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A General Solution of the Standard Magnetization Transfer Model

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The standard model of magnetization transfer consists of six coupled, first-order differential equations which describe a lossless exchange of magnetization between two sites. The system of differential equations is solved semi-analytically in full generality. The solution allows one to model any experiment generating magnetization transfer. It is especially useful in investigation spin systems subjected to pulsed magnetization transfer experiments. © 1998 Academic Press

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INTRODUCTION

Based on pioneering work (*1–3*), a macroscopic spin model which accounts for a two-site exchange of magnetization has been proposed (*4–8*). We refer to this model as the ''standard'' model of magnetization transfer (MT). Among other applications the model has been shown to account for systems containing water molecules bound to protein structures (see, e.g., (*4*)). The spin ensembles of both pools of the standard model obey the Bloch equations. Thus, the spin system is described by six coupled, first-order differential equations (DEqs). We present a general solution obtained by Laplace transformation. This technique has been used before to solve the plain Bloch equations (*9–11*) and special cases of the problem considered here (*12, 13*). The solution is ''semi-analytic'' in the sense that it is presented analytically apart from roots of a sixth-order polynomial which are computed numerically.

A *continuous-wave* MT experiment can be modeled approximately by only considering the steady state solution of the standard model (see, e.g., (*4*)). However, the including of transient effects avoids a systematic error (*12*). The transient solution of (*12*) is based on the assumption that MR-visible spins remain unaffected by continuous off-resonance RF irradiation. Hence it utilizes only four DEqs of the standard model. The transient solution is essential for modeling *pulsed* MT experiments, where RF irradiation periods are comparable to spin–spin relaxation time constants of the MR-invisible spin pool (*14, 15*). Since RF irradiation close to resonance is used, both pools are affected. Again, the case of precise on-resonant RF irradiation is modeled by four DEqs (*13*).

The general solution of the standard model extends its applicability to any experimental procedure. In addition to the cases considered in (*12, 13*) it allows one to investigate, e.g., the case of continuous off-resonance irradiation approaching resonance, or off-resonance effects arising in pulsed MT experiments. The extended applicability is particularly useful for designing MT pulse sequences and for observing MT of off-resonance spins by MR spectroscopy (see, e.g., (*16*)).

THEORY

The standard MT model describes the exchange of magnetization between two pools A and B by assuming the validity of the Bloch equations for each pool. During the presence of an RF field $\vec{B}_1$ of amplitude ω_1 and frequency offset $\Delta\omega^{A,B} = \omega - \omega_0^{A,B}$, the magnetization in the rotating frame $u'^{A,B} = M_{x,\mathrm{rot}}^{A,B}$, $u'^{A,B} \| \vec{B}_1'$, $v'^{A,B} = M_{y,\mathrm{rot}}^{A,B}$, $M_z^{A,B} = M_{z,\mathrm{rot}}^{A,B}$, is given by

$$\begin{aligned}
\frac{du'^{A,B}}{dt} &= -\frac{1}{T_2^{A,B}}u'^{A,B} - \Delta\omega^{A,B}v'^{A,B}\\
\frac{dv'^{A,B}}{dt} &= -\frac{1}{T_2^{A,B}}v'^{A,B} + \Delta\omega^{A,B}u'^{A,B} - \omega_1 M_z^{A,B}\\
\frac{dM_z^A}{dt} &= -\left(\frac{1}{T_1^A} + r_X\right)(M_z^A - M_0^A)\\
&\quad + \frac{r_X}{f}(M_z^B - M_0^B) + \omega_1 v'^A\\
\frac{dM_z^B}{dt} &= -\left(\frac{1}{T_1^B} + \frac{r_X}{f}\right)(M_z^B - M_0^B)\\
&\quad + r_X(M_z^A - M_0^A) + \omega_1 v'^B,
\end{aligned} \quad [1]$$

where r_X denotes the exchange rate, and f the ratio of equilibrium magnetizations of both pools, i.e., $f = M_0^B/M_0^A$.

Using dimensionless quantities

$$\tau = \omega_1 t,\ u^{A,B} = u'^{A,B}/M_0^{A,B},\ v^{A,B} = v'^{A,B}/M_0^{A,B},$$

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$$w^{A,B} = (M_0^{A,B} - M_z^{A,B})/2M_0^{A,B},$$
$$\delta_{A,B} = \Delta\omega^{A,B}/\omega_1,\ \alpha_{A,B} = 1/(\omega_1 T_1^{A,B}),$$
$$\beta_{A,B} = 1/(\omega_1 T_2^{A,B}),\ \alpha_X = r_X/\omega_1,\ \alpha_Y = r_X/(f\omega_1), \quad [2]$$

