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Non-Invasive evaluation of blood oxygen saturation and hematocrit from $T_1$ and $T_2$ relaxation times

Sharon Portnoy, Mike Seed, John G. Sled, and Christopher K. Macgowan

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Abstract

Purpose
We propose an analytical method for calculating both the hematocrit ($Hct$) and oxygen saturation ($sO_2$) of blood from measurements of its $T_1$ and $T_2$ relaxation times.

Theory
Through algebraic substitution, the established two-compartment relationships which describe $R_1 = T_1^{-1}$ and $R_2 = T_2^{-1}$ as a function of hematocrit and oxygen saturation were rearranged to solve for $Hct$ and $sO_2$ in terms of $R_1$ and $R_2$. The resulting solutions for $Hct$ and $sO_2$ are the roots of cubic polynomials.

Methods
The feasibility of the proposed method was assessed by comparing estimates of $Hct$ and $sO_2$ derived from $T_1$ and $T_2$ measurements in umbilical cord blood specimens ($N=86$) to ground-truth values obtained from a blood gas analyzer.

Results
Agreement between estimated and ground-truth blood properties was excellent: bias=0.011 and 0.013, 95% limits of agreement=±0.116 and ±0.123 for $Hct$ and $sO_2$, respectively. For all specimens with ground-truth $sO_2<0.83$, there was a single, unique solution for $Hct$ and $sO_2$.

Conclusion
The results of this in-vitro study demonstrate accurate quantification of both $Hct$ and $sO_2$ from a measurement of $T_1$ and $T_2$. This method can be utilized for non-invasive oximetry in fetal vessels - an application where the use of existing oximetry devices is either unfeasible or requires risky and invasive blood sampling procedures.

Keywords
umbilical cord blood, longitudinal relaxation, transverse relaxation, oxygenation, hematocrit
Introduction

Since the magnetic susceptibility of hemoglobin depends on its oxygenation state, relaxation properties of whole blood are a function of both the quantity of hemoglobin (the hematocrit, $Hct$), and the fraction of hemoglobin binding sites which are oxygenated (the oxygen saturation, $sO_2$). In spite of this dual dependence, MR measurements of $sO_2$ are typically based only on a measurement of the transverse relaxation time, $T_2$, while assuming a normal value for $Hct$ (0.4-0.5) [1-4]. In postnatal patients, the true $Hct$ can be measured non-invasively by optical means [5], or by routine blood sampling (venipuncture or finger prick) [6] and oximetry measures can be corrected accordingly. Within a fetal population, hematocrit measurement is much more difficult. One option is ultrasound-guided percutaneous umbilical cord blood sampling (PUBS), or cordocentesis; however, this procedure carries a risk of fetal death ($\sim$1%)[7]. A less invasive alternative is Doppler interrogation of the middle cerebral artery (MCA), where peak systolic blood velocity negatively correlates with $Hct$ due to the associated changes in blood viscosity [8]. This method, however, is less reliable after 35 weeks gestation [8] and is chiefly used for the diagnosis of low hematocrit or anemia – the correlation between MCA velocity and $Hct$ in cases of elevated hematocrit, or polycythemia is less clear [9].

The normal variation in fetal hematocrit across gestation is well established and relatively consistent amongst subjects ($Hct$ increases linearly from 0.3±0.03 at 17 weeks' gestation to 0.45±0.03 at 40 weeks) [10]. However, a variety of conditions, such as congenital heart disease, intrauterine growth restriction (IUGR), and maternal alloimmunization are associated with abnormal $Hct$ values [10-12]. In these cases, since MRI properties are dependent on both $Hct$ and $sO_2$, an incorrect assumption of normal hematocrit will introduce bias in $sO_2$ estimates. Moreover, knowledge of the true hematocrit is necessary for calculation of blood oxygen content, $cO_2$ ($cO_2 \propto Hct \cdot sO_2$). Measurements of $cO_2$ can be combined with blood flow data to calculate oxygen delivery and consumption, facilitating evaluation of organ metabolism.

