A General Model to Calculate the Spin-Lattice ($T_1$) Relaxation Time of Blood, Accounting for Haematocrit, Oxygen Saturation and Magnetic Field Strength

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Abstract
Many MRI techniques require prior knowledge of the T1-relaxation time of blood ($T_{1\text{bl}}$). An assumed/fixed value is often used, however, $T_{1\text{bl}}$ 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 $T_{1\text{bl}}$ as a function of $B_0$, $Hct$, and $Y$. The model was shown to predict $T_{1\text{bl}}$ from in vivo studies with a good accuracy ($\pm 87\text{ms}$). This model allows for improved estimation of $T_{1\text{bl}}$ between 1.5-7.0T 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
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 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 3. In this model, the longitudinal relaxation rate of whole blood ($R_{1bl}$, equivalent to $T_{1bl}^{-1}$), is given by:

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

where $Hct$ is the haematocrit (0 to 1), $Y$ is the oxygen saturation fraction (0 to 1), $f_e$ is the fraction of water in whole blood that resides in erythrocytes (0 to 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:

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

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

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

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 plasma3), 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 1.5-7.0 T has been shown to be linear4, and as such linear regression terms for the above parameters were substituted into equations [1] and [3] as follows ($\beta_0$ represents the ‘intercept’ term, $\beta_1$ represents the ‘gradient’ with respect to $B_0$):

$$R_{1eox} = \beta_{0R1eox} + \beta_{1R1eox} \cdot B_0 \tag{4}$$

$$r_{1deoxyHb} = \beta_{0r1deoxyHb} + \beta_{1r1deoxyHb} \cdot B_0 \tag{5}$$

$$R_{1p} = \beta_{0R1p} + \beta_{1R1p} \cdot B_0 \tag{6}$$
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), and Matlab’s `fminsearch` algorithm was used for model fitting. 42 literature values of $T_{1bl}$, acquired *in vitro* between 1.5-7.0 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 6 were increased by 12% to account for the shift in $T_{1bl}$ between 22°C and 37°C. 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 1-6, and the ability of the model to predict values of $T_{1bl}$ taken from further literature sources (Table 1), in which measurements were made *in vivo*, was tested. These comprised 48 values of $T_{1bl}$, taken from human studies performed between 1.5-7.0 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, and, where not measured, a value of $Hct$, corrected for age and gender, was estimated based on.

**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⁻¹T⁻¹, $\beta_{0,r1deoxyHb}$: 0.033 (1.8x10⁻⁹, 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 1-6, the difference between predicted and measured \( T_{1b} \) values (\( \Delta T_{1b} \)), taken from the *in vivo* literature sources\(^4\), is illustrated in Figure 1a. Predicted \( T_{1b} \) values were slightly under-estimated compared to *in vivo* literature values, with a mean \( \Delta T_{1b} \) of -108ms (predicted-literature values, mean 6% under-estimation), and a standard deviation in \( \Delta T_{1b} \) of 89ms. As such, an offset of +108ms should be added to the model when predicting *in vivo* \( T_{1b} \) values (see Discussion). The final model, valid between 1.5-7.0 T, is therefore:

\[
R_{1bl}'(Hct, Y, B_0) = \left( \frac{0.70 \cdot Hct}{0.70 \cdot Hct + 0.95 \cdot (1 - Hct)} \right) \\
\cdot \left[ 1.099 - (0.057 \cdot B_0) + \left( (0.033 \cdot [Hb]) \cdot (1 - Y) \right) \right] \\
+ \left[ \left( 1 - \left( \frac{0.70 \cdot Hct}{0.70 \cdot Hct + 0.95 \cdot (1 - Hct)} \right) \right) \cdot (0.496 - 0.023 \cdot B_0) \right]
\]

\[7\]

\[
T_{1bl}(Hct, Y, B_0) = \frac{1}{R_{1bl}'(Hct, Y, B_0)} + \Delta T_{1bl}
\]

\[8\]

where \( \Delta T_{1bl} = 0 \) and 108 ms for *in vitro* and *in vivo* studies respectively. Note 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 1b illustrates the change in both modelled and measured *in vivo* \( T_{1b} \) values as a function of Hct, shown here at 3.0 T.