Eqs. [1] read

$$\frac{du^{A,B}}{d\tau} + \beta_{A,B}u^{A,B} + \delta_{A,B}v^{A,B} = 0$$
$$\frac{dv^{A,B}}{d\tau} + \beta_{A,B}v^{A,B} - \delta_{A,B}u^{A,B} + (1 - 2w^{A,B}) = 0$$
$$\frac{dw^A}{d\tau} + (\alpha_A + \alpha_X)w^A - \alpha_X w^B + \frac{v^A}{2} = 0$$
$$\frac{dw^B}{d\tau} + (\alpha_B + \alpha_Y)w^B - \alpha_Y w^A + \frac{v^B}{2} = 0. \quad [3]$$

The definition of the dimensionless quantities requires a separate consideration of the case of no RF irradiation, i.e., $\omega_1 = 0$. In this case the six coupled DEqs [1] are reduced to three pairwise coupled DEqs. The solution for the transversal magnetization components needs to take a possible difference of the resonance frequencies of the A and B nuclei into account; the calculation is straightforward. The solution for the longitudinal components is given in (*13*). With the Laplace transformation of a function $u(t)$ denoted by $\tilde{u}(p) = \int_0^\infty u(t)e^{-pt}dt$, the Laplace transform of Eqs. [3] reads

$$(p + \beta_{A,B})\tilde{u}^{A,B} + \delta_{A,B}\tilde{v}^{A,B} = u_0^{A,B}$$
$$(p + \beta_{A,B})\tilde{v}^{A,B} - \delta_{A,B}\tilde{u}^{A,B} - 2\tilde{w}^{A,B} = v_0^{A,B} - \frac{1}{p}$$
$$(p + \alpha_A + \alpha_X)\tilde{w}^A - \alpha_X\tilde{w}^B + \frac{\tilde{v}^A}{2} = w_0^A$$
$$(p + \alpha_B + \alpha_Y)\tilde{w}^B - \alpha_Y\tilde{w}^A + \frac{\tilde{v}^B}{2} = w_0^B. \quad [4]$$

Equations [4] may be written in matrix form, $\mathbf{B}\tilde{\mathbf{x}} = \mathbf{x}_0$, where $\tilde{\mathbf{x}} = [\tilde{u}^A, \tilde{u}^B, \tilde{v}^A, \tilde{v}^B, \tilde{w}^A, \tilde{w}^B]^T$, $\mathbf{x}_0 = [u_0^A, u_0^B, v_0^A - (1/p), v_0^B - (1/p), w_0^A, w_0^B]^T$, and

$$\mathbf{B} = \begin{bmatrix} p + \beta_A & 0 & \delta_A & 0 & 0 & 0 \\ 0 & p + \beta_B & 0 & \delta_B & 0 & 0 \\ -\delta_A & 0 & p + \beta_A & 0 & -2 & 0 \\ 0 & -\delta_B & 0 & p + \beta_B & 0 & -2 \\ 0 & 0 & 1/2 & 0 & p + \alpha_A + \alpha_X & -\alpha_X \\ 0 & 0 & 0 & 1/2 & -\alpha_Y & p + \alpha_B + \alpha_Y \end{bmatrix}.$$

The solution

$$\tilde{\mathbf{x}} = \frac{1}{\det \mathbf{B}}\mathbf{B}_{\mathrm{adj}}\mathbf{x}_0 \quad [5]$$

requires computation of the adjugate and the determinant of $\mathbf{B}$. The term $\mathbf{B}_{\mathrm{adj}}\mathbf{x}_0$ is conveniently presented as $\mathbf{g} = p\mathbf{B}_{\mathrm{adj}}\mathbf{x}_0$, where $\mathbf{g}$ can be written as

$$\mathbf{g} = \begin{bmatrix} u_0^A & g_{15} & \cdots & g_{10} \\ u_0^B & g_{25} & \cdots & g_{20} \\ v_0^A & g_{35} & \cdots & g_{30} \\ v_0^B & g_{45} & \cdots & g_{40} \\ w_0^A & g_{55} & \cdots & g_{50} \\ w_0^B & g_{65} & \cdots & g_{60} \end{bmatrix} \begin{bmatrix} p^6 \\ p^5 \\ p^4 \\ p^3 \\ p^2 \\ p \\ 1 \end{bmatrix} \quad [6]$$