In this work, we propose a method for calculating both $Hct$ and $sO_2$ from vascular $T_1$ and $T_2$ measurements. The feasibility of the proposed approach is investigated using relaxometry measurements performed in-vitro on umbilical cord blood samples. Combining the two relaxometry measurements exploits the complementary nature of $T_1$ and $T_2$ relaxation times in terms of their dependence on blood properties: both $T_1$ and $T_2$ decrease with $Hct$ and increase with $sO_2$, but $T_1$ is primarily affected by $Hct$, while $T_2$ is primarily affected by $sO_2$. Determination of both $Hct$ and $sO_2$
facilitates a more complete and accurate hematological assessment. This is particularly helpful in a fetal population, where the hematocrit may be altered by pathology but cannot be easily quantified. However, the proposed method is also applicable to adult blood and may be useful in situations where logistical limitations (e.g. lack of research ethics approval for blood sampling) prevent investigators from obtaining blood for direct hematocrit measurement.

Theory
Variations in blood relaxation times as a function of blood oxygen saturation, $sO_2$, and hematocrit, $Hct$, can be described using simple biophysical models, which represent blood as a two-compartment system (plasma and erythrocytes) in the fast exchange regime [13, 14]. Briefly, the longitudinal relaxation rate of blood, $R_1 = T_1^{-1}$, is given by the compartment-weighted sum:

$$R_1 = Hct \cdot R_{1, ery} + (1 - Hct) \cdot R_{1, plas}, \quad \text{(Equation 1)}$$

where $R_{1, ery}$ and $R_{1, plas}$ are the relaxation rates of erythrocytes and plasma, respectively. Since deoxyhemoglobin (dHb) behaves as a weak paramagnetic contrast agent [15], $R_{1, ery}$ exhibits a dependence on oxygen saturation, given by:

$$R_{1, ery} = R_{1, ery, 0} + r_{1, dHb} \cdot \left( 1 - \frac{sO_2}{100\%} \right). \quad \text{(Equation 2)}$$

The transverse relaxation rate, $R_2 = T_2^{-1}$, of blood can be described by the Luz-Meiboom (L-M) model [16], which similarly includes a weighted sum of erythrocyte ($R_{2, ery}$) and plasma ($R_{2, plas}$) relaxation rates.

Also included is an exchange term, $R_{2, ex}$, to account for the effect of spin exchange between the two compartments which have an oxygen-dependent frequency difference:

$$R_2 = Hct \cdot R_{2, ery} + (1 - Hct) \cdot R_{2, plas} + R_{2, ex}. \quad \text{(Equation 3)}$$

The erythrocyte transverse relaxation rate, $R_{2, ery}$, includes plasma ($R_{2, plas}$), diamagnetic ($R_{2, dia}$), and oxygenated- ($R_{2, oxy}$) and deoxygenated ($R_{2, deoxy}$) hemoglobin contributions:

$$R_{2, ery} = R_{2, plas} + R_{2, dia} + R_{2, oxy} + (1 - sO_2) \cdot (R_{2, deoxy} - R_{2, oxy}). \quad \text{(Equation 4)}$$

The exchange component of the relaxation rate, $R_{2, ex}$, is given by:

$$R_{2, ex} = Hct \cdot (1 - Hct) \cdot (\Delta \omega)^2 \cdot \tau \left[ 1 - \frac{2\tau}{\tau_{180}} \cdot \tanh \left( \frac{\tau_{180}}{2\tau} \right) \right], \quad \text{(Equation 5)}$$

where $\tau_{180}$ is the refocusing interval and $\tau$ is the erythrocyte-plasma exchange correlation time. $\Delta \omega$, the
frequency difference between erythrocytes and plasma is given by:
\[ \Delta \omega = \gamma B_0 \left[ (\omega_{\text{dia}} + \omega_{\text{oxy}}) + (1 - sO_2) \cdot (\omega_{\text{deo}} - \omega_{\text{oxy}}) \right] \text{ (rads/s)}. \]  
(Equation 6)

The L-M model thus has 6 measurable terms: \( R_{2,\text{plas}}, (R_{2,\text{dia}} + R_{2,\text{oxy}}), (R_{2,\text{deo}} - R_{2,\text{oxy}}), \tau, (\omega_{\text{dia}} + \omega_{\text{oxy}}), \) and \( (\omega_{\text{deo}} - \omega_{\text{oxy}}) \).

