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Extension of the Rorschach–Hazlewood Theoretical Model for Spin–Lattice Relaxation in Biological Systems to Low Frequencies

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The water–biopolymer cross-relaxation model, proposed by H. E. Rorschach and C. F. Hazlewood (RH) [*J. Magn. Reson.* 70, 79 (1986)], explains the Larmor frequency dependence of T_1 in many biological systems. However, the RH theory fails at low Larmor frequencies. In this paper, a more general version of the RH theory has been developed. This theory is valid at all frequencies. Use of the new expression for the spin–lattice relaxation rate ($1/T_1$), earlier published experimental data in H_2O/D_2O bovine serum albumin, which had been measured over a wide frequency range (10 kHz to 100 MHz), were fitted over the entire frequency range. The agreement between theory and the experimental data is excellent. Theoretical expressions for the rotating-frame spin–lattice relaxation rate ($1/T_{1\rho}$) were also obtained.

INTRODUCTION

The frequency dependence of T_1 provides important insight into the relaxation mechanisms in biological tissues. It has been shown that cross relaxation between bulk protons and macromolecular protons plays an important role in the proton spin–lattice relaxation behavior of many biological systems (*1, 2*). The Larmor frequency (ν) dependence of the spin–lattice relaxation time is observed in various biological systems (*3, 4*) to have a dependence on ν which is given by $1/T_1 = B + A/\sqrt{\nu}$, where A and B are constants. The water–biopolymer cross-relaxation model proposed by Rorschach and Hazlewood (RH) (*1*) provides a satisfactory explanation for this frequency dependence. In this model, the biological system is assumed to consist of two phases: (1) a bulk water phase and (2) a macromolecular phase. The vibrational motion of the macromolecule relaxes the bulk water protons via either cross relaxation or exchange with the water molecules in the hydration shell. The RH model has been successfully applied to explain the frequency dependence of T_1 (*3*) at high Larmor frequencies (30–270 MHz). However, the assumptions of the RH theory are not valid at low frequencies; accordingly, the theory in its original form cannot explain the low-frequency dependence of T_1. In this paper, we have extended the RH model to explain spin–lattice relaxation, including that in the rotating frame, at all Larmor frequencies.

BASIC RH MODEL

In the RH model, the T_1 of a heterogeneous biological system can be considered to arise from two sources: bulk water protons (solvent phase) and macromolecular protons (protein phase). Cross relaxation can cause longitudinal magnetization to be transferred between the two phases. The z component of the proton's magnetization is designated as S or P for the solvent or protein systems, respectively. The relaxation rates of the solvent and the protein protons in the absence of cross relaxation are R_{1S} and R_{1P}, respectively, and the cross-relaxation rates R_T and R'_T represent, respectively, the transfer rate of the magnetization from the solvent to the protein protons and that from the protein protons to the solvent protons. These relaxation processes are illustrated in Fig. 1.

The time dependence of the z magnetization in the solvent and the protein phases for the two-phase biological system described in Fig. 1 is given by

$$\frac{dS}{dt} = -R_{1S}(S - S_0) - R_T S + R'_T P \qquad [1a]$$

and

$$\frac{dP}{dt} = -R_{1P}(P - P_0) + R_T S - R'_T P, \qquad [1b]$$

where S_0 and P_0 represent equilibrium values for S and P. In equilibrium, $dS/dt = dP/dt = 0$, and Eqs. [1a] and [1b] then give $R_T S_0 = R'_T P_0$.

Equations [1a] and [1b] can be rewritten as

$$\frac{d(\delta S)}{dt} = -R_{1S}\delta S - R_T\,\delta S + R_T\,\delta P \qquad [2a]$$

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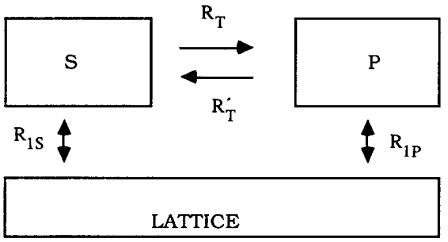

FIG. 1. The schematic representation of the spin–lattice relaxation paths of the solvent (S) protons and the protein (P) protons in a two-phase biological system. The symbols are explained in the text.

and

$$\frac{d(\delta P)}{dt} = -R_{1P}\delta P - R_T \frac{S_0}{P_0}\,\delta P + R_T \frac{S_0}{P_0}\,\delta S, \qquad [2b]$$

where $\delta S = (S - S_0)/S_0$ and $\delta P = (P - P_0)/P_0$.