with

$$g_{15} = (\gamma_1 + \beta_A + 2\beta_B)u_0^A - \delta_A v_0^A$$
$$g_{14} = [\gamma_3 + 2(\gamma_1 + \beta_A)\beta_B + \gamma_1\beta_A + 2 + \gamma_2]u_0^A - (\gamma_1 + 2\beta_B)\delta_A v_0^A - 2\delta_A w_0^A + \delta_A$$
$$g_{13} = [(\gamma_1 + \beta_A)\gamma_3 + (2\gamma_1\beta_A + 2\gamma_2 + 3)\beta_B + (\gamma_2 + 1)\beta_A + \gamma_1]u_0^A - (\gamma_3 + 2\gamma_1\beta_B + \gamma_2 + 1)\delta_A v_0^A - 2(2\beta_B + \alpha_B + \alpha_Y)\delta_A w_0^A - 2\delta_A\alpha_X w_0^B + (\gamma_1 + 2\beta_B)\delta_A$$
$$g_{12} = [(\gamma_1\beta_A + \gamma_2 + 1)\gamma_3 + 2(\gamma_2\beta_A + 0.5\beta_A + \alpha_B + \alpha_Y)\beta_B + (\alpha_X + \alpha_A)(\beta_A + \beta_B) + 1]u_0^A - [\gamma_1\gamma_3 + (2\gamma_2 + 1)\beta_B + \alpha_X + \alpha_A]\delta_A v_0^A + \delta_A\alpha_X v_0^B - [2\gamma_3 + 4(\alpha_Y + \alpha_B)\beta_B + 2]\delta_A w_0^A - 4\delta_A\beta_B\alpha_X w_0^B + (\gamma_3 + 2\gamma_1\beta_B + \gamma_2 + 1)\delta_A$$
$$g_{11} = [(\gamma_2\beta_A + \alpha_Y + \alpha_B)\gamma_3 + (\alpha_X + \alpha_A)\beta_A\beta_B + \beta_B]u_0^A + \delta_A\delta_B\alpha_X u_0^B - [\gamma_2\gamma_3 + (\alpha_X + \alpha_A)\beta_B]\delta_A v_0^A + \delta_A\beta_B\alpha_X v_0^B - [2(\alpha_Y + \alpha_B)\gamma_3 + 2\beta_B]\delta_A w_0^A - 2\gamma_3\delta_A\alpha_X w_0^B + [\gamma_1\gamma_3 + (2\gamma_2 + 1)\beta_B + \alpha_A]\delta_A$$