Equations 1-6 describe the variation in \( R_1 \) and \( R_2 \) with Hct and \( sO_2 \). Since a given relaxation rate (either \( R_1 \) or \( R_2 \)) depends on both hematocrit and oxygen saturation, each rate constrains Hct and \( sO_2 \) to a curve in \( \{\text{Hct, } sO_2\} \) space. Measurement of both \( R_1 \) and \( R_2 \) thus constrains Hct and \( sO_2 \) to the intersection of a pair of such curves. This is illustrated in Figure 1. Analytical expressions describing the values of Hct and \( sO_2 \) constrained by measurements of \( R_1 \) and \( R_2 \) can be obtained by algebraic substitution and rearrangement of terms in Eqs. 1-6. The result is a pair of cubic equations:

\[ A_1 \cdot (\text{Hct})^3 + B_1 \cdot (\text{Hct})^2 + C_1 \cdot (\text{Hct}) + D_1 = 0 \]  
(Equation 7)

and

\[ A_2 \cdot (sO_2)^3 + B_2 \cdot (sO_2)^2 + C_2 \cdot (sO_2) + D_2 = 0 \]  
(Equation 8)

Coefficients \( A_{1,2}, B_{1,2}, C_{1,2} \) and \( D_{1,2} \) are related to \( R_1 \) and \( R_2 \) as well as the biophysical parameters described above (\( R_{1,\text{plas}}, R_{1,\text{ery},0}, r_{1,dHB}, R_{2,\text{plas}}, (R_{2,\text{dia}} + R_{2,\text{oxy}}), (R_{2,\text{deo}} - R_{2,\text{oxy}}), \tau, (\omega_{\text{dia}} + \omega_{\text{oxy}}), \) and \( (\omega_{\text{deo}} - \omega_{\text{oxy}}) \)). Expressions for these coefficients are provided in the Appendix.

Note that it is not necessary to solve both cubic equations to obtain solutions for Hct and \( sO_2 \). Having solved Eq. 7 for Hct, the corresponding solution for \( sO_2 \) can be obtained (from substitution in Eq. 1), as follows:

\[ sO_2 = \frac{R_1 - R_{1,\text{plas}} - \text{Hct} \cdot (R_{1,\text{ery}} - R_{1,\text{plas}} + r_{1,dHB}^t) - r_{1,dHB}^t \cdot \text{Hct}}{R_{1,\text{ery}} - R_{1,\text{plas}} + r_{1,dHB}^t (1 - sO_2)}. \]  
(Equation 9)

Similarly, after solving Eq. 8 for \( sO_2 \), the corresponding Hct can be obtained by:

\[ \text{Hct} = \frac{R_1 - R_{1,\text{plas}}}{R_{1,\text{ery}} - R_{1,\text{plas}} + r_{1,dHB}^t (1 - sO_2)}. \]  
(Equation 10)

Thus, given a measurement of \( \{R_1, R_2\} \), the \( \{\text{Hct, } sO_2\} \) solution can be obtained using Eq. 7 and 9, or, equivalently, Eq. 8 and 10.

Depending on its coefficients, a cubic equation will have either three real roots, or one real root and two...
complex conjugate roots. In the event of three real roots, not all of them will necessarily be unique –
two, or even three of them may be repeated. However, the potential for more than one unique real root
implies multiple solutions for Hct and sO2 and additional information would be necessary to identify
the correct one. The physical range for Hct and sO2 is [0,1]. Therefore, any solutions which, taking
into account the uncertainty in Hct and sO2, fall outside this range in a statistically significant manner,
should be eliminated. Based on the established uncertainty in Hct and sO2 given typical \{R_1, R_2\}
measurement error (see Results), this corresponds to disregarding solutions beyond \{-0.1<sO2<1.1, -
0.05<Hct<1.05\}.

