, the longitudinal relaxation rate of whole blood (R_{1bl}, equivalent to ${T_{1bl}}^{-1}$) is given by

$$R_{1bl}(Hct, Y) = f_e \cdot R_{1e}(Y) + (1 - f_e) \cdot R_{1p} \quad (1)$$

where Hct is the haematocrit (0–1), Y is the oxygen saturation fraction (0–1), f_e is the fraction of water in whole blood that resides in erythrocytes (0–1), R_{1e} is the longitudinal relaxation rate of erythrocytes (s^{-1}), and R_{1p} is the longitudinal relaxation rate of plasma (s^{-1}). Under normal physiological conditions, water volume fraction in erythrocytes is approximately 70%, and water volume fraction in plasma is 94–95%,[3] which allows f_e to be expressed as a function of Hct as follows[3]

$$f_e = \frac{0.70 \cdot Hct}{0.70 \cdot Hct + 0.95 \cdot (1 - Hct)} \quad (2)$$

In addition, because deoxyhaemoglobin acts as a weak paramagnetic contrast agent, we can express R_{1e} as a function of Y

$$R_{1e}(Y) = R_{1eox} + r_{1deoxyHb} \cdot [Hb] \cdot (1 - Y) \quad (3)$$

where R_{1eox} is the longitudinal relaxation rate of erythrocytes when $Y = 1$ (100% oxygen saturation), $[Hb]$ is the mean corpuscular haemoglobin concentration (5.15 mmol Hb tetramer/L plasma[3]), and $r_{1deoxyHb}$ is the molar relaxivity of deoxyhaemoglobin (s^{-1} L plasma in erythrocyte/mmol Hb tetramer).

When analysing data collected over a range of magnetic field strengths, the possible dependence of R_{1eox}, R_{1p} and $r_{1deoxyHb}$ on B_0 must also be accounted for. The relationship between whole blood R_1 and B_0 between 1.5 and 7.0 T has been shown to be linear,[4] and as such linear regression terms for the above parameters were substituted into equations (1) and (3) as

follows (β_0 represents the 'intercept' term, β_1 represents the 'gradient' with respect to B_0)

$$R_{1eox} = \beta_{0,R1eox} + \beta_{1,R1eox} \cdot B_0 \quad (4)$$

$$r_{1deoxyHb} = \beta_{0,r1deoxyHb} + \beta_{1,r1deoxyHb} \cdot B_0 \quad (5)$$

$$R_{1p} = \beta_{0,R1p} + \beta_{1,R1p} \cdot B_0 \quad (6)$$

By combining equations (1)–(6), a general model was constructed, with R_{1bl} as the dependent variable, B_0, Hct and Y as independent variables, and the following as fitted parameters: $\beta_{0,R1eox}$, $\beta_{1,R1eox}$, $\beta_{0,r1deoxyHb}$, $\beta_{1,r1deoxyHb}$, $\beta_{0,R1p}$, $\beta_{1,R1p}$.

Data analysis

All data analysis was performed using Matlab R2014a (MathWorks Inc., Natick, MA, USA), and Matlab's *fminsearch* algorithm was used for model fitting. Forty-two literature values of T_{1bl},[3,5–8] acquired *in vitro* between 1.5 and 7.0 T in conjunction with empirically controlled variations in Hct and Y (see Table 1), were fit simultaneously to the model. The T_{1bl} values in Stefanovic and Pike[6] were increased by 12% to account for the shift in T_{1bl} between 22°C and 37°C.[5,6] Following initial model fitting, a Monte Carlo simulation was performed to determine the uncertainty on the fitted parameters. Here, the pool of $N = 42$ raw data points were randomly sampled N times (with replacement), and the model was fit to this synthetic raw data set. This process was iterated 1000 times, and the median and 95% confidence interval (CI) of the distribution of fitted values for each parameter were used as the final parameter estimate and its uncertainty, respectively. Parameters for which the 95% CI crossed zero were classified as non-significant, and the process was repeated with these terms set to zero.