$$
\begin{aligned}
g_{10} &= (\gamma_2\gamma_3 + \beta_B\alpha_A)\delta_A \\
g_{35} &= \delta_A u_0^A + (\gamma_1 + \beta_A + 2\beta_B)v_0^A + 2w_0^A - 1 \\
g_{34} &= (\gamma_1 + 2\beta_B)\delta_A u_0^A \\
&\quad + [\gamma_3 + (\gamma_1 + 2\beta_B)\beta_A + 2\gamma_1\beta_B + \gamma_2 + 1]v_0^A \\
&\quad + 2(\beta_A + 2\beta_B + \alpha_B + \alpha_Y)w_0^A \\
&\quad + 2\alpha_X w_0^B - \beta_A - 2\beta_B - \gamma_1 \\
g_{33} &= (\gamma_3 + 2\gamma_1\beta_B + \gamma_2 + 1)\delta_A u_0^A \\
&\quad + [(\gamma_1 + \beta_A)\gamma_3 + (2\gamma_1\beta_A + 2\gamma_2 + 1)\beta_B \\
&\qquad + (\gamma_2 + 1)\beta_A + \alpha_A + \alpha_X]v_0^A \\
&\quad - \alpha_X v_0^B + [2\gamma_3 + 4(\beta_A + \alpha_B + \alpha_Y)\beta_B \\
&\qquad + 2(\alpha_B + \alpha_Y)\beta_A + 2]w_0^A \\
&\quad + 2(\beta_A + 2\beta_B)\alpha_X w_0^B - \gamma_3 - 2(\gamma_1 + \beta_A)\beta_B \\
&\quad - \gamma_1\beta_A - \gamma_2 - 1 \\
g_{32} &= [\gamma_1\gamma_3 + 2\gamma_2\beta_B + \beta_B + \alpha_X + \alpha_A]\delta_A u_0^A \\
&\quad - \delta_B\alpha_X u_0^B + [(\gamma_1\beta_A + \gamma_2)\gamma_3 + (2\gamma_2 + 1)\beta_A\beta_B \\
&\qquad + (\alpha_X + \alpha_A)(\beta_A + \beta_B)]v_0^A - (\beta_A + \beta_B)\alpha_X v_0^B \\
&\quad + [2(\beta_A + \alpha_B + \alpha_Y)\gamma_3 + 4(\alpha_B + \alpha_Y)\beta_B\beta_A \\
&\qquad + 2(\beta_A + \beta_B)]w_0^A + 2(\gamma_3 + 2\beta_A\beta_B)\alpha_X w_0^B \\
&\quad - (\gamma_1 + \beta_A)\gamma_3 - (2\gamma_1\beta_B + \gamma_2 + 1)\beta_A \\
&\quad - (2\gamma_2 + 1)\beta_B - \alpha_A \\
g_{31} &= [\gamma_2\gamma_3 + (\alpha_A + \alpha_X)\beta_B]\delta_A u_0^A - \delta_B\beta_A\alpha_X u_0^B \\
&\quad + [\gamma_2\beta_A\gamma_3 + (\alpha_A + \alpha_X)\beta_A\beta_B]v_0^A \\
&\quad - \beta_A\beta_B\alpha_X v_0^B + [2(\alpha_B + \alpha_Y)\beta_A\gamma_3 + 2\beta_A\beta_B]w_0^A \\
&\quad + 2\alpha_X\beta_A\gamma_3 w_0^B - (\gamma_1\beta_A + \gamma_2)\gamma_3 \\
&\quad - (2\gamma_2 + 1)\beta_A\beta_B - (\beta_B + \beta_A)\alpha_A \\
g_{30} &= -\gamma_2\beta_A\gamma_3 - \beta_A\beta_B\alpha_A \\
g_{55} &= -0.5v_0^A + (2\beta_A + 2\beta_B + \alpha_B + \alpha_Y)w_0^A + \alpha_X w_0^B \\
g_{54} &= -0.5\delta_A u_0^A - 0.5(\beta_A + 2\beta_B + \alpha_B + \alpha_Y)v_0^A \\
&\quad - 0.5\alpha_X v_0^B + [\gamma_3 + \gamma_4 + 2(2\beta_A + \alpha_B + \alpha_Y)\beta_B \\
&\qquad + 2(\alpha_B + \alpha_Y)\beta_A + 1]w_0^A \\
&\quad + 2(\beta_A + \beta_B)\alpha_X w_0^B + 0.5 \\
g_{53} &= -0.5(2\beta_B + \alpha_B + \alpha_Y)\delta_A u_0^A - 0.5\delta_B\alpha_X u_0^B \\
&\quad - [0.5\gamma_3 + (\alpha_B + \alpha_Y)(0.5\beta_A + \beta_B) \\
&\qquad + \beta_A\beta_B + 0.5]v_0^A - (\beta_A + 0.5\beta_B)\alpha_X v_0^B \\
&\quad + [(2\beta_B + \alpha_B + \alpha_Y)\gamma_4 + (2\beta_A + \alpha_B + \alpha_Y)\gamma_3 \\
&\qquad + 4(\alpha_B + \alpha_Y)\beta_A\beta_B + 2\beta_A + \beta_B]w_0^A \\
&\quad + (\gamma_3 + \gamma_4 + 4\beta_A\beta_B)\alpha_X w_0^B \\
&\quad + 0.5(\beta_A + 2\beta_B + \alpha_B + \alpha_X + \alpha_Y) \\
g_{52} &= [-0.5\gamma_3 - (\alpha_B + \alpha_Y)\beta_B - 0.5]\delta_A u_0^A - \beta_A\delta_B\alpha_X u_0^B \\
&\quad - [0.5(\beta_A + \alpha_B + \alpha_Y)\gamma_3 + (\alpha_B + \alpha_Y)\beta_A\beta_B \\
&\qquad + 0.5(\beta_A + \beta_B)]v_0^A - (0.5\gamma_4 + \beta_A\beta_B)\alpha_X v_0^B \\
&\quad + [(1 + \gamma_3)\gamma_4 + 2(\alpha_B + \alpha_Y)(\beta_B\gamma_4 + \beta_A\gamma_3) \\
&\qquad + 2\beta_A\beta_B]w_0^A + 2(\beta_A\gamma_3 + \beta_B\gamma_4)\alpha_X w_0^B \\
&\quad + 0.5\gamma_3 + (\alpha_B + 0.5\alpha_X + \alpha_Y)\beta_B \\
&\quad + (0.5\alpha_B + \alpha_X + 0.5\alpha_Y)\beta_A + \beta_A\beta_B + 0.5 \\
g_{51} &= -0.5[(\alpha_B + \alpha_Y)\gamma_3 + \beta_B](\delta_A u_0^A + \beta_A v_0^A) \\
&\quad - 0.5\gamma_4\alpha_X(\delta_B u_0^B + \beta_B v_0^B) \\
&\quad + [(\alpha_B + \alpha_Y)\gamma_3 + \beta_B]\gamma_4 w_0^A + \gamma_3\gamma_4\alpha_X w_0^B \\
&\quad + 0.5(\beta_A + \alpha_B + \alpha_Y)\gamma_3 + 0.5\alpha_X\gamma_4 \\
&\quad + (\alpha_B + \alpha_X + \alpha_Y)\beta_A\beta_B + 0.5(\beta_A + \beta_B) \\
g_{50} &= 0.5[(\alpha_B + \alpha_Y)\beta_A\gamma_3 + \beta_B\alpha_X\gamma_4 + \beta_A\beta_B]
\end{aligned}
$$

and

$$
\begin{aligned}
\gamma_1 &= \alpha_A + \alpha_B + \alpha_X + \alpha_Y, \\
\gamma_2 &= \alpha_A\alpha_B + \alpha_X\alpha_B + \alpha_Y\alpha_A, \\
\gamma_3 &= \delta_B^2 + \beta_B^2, \quad \gamma_4 = \delta_A^2 + \beta_A^2.
\end{aligned}
$$