It is also possible for Eqs. 7 and 8 to have no physical \{Hct, sO2\} solution. This indicates the absence
of an intersection between the curves defined by R_1 and R_2 (see Figure 1). In these cases, an
approximate solution can be derived from the point in physical \{Hct, sO2\} space which bisects the
shortest path between the two curves. If, however, coefficients A_{1,2}, B_{1,2}, C_{1,2} and D_{1,2} are such that
Eqs. 7 and 8 have one non-physical real root and two complex-conjugate roots, an alternate
approximate solution can be obtained from the real component of the complex roots. This follows
from the interpretation of the complex roots of cubic equations described in [17]. While a real root is
the abscissa of a zero-crossing, the real part of a complex-conjugate root corresponds to the abscissa of
a local minimum. The imaginary part of the root is related to the proximity of this local minimum to
zero. A comparison of solutions obtained by these two strategies is provided in the Results section.

**Methods**

The feasibility of estimating blood Hct and sO2 from a measurement of R_1 and R_2 relaxation rates
using equations 7-10 was investigated using *in-vitro* umbilical cord blood relaxometry data obtained
previously [18]. Briefly, umbilical cord blood was collected from 6 placentas following caesarean
delivery. Inclusion criteria for the study were women with no maternal medical conditions or fetal
abnormalities who had reached at least 37 weeks gestation at time of delivery. Informed written
consent was obtained from each patient prior to delivery and the collection procedure and subsequent
handling of data followed institutional ethical guidelines.

The 30-50 mL volume of blood obtained from each collection was divided into multiple 1-2 mL
specimens, which were processed (by removal/addition of separated plasma and exposure to nitrogen
gas) to provide a range of Hct and sO2 values. In total, relaxometry measurements were performed on
86 samples (6 collections and approximately 15 samples/collection) with \(sO_2\) values ranging from 0.04-1.0 and \(Hct\) from 0.19-0.76. For a more detailed description of the blood collection and processing procedure, please see [18].

According to Eq. A2-A3, coefficients \(A_1\), \(B_1\), \(C_1\) and \(D_1\) (Eq. 7) were calculated from the measured \(R_1\) and \(R_2\) relaxation rates for each specimen, along with the biophysical parameters obtained from fitting all the cord blood relaxometry data to the two-compartment models described in the Theory section. Details of the fitting procedure are described in [18] and the biophysical parameters are summarized here in Table 1. \(R_1\) and \(R_2\) measurements for each specimen were obtained using a Modified Look-Locker inversion recovery (MOLLI) and a multi echo spin echo pulse sequence (refocusing interval, \(\tau_{180}=12\) ms), respectively. For more information on specific pulse sequence parameters, see [18].

Predicted \(\{Hct, sO_2\}\) values for each specimen were then obtained from the solutions of Eq. 7 and Eq. 9. The performance of the proposed approach was assessed by comparing the predicted values to the “ground truth” \(\{Hct, sO_2\}\) obtained from blood gas analysis of each specimen.

Monte-Carlo simulations were conducted to assess how uncertainty in \(R_1\) and \(R_2\) measurements propagates into uncertainty in the predictions of \(Hct\) and \(sO_2\). Using Eqs. 1-6 with \(\tau_{180}=12\) ms and the biophysical parameters in Table 1, values of \(\{R_1, R_2\}\) were calculated at 399 points on a uniform grid in \(\{Hct, sO_2\}\) space (0.05\(\leq Hct \leq\) 0.95, 0.0\(\leq sO_2 \leq\) 1.0, increments of 0.05). For each resulting \(\{R_1, R_2\}\) pair, 1000 new pairs were generated based on a normal distribution for \(R_1\) and \(R_2\) with a standard deviation equal to 5% of the given relaxation rate. The 5% standard deviation was chosen as it reflects an uncertainty typical of in-vivo relaxometry measurements. For each of the 1000 generated \(\{R_1, R_2\}\) pairs, predicted values for \(\{Hct, sO_2\}\) were obtained from Eq. 7 and 9. The \(\{Hct, sO_2\}\) measurement uncertainty was then assessed from the resulting distribution of predicted values.