**Discussion**

After correcting for the \( \Delta T_{1bl} \) offset, our model was able to predict literature measurements of *in vivo* \( T_{1b} \) with a good degree of accuracy (root mean square error = 87ms). For example, in \(^4\) the measured \( T_{1b} \) 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 1480ms, 1650ms and 2088ms respectively (males and females combined). The equivalent values predicted using our model were 1565ms, 1688ms, and 2147ms respectively (data in \(^4\) 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 \( T_{1b} \) is highly sensitive to haematocrit, but only weakly dependent on oxygenation\(^15\). Also, our fitted value for \( r_{\text{deoxyHb}} \) of 0.033 s\(^{-1}\) L plasma in erythrocyte/mmol Hb tetramer lies between the mean fitted values of 0.052 in \(^3\) and 0.012 in \(^15\) (s\(^{-1}\) L plasma in erythrocyte / mmol Hb tetramer). It should be
noted that if a full blood analysis shows mean corpuscular haemoglobin concentration to be significantly different from the assumed value used in this study, the validity of the model could be slightly impaired.

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 $T_1$. In 2, the addition of anti-coagulant was estimated to reduce $T_{1bl}$ by 7%, which agrees very well with the average under-estimation 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 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% under-estimation 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 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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Author Contribution statement
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.

Disclosure/Conflict of Interest
The authors have no conflict of interests to declare.

References

Figure legends

Figure 1 (A) Bland-Altman plot illustrating the difference between modelled and measured values of $T_{1b}$ ($\Delta T_{1b}$), between 1.5-7.0 T. The horizontal dashed lines show the mean value of $\Delta T_{1b}$ (short dashes) and the limits of agreement (long dashes, mean($\Delta T_{1b}$) ± (1.96xSD($\Delta T_{1b}$)). (B) Variation in modelled values of $T_{1b}$ (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 $T_{1b}$ values, and as such the $\Delta T_{1b} = 180$ ms offset has been added to the modelled values (equation 8).
Table 1 Sources of literature values of $R_{1\beta l}$.

<table>
<thead>
<tr>
<th>Ref.</th>
<th>$B_0$ (T)</th>
<th>No. data points</th>
<th>Blood source</th>
<th>Age range (years)</th>
<th>Gender</th>
<th>Hct</th>
<th>$Y$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stefanovic $^6$</td>
<td>1.5</td>
<td>8</td>
<td>Human (22 °C)</td>
<td>-</td>
<td>-</td>
<td>Measured</td>
<td>$0.51 \pm 0.004$</td>
</tr>
<tr>
<td>Lu $^5$</td>
<td>3.0</td>
<td>9</td>
<td>Bovine (37 °C)</td>
<td>-</td>
<td>-</td>
<td>Measured</td>
<td>$0.38-0.46$</td>
</tr>
<tr>
<td>Rane $^7$</td>
<td>7.0</td>
<td>10</td>
<td>Human (37 °C)</td>
<td>-</td>
<td>-</td>
<td>Measured</td>
<td>$0.66-0.97$</td>
</tr>
<tr>
<td>Grgac $^3$</td>
<td>7.0</td>
<td>13</td>
<td>Bovine (37 °C)</td>
<td>-</td>
<td>-</td>
<td>Measured</td>
<td>$0.4-1.0$</td>
</tr>
<tr>
<td>Dobre $^8$</td>
<td>4.7, 7.0</td>
<td>2</td>
<td>Bovine (37 °C)</td>
<td>-</td>
<td>-</td>
<td>Measured</td>
<td>$0.43$</td>
</tr>
<tr>
<td>Zhang $^4$</td>
<td>1.5, 3.0, 7.0</td>
<td>18</td>
<td>Human in-vivo</td>
<td>24-38</td>
<td>M, F</td>
<td>Estimated</td>
<td>Estimated (venous)</td>
</tr>
<tr>
<td>Wu $^9$</td>
<td>3.0</td>
<td>8</td>
<td>Human in-vivo</td>
<td>7-39</td>
<td>M, F</td>
<td>Estimated</td>
<td>Estimated (venous)</td>
</tr>
<tr>
<td>Varela $^{10}$</td>
<td>3.0</td>
<td>19</td>
<td>Human in-vivo</td>
<td>0.4-37</td>
<td>M, F</td>
<td>Measured</td>
<td>Estimated (venous)</td>
</tr>
<tr>
<td>De Vis $^{11}$</td>
<td>3.0</td>
<td>3</td>
<td>Human in-vivo</td>
<td>0.05-0.24</td>
<td>M, F</td>
<td>Measured</td>
<td>Estimated (venous)</td>
</tr>
</tbody>
</table>

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 $Y$).