The remaining coefficients g_{2ij}, $i \in \{1, 2, 3\}$, $j \in \{1, \ldots, 5\}$, are obtained from g_{2i-1j} by swapping the indices A and B, and X and Y of α, β, δ, u_0, v_0, and w_0. Note that this index permutation affects γ_3 and γ_4 as well. Further,

$$
\begin{aligned}
\det \mathbf{B} &= \Delta(p) \\
&= p^6 + c_5 p^5 + c_4 p^4 + c_3 p^3 + c_2 p^2 + c_1 p + c_0
\end{aligned} \tag{7}
$$

with

$$
\begin{aligned}
c_5 &= 2(\beta_A + \beta_B) + \gamma_1 \\
c_4 &= \gamma_2 + \gamma_3 + \gamma_4 + 2\gamma_1(\beta_A + \beta_B) + 4\beta_A\beta_B + 2 \\
c_3 &= \gamma_1(\gamma_3 + \gamma_4 + 1) + [4\gamma_1\beta_A + 2(\gamma_2 + \gamma_4) + 3]\beta_B \\
&\quad + [2(\gamma_2 + \gamma_3) + 3]\beta_A \\
c_2 &= \gamma_3\gamma_4 + (\gamma_2 + 1)(\gamma_3 + \gamma_4 + 4\beta_A\beta_B) \\
&\quad + 2\gamma_1(\gamma_3\beta_A + \gamma_4\beta_B) \\
&\quad + [\alpha_A + \alpha_X + 2(\alpha_B + \alpha_Y)]\beta_B \\
&\quad + [\alpha_B + \alpha_Y + 2(\alpha_A + \alpha_X)]\beta_A + 1
\end{aligned}
$$

$$c_1 = \gamma_1\gamma_3\gamma_4 + (\alpha_A + \alpha_X)\gamma_4 + (\alpha_B + \alpha_Y)\gamma_3 + (1 + 2\gamma_2)(\gamma_3\beta_A + \gamma_4\beta_B) + 2\gamma_1\beta_A\beta_B + \beta_A + \beta_B$$

$$c_0 = \gamma_2\gamma_3\gamma_4 + (\alpha_A + \alpha_X)\gamma_4\beta_B + (\alpha_B + \alpha_Y)\gamma_3\beta_A + \beta_A\beta_B.$$

Note that if $\omega_1 > 0$, then $c_0, \ldots, c_5 > 0$, in which case all *real* roots of $\Delta(p)$ are negative, whereas if $\omega_1 < 0$, then c_0, c_2, $c_4 > 0$, c_1, c_3, $c_5 < 0$, in which case all *real* roots are positive. Since the real parts of roots are the damping factors of the time domain solution, physical reality requires that this relation also holds for the real parts of *complex* roots. Note, however, that *neither* only the signs of the coefficients *nor* a physical principle determines the number of real roots (*17*). We assume that the roots of $\Delta(p)$ are obtained by a numerical procedure and exclude for the moment the existence of multiple roots. Then $\Delta(p)$ can be factorized as

$$\Delta(p) = \prod_{i=1}^{3} [(p + \xi_i)^2 + \eta_i^2], \quad [8]$$

regardless of whether its roots are real or complex. In case of a conjugate pair of complex roots z_i, z_i^*, ξ, and η represent $z_i = -\xi_i + i\eta_i$, $i = \sqrt{-1}$; in case of a pair of real roots x_{2i-1} and x_{2i}, ξ and η represent $\xi_i = -(x_{2i-1} + x_{2i})/2$ and $\eta_i = i(x_{2i-1} - x_{2i})/2$, where the sign of η_i can be chosen arbitrarily. This notation avoids cumbersome bookkeeping of the four possible combinations of pairs of real and complex roots, which indeed are found to occur. Given the factorization of Eq. [8], the solution $\tilde{\mathbf{x}} = \mathbf{g}/(p\Delta(p))$ is expanded in partial fractions by

$$\tilde{\mathbf{x}}(p) = \sum_{i=1}^{3} \frac{\mathbf{k}_{2i-1}(p + \xi_i) + \mathbf{k}_{2i}}{(p + \xi_i)^2 + \eta_i^2} + \frac{\mathbf{k}_7}{p}. \quad [9]$$