**Results**

A contour plot showing the set of physiologically feasible solutions for \(Hct\) and \(sO_2\) (i.e. 0\(\leq Hct \leq\) 1 and 0\(\leq sO_2 \leq\) 1) given a measurement of \(\{R_1, R_2\}\) is provided in Figure 2. Throughout most of the \(\{R_1, R_2\}\) space, a single, unique solution exists for \(\{Hct, sO_2\}\). However, the black arrow indicates an isolated region of overlapping contour lines, where \(\{R_1, R_2\}\) measurements have two solutions for \(\{Hct, sO_2\}\). Predicted \(Hct\) and \(sO_2\) values for cord blood specimens are compared to true values obtained from blood gas analysis in Figure 3. As described in the Theory, \(Hct\) solutions in the range [-0.05, 1.05] and
sO₂ solutions in the range [-0.1,1.1] were accepted. For the majority of specimens (69 out of 86), there was a single, unique solution for \{Hct, sO₂\}. Four specimens had two \{Hct, sO₂\} solutions and for thirteen specimens, there was no real-numbered, physiological solution. For all 17 specimens with either two solutions or no solution, the true oxygen saturation was above 0.83. An additional 13 specimens also had true sO₂>0.83, but produced only one solution.

For specimens with two solutions, the two \{Hct, sO₂\} predictions were similar. Among these specimens, the maximum difference between the two Hct and sO₂ predictions was 0.04 and 0.11, respectively. The proximity of the two solutions can be inferred from the similarity in color of the overlapping contour lines in Figure 1. For these specimens, both predicted values are plotted (green squares) in Figure 3.

All 13 specimens with no physiological solution had one non-physical real root (sO₂≥1.1) and two complex-conjugate roots. Two strategies, based either on the real component of the complex roots or the midpoint along the shortest line connecting the curves defined by R₁ and R₂ (determined here by a brute force search), were proposed in the Theory to handle these cases. Among the 13 specimens, the maximum difference between Hct and sO₂ values obtained using these two approaches was 0.03 and 0.01, respectively. Given the close agreement of the two strategies and relative simplicity of the real-component solution, this direct approach was adopted for Hct and sO₂ prediction in these cases. These approximate solutions are indicated by red stars in Figure 3.

A Bland-Altman analysis of the difference between true and predicted values of Hct and sO₂ indicated a mean bias of 0.011 and 0.013 and 95% limits of agreement of ±0.116 and ±0.123 in Hct and sO₂, respectively. Erring on the conservative side, for the four specimens which had two solutions, the solution which was furthest from the true \{Hct, sO₂\} was included in the analysis.

Results from the Monte-Carlo simulation, shown in Figure 4, demonstrate how 5% error in R₁ and R₂ propagates to calculated Hct and sO₂ values. These contour plots depict the interquartile range (IQR) of the predicted Hct (a) and sO₂ (b) distributions, based on 1000 Monte-Carlo iterations. When iterations of the simulation produced two solutions, both were included in the distribution analysis. In no-solution cases, if there was a pair of complex-conjugate roots, their real component was used. However, in simulations where the true Hct and/or sO₂ were near the edges of the physical space, some Monte-Carlo iterations had 3 real roots which were all non-physical (sO₂≤-0.1 or sO₂≥1.1). The frequency of this circumstance was below 10% (<100 of 1000 iterations) for simulations with
0.15<sO2<0.9 and Hct>0.1 and was zero for simulations with 0.25<Hct<0.85 and 0.25<sO2<0.85. For these iterations, the solution was set to the midpoint between the curves defined by R1 and R2 at the sO2 boundary (sO2=-0.1 or sO2=1.1).

Although the precision of Hct and sO2 predictions was variable, the IQR of both Hct and sO2 was less than 0.1 over a broad range of true values (0.25≤Hct≤0.75, sO2≤0.8). Outside this range, the uncertainty in sO2 increased (0.1≤IQR<0.6), while that of Hct was relatively stable (IQR<0.16).

Implications of the variable precision of Hct and sO2 predictions will be examined further in the Discussion.

**Discussion**

In this work, a novel approach for quantifying the hematocrit and oxygen saturation of blood based on a combined analysis of the longitudinal and transverse relaxation rates was introduced. The feasibility of this analytical approach was demonstrated by comparing estimates of Hct and sO2 derived from R1 and R2 measurements in umbilical cord blood specimens, to ground-truth values obtained from a blood gas analyzer. In general, the correspondence between calculated and ground-truth blood properties was excellent. This non-invasive approach is useful for measurements in fetal vessels, where conventional oximetry is either unfeasible or requires highly invasive and risky blood sampling procedures.