The approximate solution to the coupled Eqs. [2a] and [2b] for the solvent protons is given by

$$\delta S \cong D \exp(-t/T_1), \qquad [3]$$

where D is a constant. The solvent proton relaxation rate is then

$$\frac{1}{T_1} = \frac{1}{2}[R_{1P} + R_{1S} + R_T(M + 1)] - \frac{1}{2}\sqrt{[R_{1P} - R_{1S} + R_T(M - 1)]^2 + 4MR_T^2}\,, \qquad [4]$$

where $M = S_0/P_0$, the ratio of the number of solvent protons to protein protons, which is assumed to be much greater than one (i.e., $M \gg 1$).

The relaxation rate in Eq. [4] could also be written as

$$\frac{1}{T_1} = \frac{1}{2}\,[R_{1P} + R_{1S} + R_T(M + 1)] - \frac{1}{2}\,R_T(M + 1) \times \sqrt{1 + 2\,\frac{(R_{1P} - R_{1S})(M - 1)}{R_T(M + 1)^2} + \frac{(R_{1P} - R_{1S})^2}{R_T^2(M + 1)^2}}\,. \qquad [5]$$

In the ''fast-exchange limit,'' we assume that $(R_{1P} - R_{1S})/MR_T \ll 1$, which is equivalent to assuming that the exchange rate R_T is much faster than the relaxation rates, R_{1P} and R_{1S}, for the individual phases. This assumption should be valid at high Larmor frequencies, but cannot be valid at sufficiently low frequencies, since R_{1P} increases as the Larmor frequency is lowered (see Eq. [8] below). The third term in the square root of Eq. [5] can then be neglected and the square root can be expanded only to first order. Keeping only terms linear in R_{1P} and R_{1S}, Eq. [5] in the fast-exchange limit reduces to

$$\left(\frac{1}{T_1}\right)^{(1)} = R_1^{(1)} = \left(\frac{M}{1 + M}\right) R_{1S} + \left(\frac{1}{1 + M}\right) R_{1P}. \qquad [6]$$

The superscript $^{(1)}$ indicates that the square-root term of Eq. [5] is expanded to first order in $(R_{1P} - R_{1S})/MR_T$.

The observed relaxation rate (Eq. [6]) depends on the relaxation rates of the solvent protons and the protein protons and also on the ratio of the number of solvent to the number of protein protons. The solvent protons are characterized by a short correlation time ($\omega\tau_s \ll 1$) (*1*); hence, it is independent of the Larmor frequency. Therefore, the frequency dependence of T_1 originates only from the protein protons.

The simplest model of a protein is a chain of backbone bonds connected by completely flexible joints. The vibrational motions of these chains are represented as normal modes. According to Rouse's theory (*5*), the correlation times of these normal modes (q) are given by $\tau_c = \alpha q^{-2}$, where α is a material-dependent constant. The relaxation rate due to the vibrational motions of the polymer chain is then given by

$$R_{1P} = C \int_{\tau_{c\,min}}^{\tau_{c\,max}} \frac{\tau_c^{-3/2}\tau_c d\tau_c}{1 + \omega^2\tau_c^2} = C\nu^{-1/2} \int_{X_{min}}^{X_{max}} \frac{X^{-1/2}dX}{1 + X^2}\,, \qquad [7]$$

where C is a constant and $X = \omega\tau_c$.

Typical vibrational frequencies of a polymer chain are of order 10^{13} Hz, which is much larger than NMR Larmor frequencies ($\sim 10^8$ Hz); hence, it is reasonable to replace the lower limit by zero (since $\omega\tau_{cmin} \sim 10^{-5}$). At high Larmor frequencies, the upper limits of the integral could be replaced by infinity, in which case the value of the integral does not depend on the Larmor frequency ω and is equal to $\pi/\sqrt{2}$. So, the protein relaxation rate is given by

$$R_{1P} = A\,\nu^{-1/2}, \qquad [8]$$

where A is a constant.