Following this, the fitted parameter values were substituted into equations (1) to (6), and the ability of the model to predict values of T_{1bl} taken from further literature sources[4,9–11] (Table 1), in which measurements were made *in vivo*, was tested. These comprised 48 values of T_{1bl}, taken from human studies performed between 1.5 and 7.0 T. In these studies, measurements were made in blood in the sagittal sinus, so normal values of $Y = 0.68$ (for venous blood) were assumed,[12] and, where not measured, a value of Hct, corrected for age and gender, was estimated based on literature values.[13,14]

Results

The Monte Carlo simulation showed that the 95% CI around the fitted value of $\beta_{1,r1deoxyHb}$ crossed zero, and as such this parameter was non-significant (i.e. there was no evidence to suggest $r_{1deoxyHb}$ changes with B_0). With this term set to zero, the following values were obtained for the remaining fitted parameters (95% lower and upper CIs shown in brackets):

$\beta_{0,R1eox}$: 1.10 (0.97, 1.28) s^{-1}, $\beta_{1,R1eox}$: −0.058 (−0.085, −0.038) $s^{-1}T^{-1}$, $\beta_{0,r1deoxyHb}$: 0.033 (1.8×10^{-9}, 0.056) s^{-1} L plasma in erythrocyte/mmol Hb tetramer, and $\beta_{0,R1p}$: 0.49 (0.40, 0.57) s^{-1}, $\beta_{1,R1p}$: −0.023 (−0.035, −0.0079) s^{-1} T^{-1}.

With the above values substituted into equations (1) to (6), the difference between predicted and measured T_{1bl} values (ΔT_{1bl}), taken from the *in vivo* literature sources,[4,9,10] is illustrated in Figure 1(a). Predicted T_{1bl} values were slightly underestimated compared to *in vivo* literature values, with a mean ΔT_{1bl} of −108 ms (predicted minus literature values, mean 6% under-estimation), and a standard deviation in ΔT_{1bl} of 89 ms. As such, an offset of +108 ms should be added to the model when predicting *in vivo* T_{1b} values (see Discussion). The final model, valid between 1.5 and 7.0 T, is therefore

$$\begin{aligned} R'_{1bl}(Hct, Y, B_0) &= f_e \cdot [1.099 - (0.057 \cdot B_0) + ((0.033 \cdot [Hb]) \cdot (1 - Y))] \\ &\quad + [(1 - f_e) \cdot (0.496 - 0.023 \cdot B_0)] \end{aligned}$$

where

$$f_e = \left(\frac{0.70 \cdot Hct}{0.70 \cdot Hct + 0.95 \cdot (1 - Hct)} \right) \quad (7)$$

and

$$T_{1bl}(Hct, Y, B_0) = \frac{1}{R'_{1bl}(Hct, Y, B_0)} + \Delta T_{1bl} \quad (8)$$

where $\Delta T_{1bl} = 0$ and 108 ms for *in vitro* and *in vivo* studies respectively. Note that if a full blood analysis has been performed, a measured value for [Hb] (mean corpuscular haemoglobin concentration) can be used in equation (7), rather than the assumed value of 5.15 mmol Hb tetramer/L plasma.

Figure 1(b) illustrates the change in both modelled and measured in vivo T_{1bl} values as a function of Hct, shown here at 3.0 T.

Discussion

After correcting for the ΔT_{1bl} offset, our model was able to predict literature measurements of *in vivo* T_{1bl} with a good degree of accuracy (root mean square error = 87 ms). For example, in Zhang et al.,[4] the measured T_{1bl} values in venous blood in the sagittal sinus of healthy subjects (mean age 31 years) at 1.5 T, 3.0 T, and 7.0 T were 1480 ms, 1650 ms and 2088 ms, respectively