A limitation of the proposed approach is the lack of a single, unique \{Hct, sO2\} solution for certain \{R1, R2\} values (black arrow in Figure 2). Specifically, a small subset of cord blood specimens had two solutions (N=4) or no solution (N=13). Importantly, these circumstances only arose in specimens with high oxygen saturation (sO2>0.83). In clinical applications, such sO2 values are expected only rarely. Throughout the fetal circulation, even under normoxic conditions, the oxygen saturation does not exceed 0.85 [19]. Furthermore, in the event of no solution, an approximate solution can often be easily obtained from the real part of complex conjugate roots for Hct and sO2. In cases with two solutions, given the relatively low oxygen saturation within fetal vessels, it may be possible to rule out any solution with sO2>0.95.

As described in the Introduction, in the event that R1 data is unavailable, an estimate of sO2 can be obtained from a measurement of R2 alone by assuming a normal value for the hematocrit, Hct, and solving the following quadratic equation:

\[
(K_5 \cdot Hct - K_5 \cdot Hct^2) \cdot sO_2^2 + (K_3 \cdot Hct + K_4 \cdot Hct^2) \cdot sO_2 + (K_0 + K_1 \cdot Hct + K_2 \cdot Hct^2 - R_2) = 0, \text{(Equation 11)}
\]
where coefficients $K_0, \ldots, K_5$ are described in the Appendix. With this approach, which has been applied to both fetal and adult blood oximetry [1, 4, 20, 21], discrepancies between the assumed and true Hct can lead to systematic $sO_2$ misestimation. However, for true $sO_2 < 0.8$, the bias in estimates obtained from Eq. 11 with the assumption of a normal, late-gestation Hct of 0.45 is less than 0.05 over a wide range of true Hct values (0.35 < Hct < 0.7). This tolerance of Hct discrepancy is a result of the limited dependence of $R_2$ on hematocrit within this range.

In general, assumptions of normal Hct and application of Eq. 11 should be made with caution, particularly involving pathologies that affect Hct. Moreover, ignorance of Hct prevents accurate calculation of blood oxygen content. These observations, combined with the relative simplicity of $R_1$ measurement, argue for quantification of Hct using the described analytics. Since Hct is constant throughout the arteries and veins, protocols involving oximetry in several vessels need only measure both $R_1$ and $R_2$ in a single one. The resulting Hct estimate (Eq. 7) can then be used to calculate $sO_2$ from $R_2$ alone (Eq. 11) in the remaining vessels. Alternatively, measurements of $\{R_1, R_2\}$ in multiple vessels can be used to improve the accuracy of the estimated Hct.

The precision of $sO_2$ and Hct predictions given 5% error in relaxometry measurements was assessed through Monte-Carlo simulations. As indicated in Figure 4, the precision of the proposed method depended on the true Hct and $sO_2$. However, the IQR of the calculated Hct and $sO_2$ was less than 0.1 over a wide range of true values: $0.25 \leq \text{Hct} \leq 0.75$, $sO_2 \leq 0.8$. Values outside this range are rare in the fetus. Throughout the fetal circulation, $sO_2 \leq 0.85$. However, very low fetal hematocrits ($\text{Hct} < 0.1$) can be encountered in severe cases of red cell alloimmunization [22] and $\text{Hct} > 0.75$ can arise in extreme cases of neonatal polycythemia [23]. While the uncertainty in $sO_2$ calculations will be high in these instances, Hct calculations maintain an IQR < 0.1. In such cases, Hct is arguably the parameter of greater clinical interest.

The reduced precision of $sO_2$ calculations Hct extrema is not surprising. As described in the Introduction, $R_1$ and $R_2$ relaxation rates are complementary in terms of their dependence on blood properties: $R_1$ is primarily affected by Hct, while $R_2$ is primarily affected by $sO_2$. The dependence of $R_2$ on $sO_2$ arises from an oxygen-dependent frequency difference between plasma and erythrocytes. Spin exchange between the two frequency shifted compartments leads to an increase in $R_2$. Large reductions in the size of either compartment (i.e. very low or high Hct) will diminish this effect and decrease the precision of $sO_2$ calculations.
Assuming that the calculated $Hct$ and $sO_2$ is reported in terms of the median ± the semi-interquartile range (IQR/2), the absolute uncertainty in $Hct$ ranges from ±0.02 to ±0.08 while that of $sO_2$ ranges from ±0.02 to ±0.32 (±0.02 to ±0.10 for $0.25 \leq Hct \leq 0.75$). This level of precision is lower than many specialized oximetry devices (e.g. pulse oximeters, handheld blood gas analyzers), which typically report absolute uncertainties in $Hct$ and $sO_2$ below ±0.05 [6, 24]. However, this MRI-based method can be used for in-vivo studies of fetal vessels, where the use of such devices is impracticable and/or risky.