Therefore, the spin–lattice relaxation rate, originally obtained by Rorschach and Hazlewood by substituting Eq. [8] into Eq. [6], is valid for high Larmor frequencies and given by

$$\left(\frac{1}{T_1}\right)^{(1)} = B + A\,\nu^{-1/2}, \qquad [9]$$

where $B = [M/(M + 1)]/R_{1S}$ and $A = C\pi/[(M + 1)\sqrt{2}]$. The frequency dependence of T_1 described in Eq. [9] has been observed in various biological systems (*3, 4*).

HIGH LARMOR FREQUENCY LIMITATION OF THE RH MODEL

There are several features of the RH model which must be circumvented in developing a more general model which is applicable to all Larmor frequencies.

(1) At low Larmor frequencies, the third term in the square root of Eq. [5] cannot be neglected.

(2) At low Larmor frequencies, the expansion of Eq. [5] in powers of $(R_{1P} - R_{1S})/MR_T$ to first order may not be sufficient because R_{1P} increases at low Larmor frequencies. Hence, one should go to higher order in the expansion parameter $(R_{1P} - R_{1S})/MR_T$.

(3) At low Larmor frequencies, the upper limit of the integral in Eq. [7] cannot be replaced by infinity. When the upper limit has a finite value, the value of the integral becomes frequency dependent and should be evaluated more generally.

EXTENSION TO LOW FREQUENCIES

Spin–Lattice Relaxation ($1/T_1$)

(1) When the third term in the square root of Eq. [5] is included and the square root expanded to second order in the expansion parameter, the relaxation rate is given by

$$\left(\frac{1}{T_1}\right)^{(2)} = \left(\frac{1}{T_1}\right)^{(1)} - \frac{(R_{1P} - R_{1S})^2}{R_T}\frac{M}{(M+1)^3}, \quad [10]$$

where the superscripts $^{(1)}$ and $^{(2)}$ refer to the order of approximation.

(2) The integral in Eq. [7] can be evaluated explicitly at low frequencies using the expression (*6*)

$$\int_0^{\omega\tau_{c\,max}} \frac{X^{-1/2}\,dX}{1+X^2} = \frac{1}{\sqrt{2}}\left[\ln\left(\frac{X_m + \sqrt{2X_m} + 1}{\sqrt{1+X_m^2}}\right) + \arctan\left(\frac{X_m - 1}{\sqrt{2X_m}}\right) + \frac{\pi}{2}\right], \quad [11]$$

where $X_m = \omega\tau_{c\,max}$.

A more general expression for the spin–lattice relaxation rate which is now valid at all Larmor frequencies is obtained by combining Eqs. [6], [7], [10], and [11], and is given by

$$\left(\frac{1}{T_1}\right)^{(2)} = B + AF(\nu, \tau_{max}) - \frac{[A\cdot F(\nu, \tau_{max})]^2}{R_T}, \quad [12]$$

where

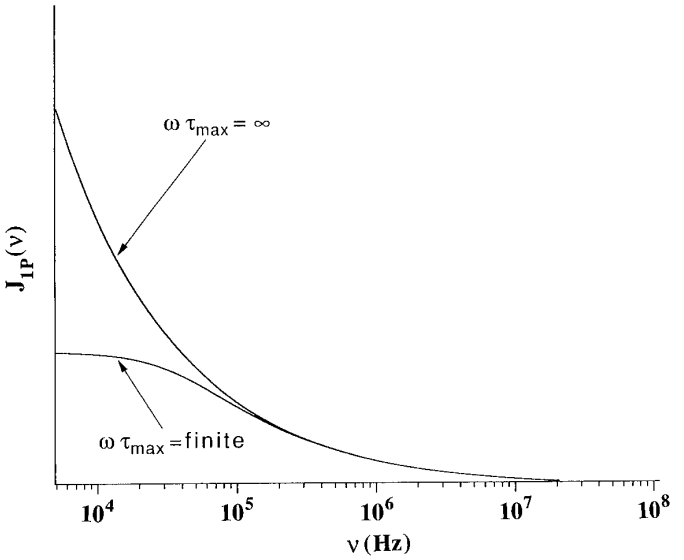

FIG. 2. The spectral density $J_{1P}(\nu)$ as a function of the Larmor frequency ν.

$$F(\nu, \tau_{max}) = \frac{\nu^{-0.5}}{\pi}\left[\ln\left(\frac{X_m + \sqrt{2X_m} + 1}{\sqrt{1+X_m^2}}\right) + \arctan\left(\frac{X_m - 1}{\sqrt{2X_m}}\right) + \frac{\pi}{2}\right]. \quad [13]$$