Inverse Laplace transformation of $\tilde{\mathbf{x}}$ yields the time domain solution:

$$\mathbf{x}(\tau) = \sum_{i=1}^{3} \left[\mathbf{k}_{2i-1}\cos(\eta_i\tau) + \frac{\mathbf{k}_{2i}}{\eta_i}\sin(\eta_i\tau) \right] \mathrm{e}^{-\xi_i\tau} + \mathbf{k}_7. \quad [10]$$

This is a real function. Terms containing an imaginary η_i can be written as

$$\left[\mathbf{k}_{2i-1}\cos(\eta_i\tau) + \frac{\mathbf{k}_{2i}}{\eta_i}\sin(\eta_i\tau) \right] \mathrm{e}^{-\xi_i\tau} = \frac{\mathbf{k}_{2i-1}\eta_i' - \mathbf{k}_{2i}}{2\eta_i'} \mathrm{e}^{-(\xi_i+\eta_i')\tau} + \frac{\mathbf{k}_{2i-1}\eta_i' + \mathbf{k}_{2i}}{2\eta_i'} \mathrm{e}^{-(\xi_i-\eta_i')\tau}, \quad [11]$$

where $\eta_i' = \eta_i/i$ is real. The steady state solution $\mathbf{k}_7$ is obtained by

$$\mathbf{k}_7 = \lim_{p\to 0} p\tilde{\mathbf{x}}(p) = \frac{\mathbf{g}(0)}{\Delta(0)}. \quad [12]$$

To obtain the remaining coefficients $\mathbf{k}_1, \ldots, \mathbf{k}_6$, one needs to consider the cases of a pair of $\mathbf{k}$'s originating from a conjugate pair of complex roots or a pair of real roots separately. Let $\mathbf{k}_{2i-1}$, $\mathbf{k}_{2i}$ correspond to a complex root represented by ξ_i, $\eta_i \in \mathbb{R}$. We then consider this limiting case of Eq. [9],

$$\lim_{p\to -\xi_i + i\eta_i} \tilde{\mathbf{x}}(p)[(p + \xi_i)^2 + \eta_i^2] = i\mathbf{k}_{2i-1}\eta_i + \mathbf{k}_{2i} \quad [13]$$

$$\frac{\mathbf{g}(-\xi_i + i\eta_i)}{(-\xi_i + i\eta_i)\Delta_R(-\xi_i + i\eta_i)} = i\mathbf{k}_{2i-1}\eta_i + \mathbf{k}_{2i}, \quad [14]$$

where $\Delta_R(p) = \Delta(p)/[(p + \xi_i)^2 + \eta_i^2]$. Each component of the left-hand side of Eq. [14] is of the form

$$f_j(p) = \frac{g_{j6}p^6 + g_{j5}p^5 + g_{j4}p^4 + g_{j3}p^3 + g_{j2}p^2 + g_{j1}p + g_{j0}}{p[(p + \xi_2)^2 + \eta_2^2][(p + \xi_3)^2 + \eta_3^2]}, \quad [15]$$

assuming $\xi_i = \xi_1$, $\eta_i = \eta_1$ without loss of generality. The real and imaginary parts of Eq. [15] are given by

$$f_j^{\mathrm{re}}(-\xi_1 + i\eta_1) = \frac{1}{h_3}[(h_{j4}\eta_1 - h_{j5}\xi_1)(h_1h_1' - h_2h_2') - (h_{j5}\eta_1 + h_{j4}\xi_1)(h_1'h_2 + h_1h_2')]$$

$$f_j^{\mathrm{im}}(-\xi_1 + i\eta_1) = \frac{1}{h_3}[-(h_{j5}\eta_1 + h_{j4}\xi_1)(h_1h_1' - h_2h_2') - (h_{j4}\eta_1 - h_{j5}\xi_1)(h_1'h_2 + h_1h_2')], \quad [16]$$

where

$$h_1 = (\xi_1 - \xi_3)^2 - \eta_1^2 + \eta_3^2,$$

$$h_1' = (\xi_1 - \xi_2)^2 - \eta_1^2 + \eta_2^2$$

$$h_2 = 2\eta_1(\xi_3 - \xi_1), \quad h_2' = 2\eta_1(\xi_2 - \xi_1)$$

$$h_3 = (\xi_1^2 + \eta_1^2)(h_1'^2 + h_2'^2)(h_1^2 + h_2^2)$$

$$h_{j4} = g_{j6}(-6\xi_1^5\eta_1 + 20\xi_1^3\eta_1^3 - 6\xi_1\eta_1^5) + g_{j5}(5\xi_1^4\eta_1 - 10\xi_1^2\eta_1^3 + \eta_1^5) + g_{j4}(-4\xi_1^3\eta_1 + 4\xi_1\eta_1^3) + g_{j3}(3\xi_1^2\eta_1 - \eta_1^3) - 2g_{j2}\xi_1\eta_1 + g_{j1}\eta_1$$