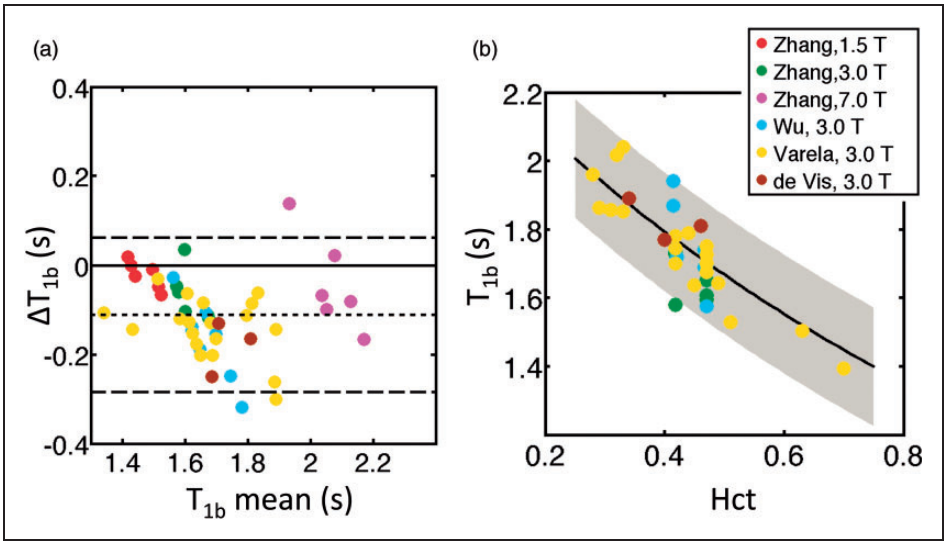

Figure 1. (a) Bland-Altman plot illustrating the difference between modelled and measured values of T_{1bl} (ΔT_{1bl}), between 1.5 and 7.0 T. The horizontal dashed lines show the mean value of ΔT_{1bl} (short dashes) and the limits of agreement (long dashes, mean(ΔT_{1bl}) $\pm$ (1.96xSD(ΔT_{1bl})). (b) Variation in modelled values of T_{1bl} (black line, with grey shading indicating limits of agreement), with literature values overlaid (legend indicates literature source in (a) and (b)). All data in (b) represent *in vivo* T_{1bl} values, and as such the $\Delta T_{1bl} = 180$ ms offset has been added to the modelled values (equation (8)).

(males and females combined). The equivalent values predicted using our model were 1565 ms, 1688 ms, and 2147 ms, respectively (data in Zhang et al.[4] were not used to 'train' the model). Our model fitting indicated that both the T_1 of plasma and fully oxygenated erythrocytes increase with B_0, and our results agree with previous findings that T_{1bl} is highly sensitive to haematocrit, but only weakly dependent on oxygenation.[15] Also, our fitted value for $r_{1deoxyHb}$ of 0.033 s^{-1} L plasma in erythrocyte/mmol Hb tetramer lies between the mean fitted values of 0.052 in Grgac et al.[3] and 0.012 in Blockley et al.[15] (s^{-1} L plasma in erythrocyte/mmol Hb tetramer).

The offset between predicted and literature T_{1bl} values arose from the fact that our model was 'trained' using data from *in vitro* studies (necessary to control the *Hct* and *Y* levels in the blood), then used to predict values from *in vivo* studies. Trisodium citrate was added to the blood in the *in vitro* studies to prevent coagulation, and higher osmolarity sodium concentrations will draw water out of erythrocytes via osmosis, shortening T_1[3]. In Grgac et al.,[3] the addition of anticoagulant was estimated to reduce T_{1bl} by 7%, which agrees very well with the average underestimation of 6% when our model was used to predict literature values acquired *in vivo*.

Implications for arterial spin labelling

When processing ASL data, an assumed value of T_{1bl} is used in the conversion of raw signal into cerebral blood flow (CBF) values (see Alsop et al.[16] for details). Certain pathologies may result in a patient having a haematocrit outside the normal range expected for their age/gender, and assuming a normal *Hct* value in these patients will result in an incorrect estimation of T_{1bl}, which in turn will lead to an incorrect calculation of CBF. For instance, sickle cell anaemia is a genetic condition in which patients have atypical haemoglobin molecules, resulting in a low number of red blood cells (anaemia). In a severely anaemic patient (say $Hct = 0.20$), the calculated value of T_{1bl} in arterial blood ($Y = 0.97$) using our model would be 2.09 s at 3.0 T. If we assumed a normal *Hct* value in this subject (say $Hct = 0.47$ for a 30 year old male), the calculated value of T_{1bl} drops to 1.70 s. This 18% underestimation of T_{1bl}, resulting from an assumed normal value for T_{1bl} rather than a *Hct*-corrected value, would lead to an overestimation in the calculated CBF of approximately 30%, based on a typical pseudo-continuous ASL acquisition (see equation 1 in Alsop et al.[16]).

Conclusions

MRI applications such as ASL are dependent on accurate knowledge of T_{1bl}, which is rarely measured on a patient-by-patient basis. We have presented a mathematical model which brings together previous empirical measurements of T_{1bl}, and provides a general tool for estimation of this parameter in individual subjects, adjusted for magnetic field strength, haematocrit and oxygenation of the blood. In healthy subjects, this

model can be used with assumed normal values of *Hct* (corrected for age/gender) and *Y*, whereas in patients measured *Hct* and *Y* values may be required, which will require blood sampling and non-trivial steps for accurate assessment. Following this, the model presented here will account for the influence of a patient's atypical *Hct* and *Y* values on the estimated value of T_{1bl}. This in turn will have a significant influence on the quantification of CBF using ASL, and considerable errors in CBF quantification will occur if normal values of T_{1bl} are assumed.

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Authors' contributions

PWH designed the research, analysed data and wrote the manuscript; CAC, FJK edited the manuscript and provided clinical input. All authors approved the final manuscript.

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