In the limit of high Larmor frequencies, $X_m \to \infty$ and $F(\nu, \tau_{max}) = \nu^{-0.5}$. Then, Eq. [12] reduces to Eq. [6], since the third term in Eq. [12] becomes negligible. Equation [12] can explain the frequency dependence of T_1 over a wide frequency range. Figure 2 shows a calculation using Eq. [7] of the spectral density $J_{1P}(\nu)$ (proportional to R_{1P}) for two cases: (1) the upper limit is infinite and (2) the upper limit is finite. Note that the spectral densities of both curves are almost the same at high frequencies but are quite different at low frequencies.

Rotating-Frame Relaxation ($1/T_{1\rho}$)

The low-frequency relaxation can also be conveniently determined by measuring the spin–lattice relaxation time ($T_{1\rho}$) in the rotating frame. In this measurement, the Larmor frequency ν ($=\gamma B_0/2\pi$, where γ is the gyromagnetic ratio) is replaced by ν_1 ($=\gamma B_1/2\pi$, where B_1 is the RF magnetic field). Furthermore, the constant C in Eq. [7] contains the mean-square local field. In the rotating frame, this constant is only one-third its value in the laboratory frame (*7*). Hence, the spin–lattice relaxation in the rotating frame is given by

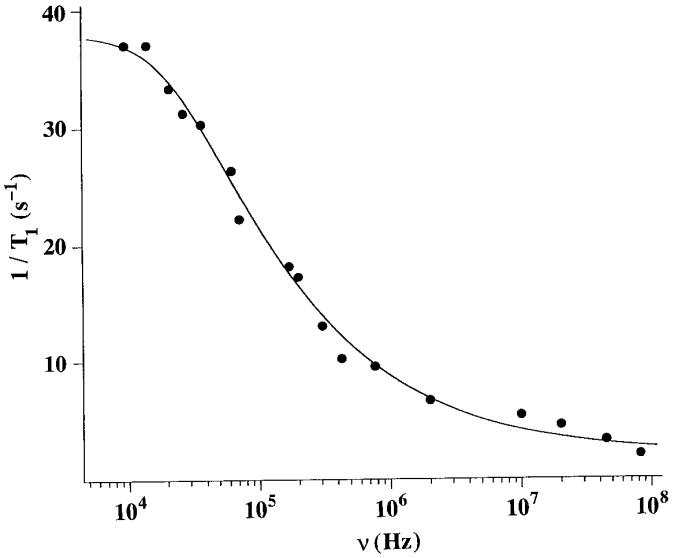

FIG. 3. The spin–lattice relaxation rate ($1/T_1$) as a function of the Larmor frequency ν for a mixed H_2O/D_2O serum albumin solution [from Ref. (*8*)]. The solid line is the theoretical calculation using our model (Eq. [12]), with $\tau_{cmax} = 8 \times 10^{-6}$ s, $R_T = 230$ s^{-1}, $A = 7.0$ (MHz)$^{1/2}$/s, and $B = 2.0$ s^{-1}.

$$\left(\frac{1}{T_{1\rho}}\right)^{(2)} = B + \frac{1}{3}AF(\nu, \tau_{\max}) - \frac{[(1/3)AF(\nu, \tau_{\max})]^2}{R_T}. \qquad [14]$$

VERIFICATION OF THEORY

To demonstrate that our expression for $1/T_1$ (Eq. [12]) can be applied over a much wider range of frequencies, we reexamined the previously published T_1 data of Kimmich and Noack (*8*) measured over the range 10 kHz to 100 MHz for a mixed H_2O/D_2O serum albumin solution (see Fig. 3). A fit of our theory to the data required only four parameters ($\tau_{c\,max}$, R_T, B, and A) and resulted in excellent agreement between theory and the experiment.

CONCLUSION

We have extended the Rorschach–Hazlewood theory for spin–lattice relaxation in biological systems to low frequencies and have derived expressions for the spin–lattice relaxation rate in the laboratory frame and in the rotating frame. Our expression for $1/T_1$ is valid over a wide frequency range. Excellent agreement was obtained between our theory and published experimental data on serum albumin solution, thereby confirming the validity of our model in this system at all frequencies investigated. This theory has also been successfully applied to rat lung (*9*).

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