$$\begin{aligned} h_{j5} &= g_{j6}(\xi_1^6 - 15\xi_1^4\eta_1^2 + 15\xi_1^2\eta_1^4 - \eta_1^6) \\ &\quad + g_{j5}(-\xi_1^5 + 10\xi_1^3\eta_1^2 - 5\xi_1\eta_1^4) \\ &\quad + g_{j4}(\xi_1^4 - 6\xi_1^2\eta_1^2 + \eta_1^4) + g_{j3}(-\xi_1^3 + 3\xi_1\eta_1^2) \\ &\quad + g_{j2}(\xi_1^2 - \eta_1^2) - g_{j1}\xi_1 + g_{j0}. \end{aligned}$$

Then,

$$\mathbf{k}_1 = \frac{1}{\eta_1}\mathbf{f}^{\,\mathrm{im}}(-\xi_1 + i\eta_1), \quad \mathbf{k}_2 = \mathbf{f}^{\,\mathrm{re}}(-\xi_1 + i\eta_1). \quad [17]$$

If $\mathbf{k}_{2i-1}$, $\mathbf{k}_{2i}$ correspond to a pair of real roots x_{2i-1}, x_{2i} represented by ξ_i, η_i and $\eta_i' = \eta_i/i$, we consider

$$\begin{aligned} \lim_{p\to-\xi_i+\eta_i'} \tilde{\mathbf{x}}(p)[(p+\xi_i)^2 + \eta_i^2] &= \mathbf{f}(-\xi_i + \eta_i') \\ &= \mathbf{k}_{2i-1}\eta_i' + \mathbf{k}_{2i} \end{aligned}$$

and

$$\begin{aligned} \lim_{p\to-\xi_i-\eta_i'} \tilde{\mathbf{x}}(p)[(p+\xi_i)^2 + \eta_i^2] &= \mathbf{f}(-\xi_i - \eta_i') \\ &= -\mathbf{k}_{2i-1}\eta_i' + \mathbf{k}_{2i}. \quad [18] \end{aligned}$$

Hence,

$$\begin{aligned} \mathbf{k}_{2i-1} &= \frac{1}{2\eta_i'}[\mathbf{f}(-\xi_i + \eta_i') - \mathbf{f}(-\xi_i - \eta_i')], \\ \mathbf{k}_{2i} &= \frac{1}{2}[\mathbf{f}(-\xi_i + \eta_i') + \mathbf{f}(-\xi_i - \eta_i')]. \quad [19] \end{aligned}$$

This result simplifies Eq. [11] further; i.e.,

$$\begin{aligned} &\left[\mathbf{k}_{2i-1}\cos(\eta_i\tau) + \frac{\mathbf{k}_{2i}}{\eta_i}\sin(\eta_i\tau)\right]e^{-\xi_i\tau} \\ &= \frac{\mathbf{f}(x_{2i-1})}{x_{2i-1} - x_{2i}}e^{x_{2i-1}\tau} + \frac{\mathbf{f}(x_{2i})}{x_{2i} - x_{2i-1}}e^{x_{2i}\tau}. \quad [20] \end{aligned}$$

Equations [17] and [20] allow one to compute all coefficients of the transient solution terms. Alternatively, the last two unknown coefficients may be computed directly from the initial conditions and the four known coefficients.

DISCUSSION

As mentioned above, the presented algorithm includes the solutions of (*12, 13*). It is complete insofar as Eq. [8] considers all possible factorizations of the determinant. Unnecessarily specializing the factorization at this point by assuming the existence of a pair of real roots (*12, 13*) severely limits the applicability of the solution, especially for the on-resonant case. Compared to a solution by projection operators, this solution avoids the asymptotic approximation (Eq. [10] of (*18*)) and provides the time development of all magnetization components, a useful feature particularly with respect to pulse design.

The solution was thoroughly validated by comparing its behavior with solutions of the plain Bloch equations (*10*) and of the specialized binary systems of (*12, 13*) for various pulse sequences. Equations [6], [7], and [16] were computed by the symbolic calculation program Maple V R3 (Waterloo Maple, Inc., Waterloo, Canada), manually rewritten in a compact form and checked against the original solution.

The implementation uses Laguerre's method as described in (*19*) for computing the roots of $\Delta(p)$, Eq. [7]. Multiple roots have been found to occur if $T_1^A = T_1^B$, $T_2^A = T_2^B$, and $\delta_A = \delta_B = 0$. However, since an infinitesimal variation of a coefficient is sufficient to resolve the degeneracy (*20*), multiple roots pose no problem if the coefficients represent physical parameters of finite precision. Variation of one parameter such as T_2^A by less than a factor $(1 + 10^{-4})$ resolves the degeneracy, a fact which proves the robustness of the algorithm.