While further validation with in-vivo relaxometry data is necessary, the current in-vitro investigation demonstrates the feasibility of the proposed technique. This analytical method for determination of both $Hct$ and $sO_2$ is simple and robust, facilitating greater accuracy in studies of the fetal circulation.
Appendix

Solutions for Hct and sO2, given a measurement of $R_1$ and $R_2$, are described by the following pair of cubic polynomials:

\[ A_1 \cdot \text{Hct}^3 + B_1 \cdot \text{Hct}^2 + C_1 \cdot \text{Hct} + D_1 = 0 \]  
\[ A_2 \cdot (sO2)^3 + B_2 \cdot (sO2)^2 + C_2 \cdot (sO2) + D_2 = 0 \].

(Equation A1)

Coefficients $A_{1,2}, B_{1,2}, C_{1,2}$ and $D_{1,2}$ can be expressed in terms of $R_1$ and $R_2$ and intermediate constants $K_0, K_1, K_2, K_3, K_4, K_5$, and $M_0, M_1, M_2$:

\[ A_1 = K_2 M_2^2 - K_4 M_1 M_2 - K_5 M_1^2 \]
\[ A_2 = K_5 \cdot (R_1 M_2 - M_0 M_2) \]
\[ B_1 = K_1 M_2^3 + K_3 M_1 M_2 + K_4 \cdot (R_1 M_2 - M_0 M_2) + K_5 \cdot (M_1^2 + 2R_1 M_1 - 2M_0 M_1) \]
\[ B_2 = K_5 \cdot (R_1 M_1 - M_0 M_1)^2 + K_3 \cdot (R_1 M_2 - M_0 M_2) + K_4 \cdot (R_1 - M_0)^2 M_1^2 \]
\[ C_1 = K_0 M_2^2 + K_5 \cdot (R_1 M_2 - M_0 M_2) + K_5 \cdot (2M_0 M_1 - 2M_1 R_1 (R_1 - M_0)^2) R_2 M_2^2 \]
\[ C_2 = K_4 \cdot (M_0 - R_1)^2 + K_3 \cdot (R_1 M_1 - M_0 M_1) + K_1 \cdot (R_1 M_2 - M_0 M_2) + 2K_0 M_1 M_2 - 2R_2 M_1 M_2 \]
\[ D_1 = K_5 \cdot (R_1 - M_0)^2 \]
\[ D_2 = K_2 \cdot (M_0 - R_1)^2 + K_1 \cdot (R_1 M_1 - M_0 M_1) + K_0 M_1^2 - R_2 M_1^2 \].

(Equation A2)

Intermediate constants $K_0, K_1, K_2, K_3, K_4, K_5$, and $M_0, M_1, M_2$ are, in turn, related to biophysical parameters $R_{1,\text{plas}}, R_{1,\text{ery}}, R_{1,dHb}, R_{2,\text{plas}}, R_{2,\text{di}a + \text{R}_{2,\text{oxy}}}, R_{2,\text{deo} + \text{R}_{2,\text{oxy}}}, \tau, \text{ dia} + \omega_{\text{oxy}}$, and $\omega_{\text{deo}} - \omega_{\text{oxy}}$ as follows:

\[ K_0 = R_{2,\text{plas}} \]
\[ K_1 = (R_{2,\text{dia}} + R_{2,\text{oxy}}) + \mu \cdot [(\omega_{\text{dia}} + \omega_{\text{oxy}}) + (\omega_{\text{deo}} - \omega_{\text{oxy}})]^2 \]
\[ K_2 = \mu \cdot [(\omega_{\text{dia}} + \omega_{\text{oxy}}) + (\omega_{\text{deo}} - \omega_{\text{oxy}})]^2 \]
\[ K_3 = (R_{2,\text{deo}} + R_{2,\text{oxy}}) \cdot 2\mu \cdot (\omega_{\text{deo}} - \omega_{\text{oxy}}) \cdot [(\omega_{\text{dia}} + \omega_{\text{oxy}}) + (\omega_{\text{deo}} - \omega_{\text{oxy}})] \]
\[ K_4 = 2\mu \cdot (\omega_{\text{deo}} - \omega_{\text{oxy}}) \cdot [(\omega_{\text{dia}} + \omega_{\text{oxy}}) + (\omega_{\text{deo}} - \omega_{\text{oxy}})] \]
\[ K_5 = \mu \cdot (\omega_{\text{deo}} - \omega_{\text{oxy}})^2 \]
\[ M_0 = R_{1,\text{plas}} \]
\[ M_1 = R_{1,\text{ery}} - R_{1,\text{plas}} + R_{1,dHb} \]
\[ M_2 = -R_{1,dHb} \].

(Equation A3)

where the constant $\mu$ in coefficients $K_1, \ldots, K_5$ relates to the refocusing interval, $\tau_{180}$:

\[ \mu = \tau \cdot \frac{2\tau}{\tau_{180}} \cdot \tanh \left( \frac{\tau_{180}}{2\tau} \right) \].

(Equation A4)
## Tables

Table 1: Biophysical parameters for the description of umbilical cord blood relaxation rates.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_{1,\text{plas}}$ (s^{-1})</td>
<td>0.44</td>
</tr>
<tr>
<td>$R_{1,\text{ery,0}}$ (s^{-1})</td>
<td>0.95</td>
</tr>
<tr>
<td>$r'_{dHb}$ (s^{-1})</td>
<td>0.29</td>
</tr>
<tr>
<td>$R_{2,\text{plas}}$ (s^{-1})</td>
<td>1.60</td>
</tr>
<tr>
<td>$R_{2,\text{dia}} + R_{2,\text{oxy}}$ (s^{-1})</td>
<td>5.1</td>
</tr>
<tr>
<td>$R_{2,\text{deoxy}} - R_{2,\text{oxy}}$ (s^{-1})</td>
<td>-3.1</td>
</tr>
<tr>
<td>$\omega_{\text{dia}} + \omega_{\text{oxy}}$ (ppm)</td>
<td>-0.071</td>
</tr>
<tr>
<td>$\omega_{\text{deoxy}} - \omega_{\text{oxy}}$ (ppm)</td>
<td>-0.62</td>
</tr>
<tr>
<td>$\tau$ (ms)</td>
<td>2.27</td>
</tr>
</tbody>
</table>
Figures

Figure 1: Constraining Hct and sO₂ with R₁ and R₂ measurements. R₁=0.85 s⁻¹ confines {Hct, sO₂} to the solid line. R₂=14 s⁻¹ limits {Hct, sO₂} to the dashed line. A single solution, {Hct=0.6, sO₂=0.4}, is derived from the intersection of these two lines.
Figure 2: Contour plots indicating solutions for Hct (a) and sO2 (b) based on a measurement of \{R_1, R_2\}. For example, \{R_1=0.85 \text{ s}^{-1}, R_2=14 \text{ s}^{-1}\} (dashed lines) corresponds to \{sO2=0.4, Hct=0.6\}. The black arrow highlights a region with overlapping contour lines, where \{R_1, R_2\} yields two solutions for \{Hct, sO2\}. 
Figure 3: Comparison of predicted Hct (a) and sO₂ (b) values obtained from Eq. 7 and 9 to true values obtained from blood gas analysis. In specimens with no solution (N=13), the real value of the complex-conjugate roots (Re{Hct}, Re{sO₂}) is plotted (red stars). For specimens with two solutions (N=4), both solutions are plotted (green squares). Agreement between true and predicted values is demonstrated by the proximity of plotted points to the identity line.
Figure 4: Uncertainty in calculated Hct (a) and sO₂ (b) given 5% error in R₁ and R₂ measurement. Uncertainty is represented by the interquartile range, as a function of the true Hct and sO₂ used in Monte-Carlo simulations.
References