Compared to numerical integration methods, the main advantage of the algorithm is its black box capability. Pulse sequences consisting of pulses of some microseconds or seconds duration are readily realized; spin system parameters may vary over several orders of magnitudes. The algebraic complexity of the algorithm is manageable. Even solutions of higher-order systems such as a three-compartment model can be realized by taking advantage of the well-defined structure of the algorithm and a symbolic calculation program. Regarding the computational cost of the algorithm it should be mentioned that solving for a period of constant RF irradiation requires 1.2 ms on an old-fashioned SuperSPARC, 60-MHz microprocessor (SUN Microsystems, Inc., Mountain View, USA). The algorithm is available as C++ code from the authors.

REFERENCES

1. S. Forsén and R. A. Hoffman, Study of moderately rapid chemical exchange by means of nuclear magnetic double resonance, *J. Chem. Phys.* **39**(11), 2892–2901 (1963).
2. S. H. Koenig, R. G. Bryant, K. Hallenga, and G. S. Jacob, Magnetic cross-relaxation among protons in protein solutions, *Biochemistry* **17**(20), 4348–4358 (1978).
3. H. T. Edzes and E. T. Samulski, The measurement of cross-relaxation effects in the proton NMR spin–lattice relaxation of water in biological systems: Hydrated collagen and muscle, *J. Magn. Res.* **31,** 207–229 (1978).
4. J. Grad and R. G. Bryant, Nuclear magnetic cross-relaxation spectroscopy, *J. Magn. Res.* **90,** 1–8 (1990).
5. J. Eng, T. L. Ceckler, and R. S. Balaban, Quantitative ^{1}H magnetization transfer imaging, *Magn. Res. Med.* **17,** 304–314 (1991).

6. G. H. Caines, T. Schleich, and J. M. Rydzewski, Incorporation of magnetization into the formalism for rotating-frame spin–lattice proton NMR relaxation in the presence of an off-resonance-irradiation field, *J. Magn. Res.* **95,** 558–566 (1991).

7. S. H. Koenig, R. D. Brown III, and R. Ugolini, A unified view of relaxation in protein solutions and tissue, including hydration and magnetization transfer, *Magn. Res. Med.* **29,** 77–83 (1993).

8. R. M. Henkelman, X. Huang, Q. Xiang, G. J. Stanisz, S. D. Swanson, and M. J. Bronskill, Quantitative interpretation of magnetization transfer, *Magn. Res. Med.* **29,** 759–766 (1993).

9. H. C. Torrey, Transient nutations in nuclear magnetic resonance, *Phys. Rev.* **76,** 1059–1063 (1949).

10. G. A. Morris and P. B. Chilvers, General analytical solutions of the bloch equations, *J. Magn. Res. A* **107,** 236–238 (1994).

11. G. A. Morris and P. B. Chilvers, Correction to: General analytical solutions of the bloch equations, *J. Magn. Res. A* **111,** 232 (1994).

12. H. N. Yeung and S. D. Swanson, Transient decay of longitudinal magnetization in heterogeneous spin systems under selective saturation, *J. Magn. Res.* **99,** 466–479 (1992).

13. H. N. Yeung, Transient response of a heterogeneous spin system to binomial pulse saturation, *J. Magn. Res. A* **102,** 8–15 (1993).

14. R. A. Jones and T. E. Southon, Improving the contrast in rapid imaging sequences with pulsed magnetization transfer contrast, *J. Magn. Res.* **97,** 171–176 (1992).

15. B. S. Hu, S. M. Conolly, G. A. Wright, D. G. Nishimura, and A. M. Macovski, Pulsed saturation transfer contrast, *Magn. Res. Med.* **26,** 231–240 (1992).

16. S. A. Röll, W. Dreher, E. Busch, and D. Leibfritz, Magnetization transfer in localized proton spectroscopy of rat brain using pulsed on-resonant rf-irradiation, *in* ''Proc. ISMRM, 4th Annual Meeting, New York,'' p. 1671 (1996).

17. M.-F. Roy, Basic algorithms in real algebraic geometry and their complexity: From Sturm's theorem to the existential theory of reals, *in* ''Lectures in Real Geometry'' (F. Broglia, Ed.), pp. 1–67, de Gruyter, Berlin (1996).

18. R. S. Adler and H. N. Yeung, Transient decay of longitudonal magnetization in heterogeneous spin systems under selective saturation. iii. solution by projection operators, *J. Magn. Res. A* **104,** 321–330 (1993).

19. W. H. Press, S. Teukolsky, W. T. Vetterling, and B. P. Flannary, ''Numerical Recipes in C,'' Cambridge Univ. Press, Cambridge, UK (1994).

20. H. Weber, ''Lehrbuch der Algebra,'' Vieweg und Sohn, Braunschweig (1898).